IOWA STATE UNIVERSITY
Digital Repository

Retrospective Theses and Dissertations

Iowa State University Capstones, Theses and Dissertations

1963

The structures of certain base-catalyzed condensation products

Sujit Kumar Bhattacharya
Iowa State University

Follow this and additional works at: https://lib.dr.iastate.edu/rtd

Part of the Organic Chemistry Commons

Recommended Citation

Bhattacharya, Sujit Kumar, "The structures of certain base-catalyzed condensation products " (1963). *Retrospective Theses and Dissertations*. 2334.
https://lib.dr.iastate.edu/rtd/2334

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

المنارة للاستشارات

www.manaraa.com

This dissertation has been 63–5168
microfilmed exactly as received

BHATTACHARYA, Sujit Kumar, 1927–
THE STRUCTURES OF CERTAIN BASE–
CATALYZED CONDENSATION PRODUCTS.

Iowa State University of Science and Technology
Ph.D., 1963
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THE STRUCTURES OF CERTAIN BASE-CATALYZED CONDENSATION PRODUCTS

by

Sujit Kumar Bhattacharya

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa
1963

TABLE OF CONTENTS

Page

PART I. THE SELF-CONDENSATION OF METHYL GLUTACONATE... 1

INTRODUCTION 2

HISTORICAL 3

DISCUSSION 7

SPECTRA 19

PART II. THE STRUCTURE OF THE ETHYLOXALATE-CYCLOHEXENYLCYCLOHEXANONE CONDENSATION PRODUCT........ 38

INTRODUCTION 39

HISTORICAL 40

DISCUSSION 46

SPECTRA 52

EXPERIMENTAL 69

SUMMARY 88

LITERATURE CITED 89

ACKNOWLEDGEMENTS 92

PART I - THE SELF-CONDENSATION OF METHYL GLUTACONATE

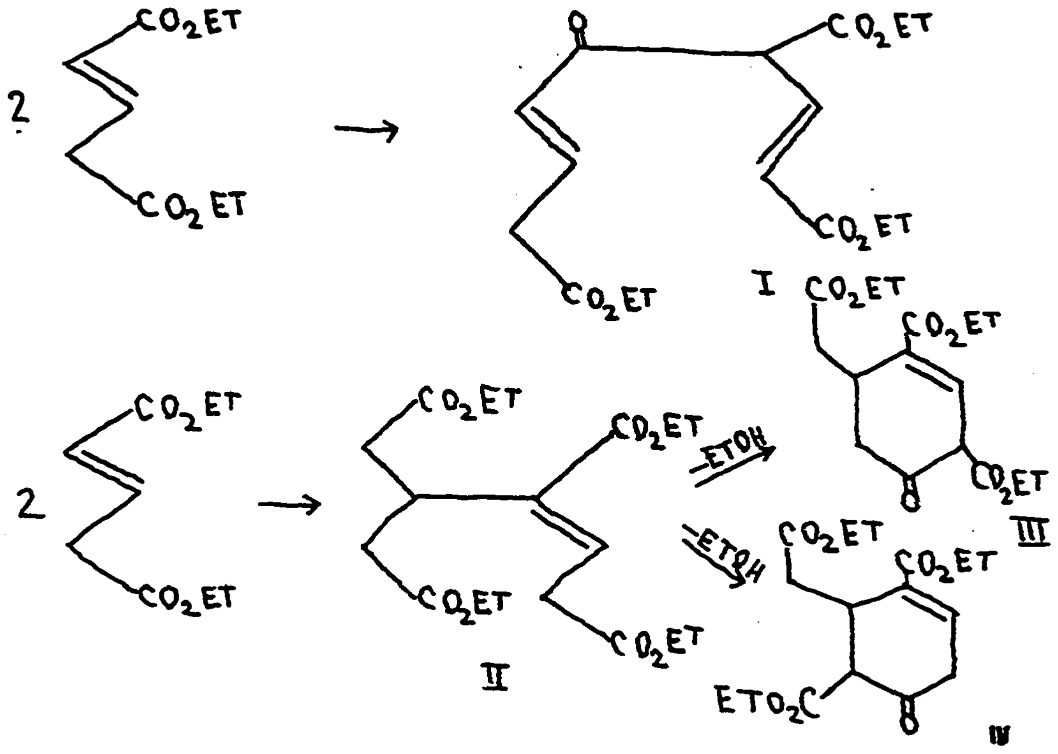
INTRODUCTION

The purpose of the present research is to determine the structure of the substance derived from self-condensation of methyl glutaconate and to investigate its chemistry, particularly with a view to transforming it into the ring E moiety of yohimbine-like alkaloids.

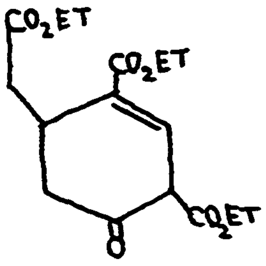
HISTORICAL

Dialkylation of ethyl glutaconate with methyl iodide has been reported to yield ethyl α,α- and α,γ- dimethylglutaconates (1,2,3). Following these reports, Fecht (4) and Curtis and Kenner (5) have examined the possibility of forming either a cyclopropane or a cyclopentane ring by alkylation of ethyl glutaconate with ethylene dibromide and sodium ethoxide. Although Fecht (4) obtained evidence of the formation of the cyclopropane derivative, Curtis and Kenner (5) showed that this compound constituted no more than 10% of the product mixture. The major product was a crystalline compound which had been formed without the participation of ethylene dibromide. It gave a positive ferric chloride test. Elemental analysis showed it to be derived from two moles of glutaconic ester by elimination of one mole of alcohol. The same compound was obtained when glutaconic ester alone was treated with sodium ethoxide (3,5,6).

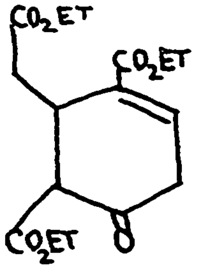
Blaise (3) postulated structure I for the compound. He called it ethyl glutaconyl-glutaconate and considered it the consequence of a Claisen condensation between two moles of glutaconic ester. Pechmann _et_ _al_. (6), on the other hand, postulated II as the reaction intermediate and III or IV, obtained by elimination of a mole of alcohol, as the final product.



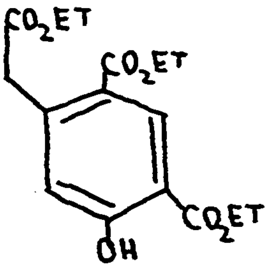
The gross structure (III or IV) has been settled. Pechmann <u>et al</u>. (6) aromatized the compound with bromine. The product (V or VI) formed a methyl ether and an acetate, showing the presence of an hydroxyl group. The ester groups could be hydrolyzed with potassium hydroxide solution to give a triacid (VII or VIII). The meta orientation of the two carboxyl groups with respect to each other was indicated by a negative fluroescein test. When heated with hydrochloric acid, the acid gave a compound IX which proved identical with m-hydroxyphenylacetic acid. Hydrolysis and decarboxylation of the two carboxyl groups had evidently occurred. This clearly showed the meta relationship of the hydroxy group with the acetic acid side chain. m-Hydroxyphenylacetic acid could be brominated to give a tribromo derivative X. These facts were consistent with both structure III and IV for the original product. Although no compelling reasons were advanced, Curtis and Kenner seemed to prefer structure IV.



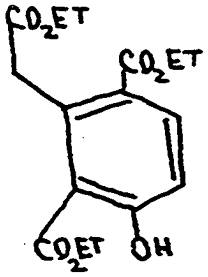
III



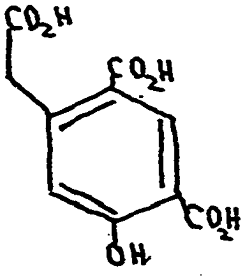
IV



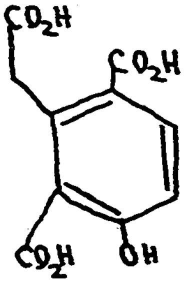
V



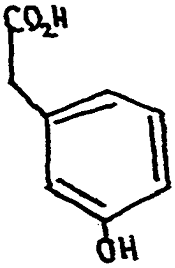
VI



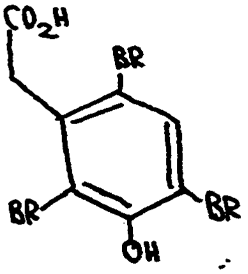
VII



VIII

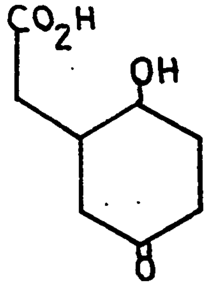


IX



X

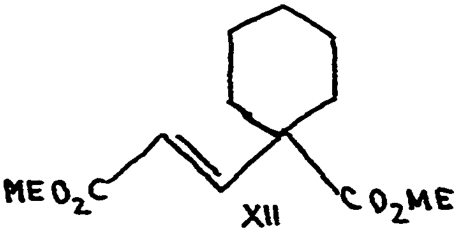
Hydrolysis of III (or IV) with mineral acid yielded a monobasic acid $C_8H_{12}O_4$ from which a lactone could be prepared (3,6). Structure XI was assigned to the hydroxy acid (3,5).



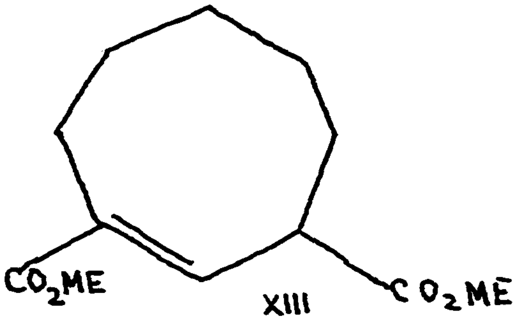
XI

DISCUSSION

In connection with another problem it was necessary to investigate whether a six-membered ring could be formed on the methylene carbon of dimethyl glutaconate by its alkylation with pentamethylene dibromide. As a consequence, a mixture of dimethyl glutaconate (7), pentamethylene dibromide and sodium methoxide were refluxed in methanol solution. Neutral and acidic products were obtained. Although the infrared spectrum of the neutral product looked similar to that of methyl glutaconate, its n.m.r. spectrum was incompatible with either the cyclohexane structure XII or the alternate cyclooctane system XIII. While this product remained unidentified, this experience suggests that the structure proposed by Fecht (4) for the product of alkylation of ethyl glutaconate with ethylene dibromide may need reinvestigation.



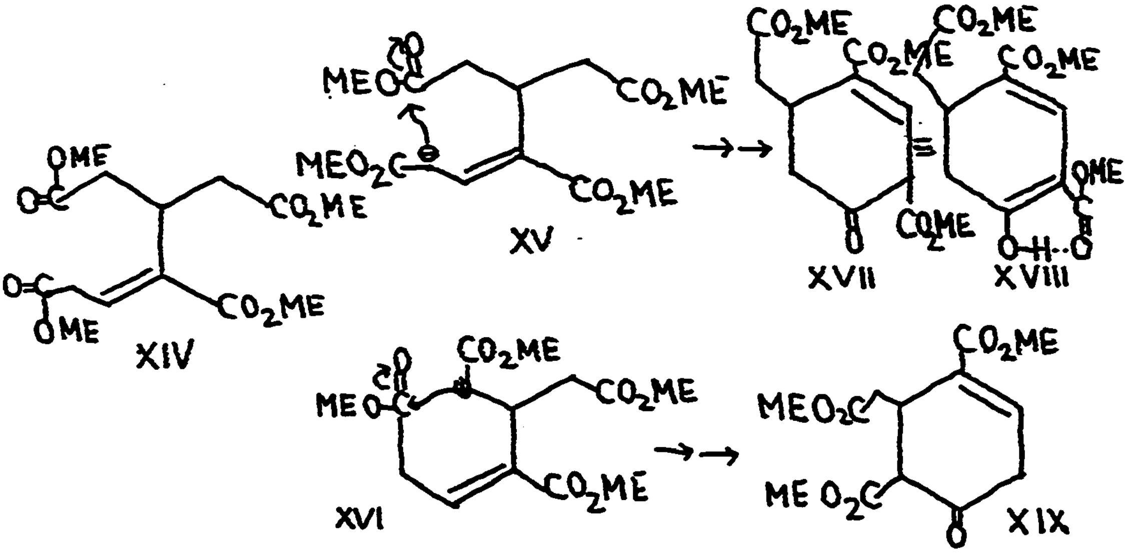
XII



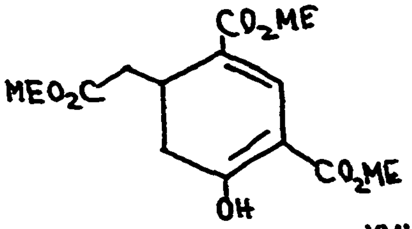
XIII

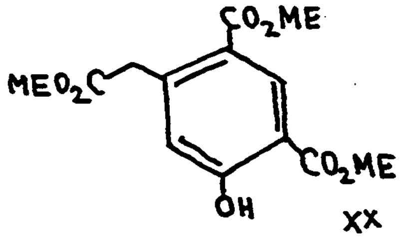
The acidic product gave a ferric chloride test and seemed similar to the product of self-condensation already reported for ethyl glutaconate (3,4,5,6). Furthermore, the same compound could be prepared by refluxing a methanol solution of dimethyl glutaconate and sodium methoxide without alkylating agent. Since the structure of the product was ambiguous (XVII or XIX), the position of the carbomethoxy group β to the ketone had to be settled.

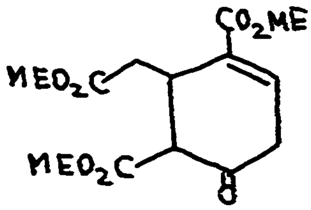
The speed of the condensation reaction of esters of glutaconic acid strongly suggests the first step to be a Michael condensation, cf. Pechmann et al. (6), rather than a Claisen condensation, cf. Blaise (3). A Dieckmann condensation of the intermediate XIV or one of its double bond isomers, can lead to either of two possible products, XVII or XIX. A build-up of concentration of the anion XV, however, is favored over that of XVI since XV is stabler, being a vinylogous malonic ester anion. Furthermore, cyclization in the manner indicated in XV is sterically more favorable than that shown in XVI. Therefore, theory would predict XVII to represent the structure of the condensation product.

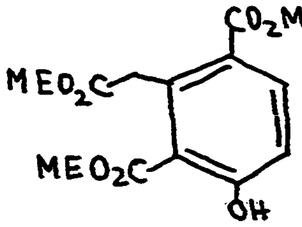


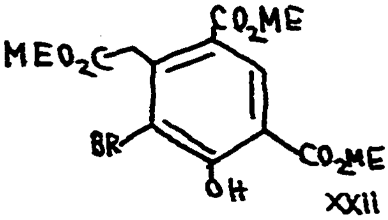
Attempts to dehydrogenate XVII (or XIX) by Pd-C failed. It was, therefore, aromatized to the phenol XX (or XXI) by bromine, —— the original method of Pechmann et al. (6). When more than the theoretical amount of bromine was used or when, in a separate reaction, the phenol was treated with bromine, a new compound was formed. This turned out to be the monobromophenol XXII (XXIII). The methyl ether of XX (or XXI) was prepared by refluxing the latter in acetone with dimethyl sulfate and anhydrous potassium carbonate. The product was XXIV (XXV).

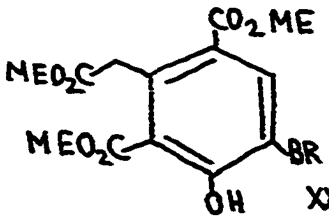

XVIII

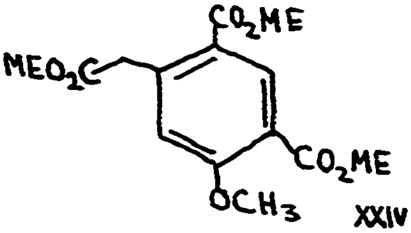

XX

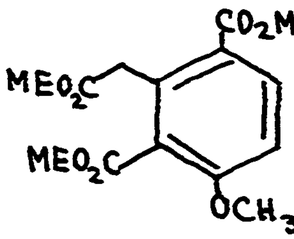

XIX


XXI


XXII


XXIII

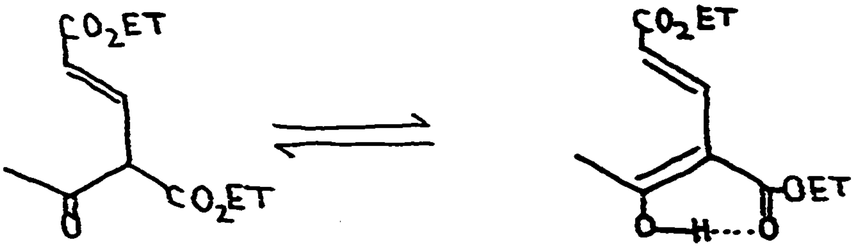

XXIV


XXV

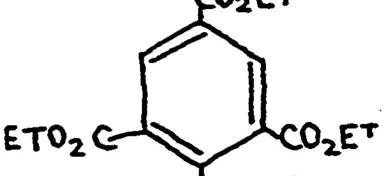
The olefinic proton region of the n.m.r. spectrum of XVII (or XIX) showed a one-proton singlet at 454 c.p.s. (relative to tetramethylsilane). The proton count indicated 100% enol content in deuterochloroform solution, while the multiplicity favored structure XVIII over XIX. The OH proton showed up at 786 c.p.s. and disappeared when the solution was shaken with deuterium oxide. The extraordinarily high value of 786 c.p.s. for the enol proton indicated its tight hydrogen bonding with the carbonyl function of the neighboring carbomethoxy group. This fact also was apparent from the infrared spectrum which showed no OH peak in the customary 2.8 - 3.3 μ region while revealing carbonyl peaks at 5.76 μ (saturated ester), 5.87 μ (conjugated ester), 6.04 μ (hydrogen bonded ester) and 6.13 μ (double bond).

