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STRUCTURE AND STEREOCHEMISTRY OF THE KETOACIDS DERIVED FROM MENTHOFURAN PHOTOPEROXIDE[1a]

C. S. FOOTE,[1b] M. T. WUESTHOFF and I. G. BURSTAIN[1c]
Department of Chemistry, University of California, Los Angeles,
California 90024[*]

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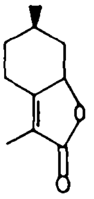
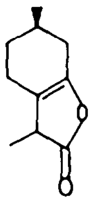
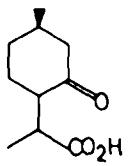
Abstract—The four diastereomeric keto acids related to the lactones produced by reduction of the menthofuran photoperoxide have been assigned structure and stereochemistry by alternate synthesis from pseudoacid IV, by stereospecific interconversions, and by ORD spectra.

IN CONNECTION with the structure determination of the menthofuran photoperoxide, an α,β-unsaturated and a β,γ-unsaturated lactone (structures I and II) were isolated.[2] In order to place the structures of these compounds on a firm basis, the four diastereomeric keto acids IIIa–d which are derived from lactones I and II were studied.[3]


I


II


IIIa-d

Saponification of the α,β-unsaturated lactone I[2] produced a mixture of all four keto acids;[4] the relative amounts were determined to be 18, 37, 41 and 4% of IIIa, IIIb, IIIc and IIId, respectively. From this mixture, one acid (IIIa, m.p. 143–144°) crystallizes readily; this acid is presumably identical to the acid (m.p. 146–147°) isolated by reduction of the pseudoacid IV with sodium amalgam.[6]

This compound was free of its isomers; the IR spectrum had bands at 2·9 and 5·68 μ in $CHCl_3$, indicating that the acid exists largely in the pseudoacid (lactol) form V in this solvent.[7] In addition, the NMR spectrum had no carboxyl absorption below 0 τ.

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[2a] C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain and R. Denny; G. O. Schenck and K.-H. Schulte-Elte, *Tetrahedron* 23, 2583 (1967); [b] all compounds in this series are ultimately derived from (+)-pulegone, and thus have the absolute configurations shown.

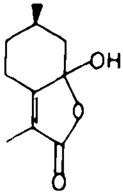
[3] See Experimental for details of the analysis of mixtures of IIIa–d.

[4] The saponification presumably proceeds by way of the β,γ-unsaturated lactone II. Ample analogy is available.[5]

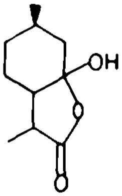
[5a] W. Cocker and S. Hornsby, *J. Chem. Soc.* 1157 (1947); [b] R. B. Woodward and P. Yates, *J. Am. Chem. Soc.* 85, 551 (1963).

[6] R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.* 72, 399 (1950).

[7] Even in the case of IIIa (which IR spectroscopy shows to be the most completely in the lactol form of the three isolated isomers) the equilibrium constant for closure is far smaller than that for the unsaturated keto acid corresponding to IV, since IIIa, unlike IV,[6] dissolves readily in bicarbonate.



IV



V

The mother liquor from the first acid slowly deposited a second keto acid IIIb (m.p. 97–98°), which is probably the same as the reported second acid[6] (m.p. 89–91°). This acid was much more difficult than IIIa to free of its isomers, and usually contained traces of IIIa and up to 10% of a third acid IIIc. The IR spectrum of keto acid IIIb showed no lactol absorption near 5·7 μ ($CHCl_3$), but typical carboxyl absorption 3·4 and 5·87 μ); in addition, the NMR spectrum had a one-proton peak at −1·2 τ (CO_2H).[7]

The third keto acid IIIc was isolated by epimerization of acid IIIa with aqueous potassium hydroxide (described in more detail below) to a mixture of keto acids containing about 65% of IIIc and 35% IIIa. Acid IIIa was removed by crystallization to leave a mother liquor which was shown by gas chromatography to contain IIIc contaminated with less than 10% of its isomers. This acid could not be made to crystallize; the IR spectrum showed bands characteristic of both pseudoacid (lactol, V; 5·65 μ) and open keto acid (5·85 μ) in chloroform.[7] The NMR spectrum ($CDCl_3$) had a one-proton peak at 1·2 τ, considerably upfield from the normal carboxyl position (∼ −1 τ); this is presumably the time-averaged absorption of the lactol and keto acid OH groups, which undergo rapid exchange.

