Structures and Reactions of Condensation Products
of Benzaldehyde and Acetoacetic Ester

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The configurations of the three known isomers of 1-methyl-3-phenyl-1-cyclohexanol-5-one-2,4-dicarboxylate esters are assigned on the basis of nmr spectra. The predominant condensation product has all equatorial substituents except hydroxyl. The next highest yield product has an axial 2-carbomethoxy and an axial hydroxyl group; other groups are equatorial. The minor product has an axial 1-methyl and an axial 2-carbomethoxy group. In the nmr spectrum of the first product, long-range coupling to the hydroxyl proton is observed. The large magnitude of this four-bond coupling to the hydroxy proton is considered the result of a preferential hydrogen-bonded conformation which holds the coupled protons in the W conformation. A mechanism is proposed for the unusual base-catalyzed loss of the 4-carbomethoxy and 1-hydroxyl functions which accounts for the fact that the first two isomers undergo this reaction much more readily than the third isomer.

The somewhat acrimonious history of the reaction products from the condensation of acetoacetic ester and benzaldehyde began in 1885 when Hantzsch[1] isolated a product, mp 149–150°, from the reaction the structure of which he considered to be 1. Some time later Knoevenagel[2] also proposed 1 as the structure of the product. In those days of difficult structure proof, Schiff[3] first considered structure 2 for the same material.


1

2
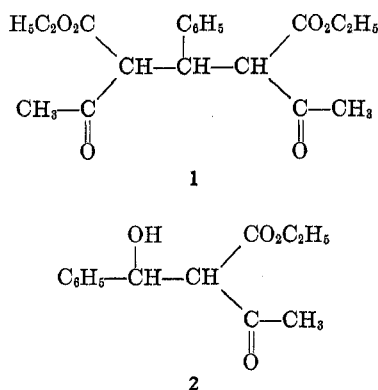
Later Schiff isolated three isomeric products from the condensation, mp 150, 134, and 120°, which he then considered to be the three isomers of 1.

Rabe[4-9] began an extensive series of investigations of the condensation, in which he criticized Schiff on the basis that some of Schiff's materials were actually mixtures. Rabe gave 150, 154, and 107–108° as the melting points of the three isomers of 1 which he termed β_1, β_2, and β_3. Later Rabe realized that these compounds were cyclic and proposed structure 3, which would demand the existence of eight diastereomers.[5,6] The cyclic nature of the products is generally ac-

cepted[10-12] and is consistent with the nmr data reported herein.

It was the purpose of this study to elucidate the configurations of the three known isomers and to study the very interesting reaction shown in eq 1.[8,9] Rabe and

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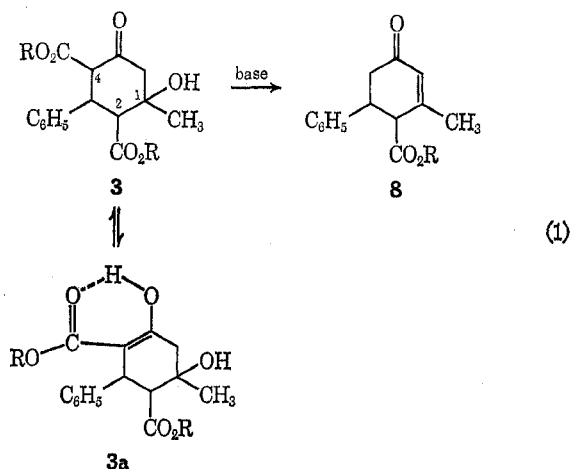
coworkers were also able to separate the enols 3a of the three isomeric ketones. These enols were shown to revert to their respective original ketones without additional isomerization. The reason for the specificity of the enolization–ketonization process was not investigated by Rabe, but becomes apparent upon proof of the configurations of 3, as explained below.