The downfield region of the n.m.r. spectrum of the phenol XX or (XXI) revealed three singlets at 412, 516 and 665 c.p.s. Since the last represented the hydroxyl proton, the first two had to be aromatic hydrogens. The multiplicity of the signals ruled out structure XXI, while their chemical shift was indicative of C(5)-H and C(2)-H, respectively. The 516 c.p.s. signal compared favorably with one at 525 c.p.s. for the hydrogen ortho to both carbomethoxy groups in dimethyl isophthalate (8). The n.m.r. spectrum of the bromophenol XXII showed the same hydrogen at 517 c.p.s. while its OH group revealed a signal at 723 c.p.s. The tight hydrogen bonding between the hydroxyl and carbomethoxyl groups in this compound was corroborated by its infrared spectrum: no OH bond in the proper region, while 5.75μ, 5.80μ, 5.95μ (hydrogen-bonded carbomethoxy group) and 6.20μ in the double bond region. The methyl ether XXIV showed two aromatic one-proton singlets at 412 (c(5)-H and 512 c.p.s. (C(2)-H).

Ethyl α-acetylglutaconate XXVI was prepared to serve as a model for comparison of its ultraviolet spectrum with that of XVIII. However, it was anticipated that the difference of the cyclic vs. acyclic structures might make a difference in the spectral properties of the two substances. Compound XXVI was prepared by the method of Simonsen (9), the condensation of ethyl acetoacetate with ethyl propiolate (10) in the presence of sodium ethoxide. The by-product, which Simonsen (9) had proved to be triethyl methyltrimesate XXVIII, was obtained also.



XXVI XXVII



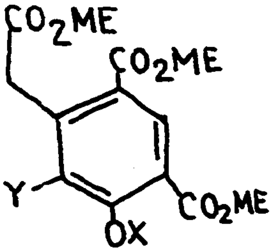
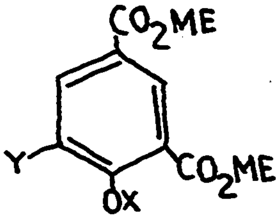
XXVIII

The following table shows the u.v. spectra of the two compounds. The agreement was best in basic solution. While their anions are apparently identical, the model compound is less enolized in acid or neutral media than XVIII. The lower tendency for XXVI to enolize was indicated also by its infrared spectrum (as film) which showed carbonyl peaks at 5.75μ, 5.80μ and 5.85μ (hydrogen-bonded ester), 6.14μ. Its n.m.r. spectrum showed a hydroxyl signal of less than one proton at 855 c.p.s.

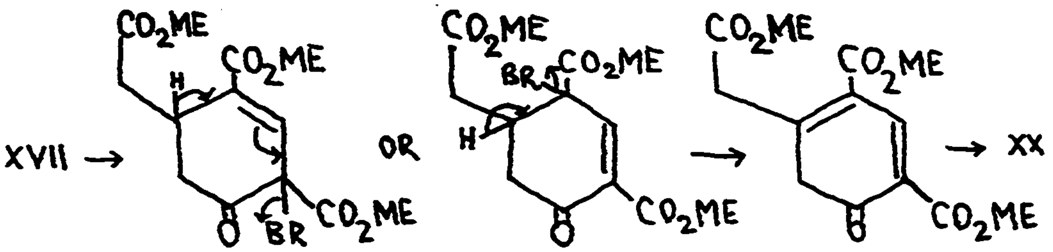
	Neutral				Basic			
	λ_{max} mμ	log ε	λ_{min} mμ	log ε	λ_{max} mμ	log ε	λ_{min} mμ	log ε
XVIII	320	3.63	287	3.36	357	4.24	318	3.76
	262	3.99			292	4.24	245	3.54
	300	3.54 (shoulder)						
XXVI $\rightleftharpoons$ XXVII	278	4.30	240	3.99	347	4.35	303	3.74
	230	4.10			280	4.04		

The u.v. spectra of the phenol XX, methyl ether XXIV and bromophenol XXII could be compared with the data of Hunt et al. (11), who in recent years had prepared a large number of derivatives of dimethyl 4-hydroxyisophthalates for pharmacological study.

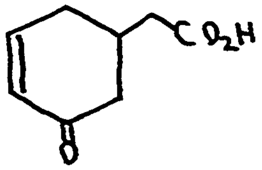
λ max. in mμ (log ε)

	X = H	X = CH_3	X = H
	Y = H	Y = H	Y = Br
	226 (4.67)	224 (4.63)	231 (4.58)
	251 (4.14)	258 (4.25)	255sh(3.58)
	306 (3.51)	290 (3.74)	313 (4.10)
	221.2(4.58)	219 (4.48)	228 (4.56)
	253.5(4.02)	255 (4.15)	246sh(3.98)
	303 (3.49)	294 (3.43)	309.5(3.66)

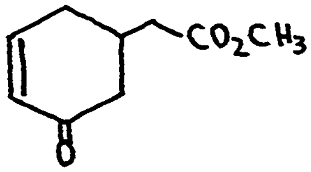
The mechanism of aromatization of XVIII by bromine probably is as follows:



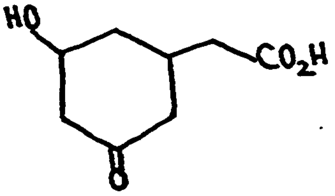
Having settled the structure of the self-condensation product of methyl glutaconate as XVIII, its reaction in mineral acid was investigated next. On refluxing with 10% hydrochloric acid for 24 hrs., an unsaturated keto acid XXIX was obtained. Its infrared peaks at 5.80μ and 5.98μ showed the presence of carboxyl and α,β- unsaturated ketone functions, respectively. The methyl ester was prepared and its structure as XXX confirmed on the basis of the following facts: 1) an elemental analysis checking for a $C_9H_{12}O_3$ formula; 2) infrared bands at 5.78μ, 5.96μ and 6.17μ; 3) an ultraviolet maximum at 225 mμ in conformity with Woodward's generalization for α, β -unsaturated ketones (12,13,14) and 4) a n.m.r. spectrum showing olefinic proton signals at 365 (broad one-proton doublet) and at 420 c.p.s. (one-proton multiplet). The hydroxy acid reported by Blaise (3) and Curtis and Kenner (5) was not obtained. As the hydroxy acid may have been formed by the hydroxylation of the enone XXIX, the most probably structure for this compound is XXXI.



XXIX

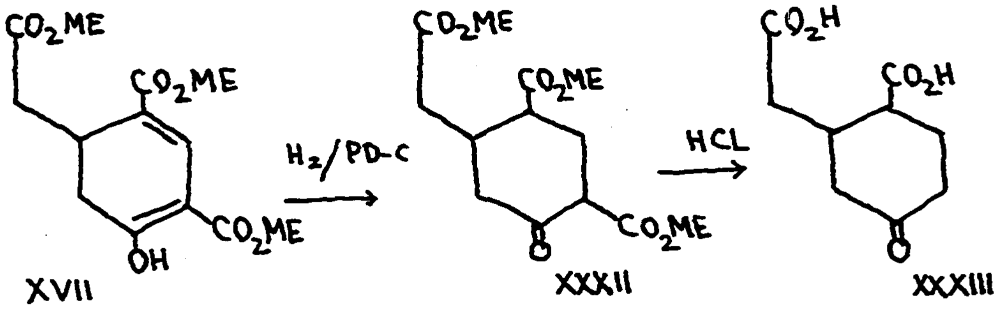


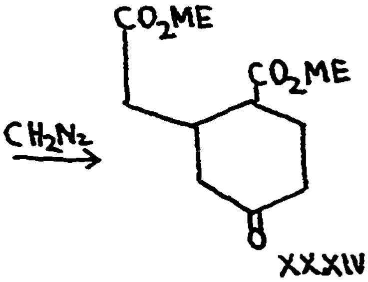
XXX

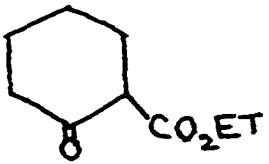


XXXI

Compound XVII was hydrogenated catalytically to XXXII. The u.v. spectrum of the product showed a peak at 245mμ (log ε 3.92), identical [254mμ (log ε 3.90)] with that of 2-carboethoxycyclohexanone (XXXV). The infrared spectrum of XXXII showed peaks at 5.75μ (saturated ester), 6.01μ (chelated ester) and 6.17μ (double bond). Decarboxylation of the carbomethoxy group β to the keto function proved difficult. Refluxing with base or mineral acid led to incomplete decarboxylation. The reaction was finally accomplished by heating with 20% hydrochloric acid in a sealed tube. The resulting diacid XXXIII was converted to its methyl ester XXXIV.

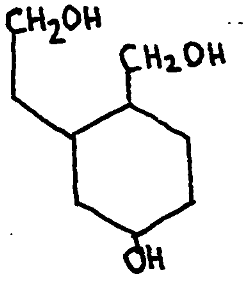




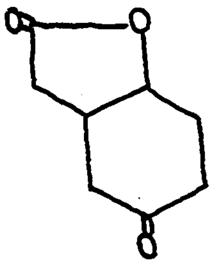


XXXV

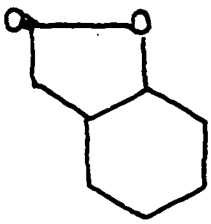
One incomplete aim in the present work was the transformation of the condensation product of methyl glutaconate XVIII to a form which could serve as the ring E moiety of yohimbine-like alkaloids. For this purpose, XXXIV needs to be converted to XXXVI and XXXVII. van Tamelen and Shamma (15) have already converted XXXVIII into XXXIX with alcoholic hydrobromic acid. On reaction with tryptamine, followed by two further transformations, they have transformed XXXIX to yohimbane. Subjection of compound XXXVII to the same reaction sequence might be expected to yield yohimbone.



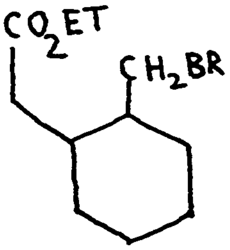
XXXVI



XXXVII



XXXVIII



XXXIX

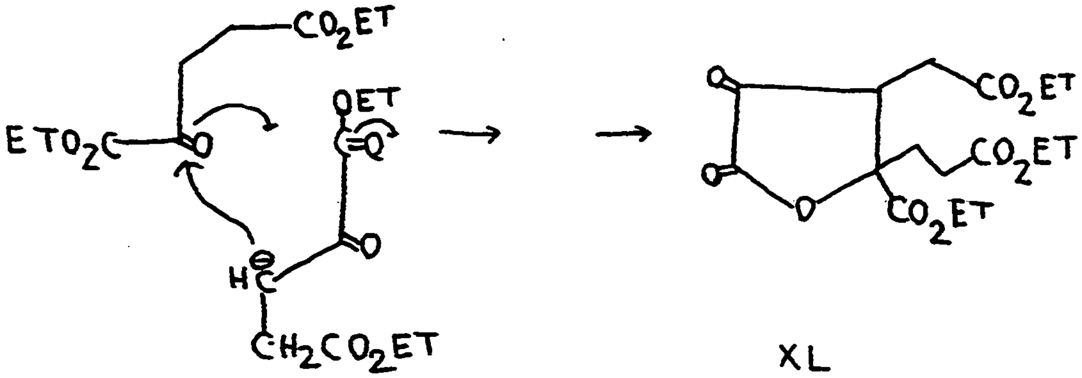
The self-condensation of esters of glutaconic acid finds a parallel in the self-condensation of ester of α-ketoglutaric acid. Garrett* observed that in a Fischer esterification of this acid, an acidic product was also obtained in addition to the neutral diester. The carbonyl peaks in its infrared spectrum were noted as 5.60(m)μ and

---

*Dr. Sheila Garrett, Chemistry Department, Iowa State University, Ames, Iowa. Private Communication (1960).

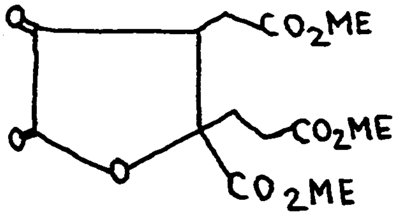
5.76(s)μ. This suggested a lactone structure. Repetition of Garrett's work using methanol confirmed her observations. Elemental analysis revealed a formula corresponding to two moles of dimethyl α-ketoglutarate minus one mole of methanol. The molecular weight was found to be 338. It gave a faint ferric chloride test. Its ultraviolet maximum at 242 mμ was shifted bathochromically 33mμ in basic solution. The compound was converted to a methyl ether with diazomethane whose infrared spectrum showed carbonyl peaks at 5.65μ, 5.78μ and a double bond peak at 5.99μ.

Gault (16) in his study of self-condensation of ethyl ester of α-keto acids had reported similar products. He postulated the reaction as follows:

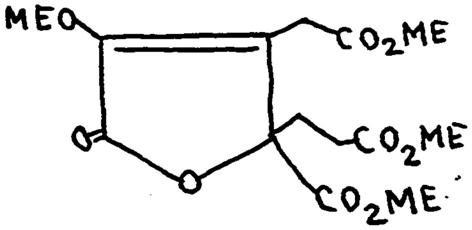


XL

As the spectral data of our acidic product and its enol ether are consistent with a structure like XL, Gault's and our compounds probably are similar. Thus our acidic product and its methyl ether probably are XLI and XLII, respectively. A rigorous proof, of course, is necessary before the structures are finally determined.



XLI



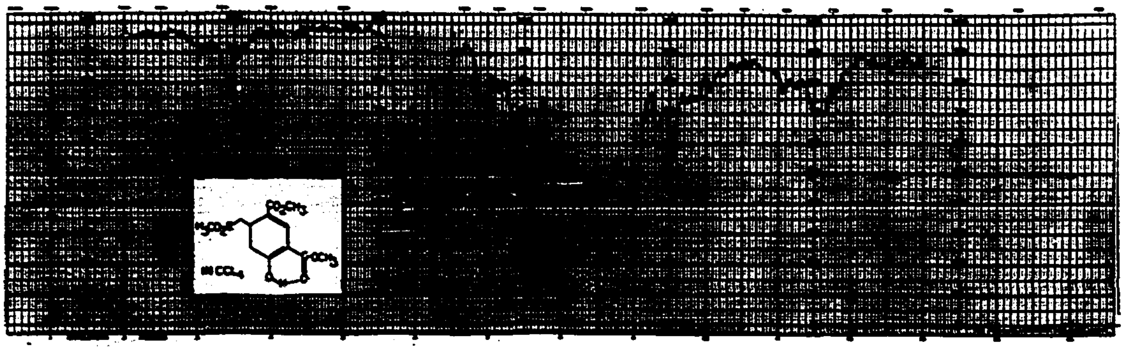
XLII

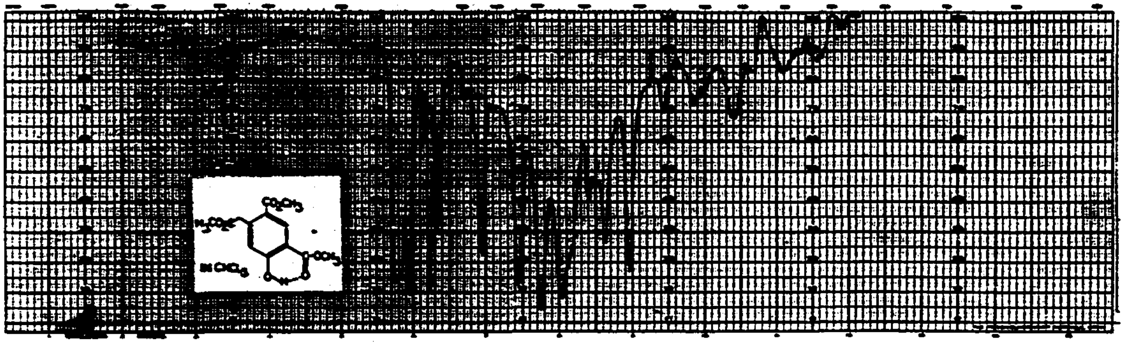
SPECTRA

All infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer. The ultraviolet spectra were run in 95% ethanol using a Carey model 14 recording spectrophotometer.

The nuclear magnetic resonance spectra were obtained from dilute deuterochloroform solutions using a Varian Model A-60 Spectrometer. Resonance positions were determined by pre-calibrated charts relative to tetramethylsilane as internal standard. Peak positions were expressed in c.p.s. (cycles per second).