Structural and stereochemical assignments

The structures of the keto acids follow directly from their spectra and chemical properties, and from the interconversions described below, which also permit complete stereochemical assignments. Saponification of the β,γ-unsaturated lactone II produced a mixture of all four keto acids (IIIa, IIIb, IIIc and IIId, in relative amounts, 7, 52, 38 and 3%). Hydrogenation of the Woodward-Eastman pseudoacid IV on Pd in ethanol gave a mixture which contained only keto acids IIIc and IIId (relative amounts 40 and 60%, respectively). Hydrogenation normally gives predominantly *cis*-addition of hydrogen to the double bond,[8] thus since only two isomers were formed, these are probably the products of *cis* addition from the two sides of the molecule; acids IIIa and IIIb would then be the corresponding *trans*-compounds.[2b]

The acids IIIa and IIIb were heated with 10% aqueous KOH. Under these conditions, the proton α to the ketone would be expected to be far more easily exchanged and thus epimerized than that next to the carboxylate group. In agreement with this expectation, only one acid other than the starting material was found in each reaction (after correction for the presence of small amounts of isomeric impurities in the starting material). The product from IIIa was a mixture of IIIc and IIIa in relative proportions 2:1; that from IIIb was a mixture of IIIb and IIId in relative proportions

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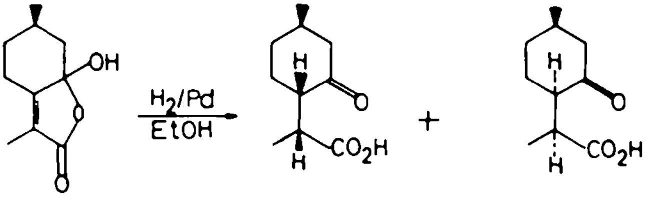
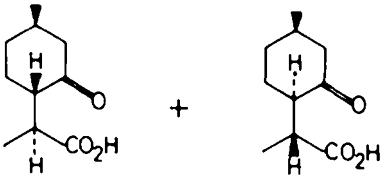
[8] E. L. Eliel, *Stereochemistry of Carbon Compounds*. McGraw-Hill, New York (1962).



IV

IIIc and IIId



IIIa and IIIb

2:1. These results indicate that IIIc is more stable than IIIa; the relative stabilities of IIIb and IIId cannot be assessed from these data alone, since equilibrium may not have been reached. The results also confirm that IIIa and IIIb are epimeric at least at the position α to the carboxyl, since otherwise epimerization α to the ketone would have interconverted them.

The results of the hydrogenation of pseudoacid IV and the above epimerization together indicate that the *cis* acid IIIc and the *trans* acid IIIb have one configuration α to the ketone, and that the *cis* acid IIId and the *trans* acid IIIa have the other configuration. Thus assignment of configuration to any one of the acids is sufficient for the assignment to all.

Very small amounts of the methyl esters of acids IIIa and IIIb were heated with methanolic sodium methoxide; from each, mixtures containing all four esters were formed, showing that both positions are subject to epimerization under these conditions. In the reaction mixtures from both IIIa and IIIb, the proportion of IIIb was larger than that of IIId. In addition, in each of the other reactions carried out under basic conditions (hydroxide epimerization of IIIb, and saponification of both conjugated and unconjugated lactones), IIIb was present in larger amount that IIId, so that IIIb is almost certainly more stable than IIId.

Thus, since IIIc was already shown to be more stable than IIIa, and since IIIb and IIIc have the same configuration α to the ketone, IIIb and IIIc can be confidently assigned the diequatorial configurations, in which the two ring substituents are *trans*; the other two then have *cis* ring substituents.[2b] Table 1 summarizes the reactions carried out and the stereochemical assignments.