Results and Discussion

The ethyl esters were rather inconvenient for nmr analysis, and therefore the methyl esters were prepared by reaction of methyl acetoacetate and benzaldehyde catalyzed by piperidine. The main product 4 (usually about 65% of theoretical), mp 189.5–190.5°, was shown to be analogous to β_1 by nmr and infrared spectra. The second product 5 (usually 5–10%), mp 175.5–176.1°, was similar to β_2. A third product, 8 (R = CH₃), mp

(1) R. Hantzsch, *Chem. Ber.*, **18**, 2579 (1885).
(2) E. Knoevenagel, *ibid.*, **31**, 738 (1898).
(3) R. Schiff, *ibid.*, **31**, 105 (1898); **32**, 332 (1899).
(4) P. Rabe, *Justus Liebigs Ann. Chem.*, **313**, 129 (1900).
(5) P. Rabe and F. Elze, *ibid.*, **323**, 83 (1902).
(6) (a) P. Rabe, *ibid.*, **332**, 1 (1904). (b) P. Rabe and F. Rahm, *ibid.*, **332**, 10 (1904).
(7) P. Rabe and F. Billmann, *ibid.*, **332**, 22 (1904).
(8) (a) R. Rabe and D. Spence, *ibid.*, **342**, 327 (1906). (b) P. Rabe and F. Rahm, *Chem. Ber.*, **38**, 970 (1905).
(9) W. Dieckmann, *Chem. Ber.*, **44**, 975 (1911); **45**, 2609 (1912).

(10) (a) B. D. Wilson, *J. Org. Chem.*, **28**, 314 (1963). (b) D. F. Martin, M. Shamma, and W. C. Fernelius, *J. Amer. Chem. Soc.*, **80**, 5851 (1958).
(11) (a) J. K. O'Loane, C. M. Combs, and R. L. Griffith, *J. Org. Chem.*, **29**, 1730 (1963). (b) I. L. Finar, *J. Chem. Soc.*, 674 (1961).
(12) A. Dunlop and F. Peters, "The Furans," Reinhold, New York, N. Y., 1963, p 613.

TABLE I

NMR PARAMETERS[a] FOR 4-9

Compd	Chemical shifts, ppm							Coupling constants,[b] Hz				
	H1	H2	H3	H4	H6a	H5e	CH3	J16a	J23	J34	J26e	J6a6e
4	3.56	3.05	4.00	3.70	2.51	2.69	1.32	2.4	12.2	12.4		14.2
5	...[c]	3.04	4.22	4.60	3.32	2.47	1.32		4.9	13.1	1.6	14.6
6[d]	2.01	3.53	2.71	4.87	Ca. 2.97[c]	2.38	1.09		5.2	13.2	1.4	13.2
7	3.95	3.36	3.91	3.78	2.47	2.65	1.20	2.2	11.0	12.0		14.2

	Chemical shifts, ppm						Coupling constants,[b] Hz						
	H2	H4	H5	H6a	H6e	CH3	J6a6e	J2CH3	J24	J4CH3	J45	J56a	J56e
8[d]	5.93	3.23	3.46	2.31	2.34	1.55	16.4	1.2	0.4	1.2	9.1	12.4	3.7
9[d]	5.86	3.28	4.08	3.56		1.51		1.2	1.3	1.3	11.2	13.4	

[a] All 100 MHz; the parameters were varied until the California Computer Products plot of the computer calculated (LAOCOON program) spectrum was superimposible on the original spectrum. [b] The sign of the coupling constant is not implied. [c] Obscured by other peaks. [d] Solvent C6D6. All others, CDCl3.

85.0–85.7° (about 5–10% in most runs), was the olefinic structure carefully elucidated by Dieckmann[9] and Rabe.[8] The third isomer 6, mp 141–142°, proved to be very difficult to isolate, and eventually was obtained in minute yield as described in the Experimental Section.

The 100-MHz spectral parameters of 4–6, and 8 (R = CH3) as duplicated by computer simulation, are recorded in Table I. Considering first of all the major product, 4, the large coupling constants J_{23} and J_{34} (ca. 12 Hz) are clearly indicative of trans diaxial protons.[13–17] The large substituents at neighboring carbon then must occupy the preferred equatorial positions. *The hydroxyl proton was observed to be a doublet, J = 2.4 Hz, coupled to the axial proton H6a,* the resonance of which appeared as a doublet of doublets. This is one of the few instances known of long-range coupling to hydroxyl.[18–20] As Figure 1 shows, one member of the hydroxyl doublet was obscured by the methoxyl absorption, but computer simulation proved it had to be present. Addition of deuterium oxide caused the disappearance of the hydroxyl doublet and concurrent simplification of the H6a pattern.
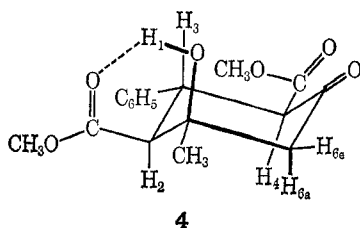