Figure 1. Infrared spectra


CO2CH3
H3CO2C
OCH3
in CCl4


CO2CH3
H3CO2C
OCH3
in CHCl3

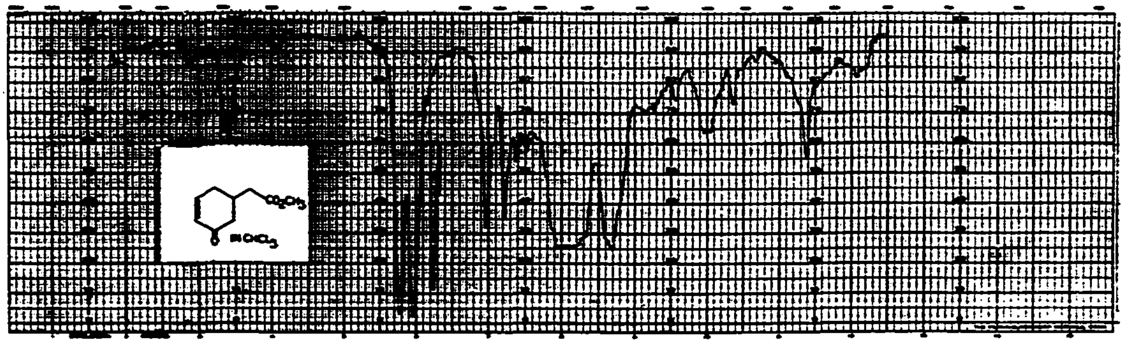
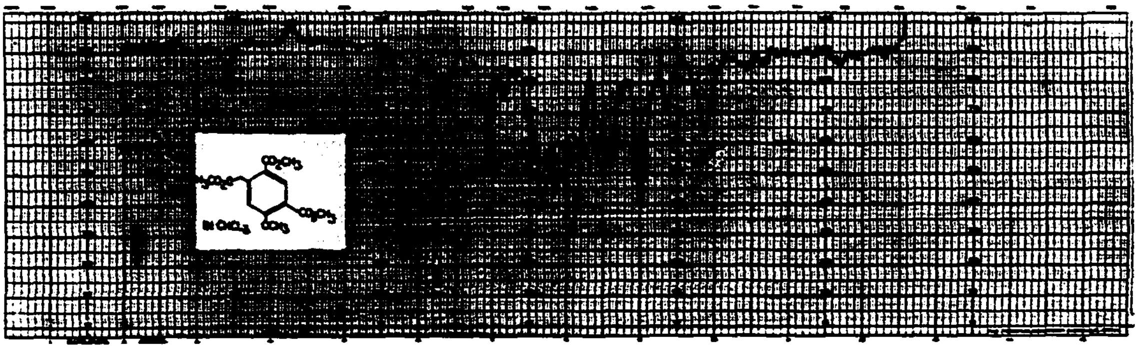
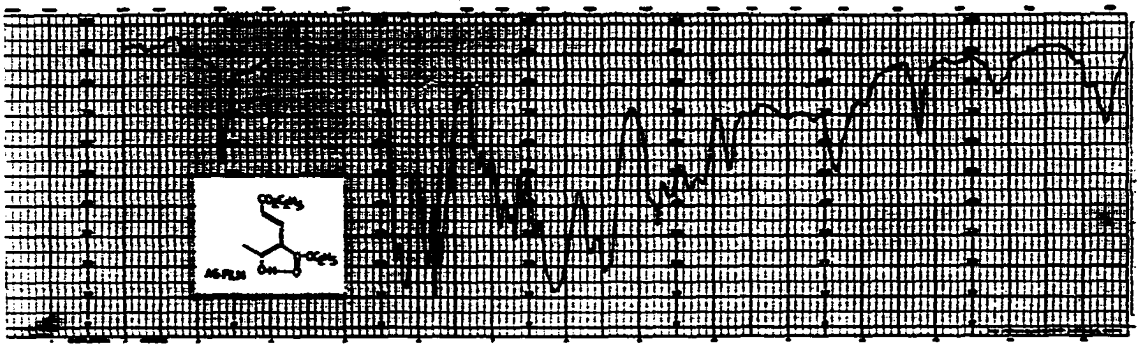

CO2CH3
in CHCl3

Figure 2. Infrared spectra


H3CO2C
CO2CH3
CO2CH3
OCH3
IN CHCl3


CO2C2H5
OC2H5
AS FILM

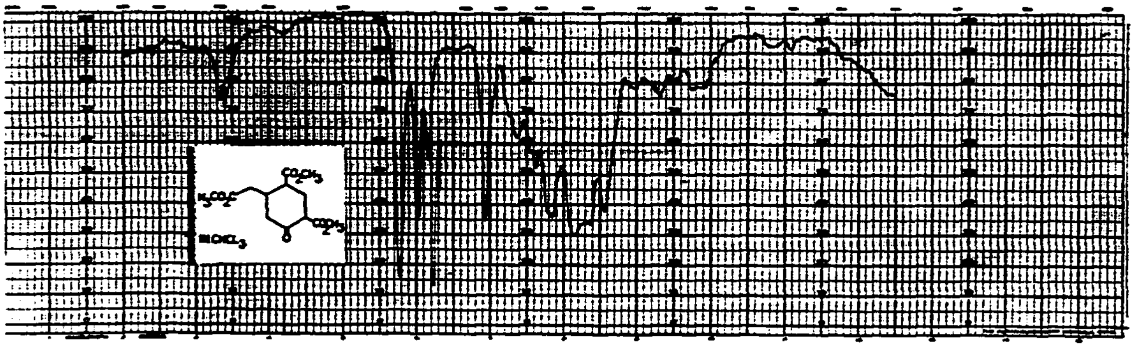
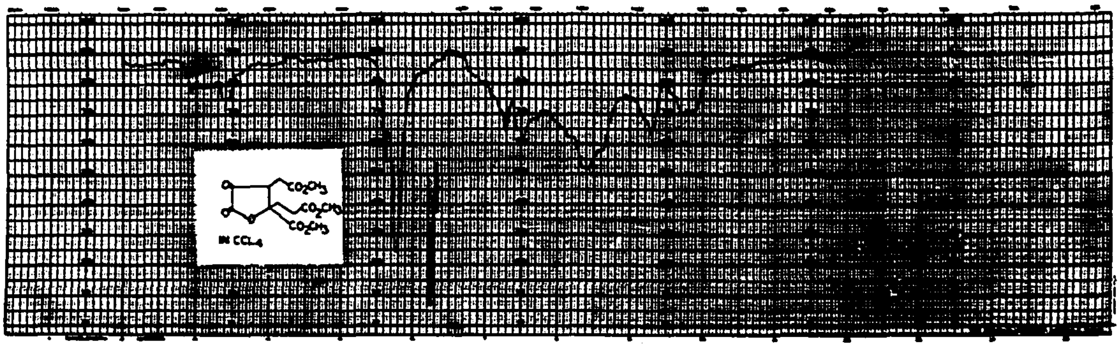

H3CO2C
CO2CH3
CO2CH3
IN CHCl3

Figure 3. Infrared spectra


CO2CH3
CO2CH3
CO2CH3
IN CCL4


CO2H
CO2H
IN NUJOL

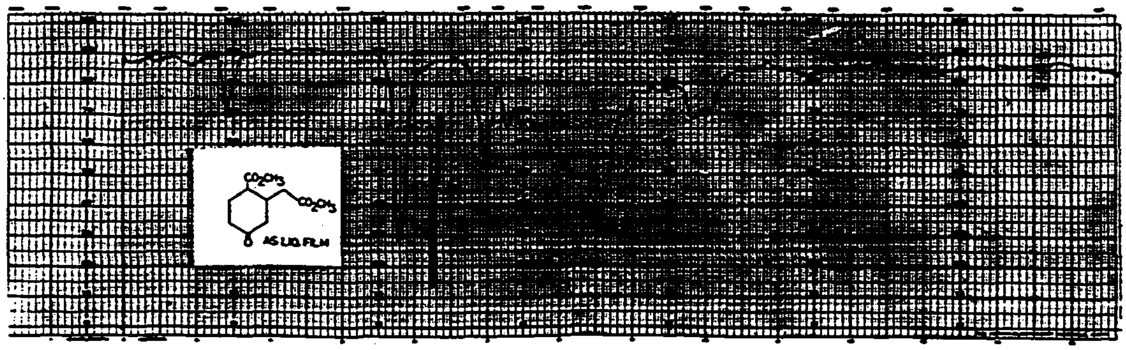

CO2CH3
CO2CH3
AS LIQ.FILM

Figure 4. Infrared spectra

(27)

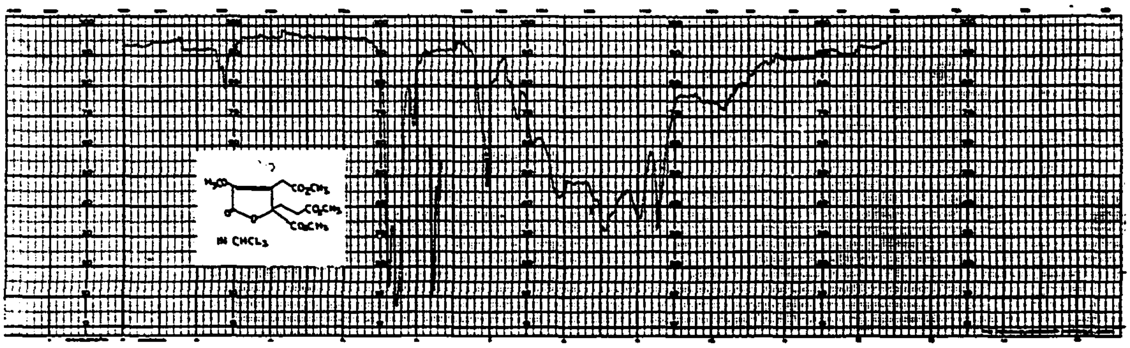
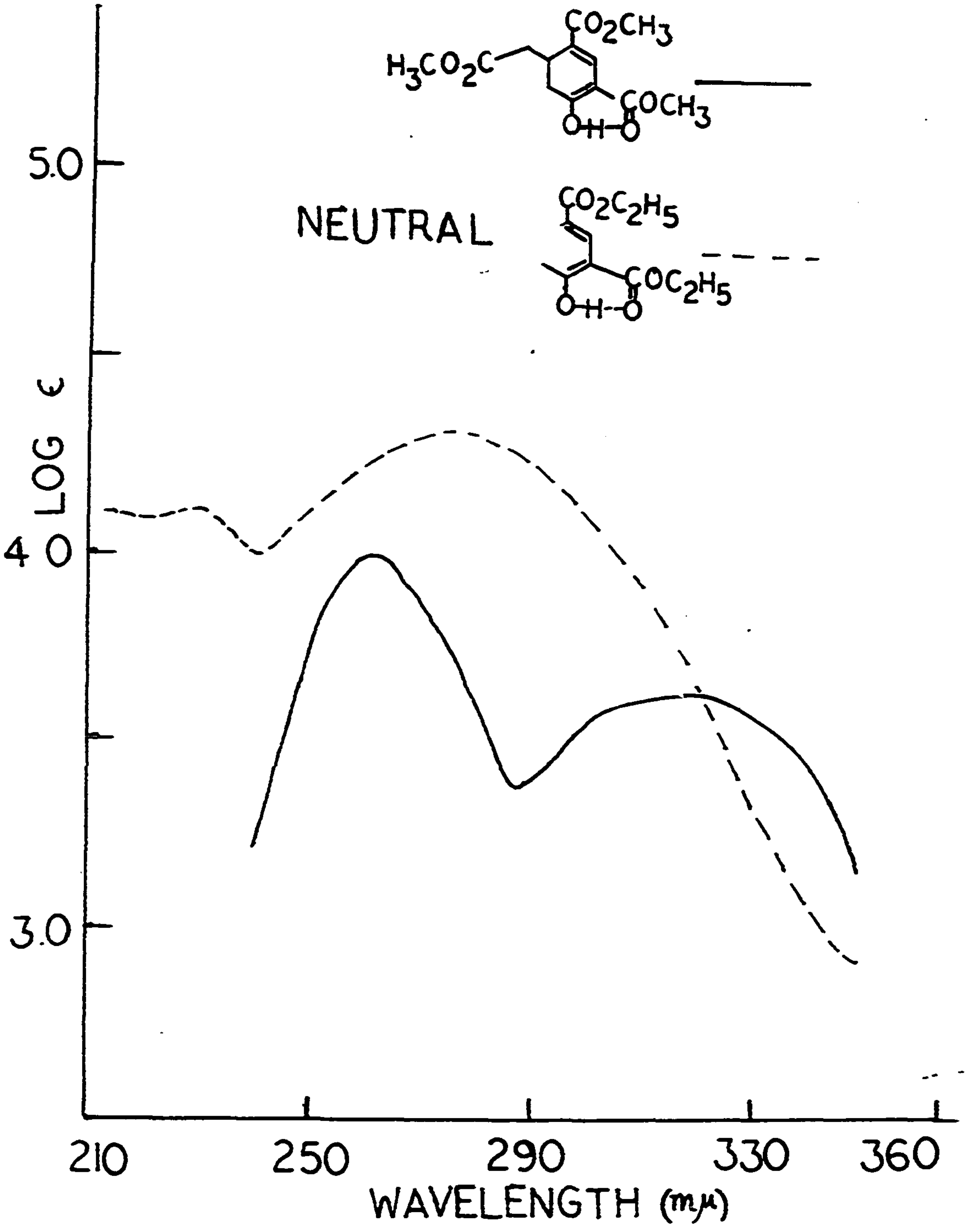


Figure 5. Ultraviolet spectra



H_3CO_2C
CO_2CH_3
$COCH_3$
O-H-O
NEUTRAL
$CO_2C_2H_5$
COC_2H_5
O-H-O
5.0
LOG ε
4 0
3.0
210
250
290
330
360
WAVELENGTH (mμ)

Figure 6. Ultraviolet spectra

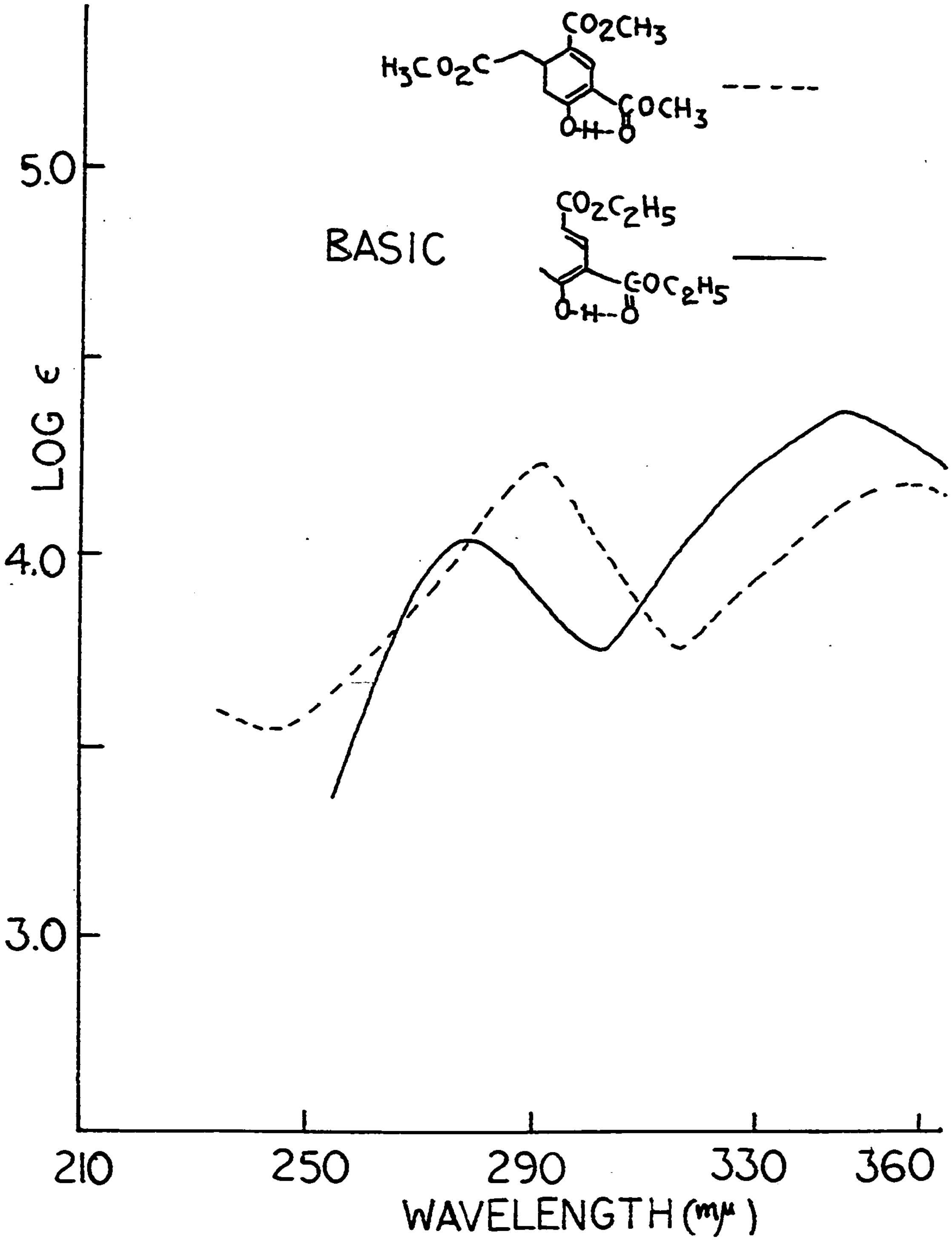

CO_2CH_3
H_3CO_2C
$COCH_3$
O-H--O
BASIC
$CO_2C_2H_5$
COC_2H_5
O-H--O
5.0
4.0
3.0
LOG ε
210
250
290
330
360
WAVELENGTH (mμ)