The ORD curves for the esters of IIIa–d were taken; the results are listed in Table 2. These results clearly separate the esters into two groups: IIIa and IIId have large values for the Cotton effects, whereas IIIb and IIIc have small values; all are positive. Excellent models for these compounds are provided by menthone and isomenthone, whose ORD spectra have been analyzed and discussed in detail.[9] (−)-Menthone

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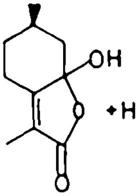
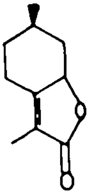
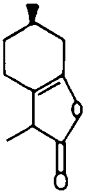
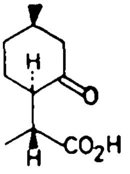
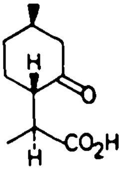
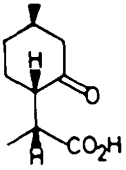
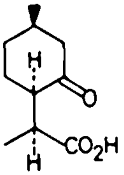
[9] C. Djerassi, *Optical Rotatory Dispersion; Applications to Organic Chemistry*. McGraw-Hill, New York (1960).

TABLE 1. INTERCONVERSIONS OF KETOACIDS

Reaction	Per cent of acid (or ester) in product[a]			
	IIIa	IIIb	IIIc	IIId
IIIa + OH^-/H_2O	32	3	65	tr.
IIIb + OH^-/H_2O	[b]	63	[b]	27
 + H_2/Pd	—	—	40	60
IIIa Ester + OMe^- [c]	37	13	41	9
IIIb Ester + OMe^- [c]	14	33	43	9
 I + OH^-	18	37	41	4
 II + OH^-	7	52	38	3
Structure assigned				

[a] Determined by gas chromatography of the methyl ester.

[b] Both the starting acid and the final product contained 2-3% IIIa and 8% IIIc.

[c] Product remethylated before analysis; reaction may not have been complete.

(VII) has a weak positive Cotton effect, while the epimeric (+)-isomenthone (VIII) has a strongly positive effect. Similar effects are observed with the isopulegones.[10]

Thus, by analogy, the two keto esters with the small Cotton effects would be expected to be those with the ring substituents *trans*, while those with the large Cotton effects should have *cis* configurations of the substituents. These are precisely the configurations assigned above to the four keto acids on the basis of chemical evidence.

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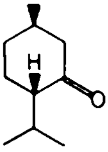
[10] G. Ohloff, J. Osieki and C. Djerassi, *Chem. Ber.* **95**, 1400 (1962).

Each of the three isolable keto acids IIIa–c was dehydrated by distillation both from potassium bisulfate and from phosphorus pentoxide.[11] The products were in each case a mixture containing predominantly the β,γ-unsaturated lactone II and small amounts of unidentified materials. Some of the α,β-unsaturated lactone I was also present, apparently produced by rearrangement of the β,γ-isomer during reaction or gas chromatography.[2a] Samples of both lactones were collected from the gas chromatograph; the IR spectra of all samples of each were always identical no matter which acid they were produced from. Gas chromatography on a wide variety of efficient columns failed to disclose any retention time differences between samples of various origins, although small amounts of other unidentified materials were present in many of the reaction mixtures. The two diastereomeric forms of each lactone may be so similar that no separation is possible under the conditions tried; all saponifications of II would have caused loss of stereochemistry. For these reasons, no stereochemistry can be assigned to lactone II; tentative assignment of stereochemistry of lactone I is made in the accompanying paper[3a] but this stereochemistry would also be lost during saponification.[4]

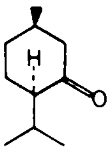
TABLE 2. OPTICAL ROTATORY DISPERSION DATA FOR THE KETO ESTERS IIIa–d

	Extrema					Zero rotation,
Ester	λ, mμ	[α]	λ, mμ	[α]	[A][a]	mμ
IIIa	311	560	267	−1180	34	293
IIIb	313	38	280	- 500	11	309
IIIc	313	- 12	275	- 436	8	296
IIId	314	817	269	- 1180	40	297

[a] As defined by W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* 83, 4013 (1961), the difference between peak and trough values for [ϕ]/100 in standard Cotton effect curves.