4

The magnitude of the long-range coupling to the hydroxyl proton is substantially larger than other literature examples.[18–20] It is suggested that strong hydro-

gen bonding of the hydroxyl proton with the neighboring carbomethoxy function holds the hydroxyl proton in a conformation favorable for long-range coupling, namely the well-known W arrangement.[19,21] Thus, the observation of long-range coupling is strong evidence for an axial hydroxyl function. An equatorial hydroxyl group could not meet the geometric requirements considered necessary for a four-bond coupling of this magnitude.[18]

The predominant condensation product[22] of acetylacetone and benzaldehyde, 7, clearly is very similar to
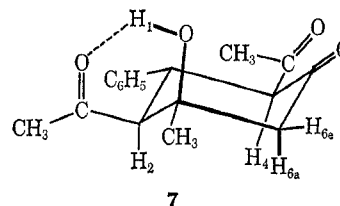
7

4. The resonance of the hydroxyl proton is again a doublet, coupled to H6a. Again the hydroxyl doublet is eliminated on deuterium oxide addition and H6a is simplified. In this case the hydroxyl absorption is not obscured by other absorptions, as Figure 2 shows.

Nmr evidence (Table I) indicates the second (ester) isomer, analogous to Rabe's β_2, to have structure 5, in
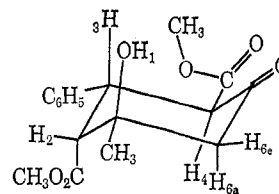

5

which the C-2 carbomethoxy group is now axial. The magnitude of J_{34} = 13.1 Hz is indicative of trans diaxial protons. The smaller J_{23} = 4.9 Hz shows that these protons are gauche; H2 is therefore equatorial. In moving from 4 to 5 the ca. 0.9-ppm downfield shift of the resonances ascribed to H6a and H4 is also consistent with the axial C-2 carbomethoxy group. The hydroxyl proton cannot hydrogen bond to the C-2 carbomethoxy group. Its resonance is markedly concentration sensitive. Since the hydroxyl proton is no longer conforma-

(13) N. C. Franklin, *Angew. Chem., Int. Ed. Engl.*, **4**, 774 (1965).

(14) A. A. Bothner-By, *Advan Magn. Resonance*, **1**, p 195; A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962).

(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 77–82.

(16) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964).

(17) See also R. A. B. Bannard, *Can. J. Chem.*, **44**, 775 (1966), and references cited therein.

(18) (a) J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. Driesen, *Tetrahedron Lett.*, 4363 (1967). (b) J. C. Jochims, W. Otting, A. Seeliger, and G. Taigel, *Chem. Ber.*, **102**, 255 (1969). (c) J. C. Jochims and G. Taigel, *Tetrahedron Lett.*, 5483 (1968).

(19) (a) C. W. Schoppee, F. P. Johnson, R. Lack, J. Shannon, and S. Sternhell, *Tetrahedron, Suppl.*, **8**, Part II, 421 (1966). (b) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, **87**, 302 (1965).

(20) See also (a) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964). (b) R. R. Fraser, M. Kaufman, P. Morand, and G. Gavil, *Can. J. Chem.*, **47**, 403 (1969). (c) C. P. Rader, *J. Amer. Chem. Soc.*, **91**, 3248 (1969). (d) E. F. Kiefer, W. Gerible, and S. Amimoto, *ibid.*, **90**, 6246 (1968).

(21) C. W. Jefford, J. Gunsher, and K. C. Ramey, *ibid.*, **87**, 4384 (1965).