Figure 7. Ultraviolet spectra

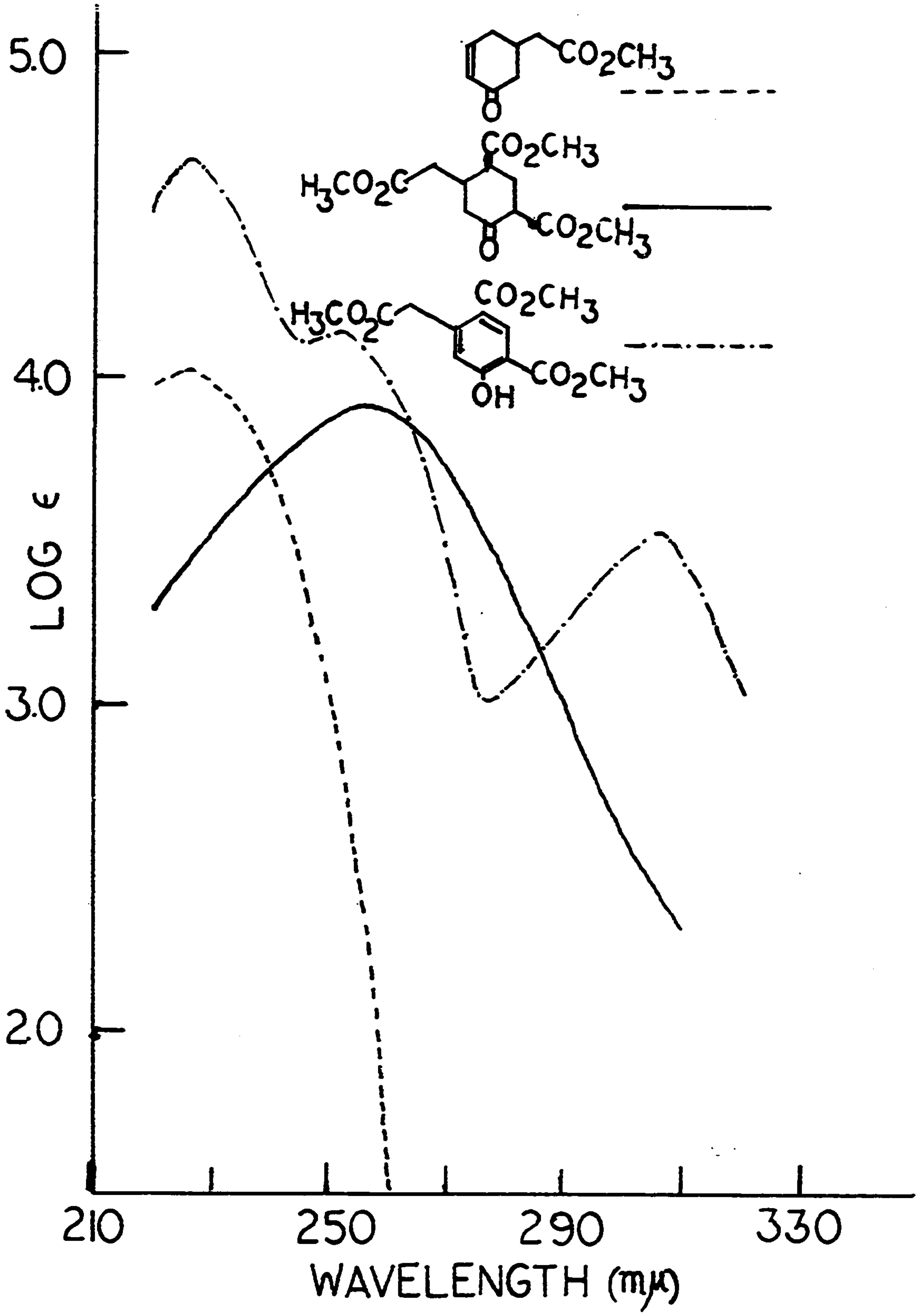
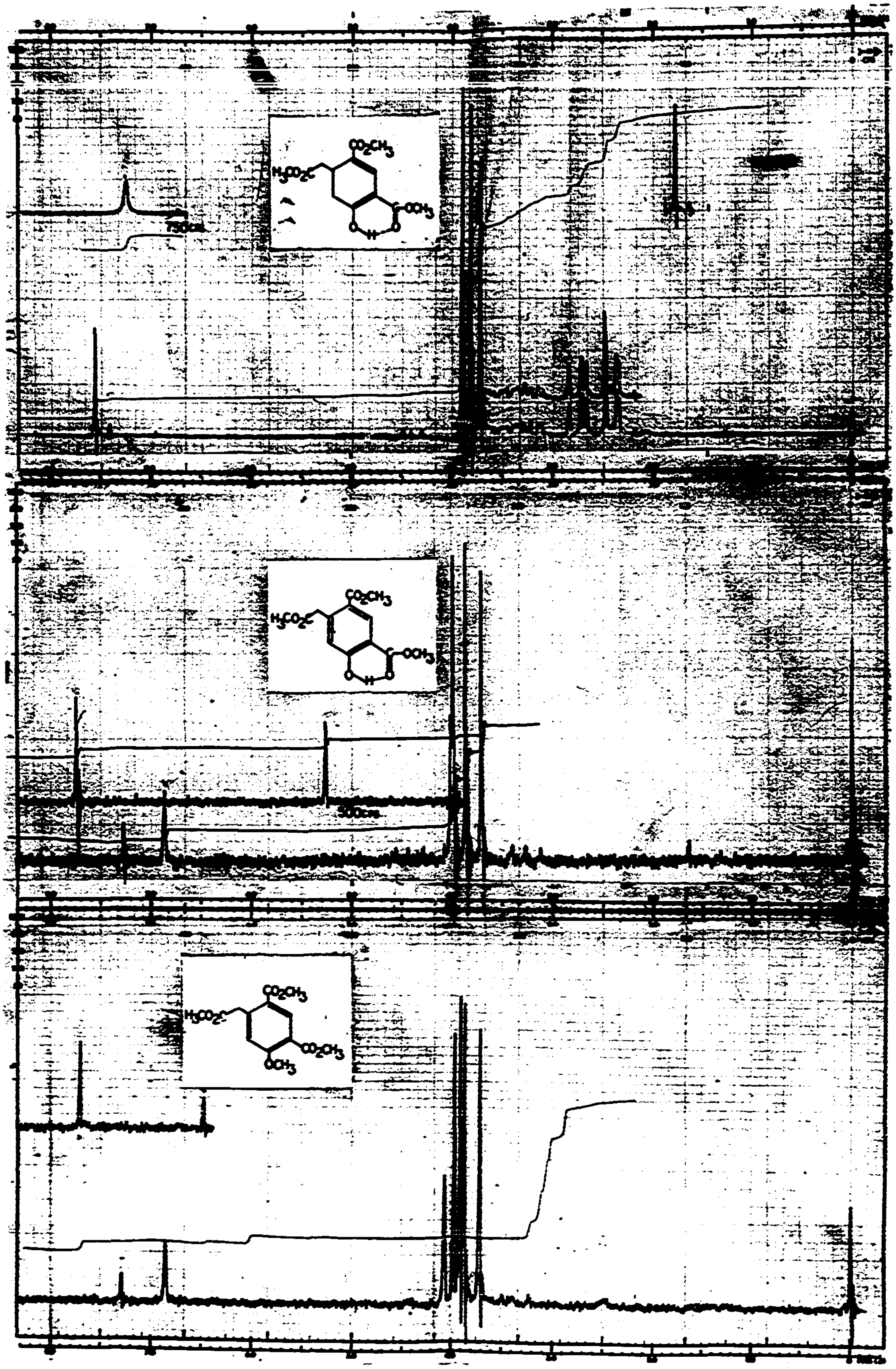
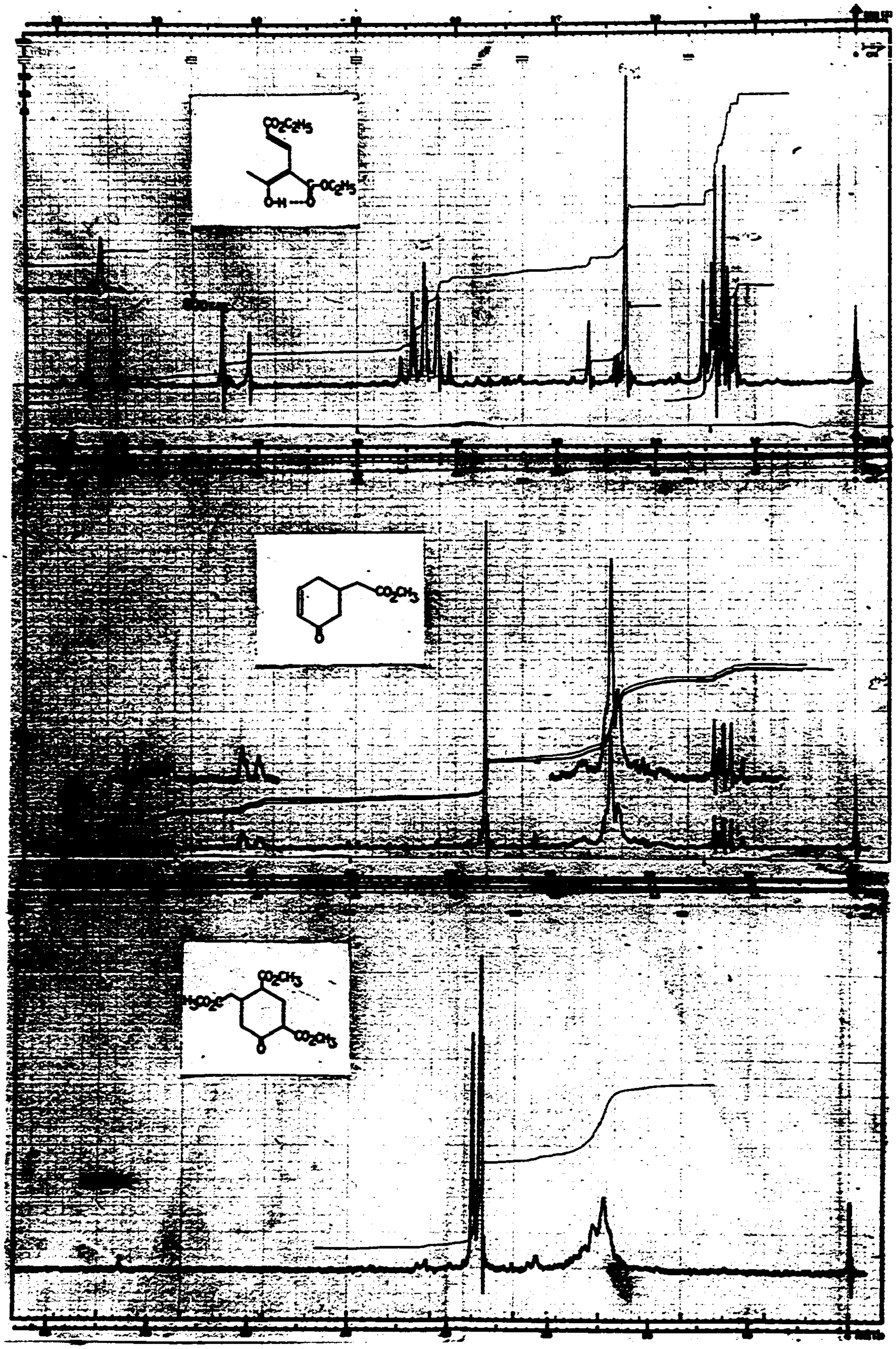

5.0
4.0
3.0
2.0
LOG ε
210
250
290
330
WAVELENGTH (mμ)
CO2CH3
O
H3CO2C
CO2CH3
CO2CH3
O
H3CO2C
CO2CH3
CO2CH3
OH

Figure 8. Nuclear magnetic resonance spectra



750cps
CO2CH3
H3CO2C
OCH3
500cps
CO2CH3
H3CO2C
OCH3
CO2CH3
H3CO2C
CO2CH3
OCH3

Figure 9. Nuclear magnetic resonance spectra


CO2C2H5
OC2H5
O-H
O
CO2CH3
O
CO2CH3
H3CO2C
CO2CH3
O

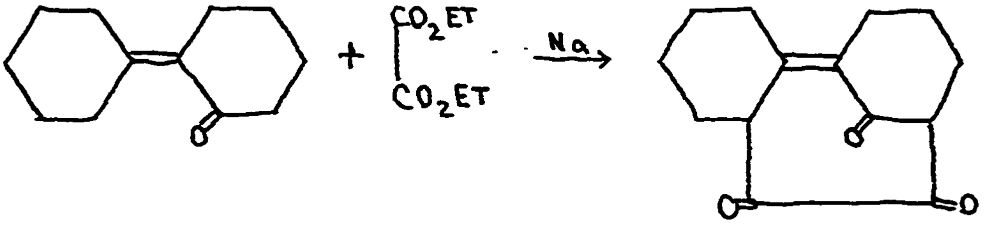
PART II - THE STRUCTURE OF THE ETHYLOXALATE-CYCLOHEXENYLCYCLOHEXANONE CONDENSATION PRODUCT

INTRODUCTION

The structure of the product of the base-catalyzed condensation of cyclohexenylcyclohexanone and ethyl oxalate is to be determined.

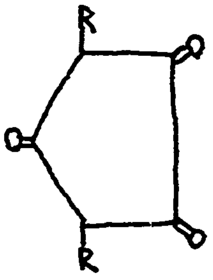
HISTORICAL

Jager *et al.* (17) reported that a condensation of cyclohexylidenecyclohexanone XLIII with ethyl oxalate in the presence of sodium gave a yellow product whose carbonhydrogen analysis showed it to be derived from one mole each of XLIII and ethyl oxalate minus the elements of two moles of ethenol. The reaction was carried out in ether, whence the sodium salt had precipitated. This meant that the product was enolizable. The enolizable nature of the compound was also evident from the preparation of a tosylate and a p-bromophenacyl ether. When condensed with o-phenylenediamine, the product gave a compound whose empirical formula fitted an addition product minus one mole of water. By analogy with the products of condensation of diethyl ketone and dibenzyl ketone with ethyl oxalate, XLV (18) and XLVI (19), respectively, Jager *et al.* have postulated XLIV for the structure of their product.



XLIII

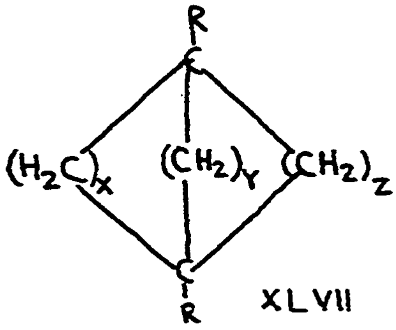
XLIV



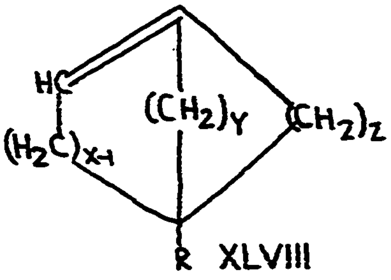
XLV R= CH_3

XLVI R= C_6H_5

In view of the comments on the Jager structure XLIV in the Discussion Section an inspection of Bredt's rule (20,21) seems appropriate. The rule forbids a double bond at a bridgehead in certain bridged ring system,—structures XLVII wherein three or more ring atoms are common to two rings. Ring sizes determine whether or not a double bond at the bridgehead would be possible. The rule, however, does not divide ring sizes sharply into these two categories. Only insufficient data are available in the borderline area. A study of models of bicyclo (x, y, z) alkene ($x \geq y \geq z \neq 0$) structures like XLVIII shows that a double bond at the bridgehead can be made strainlessly when $x + y + z = S = 11$. Many structures with a bridgehead double bond can be formed with little strain when $S = 10$ and even 9. But when $S = 8$, the strain becomes too large for room temperature stability.

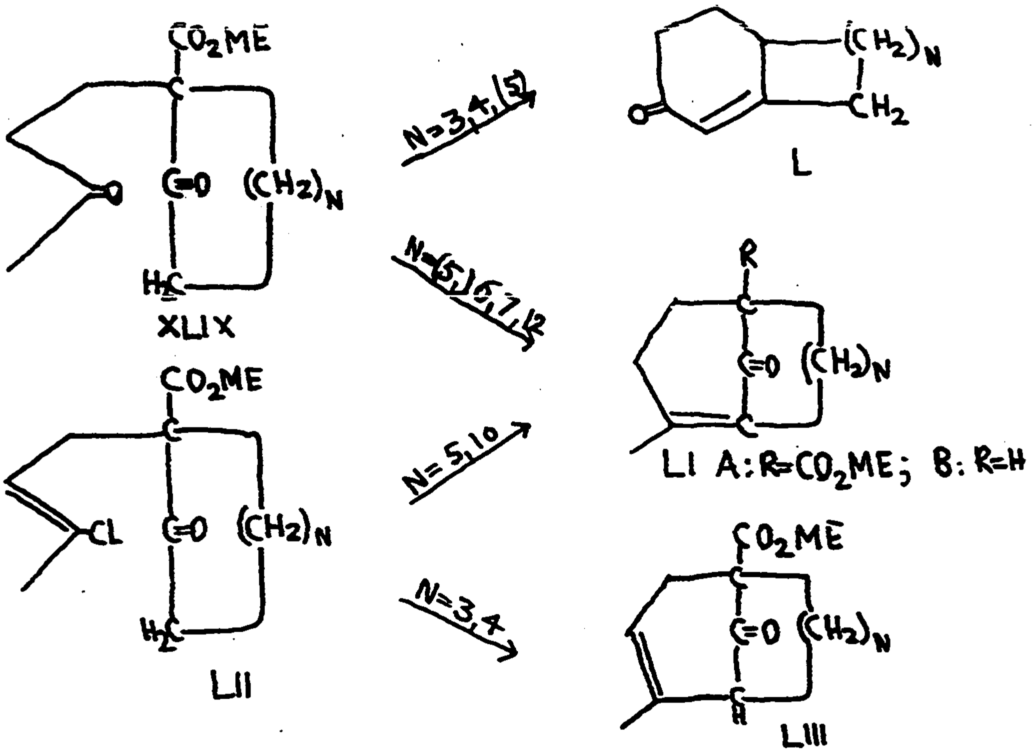


XLVII



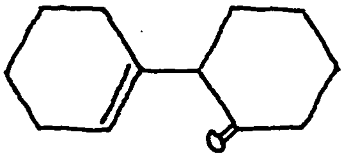
XLVIII

Prelog *et al.* (22,23,24) studied the cyclization of a series of 2-carbomethoxy-2-(3-ketobutyl)-cycloalkanones XLIX and 2-carbomethoxy-2-(3-chlorocrotyl)-cycloalkanones LII, in which the ring size varied from six to fifteen carbon atoms. The products obtained were bicycyclic unsaturated ketones or β-keto esters. Cyclization of XLIX through an intramolecular aldol condensation was accomplished by heating with acetic acid containing aqueous hydrochloric acid. Decarboxylation also occurred giving α, β -unsaturated ketones, the structure of which depended upon the ring size of the starting material. With a small ring $n = 3,4$, a fused ring bicyclic structure L was formed, but with a large ring $n = 6,7,12$, the product was a bridged ring bicyclic derivative LI(b). With a ring of intermediate size $n = 5$, a mixture of both L and LIb. was obtained. Cyclization of LII with conc. sulfuric acid gave no decarboxylation but led to a bridged ring bicyclic unsaturated β-ketoester irrespective of ring size. The size of the ring determined the position of the double bond. With a small ring (LII: $n = 3$ or 4), the product LIII had a non-conjugated double bond, while a large-ring structure (LII: $n = 5$ or 10) produced the conjugated double bond isomer LI(a). Thus for the latter case a double bond at the bridge head is possible.