VII



VIII

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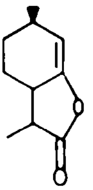
[11] Treatment of the acids with acetic anhydride, the more usual reagent[4a] apparently produced a third isomer, VI, rather than I or II.



VI

EXPERIMENTAL

All m.p.s are uncorrected. Microanalyses were by Miss Heather King, UCLA, IR spectra were taken on a Perkin–Elmer Model 137 Infracord, calibrated with polystyrene films. NMR spectra were taken on a Varian A-60 spectrometer (purchased with NSF Grant No. G-20207) and are relative to internal TMS. UV spectra were taken on a Cary Model 14 spectrophotometer. Gas chromatography was carried out with a Perkin–Elmer Model 154 (thermal conductivity detector) or Model 800 (flame ionization detector) chromatograph. ORD spectra were taken on a Cary Model 60 spectropolarimeter (purchased with NSF Grant No. GP-1682).

Analysis of acid mixtures. In the following experiments, analysis of acid mixtures was carried out by gas chromatography of the Me esters. The acids were methylated with excess diazomethane in ether; the solns were washed with bicarbonate to remove unreacted acids, as it was found that IIIa is methylated only to the extent of 67%, presumably because it is partially in the lactol form. Percentages given have been corrected for the fraction of unmethylated IIIa; it is to be expected that IIIc is also incompletely methylated since it also shows a substantial amount of lactol absorption in the IR; however, lack of pure material prevented testing this point, and no correction has been made. Errors introduced by failure to make this correction would not affect the conclusions presented, since the amount of IIIc could only increase. The esters were separated on a 10-foot 1/8" column of 3% *tris*-[2-cyano-ethoxy]propane (TCEP) on Chromosorb W at 130° at a flow rate of 50 ml/min; under these conditions, the relative retention times for the esters IIIc, IIId, IIIa and IIIb are 75, 83, 89 and 100, respectively.

Saponification of the α,β-unsaturated lactone (I)

Preparation of keto-acids IIIa *and* IIIb. A soln of 894 mg (5·39 mmoles) lactone I[14] in 30 ml 25% methanolic KOH was refluxed 1 hr. The soln was diluted with H_2O, and extracted with ether, which was discarded. The aqueous layer was acidified with 6N HCl, and extracted again with ether. The extract from the acidic soln was concentrated to a small volume, and the residue taken up in benzene. The soln was washed with H_2O, filtered through anhyd Na_2SO_4, and evaporated to give an oily residue containing some crystals (755 mg, 4·10 mmoles, 76%). VPC analysis (see above) showed the residue to be a mixture containing 18, 37, 41 and 4% of IIIa, IIIb, IIIc and IIId, respectively.

The residue was taken up in benzene and diluted with a large amount of hexane. Two crops of flat needles of IIIa were collected (150 mg, 806 mmoles, 15%, based on lactone). The product was recrystallized to a constant m.p. of 143–144° (reported for one of the acids obtained by Na(Hg) reduction of pseudo acid: 146–147°[6]). (Found: C, 65·2; H, 8·4. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·7%.) The IR spectrum ($CHCl_3$) had bands at 2·9 (w), 5·68 (s), 5·85, 9·32, 10·50 (s), 10·60 (s), and 12·0 μ; the NMR spectrum ($CDCl_3$) had bands at 7–8·5 (unresolved), 8·80 (d, J = 7, 3H), and 9·05 τ (d, J = 6, 3H). The UV spectrum (MeOH) had $\varepsilon_{311} = 290$, $\lambda_{max} = 269$ mμ ($\varepsilon = 10$). The Me ester of this acid had IR bands ($CHCl_3$) at 5·78, 5·85, 7·80, 7·90, 8·40, 8·55 (s) and 9·43 μ among others.