(22) (a) R. Schiff, *Justus Liebigs Ann. Chem.*, **309**, 206 (1899). (b) E. Knoevenagel, *Chem. Ber.*, **36**, 2118 (1903).

tionally rigid, its resonance appears as a singlet. Weak π bonding to the ketone function is possible, however.[23]

The isomer isolated in smallest yield, 6, has spectral parameters rather similar to 5. We have no information whether 6 is similar to Rabe's β_3, since the latter was not available, but it seems likely the two are analogous. The magnitudes of the coupling constants again indicate *trans* diaxial protons H_3 and H_4 and *gauche* protons H_2 and H_3. Long-range coupling (J = 0.9 Hz) is observed between the methyl group at C-1 and the axial proton 6a. The W orientation is possible between H_{6a} and one of the three conformationally mobile protons of the axial methyl function. The assignment of the C-1 methyl as axial has several analogies to axial steroid angular methyl groups, in which long-range coupling is also observed.[19]

6
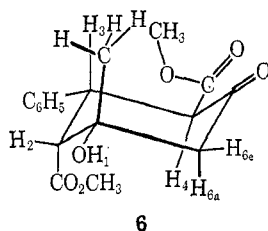
The chemical shift of the methyl group (δ 1.45 in $CDCl_3$) was also different from the corresponding group in 4 and 5 (both δ 1.32), which is consistent with their different configurations.[19] Unfortunately, too little of 6 was available to pursue hydrogen bonding studies; however, no long-range coupling involving hydroxyl was evident.

A nuclear Overhauser effect (NOE) experiment[24] was attempted in which the C-1 methyl group was irradiated and attempts were made to observe an increase in intensity of H_3, which is very close to the C-1 methyl in space. Based on peak heights, a 17% increase in intensity was observed for H_3. Integration showed only an 8% increase. Molecular models show that one *ortho* proton of the phenyl is also very close in space to H_3. Efficient relaxation of H_3 by this *ortho* proton prevents the expected >30% intensity increase on irradiation of methyl.

Thus, the yields of these three isomers parallels their stabilities. The major product, 4, has all major groups equatorial save hydroxyl. The minor product, 5, has an axial C-2 carbomethoxy function. The minute yield product, 6, has axial C-1 methyl and C-2 carbomethoxy groups.[25]

As pointed out earlier, Rabe and coworkers were able to convert the ketones, β_1, β_2, and β_3, into their respective enols, which were termed α_1, α_2, and α_3. These enols stereospecifically ketonized to form the original ketone. In our hands, the base catalyzed enolization of 4 and 5 was also accompanied by formation of 8, but generally speaking the observations of Rabe and coworkers are confirmed for these two compounds. In 4–6, the C-4 carbomethoxy group is in the equatorial

(23) L. Joris and P. Schleyer, *J. Amer. Chem. Soc.*, **90**, 4599 (1968).

(24) (a) F. A. L. Anet and A. J. R. Baum, *ibid.*, **87**, 3250 (1965). (b) J. G. Colson, P. T. Lansbury, and F. D. Saeva, *ibid.*, **89**, 7163 (1967).

(25) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, pp 208, 236. Data in a cyclohexanone system is preferable, but not complete; N. L. Allinger, H. Blatter, L. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966), report a conformational free-energy preference of 1.4 kcal for the 3-methyl case.
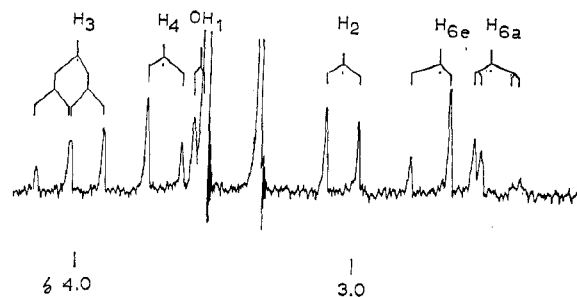

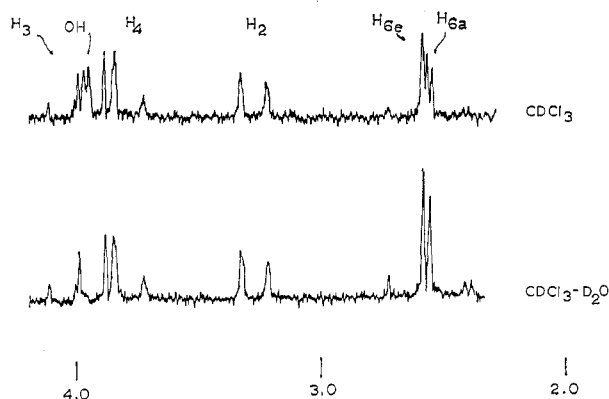Figure 1.—Partial 100-MHz spectrum of condensation product, 4 and computer simulation of the spectrum.