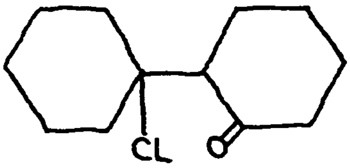


From the above studies the tentative upper limit of ring size for which an extended rule forbids a double bond in an isolable compound has been put at S = 8.

Cyclohexylidenecyclohexanone XLIII is one of two known bimolecular self-condensation products of cyclohexanone. The other and first to be known is cyclohexenylcyclohexanone LIV. It was first prepared by Wallach (25) by the action of sodium ethoxide on cyclohexanone over a period of many days. Since then it has been prepared by treating cyclohexanone with sulfuric acid (26), calcium hydride (27,28), sodium amide (29), etc. On passing gaseous hydrochloric acid through pure cyclohexanone, Wallach (30) has prepared chlorocyclohexylcyclohexanone LV which he converted to LIV by base treatment. The chemical reactions of LIV seemed ambiguous. In reactions with benzaldehyde and cyclohexanone (31) and in condensation with ethyl sodiocyanoacetate (32) it behaved as an α,β-unsaturated ketone. On the other hand, it behaved as a β,γ-unsaturated ketone in oxidation with ozone (32), potassium permanganate (33) and methylation with methyl iodide (32).



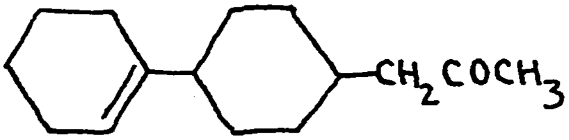
LIV



LV

Reese discovered cyclohexylidenecyclohexanone XLIII, when he treated chlorocyclohexylcyclohexanone LV with sodium methoxide in the cold. It is a solid and is comparatively unstable changing on heating into the liquid ketone LIV. It has been known from the work on cyclohexenylacetone LVI of Kon and Speight (34) that in such a cyclohexene system, the more favored position of the double bond is endo- and not exo-cyclic. Based on this fact, the more stable condensation product was given the structure LIV and the less stable one XLIII.

LVI



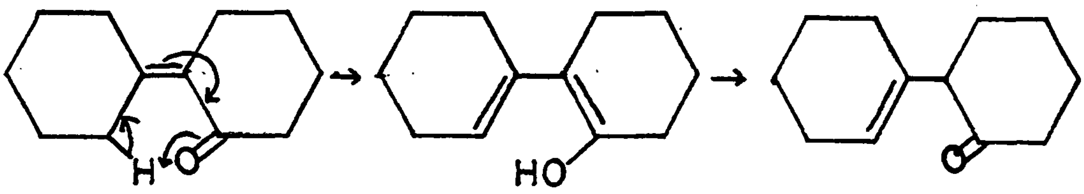
The ultraviolet spectrum of XLIII (35,36) was known to have a peak at 255 mμ characteristic of a α,β-unsaturated ketone. The infrared spectrum (36) showed peaks at 5.98μ and 6.2μ, again showing a conjugated ketone system. Recently Roginskaia et al. (37) have studied the infrared and Raman spectra of these two ketones. In their hands, the infrared spectra of the ketone LIV also revealed peaks like those of ketone XLIII,— a conjugated carbonyl bond at 5.95μ and a double bond peak at 6.15μ. A Raman spectrum of the ketone LIV also revealed characteristic peaks for an α,β-unsaturated ketone,— 5.90μ and 6.10μ. No lines were obtained at 5.85μ and between 6.02-6.06μ, characteristic of ketones with unconjugated double bonds. The ultraviolet spectra of both the ketones showed absorbtion at 255mμ, only the extinction coefficient of LIV was much lower than that of XLIII. From these observations, Roginskaia et al. concluded that both the compounds XLIII and LIV were conjugated ketones. They postulated that the difference lay only in the configuration of the cyclohexane ring. Ketone XLIII, which is less stable, was assigned a 'half-boat' conformation while the more stable LIV was given a 'half-chair' conformation.

DISCUSSION

The total number of atoms in the bridges of XLIV, the Jager bridge-ring system is $S = 8$. In such a system Bredt's rule prohibits a double bond at a bridgehead. Since enolization of the compound produces yet another double bond at a bridgehead, the Jager structure can be dismissed. Therefore, a reinvestigation of the structure of the compound was thought necessary.

The comments of Roginskaia et al. (37) about the structure of the two bimolecular self-condensation products of cyclohexanone were examined first. Their arguments of both the two compounds being α,β-unsaturated ketones, their difference lying in the conformations of the cyclohexane rings are difficult to understand. No such cases of isomerism in simple cyclohexane ring systems is known. Contrary to their observations, the infrared structure of LIV was found to have a saturated carbonyl peak at 5.85μ, while XLIII had a conjugated carbonyl peak at 5.96μ as reported (19,20). The n.m.r. spectrum of LIV revealed a one-proton olefinic signal at 330 c.p.s. There was no olefinic proton signal in the n.m.r. spectrum of XLIII. The ultraviolet spectrum of LIV, of course, showed absorption at $255 m\mu$ ($\log \varepsilon$ 3.52). This has to be explained by the assumption that in dilute ethanol solution a part of LIV isomerizes to XLIII. As a consequence the extinction coefficient of the absorption maximum of LIV is only one half of that of XLIII.

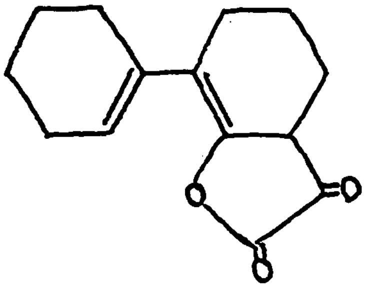
The mechanism of the transformation of XLIII to LIV on heating may be similar to that of a photochemical reaction:



XLIII LIV

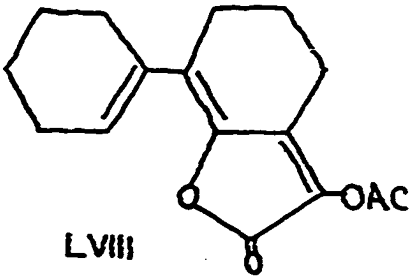
When cyclohexylidenecyclohexanone was condensed with diethyl oxalate as described by Jager, a dark oil rather than a yellow crystalline solid was obtained. Inspection of his exact mode of preparation (38) revealed that his cyclohexanone condensation product probably had been the double-bond isomer, cyclohexenylcyclohexanone LIV. Repetition of the condensation reaction of diethyl oxalate with LIV did indeed yield a yellow crystalline product. It gave a ferric chloride test. Its infrared peaks at 5.80μ and 5.98μ gave the first indication of its being an enol lactone. The ultraviolet spectrum showed maxima at 225mμ and 326mμ which in basic solution were shifted bathochromically to 241mμ and 351mμ. A maximum at such a high wavelength (326mμ) pointed towards extensive conjugation. The olefinic region of its n.m.r. spectrum showed a one-proton multiplet at 364 c.p.s.

From these data the structure for the compound was postulated as LVII.

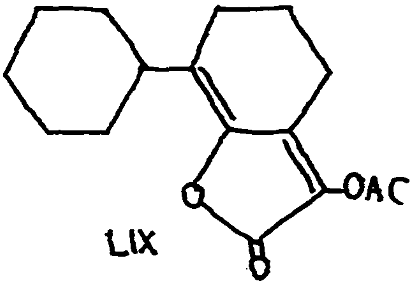


LVII

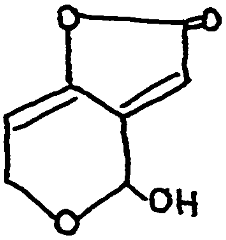
Its enol acetate LVIII, a thick oil, was prepared. Though the latter solidified on standing for a few days, it could not be purified properly. Spectral studies were made on a small amount obtained by distillation. The infrared spectrum showed a shoulder at 5.61 μ (enol acetate), and peaks at 5.79 μ (lactone c = o), 6.02 μ (enol c = c). The ultraviolet spectrum was the same as the parent compound. The n.m.r. spectrum still showed an olefinic one-proton multiplet at 371 c.p.s. A three-proton methyl singlet (of the acetate group) appeared at 138 c.p.s. With a view to hydrogenolizing the acetate group, the compound was subjected to hydrogenation in ethanol solution in the presence of 10% Pd-C. The product, a heavy oil, was distilled with difficulty. The infrared spectrum was almost identical with that of the acetate. The n.m.r. spectrum still had the three-proton methyl singlet at 138 c.p.s., indicating that the acetate group had not been hydrogenolyzed. The olefinic proton peak had disappeared. The ultraviolet spectrum showed maxima at 215mμ and 292mμ. As the higher peak had moved only by 34mμ, it seemed probable that in hydrogenation only one double bond had been reduced. The ultraviolet maximum (292mμ) for the resulting structure LIX compares favorably with the maximum (276mμ) of patulin LX (39,40,41), a natural product with similar chromophore. Unfortunately the elemental analysis of the product fitted a tetrahydro derivative of the acetate LVIII better than the dihydro derivative LIX.



LVIII

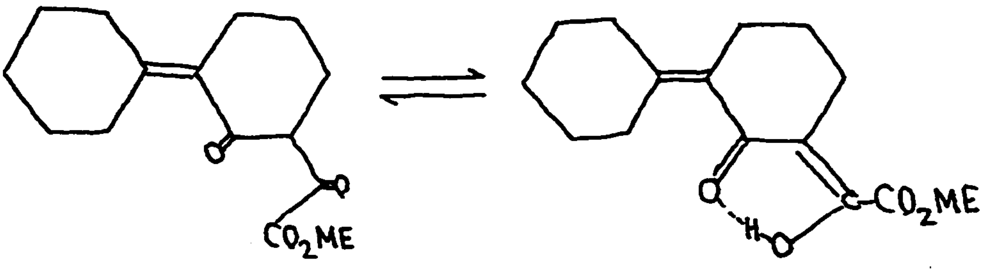


LIX



LX

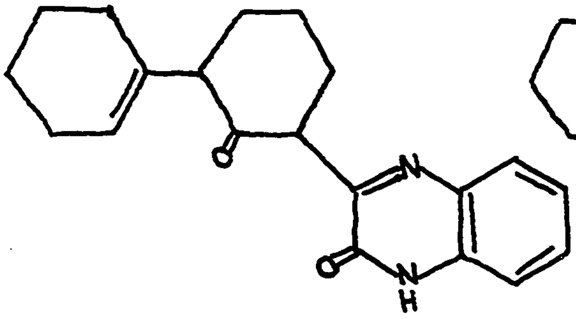
When Jager's compound was left standing at room temperature in contact with methanol for 24 hrs., it slowly dissolved. On evaporation of the solvent a dark oil was obtained, which could not be purified. The crude material showed infrared peaks at 5.75μ and 6.25μ. Probably methanolysis of the lactone had occurred. The resulting diketoester LXI exists most likely in the hydrogen-bonded enol form LXII. The β-diketone monoenol chelated carbonyl moiety accounts for the infrared 6.25μ peak while the ester accounts for the 5.75μ infrared peak.



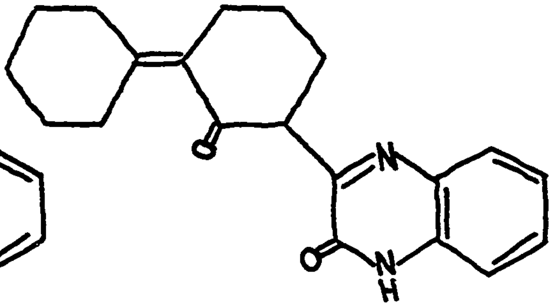
LXI LXII

When the Jager compound was condensed with o-phenylenediamine, the product described by him was obtained. Its structure is best described as either LXIII or LXIV. The infrared spectrum showed bands at 5.85(w)μ, 6.02(s)μ and 6.22(m)μ, which may be explained by assuming the product to be LXIII and/or LXIV. The weak 5.85μ peak represents a saturated carbonyl group while the strong 6.02μ band may be a superimposition of a conjugated carbonyl and imine bands (42). The absence of an N-H peak in the 3μ region is however puzzling.

Comparison of the ultraviolet spectra of the o-phenylenediamine product (LXIII and/or LXIV) and of an equimolecular mixture of 3-methylquinoxalone and cyclohexylidenecyclohexanone revealed a similarity in neutral solution and identity in a basic medium.



LXIII



LXIV

The above study makes the structure LVII as the only acceptable one for the Jager product.

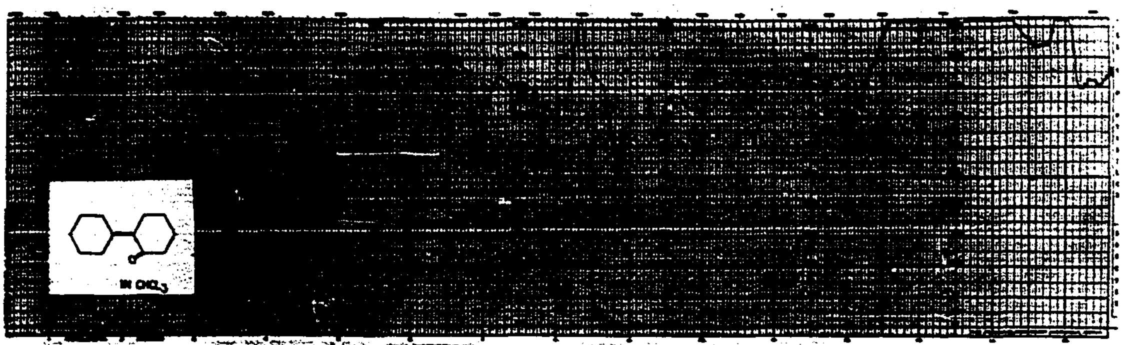
The condensations of diethyl (18) and dibenzyl ketones (19) with diethyl oxalate, referred to by Jager, seem to be only two isolated instances of α-, α-diacylation of a ketone by diethyl oxalate. The Jager case thus appears to be unique in its representation of a case of O,C-diacylation.

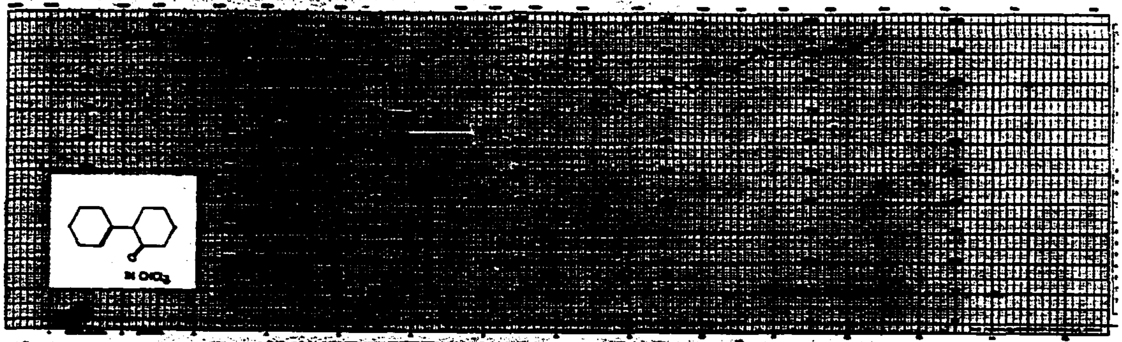
SPECTRA

All infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer. The ultraviolet spectra were run in 95% ethanol using a Carey model 14 recording spectrophotometer.

The nuclear magnetic resonance spectra were obtained from dilute deuterochloroform solutions using a Varian Model A-60 Spectrometer. Resonance positions were determined by pre-calibrated charts relative to tetramethylsilane as internal standard. Peak positions were expressed in c.p.s. (cycles per second).