The mother liquor from the crystallization of IIIa was allowed to stand in benzene–hexane at 10° for several weeks; the impure crystals which had separated were redissolved in benzene; a small insoluble residue of IIIa was filtered off and the soln again saturated with hexane to yield 110 mg (0·539 mmole, 11%) of flat needles of IIIb, which were recrystallized to a constant m.p. of 97–98° (reported[6] for the second ketoacid obtained by Na(Hg) reduction of pseudoester: 89–91). (Found: C, 65·3; H, 8·8. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·7%.) The IR spectrum ($CHCl_3$) was: 2·7–4·1, 5·87 (s), 9·01 (w), 9·29 (w), 10·30 (w), 10·60 (w), 10·80 (w), 11·2 (w), and 11·6 μ (w); in the NMR ($CDCl_3$) there were bands at −1·2 τ (1H), 7·0–7·5 τ (unresolved, 2H), 8·78–9·1 τ (unresolved, 6 + H) in addition to broad absorption from 7·5–8·5 τ. The UV spectrum (MeOH) had $\varepsilon_{310} = 99$, $\lambda_{max} = 284$ mμ ($\varepsilon = 18$). The Me ester of this acid had IR absorption (CCl_4) at 5·77, 5·85, 8·30, 8·40, 8·58, 9·32 and 9·45 μ.

Epimerization of keto acids IIIa *and* IIIb *in aqueous base*

Preparation of acid IIIc. Roughly 5 mg each of purified acids IIIa and IIIb were refluxed 1–2 hr in 0·5 ml 10% KOHaq; the solns were acidified with 6N HCl and extracted with benzene. The benzene solns were filtered through anhyd Na_2SO_4 and analyzed as described above; the purities of the starting acids were simultaneously checked. The results are listed in Table 3.

The epimerization of IIIa was repeated on a somewhat larger scale (10 mg). The aqueous soln was acidified, extracted with benzene and dried, and the remaining starting material removed by crystallization (benzene–hexane). The mother liquors were evaporated, and the residue found (by the above procedure) to be acid IIIc, containing less than 10% of isomeric acids. This acid has not been obtained crystalline; insufficient material was available for elemental analysis. The characteristic IR bands ($CHCl_3$) are: 2·7–4·1, 5·65, 5·85 (s), 9·72 (w), 10·73. The NMR spectrum ($CDCl_3$) had a broad peak at 1·9 τ (S, 1H), an unresolved multiplet at 6·8–8·7 τ (8H) and doublets at 8·81 (3H, J = 7) and 8·99 τ (3H, poorly resolved).

TABLE 3.—HYDROXIDE EPIMERIZATION OF KETO ACIDS

Mixture		Composition, %			
		IIIa	IIIb	IIIc	IIId
IIIa	Initial	100	—		—
	Final	32	3	65	tr.
IIIb	Initial	3	88	8·5	tr.
	Final	2	63	8	27

Saponification of the unconjugated lactone (II). The solvent was evaporated from a portion of the mixture obtained by reduction of the menthofuran photoperoxide with excess triphenylphospine (which was nearly pure II).[3a] A soln of 1 g of this mixture in 10 ml 10% methanolic NaOH was refluxed for 1 hr, then diluted with twice its volume of water and extracted with benzene, which was discarded. The aqueous soln was acidified with 6N HCl and extracted with benzene. The benzene soln was washed with 5% HCl, dried over anhyd Na_2SO_4 and evaporated. The extract from the acidic soln contained approximately 40 mg of a brownish-yellow oil. Analysis of this mixture in the usual way showed the approximate composition to be 38% IIIc, 3% IIId, 52% IIIb and 7% IIIa.

Hydrogenation of pseudoacid (IV). A soln of 91·8 mg (0·505 mmoles) of the pseudoacid[6] IV in 10 ml 100% EtOH was stirred over 10% Pd/C for 2·5 hr at room temp and atm press, under an atm of H_2. The H_2 uptake was 8·5 ml (STP, 0·75 moles H_2 per mole pseudoacid). The reaction mixture was filtered, diluted with water (approx. 250 ml), and acidified with 6N HCl. The soln was extracted twice with ether, the combined ether extracts were evaporated, and the residue taken up in benzene. The benzene soln was filtered through anhyd Na_2SO_4. Gas chromatography (as described above) showed two products to be present, IIIc (40%), and IIId (60%), in addition to some unreacted pseudoacid.