Figure 10. Infrared spectra


IN CHCl3


IN CHCl3

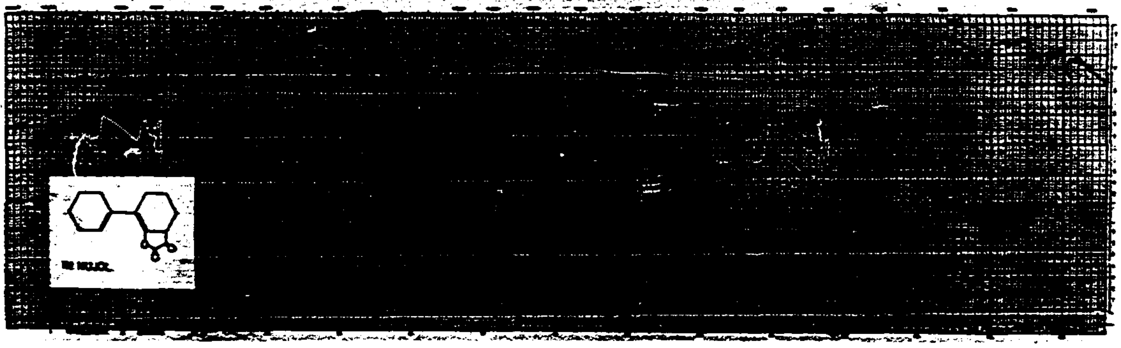
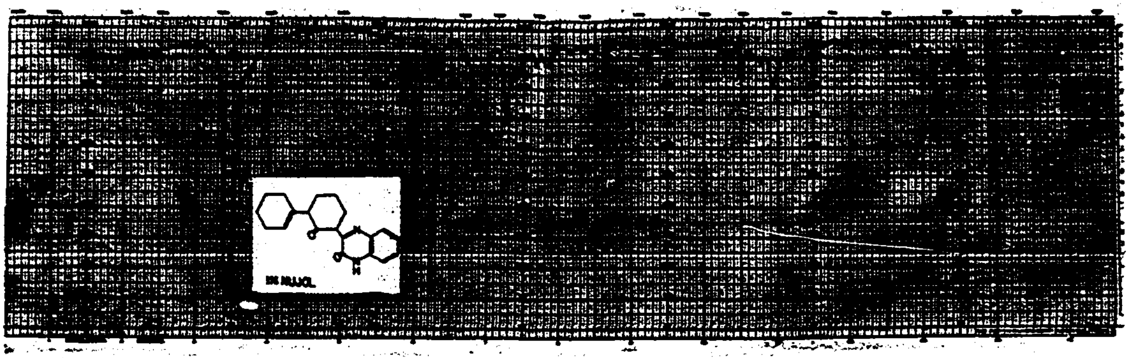

IN NUJOL

Figure 11. Infrared spectra


O
O
N
H


O
O
OAC

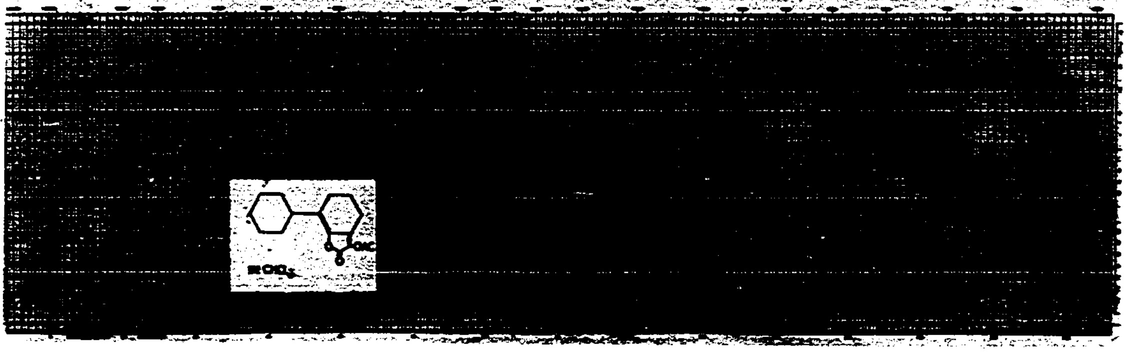

O
O
OAC

Figure 12. Ultraviolet spectra

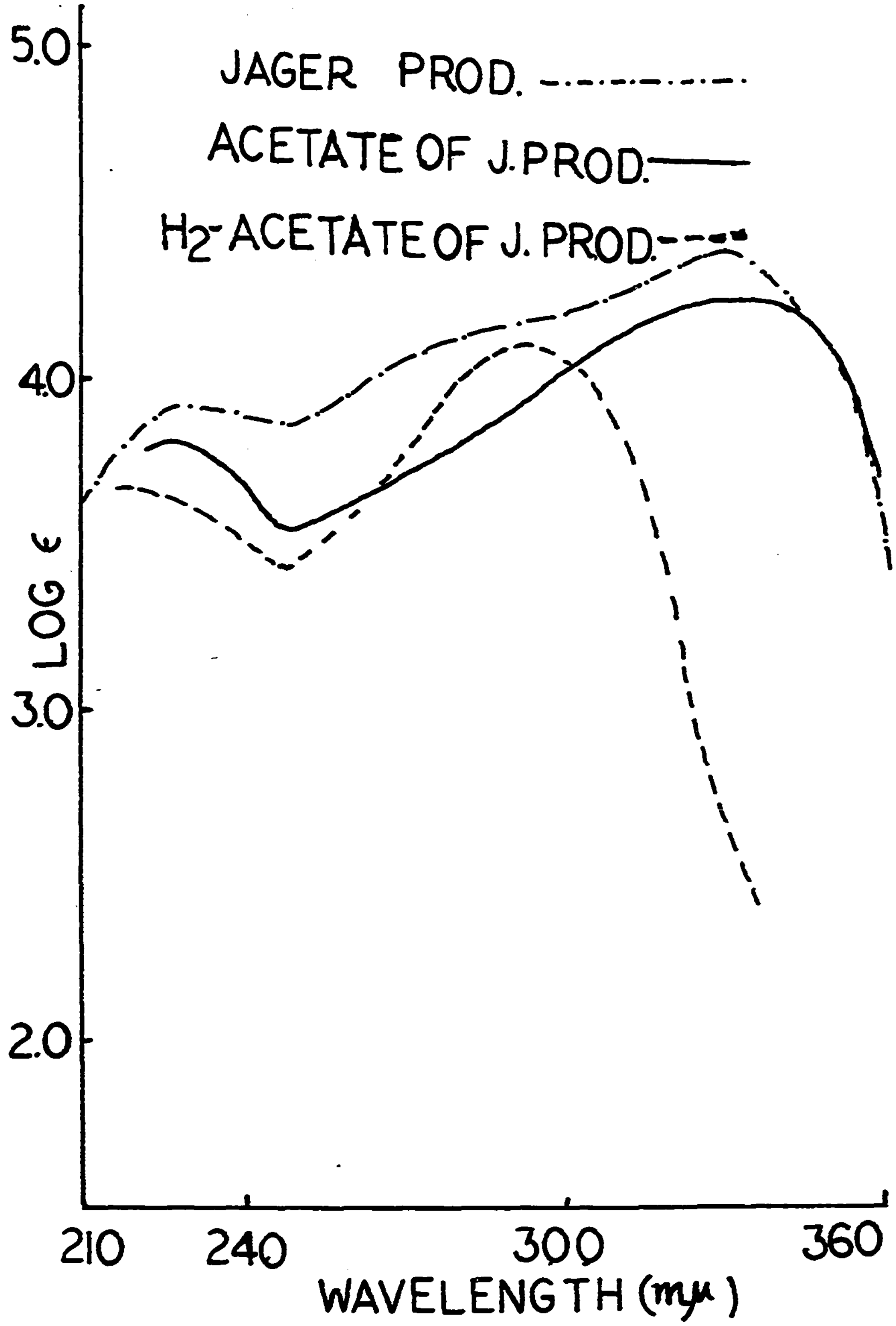

5.0
4.0
3.0
2.0
LOG ε
210
240
300
360
WAVELENGTH (mμ)
JAGER PROD.
ACETATE OF J. PROD.
H2-ACETATE OF J. PROD.

Figure 13. Ultraviolet spectra

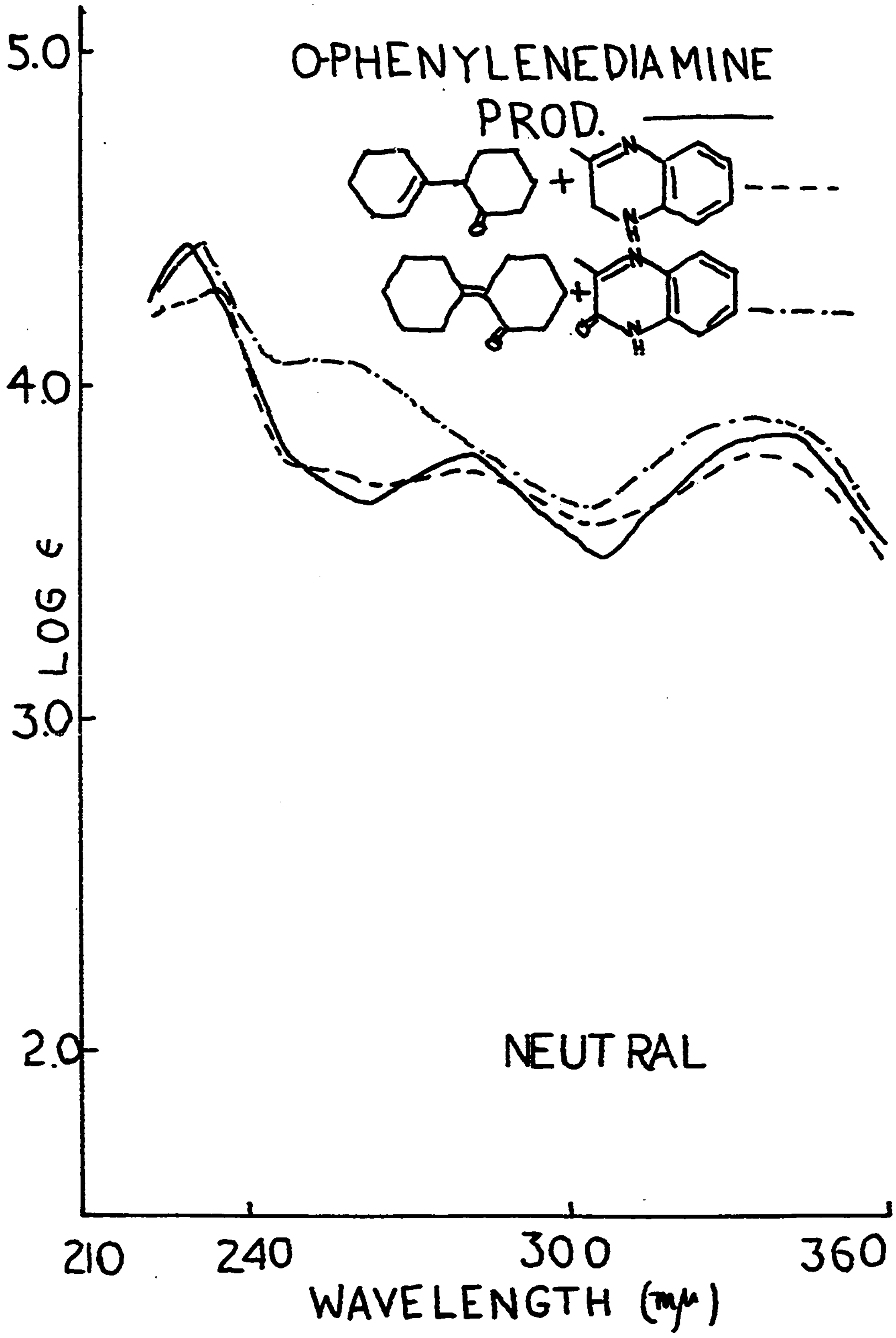

O-PHENYLENEDIAMINE
PROD.
N
N
H
+
N
N
H
5.0
4.0
3.0
2.0
LOG ε
NEUTRAL
210
240
300
360
WAVELENGTH (mμ)

Figure 14. Ultraviolet spectra

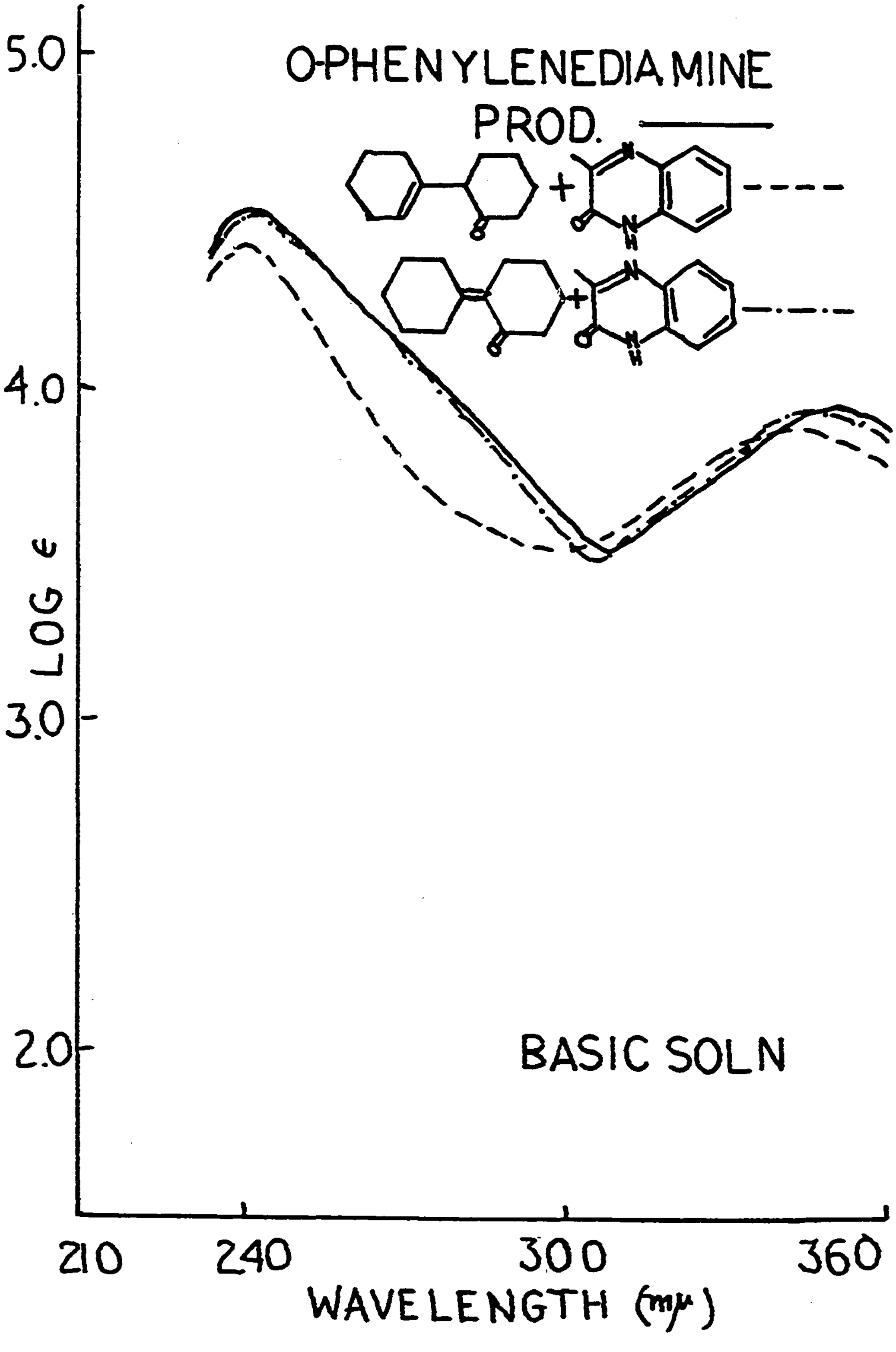

5.0
4.0
3.0
2.0
LOG ε
O-PHENYLENEDIAMINE PROD.
+
+
BASIC SOLN
210
240
300
360
WAVELENGTH (mμ)

Figure 15. Ultraviolet spectra

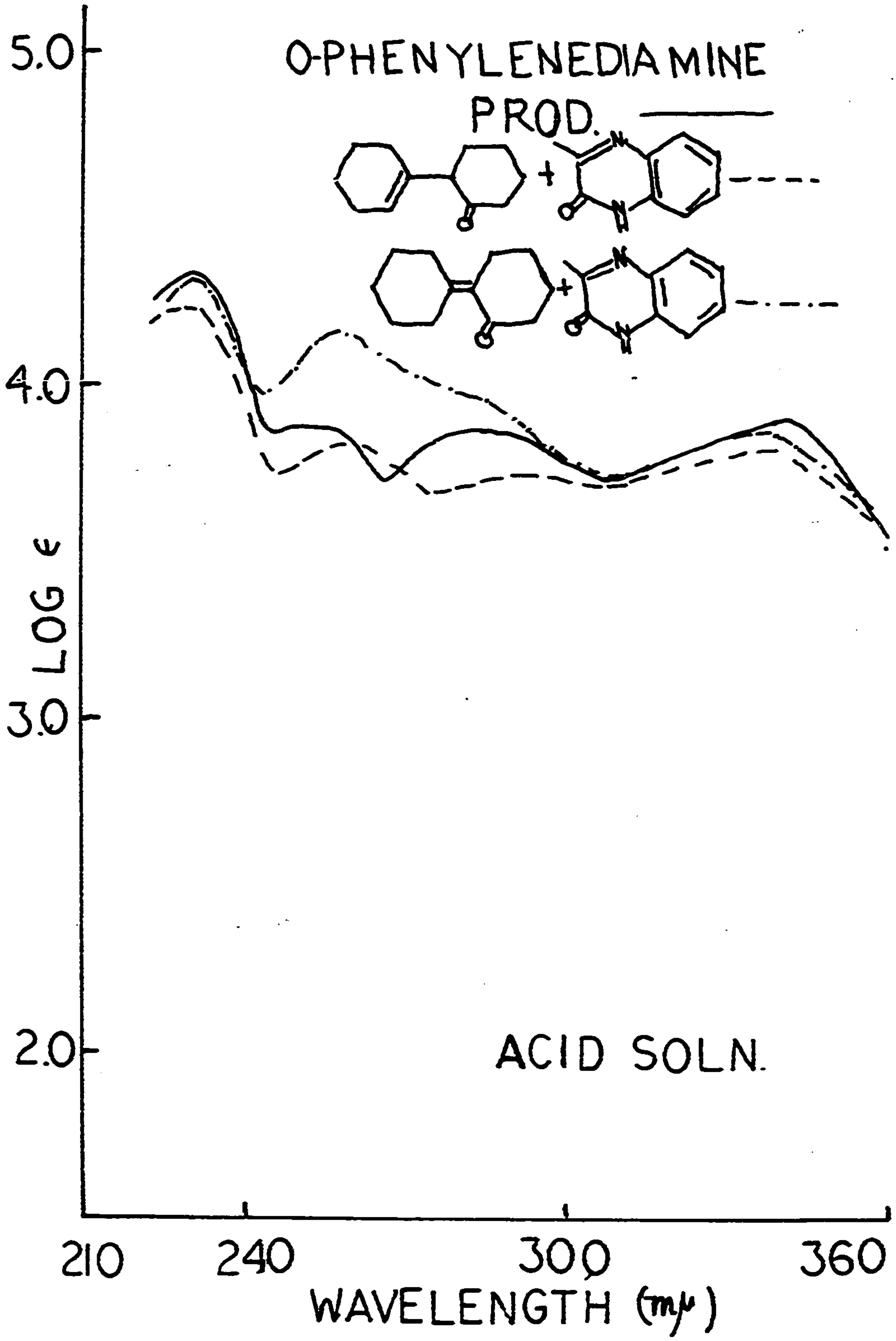

O-PHENYLENEDIAMINE PROD.
5.0
4.0
3.0
2.0
LOG ε
210
240
300
360
WAVELENGTH (mμ)
ACID SOLN.

Figure 16. Nuclear magnetic resonance spectra

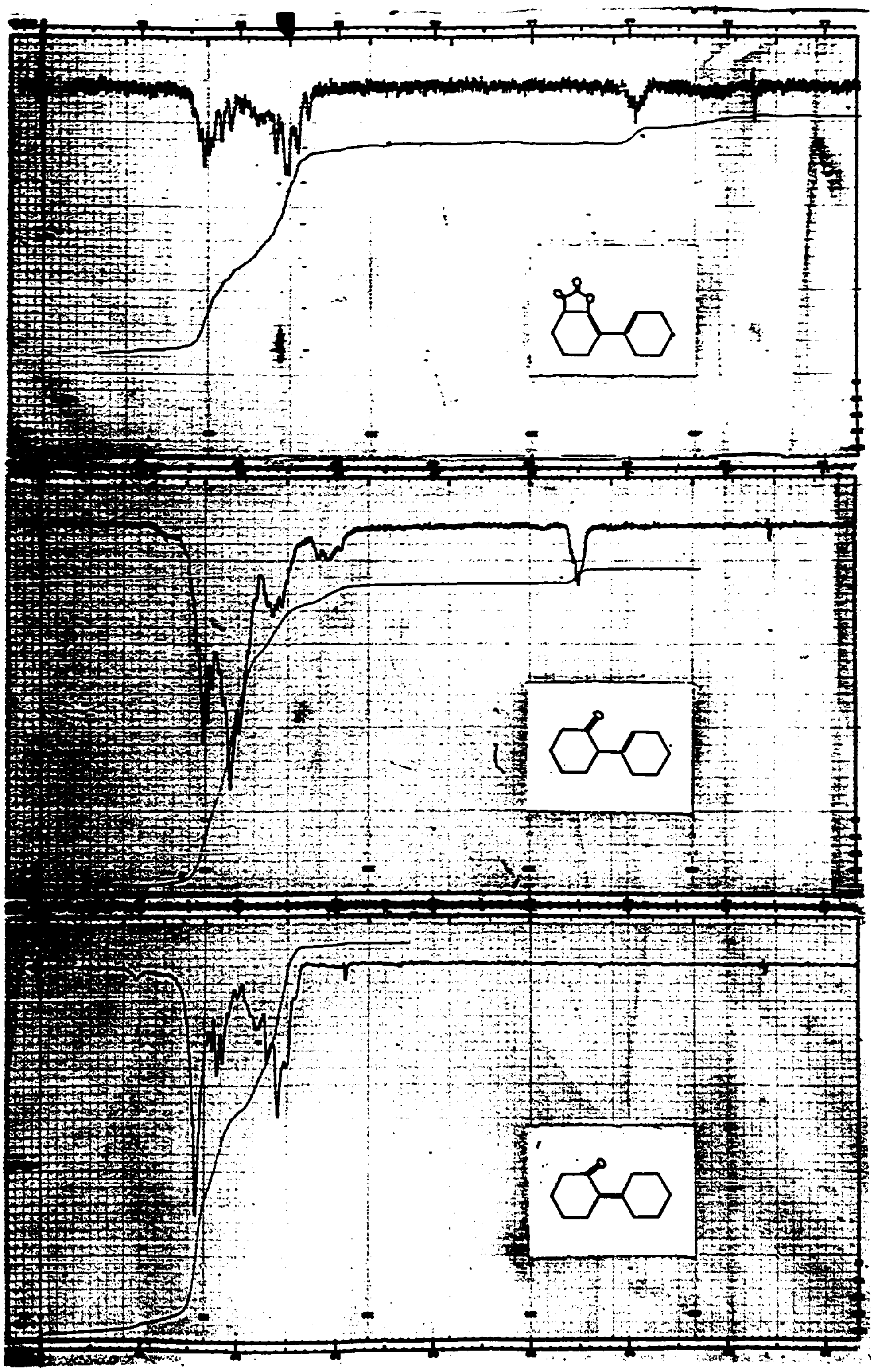
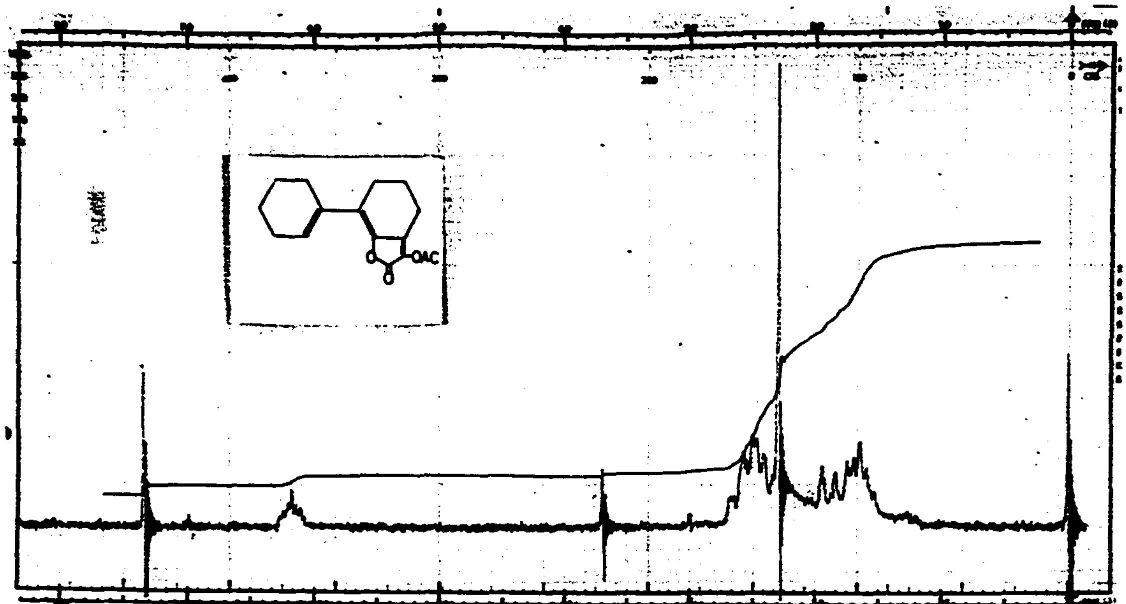
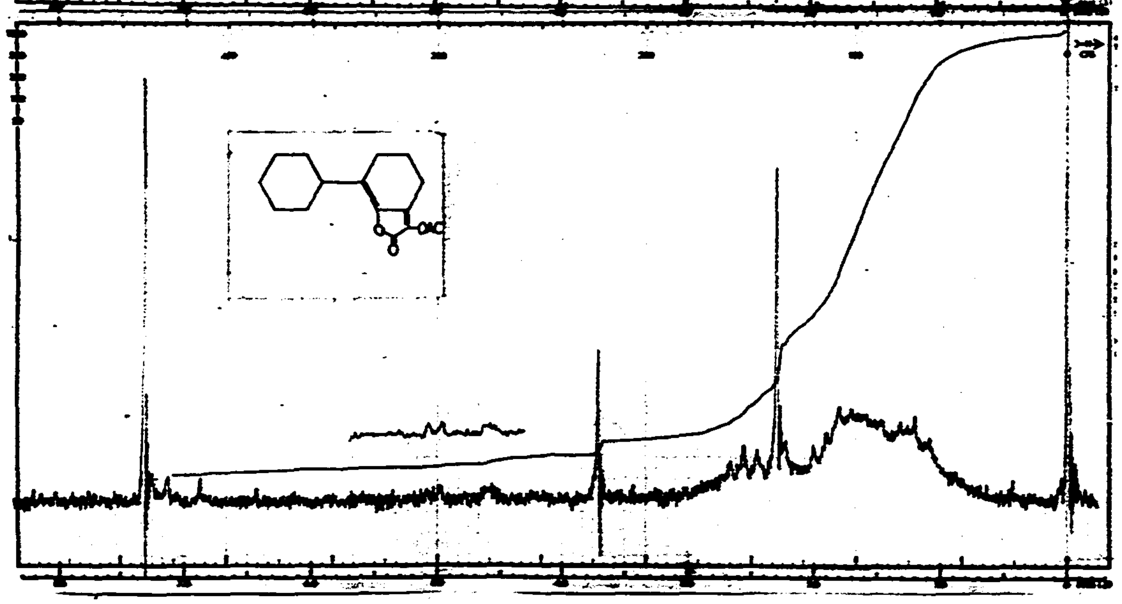


Figure 17. Nuclear magnetic resonance spectra


O
O
OAC


O
O
OAC

EXPERIMENTAL

All melting and boiling points are uncorrected. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana, and Alfred Bernhardt, Mikroanalytisches Laboratorium, Mulheim (Ruhr), Germany. The ultraviolet spectra were run in 95% ethanol using a Carey model 14 recording spectrophotometer.

Silica for chromatography was 50-200 mesh, supplied by G. Frederick Smith Chemical Co., Columbus, Ohio. Iron-free silica was made by allowing it to stand 12 hrs. in contact with conc. hydrochloric acid and then washing it with distilled water. It was dried in an oven at 100 - 120° for 12 hrs.

Dimethyl glutaconate

Dimethyl glutaconate b.p. 90° (2 mm.) was made by a standard method (7)

Attempted alkylation of dimethyl glutaconate with pentamethylene dibromide

1.6 g. of sodium was dissolved in 60 ml. of anhydrous methanol. While stirring under nitrogen 5.0g. of dimethyl glutaconate and 7.2g. of pentamethylene dibromide were added. After stirring at room temp. for 22 hrs., the solution was refluxed for 2 more hrs. It was cooled, water was added and the solution concentrated. It was extracted with ether and the extract washed with water and dried over sodium sulfate. The solvent was evaporated and the residue, 2g. was distilled. A fraction, 0.8g., with broad boiling range (up to 140°/6mm.) was obtained but not identified.

The remaining alkaline solution was acidified with 5% hydrochloric acid and then extracted with ether. The extract was washed with water and dried over sodium sulfate. On evaporation of the solvent 2.6g. of a white solid material was obtained. Chromatography over iron-free silica and elution with 7:1 benzene-ether yielded 1.5g. of a solid. Crystallization from n-hexane gave a crystalline solid, m.p. 81-85°, which proved identical with dimethyl 5, 6 dihydro-4-hydroxy-6-carbomethoxymethylisophthalate. (see below)

Dimethyl 5, 6 dihydro-4-hydroxy-6-carbomethoxymethylisophthalate XVII.

2.4g. of sodium was dissolved in 60 ml. of anhydrous methanol and 20g. of dimethyl glutaconate added. The mixture was refluxed for 40 min. After cooling, it was acidified with 5% hydrochloric acid and extracted with ether. The extract was washed with water and dried, and the solvent removed. 17.5g. of crude solid was obtained. Five crystallizations from n-hexane and one crystallization from methanol gave a crystalline compound, m.p. 83-84°.

Analysis

Calculated for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.93; H, 5.74.

Infrared spectrum

$C=O$ 5.76(s)μ, 5.87(s)μ ; 6.04(s)μ ; $C=C$ 6.13(w)μ; see Fig. 1.

Ultraviolet spectrum

λmax. 262mμ (log ε 3.9), 320mμ (log ε 3.6).

λshoulder 300mμ (log ε 3.5)

λmin. 287mμ (log ε 3.4)

$\lambda_{max}^{0.5N\ NaOH}$ 292mμ (log ε 4.2), 357mμ (log ε 4.2)

$\lambda_{Min}^{0.5\ N\ NaOH}$ 245mμ (log ε 3.5), 318mμ (log ε 3.8)

see Fig. 5.

N.M.R. spectrum

C(2)-H singlet at 454 c.p.s.

O-H singlet at 786 c.p.s.

see Fig. 8.

Dimethyl 4-hydroxy-6-carbomethoxymethylisophthalate XX

A solution of 3 g. of bromine in 20 ml. of chloroform was added with stirring to 5.0g. of XVII dissolved in 20 ml. of chloroform. After a half hr. of further stirring at room temp., it was stirred at 50° for 3 hrs. The solution was cooled, washed with water and dried. The solvent was removed and the residue chromatographed over iron-free silica. Elution with 16:1 benzene-ether gave 3.7g. of a solid. Two crystallizations from n-hexane gave a crystalline product, m.p. 78-80°.

<u>Analysis</u>

Calculated for $C_{13}H_{14}O_7$: C, 55.32; H, 500. Found: C, 55.95; H, 4.98.

<u>Infrared spectrum</u>

$C{=}O$ 5.75(s)μ, 5.80(s)μ, 5.95(s)μ ; $C{=}C$ 6.20(w)μ ; see Fig. 1.

<u>Ultraviolet spectrum</u>

λ max 226mμ(log ϵ 4.7), 251mμ(log ϵ 4.1), 306mμ(log ϵ 3.5)

λ min 243mμ (log ϵ 4.1), 277mμ(log ϵ 3.0)

see Fig. 7.

<u>N.M.R. spectrum</u>

C(5)-H singlet at 412 c.p.s.
C(2)-H singlet at 516 c.p.s. see Fig. 8.
O-H singlet at 665 c.p.s.

Dimethyl 4-hydroxy-5-bromo-6-carbomethoxymethylisophthalate XXII

A solution of 6.3g. of bromine in 100 ml. of chloroform was added with stirring to 4.5g. of XVII dissolved in 100 ml. of chloroform. After a half hr. of further stirring at room temp., the mixture was stirred at 60° for 7 hrs. and then left at room temp. overnight. It was washed with water and dried, and the solvent removed. On addition of methanol to the residue 1.3g. of a solid compound separated. Two crystallizations each from methanol and n-hexane yielded a crystalline compound, m.p. 123-124°. The mother liquor of the methanol precipitation experiment yielded a mixture of this bromophenol and the phenol XIX.

Analysis

Calculated for $C_{13}H_{13}O_7$ Br: C, 43.23, H, 3.62. Found: C, 43.14; H, 3.71.

Infrared spectrum

C=O 5.76(s)μ, 5.81(s)μ, 5.95(s)μ ; C=C 6.21(w)μ.

Ultraviolet spectrum

λ max. 231mμ (logϵ 4.6), 313mμ (logϵ 4.1)

λ shoulder 255mμ (logϵ 3.6)

λ min. 282mμ (logϵ 3.4)

N.M.R. spectrum

C(2)-H singlet at 515 c.p.s.

O-H singlet at 721 c.p.s.

Dimethyl 4-methoxy-6-carbomethoxymethylisophthalate XXIV

0.5g. of dimethyl sulfate and 10 g. of anhydrous Potassium carbonate were added to a solution of 0.5g. XX in 100 ml. of anhydrous acetone. The mixture was refluxed for 15 hrs. After cooling and filtration of the solid, water was added and the solution concentrated under reduced pressure and extracted with ether. The extract was washed with water and dried. After removal of the ether the 0.5g. of crude product was crystallized three times from n-hexane, yielding a crystalline solid, m.p. 113-119°.

Analysis

Calculated for $C_{14}H_{16}O_7$: C, 56.75; H, 5.44. Found: C, 56.47; H, 5.14.

Infrared spectrum

C=O 5.80(s)μ, 5.82(s)μ. C=C 6.20(m)μ;
see Fig. 2.

Ultraviolet spectrum

λ max 224mμ (log ε 4.6), 258mμ (log ε 4.2).
λ shoulder 290mμ (log ε 3.7).
λ min. 244mμ (log ε 4.1).

N.M.R. spectrum

C(5)-H singlet at 412 c.p.s.
C(2)-H singlet at 512 c.p.s.
see Fig. 8.

Dimethyl isophthalate

Dimethyl isophthalate was made by a standard method m.p. 64° (8).

N.M.R. spectrum

C(2)-H singlet at 525 c.p.s.

Ethyl α-acetylglutaconate XXVI

Ethyl propiolate was prepared by a standard method (10).