Methoxide epimerization of IIIa *and* IIIb *esters*. A small cube of Na, freshly cut under hexane, was placed in one bulb of a carefully dried apparatus arranged for bulb-to-bulb distillation and fitted with a septum; the apparatus was flushed with dry N_2, and about 1 ml MeOH was distilled from CaH_2 onto the Na from the other bulb. A soln of the Me ester to be epimerized in about 50 ml of benzene (prepared by methylating the acid with diazomethane in benzene, drying and concentrating[18]) was added through the septum with a microsyringe. Aliquots were withdrawn with a syringe and quenched immediately in 3% aqueous HCl. The aqueous solns were extracted with benzene, methylated by adding diazomethane in ether,[19] filtered through dry Na_2SO_4, concentrated, and analyzed by gas chromatography.

Solns of 3 mg of the Me ester of IIIa and 16 mg of the Me ester of IIIb were allowed to react for 3 hr, at 60° for the soln from IIIa, and at 25° for that from IIIb. The compositions of the reaction mixtures are given in Table 4.

Optical rotatory dispersion measurements. The ORD curves of the 3 isolable ketoacids were taken in an attempt to measure the Cotton effects resulting from the ketone chromophores. All the acids had positive Cotton effects in the 300 mμ region, but the large contribution from the carboxyl chromophore made it impossible to measure the ketone contribution with any certainty. As the Me esters

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[18] The benzene solution from IIIa was also washed with 10% $NaHCO_3$aq to remove unmethylated acid, a precaution which was necessary for this acid (*vide supra*).

[19] This methylation was necessary since it was found that despite all precautions, up to half of the initial ester had been hydrolyzed, either during reaction or workup.

had a much smaller interference from the carbomethoxyl group, ORD curves (in MeOH) were made of the Me ester of each isolable acid, and of the esterified acid mixture from pseudoacid hydrogenation. The curve for this mixture was corrected by subtraction of the (small) calculated contribution from the known proportion of isomeric esters (IIIc, 39·0% and IIIa, 1·5%). In this way, the curve for pure IIId ester (59·5%) could be estimated, although this ester was never isolated. These values are only qualitatively meaningful, because of the small interference from the carbomethoxyl chromophore, which was serious only in the case of IIIc; correction for this contribution would reduce the observed amplitude for IIIc by about one fourth. The results are listed in Table 2.

Dehydration of keto acids IIIa–c. The acid to be dehydrated, 5–10 mg, was placed in a bulb with a large excess of P$_2$O$_5$. The system was evacuated and sealed off, and the contents of the bulb were heated gradually to 150° over the period of ½ hr; during this time, the dehydration product distilled into a sidearm which was cooled with liquid N$_2$. The distillate was washed out with CCl$_4$. Both the IR spectrum of the crude distillate and gas chromatography indicated the principal product to be the unconjugated lactone II with the conjugated lactone I as the impurity. The retention times (150′ Silicone oil capillary and 10′ × ¼″ 25% TCEP on 70–80 Anakrom ABS columns) of the peaks corresponding to lactones I and II from each of the three acids were identical. In addition to I and II, small amounts of unidentified compounds were also produced. The retention time of the unidentified material from IIIc was identical to that from IIIa, but differed from that from IIIb. The unidentified compounds were not isolated, as they could not be separated from II except in microscopic amounts on high-resolution gas chromatography columns using a flame-ionization detector.

TABLE 4. METHOXIDE EPIMERIZATION OF KETO ESTERS

Mixture		Composition, %			
		IIIa	IIIb	IIIc	IIId
IIIa	Initial	100	—	—	—
	Final	37	13	41	9
IIIb	Initial	4	86	9	2
	Final	14	33	43	9

The acids were also dehydrated in a similar way over KHSO$_4$; the results of these dehydrations were very similar to those with P$_2$O$_5$, except that the proportions of I in the reaction mixture were somewhat higher. The infrared spectra of samples of I and II collected from the v.p.c. were identical to those of samples prepared by peroxide reduction.[26] Small amounts of unidentified compounds were also produced in these reactions.

Dehydration of the acids with refluxing Ac$_2$O produced complex mixtures of compounds, including a compound whose retention time on Silicone oil columns was very similar to that of II, and which had similar IR absorption in the CO region, but a very different spectrum in the fingerprint region; and which is believed to be the double-bond isomer VI.