Condensation of ethyl acetoacetate with ethyl propiolate was carried out by the method of Simonsen (7). 0.9g. of sodium was dissolved in 30 ml. of anhydrous ethanol. 5.4g.

of ethyl acetoacetate and 4.1g. of ethyl propiolate were added with cooling. The red mixture was left standing overnight. Water was added and the mixture extracted with ether. The extract was washed and dried, and the solvent removed. The residue was distilled but the resulting ethyl methyltrimesate (7), 1.0g., was not investigated.

The alkaline mother liquor was rendered acidic with 5% hydrochloric acid and extracted with ether. The extract was washed with a small amount of 5% sodium carbonate and with water. After drying over sodium sulfate the solvent was removed. The product was distilled, b.p. 152°/12mm.; yield 3.2g.

Infrared spectrum

$C{=}O$ 5.75(s)μ, 5.80(s)μ, 5.85(s)μ; $C{=}C$ 6.14(s) μ; see Fig. 2.

Ultraviolet spectrum

λ max 230mμ (log ε 4.1), 278mμ (log ε 4.3)

λ min 222mμ (log ε 4.1), 240mμ (log ε 4.0)

$\lambda_{\text{max}}^{0.5\text{ N NaOH}}$ 280mμ (log ε 4.0), 347mμ (log ε 4.4)

$\lambda_{\text{min}}^{0.5\text{ N NaOH}}$ 303mμ (log ε 3.7)

see Fig. 5.

N.M.R. spectrum

O-H singlet at 855 c.p.s. see Fig. 9.

5-Carbomethoxymethylcyclohexen-2-one XXIX

4.0g. of XVII was refluxed for 20 hrs. with 100 ml. of 10% aqueous hydrochloric acid. After cooling, the mixture was extracted with ether. The extract was dried and evaporated and the residue chromatographed over acid-washed silica. 0.81g. of an oil was eluted in 7:3 benzene-ether. The infrared spectrum of this crude product showed bands at 2.80μ (-OH), 5.85μ (C=O of corboxylic acid) and 5.96μ (conjugated C=O). It was esterified with an excess of diazomethane. The product was chromatographed over silica and was eluted with 9:1 benzene-ether. Then it was distilled (bath temp. 135-155°/6mm).

Analysis

Calculated for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.75; H, 7.25.

Infrared spectrum

C=O 5.78(s)μ, 5.96(s)μ ; C=C 6.17(w)μ; see Fig. 1.

Ultraviolet spectrum

λmax. 225mμ (log ε 4.0), 317mμ (log ε 1.5).

λmin. 274mμ (log ε 1.2).

see Fig. 7.

N.M.R. spectrum

C(2)-H broad doublet at 365 c.p.s.
C(3)-H multiplet near 420 c.p.s.
see Fig. 8.

2,4 Dicarbomethoxy-5-carbomethoxymethylcyclohexanone XXXII

4.3g. of XVII was dissolved in 160ml. of ethyl acetate and 700mg. of 10% Pd-C was added. The mixture was hydrogenated at atmospheric pressure. The uptake of hydrogen was complete after one hr. The catalyst was filtered and the solvent removed, leaving 4.8g. of a thick oil. It was chromatographed over iron-free silica and eluted with 7:3 benzene-ether. Then it was distilled (bath temp. 165-185°/ 2.6mm.).

Analysis

Calculated for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.40; H, 6.49.

Infrared spectrum

$C=O$ 5.78(s)μ, 6.03(s)μ, 6.18(m)μ ; see Fig. 2.

Ultraviolet spectrum

λmax. 254mμ (log ε 3.92)
λ shoulder 300mμ (log ε 1.9). see Fig. 7.

N.M.R. spectrum showed no vinyl protons. see Fig. 8.

3-Carboxymethyl-4-carboxycyclohexanone XXXIII

2.0g. of XXXII and 2 ml. of 20% hydrochloric acid were heated in a sealed tube for 3.5 hrs. in an oven at 185-195°. After cooling the tube contents were concentrated and extracted with ether. The extract was dried and the solvent removed leaving 0.8g. of a residual oil. The latter was chromatographed over acid-washed silica and eluted with 7:3 benzene-ether. The eluate was crystallized from acetone-cyclohexanone mixture yielding a crystalline solid, m.p. 143-145°.

Analysis

Calculated for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found: C, 53.96; H, 5.97.

Infrared spectrum (Nujol)

OH 2.35(w)μ ; C=O 5.75(s)μ, 5.80(s)μ; see Fig. 3.

3-Carbomethoxymethyl-4-carbomethoxycyclohexanone XXXIV

XXXII was esterified with a slight excess of diazomethane. The product was chromatographed over silica and eluted with

4:1 benzene-ether. It then was distilled (bath temp. 180-190°/2.6mm.).

Analysis

Calculated for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.12; H, 7.02.

Infrared spectrum

$C{=}O$ 5.79(s) μ and 5.85(m) μ ; see fig. 3.

Esterification of α -ketoglutaric acid

5.0g. of α-ketoglutaric acid was refluxed for 1.5 hrs. with 70 ml. of anhydrous methanol and 20 drops of conc. sulfuric acid. After cooling the solution was basified with 5% sodium carbonate and concentrated. It then was extracted ether and the extract was dried. The solvent was removed leaving 2.7g. of dimethyl α-ketoglutarate. The mother liquor was made acidic and again extracted with ether. The extract was dried and the solvent removed yielding 2.0g. of a thick oil XLI . It was chromatographed over silica and eluted with 3:1 benzene-ether. It was distilled (bath temp. 160-180°/1.5mm.). Molecular weight determination by the Rast method gave a value of 327.

Analysis

Calculated for $C_{13}H_{16}O_9$: C, 49.37; H, 5.10. Found:

C, 49.36; H, 5.28.

Infrared spectrum

C=O 5.60(m)μ, 5.76(s)μ; see Fig. 3.

Ultraviolet spectrum

λ max. 242 mμ(log ε 4.0)

$\lambda^{0.5\ N\ NaOH}_{max}$ 275mμ.

Enol ether of XLI - XLII

XXXV was converted to its enol ether by exposure to diazomethane. Then the product was distilled (bath temp. 150-170°/2mm.).

Analysis

Calculated for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 50.82; H, 5.55.

Infrared spectrum

C=O 5.65(s)μ, 5.78(s)μ; C=C 5.99(w)μ. See Fig. 4.

Ultraviolet spectrum

max. 242mμ (log ε 3.8).

Cyclohexenylcyclohexanone LIV

Compound LIV was prepared by the method of Gault (26); b.p. 153-156°/11mm. reported b.p. 134-136°/11mm. (26).

Infrared spectrum

c=o 5.80(s)μ, c=c 6.05(w)μ. see Fig. 10.

Ultraviolet spectrum

λ max. 255mμ (log ϵ 3.50)

N.M.R. spectrum

An olefinic less than one-proton multiplet at 330 c.p.s. see Fig. 16.

Cyclohexylidenecyclohexanone XLIII

Cyclohexanone was purified through its bisulfite addition compound (43, p. 342).

Chlorocyclohexylcyclohexanone LV was prepared by the method of Huckel *et al*. (44).

Compound LV was converted to XLIII by the method of Reese (33). 10.3g. of LV was dissolved in 30 ml. of dry ether and the solution stirred. A solution of 1.7g. of sodium in 50 ml. of anhydrous methanol was added to the ether solution and the temperature kept below 10°. Stirring was continued for two hrs. whereupon water was added. The ether layer was washed with acid and dried and the solvent was evaporated. On distillation (b.p. 140-145°/11mm.) 5.7g. of XLIII was obtained. It was crystallized from 80% methanol; m.p. 56°.

Infrared spectrum

$C=O$ 5.95(s)μ, $C=C$ 6.20(m)μ. see Fig. 10.

Ultraviolet spectrum

λ max. 255 mμ(logϵ 3.9).

The n.m.r. spectrum showed no olefinic protons. see Fig. 16.

Condensation of cyclohexylidenecyclohexanone XLIII with diethyl oxalate

The condensation was carried out as described by Jager (17). But the product obtained was a dark oil rather than a yellow crystalline solid. It was not investigated further.

Infrared spectrum

$C=O$ 5.70(s)μ.

Condensation of cyclohexenylcyclohexanone LIV with diethyl oxalate

1.53g. of sodium sand was stirred in 40 ml. of anhydrous ether. A solution of 9.8g. diethyl oxalate and 12.2g. of in 50ml. ether was added at first slowly at room temperature and upon the start of evolution of hydrogen with cooling. Yellow crystals started precipitating after a while. The mixture was left standing overnight. The precipitated solid was filtered, washed with ether and dissolved in water. The solution was acidified with 5N sulfuric acid and the resulting precipitate of yellow crystals LVII filtered. Extraction of the ethereal mother liquor with water and acidification of the extract gave more yellow compound. The total yield was 8.2g. The product was crystallized once from methanol and four times from 1:1 benzene-hexane; m.p. 168-178° (reported m.p. 182° (17)).

Analysis

Calculated for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.58; H, 6.92.

Infrared spectrum (Nujol)

OH 2.85(w)μ, c = o 5.80(s)μ, c = c 5.98(w)μ.

see fig. 10.

Ultraviolet spectrum

λ max. 225mμ (log ε 3.90), 326mμ (log ε 4.41)

λ min. 247mμ (log ε 3.89)

$\lambda^{0.5\text{ N NaOH}}_{\text{max}}$ 241mμ (log ε 4.00), 351mμ (log ε 4.40)

$\lambda^{0.5\text{ N NaOH}}_{\text{min}}$ 277mμ (log ε 1.35)

see Fig. 12.

The <u>n.m.r.</u> spectrum showed an olefinic one-proton multiplet at 364 c.p.s. see Fig. 16.

3-Methylquinoxalone

3-Methylquinoxalone was prepared by a standard method (45).

Condensation of LVII with O-phenylenediamine.

The reaction was carried out by the method of Jager (17) m.p. 260-265° (dec.); reported m.p. 267-270° (17).

<u>Analysis</u>

Calculated for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 73.91; H, 6.84; N, 8.81.

<u>Infrared spectrum</u> (Nujol)

$c=o$ 5.85(w)μ, 6.02(s)μ; $c=c$ 6.22(m)μ.

see Fig. 11.

<u>Ultraviolet spectrum</u>

λ max. 229mμ(log ε 4.42), 280mμ(log ε 3.78), 341mμ (log ε 3.81);

λ shoulder 255mμ(log ε 3.70), 330mμ(log ε 3.80);

λ min 2.63mμ (log ε 3.63), 306mμ (log ε 3.48);

$\lambda^{0.5\ N\ NaOH}_{max}$ 241mμ (log ε 4.53), 351mμ (log ε 3.95);

$\lambda^{0.5\ N\ NaOH}_{min}$ 305mμ (log ε 3.51)

see Fig. 13, 14, 15.

Enol acetate of LVII —— LVIII

2.0g. of LVII and a little of sodium acetate were dissolved in 40 ml. of acetic anhydride. The solution was stirred at room temperature for two hrs. Methanol then was added and the solvent evaporated. After repetition of this procedure for a few times, the solution was cooled and water added. The aqueous solution was extracted with ether. The extract was washed with 4% sodium bicarbonate solution and then with water. After drying, the solvent was evaporated. A yellow oil, 1.5g., was obtained. It was not purified further.

Infrared spectrum

$C{=}O$ 5.61(s)μ, 5.79(s)μ ; $C{=}C$ 6.02(m)μ.

see Fig. 11.

Ultraviolet spectrum

λ max 329mμ (log ε 4.28), 225mμ (log ε 3.84)

λ min 244mμ (log ε 3.6)

see Fig. 12.

N.M.R. spectrum

An olefinic one-proton multiplet at 371 c.p.s.; a methyl three-proton singlet (of the acetate group) at 138 c.p.s.

see Fig. 17.

Hydrogenation of the enol acetate LVIII —— LIX

1.0g. of LVIII in 80 ml. of 95% ethanol was hydrogenated with 700 mg. of 10% Pd-C at atmospheric pressure. The uptake of hydrogen was complete in two hrs. The catalyst was filtered and the solvent evaporated. 1.0g. of a thick oil was obtained. It was distilled; bath temp. 260-280°/2.5mm.

Analysis

Calculated for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30.

$C_{16}H_{22}O_4$: C, 69.04; H, 7.97.

Found: : C, 68.72; H, 7.61.

Infrared spectrum

$C=O$ 5.61(s)μ, (shoulder), 5.79(s)μ ; $C=C$ 6.02(w)μ.

see Fig. 11.

Ultraviolet spectrum

λ max 292mμ (log ε 4.1), 215mμ (log ε 3.7)

λ min 244mμ (log ε 3.4)

see Fig. 12.

SUMMARY

The structure of the base-catalyzed self-condensation product of methyl glutaconate has been investigated. Its structure is shown to be dimethyl 5,6-dihydro-4-hydroxy-6-carbomethoxymethylisophthalate. The chemistry of this product has been studied. It has been degraded to 3-carbomethoxymethyl-4-carbomethoxyclohexanone, which might be incorporated into rings D and E in yohimbine-like alkaloids through several further reactions.

The assigned structure of the base-catalyzed condensation product of cyclohexenylcyclohexanone and diethyl oxalate has been shown corrected.

LITERATURE CITED

1. F. Henrich, Monatsh., 20, 539 (1899)
2. E.E. Blaise, Bull. Soc. Chim. France, 1015 (1903)
3. E.E. Blaise, Bull. Soc. Chim. France, 1028 (1903)
4. H. Fecht, Ber., 40, 3883 (1907)
5. R. Curtis and J. Kenner, J. Chem. Soc., 105, 282 (1914)
6. H. Pechmann, W. Bauer and J. Obermiller, Ber., 37, 2113 (1903)
7. E. P. Kohler and G.H. Reid, J. Am. Chem. Soc., 47, 2803 (1925)
8. O. Stark and O. Garben, Ber., 46, 659 (1913)
9. J.L. Simonsen, J. Chem. Soc., 97, 1910 (1910)
10. E.H. Ingold, J. Chem. Soc., 127, 1199 (1925)
11. S.E. Hunt, J. Idris Jones, and A.S. Lindsey, J. Chem. Soc., 1956, 3099
12. R.B. Woodward, J. Am. Chem. Soc., 63, 1123 (1941)
13. R.B. Woodward, J. Am. Chem. Soc., 64, 72 (1942)
14. R.B. Woodward, J. Am. Chem. Soc., 64, 76 (1942)
15. E.E. van Tamelen and M. Shamma, J. Am. Chem. Soc., 76, 950 (1954)
16. H. Gault, Compt. Rend., 153, 107 (1911)
17. H. Jager, W. Farber and N. Poonawalla, Archiv der Pharmazie, 295, 205 (1962)
18. L. Claisen, Ber., 27, 1353 (1894)
19. L. Claisen and Th. Edwan, Ann., 284, 245 (1895)
20. J. Bredt, Ann., 437, 1 (1924)
21. F.S. Fawcett, Chem. Rev., 47, 219 (1950)

22. V. Prelog, J. Chem. Soc., 1950, 420.

23. V. Prelog, P. Barman and M. Zimmermann, Helv. Chim. Acta, 32, 1284 (1949).

24. V. Prelog, L. Ruzicka, P. Barman and L. Frenkiel, Helv. Chim. Acta, 31, 92 (1948)

25. O. Wallach, Ber., 29, 2965 (1896)

26. H. Gault, L. Daltroff and J. Ecktridon, Bull. Soc. Chim. France, 12, 952 (1945)

27. F. Taboury and M. Godchot, Compt. Rend., 169, 62 (1918)

28. G. Vavon, Anziani and Herynk, Bull. Soc. Chim. France, 39, 1138 (1926)

29. A. Haller and E. Bauer, Compt. Rend., 162, 551 (1911)

30. O. Wallach, Ber., 40, 70 (1907)

31. F. Kunze, Ber., 59, 2085 (1926)

32. G.A.R. Kon and J.H. Nutland, J. Chem. Soc., 1926, 3101

33. J. Reese, Ber., 75, 384 (1942)

34. G.A.R. Kon and E.A. Speight, J. Chem. Soc., 1926, 2727

35. H.S. French and L. Wiley, J. Am. Chem. Soc., 71, 3702 (1949)

36. H.O. House and R.L. Wason, J. Am. Chem. Soc., 78, 4394 (1956)

37. Ts.N. Roginskaia, S.V. Svetozarskii, A.I. Finkel'shtein and E.N. Zil'berman, J. Gen. Chem., of U.S.S.R. 28, 2266 (1958)

38. H. Jager, Ber., 95, 242 (1962)

39. R.B. Woodward and G. Singh, Experientia, 6, 238 (1950)

40. R.B. Woodward and G. Singh, J. Am. Chem. Soc., 72, 1428 (1950)

41. R.B. Woodward and G. Singh, J. Am. Chem. Soc., 72, 5351 (1950)

42. S.F. Mason, *J. Chem. Soc.*, *1957*, 4874

43. A.I. Vogel, *A Text-Book of Practical Organic Chemistry*, Longmans, Green and Co., Ltd., London (1961)

44. W. Huckel, O. Neunhoeffer, A. Gercke and E. Frank, *Ann.*, *477*, 99 (1930)

45. O. Hinsberg, *Ann.*, *292*, 245 (1896)

ACKNOWLEDGEMENTS

The author is indebted to Dr. Ernest Wenkert for suggesting this problem and for guidance during the course of the investigation.

He wishes to thank Mr. Curtis Leight and Mr. James McChesney who have taken the n.m.r. spectra and helped interpreting them.

He wishes to thank Texaco Inc., for a Research Fellowship during 1960-61 and to CIBA Pharmaceutical Company, Summit, New Jersey for financial support during 1961-62.