Figure 2.—Partial 100-MHz spectrum of the condensation product, 7, of benzaldehyde and acetylacetone, showing the hydroxyl doublet and the collapse of long range coupling to H_6 on addition of D_2O.

position. Axial approach of a proton to the C-4 position of the enol then simply permits the C-4 carbomethoxy group to return to the favored equatorial orientation. Considerable precedent for this type of ketonization now exists.[26]

Base-Catalyzed Dehydration–Decarbomethoxylation. —In this unusual reaction the C-4 carbomethoxy group and the C-1 hydroxy group are lost, producing an α,β unsaturated ketone, 8, as shown in eq 1.[8,9] Extensive long range coupling is observed in the nmr spectrum of 8 (Table I). However, it is clear that its structure is analogous to 4 with major groups equatorial or pseudoequatorial. In particular the large J_{45} = 9.1 and the pattern J_{56a} = 12.4, J_{56e} = 3.7 are consistent with *trans* diaxial protons 4 and 5, and therefore equatorial carbomethoxy and phenyl groups.[27]


8
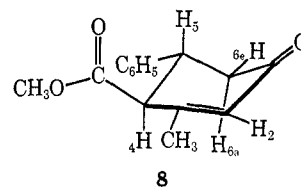
In the 4 → 8 conversion, we feel that it is more than a coincidence that the C-1 carbomethoxy and the C-4

(26) (a) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956). (b) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **81**, 4305 (1959), and earlier papers.

(27) H. L. Jakobsen, *Tetrahedron Lett.*, 1991 (1967).

hydroxyl functions are both eliminated. Observation of the course of reaction by nmr (in deuteriochloroform with *t*-butyl amine) and also by thin layer chromatography (sodium methoxide catalyst in methanol) revealed that **8** was formed virtually concurrent with the loss of **4**. Only a hint of an intermediate was discernible.

The pathway shown in eq 2 can be eliminated from consideration. The olefin **9** was prepared by acid-

$$4 \longrightarrow \qquad \longrightarrow \longrightarrow 8 \quad (2)$$

9
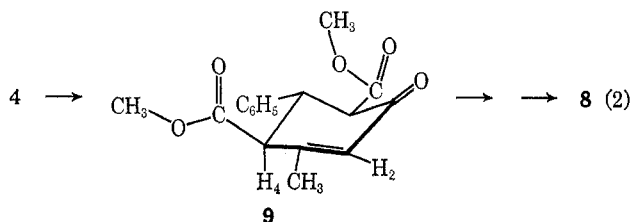
catalyzed dehydration[8] of **4**, and was shown by nmr (Table I) to have the same configuration at relevant centers as **4** and **8**. In parallel experiments, **9** did not form **8** during the same period in which **4** was smoothly converted to **8**.

A number of other possible pathways should be considered. The cyclic structure, **4** could open and various types of decarboxylation and dehydration steps are possible, with subsequent recyclization occurring. Monitoring the course of the reaction by nmr revealed that no open-chain material was observable in the dehydration–decarbomethoxylation of **4**. A model compound, **10a**, was prepared, in which cyclization is not possible. In **10a** separate resonances were noted for

10a

10b

10c
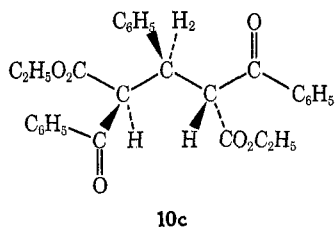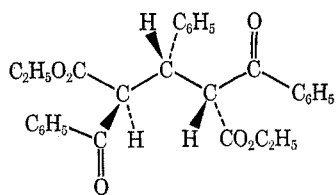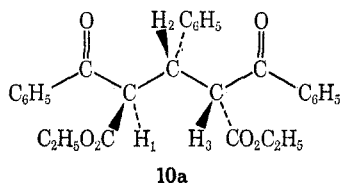
protons 1 and 3 and the two ethyl groups ($J_{12} = 8.6$ Hz, $J_{23} = 9.3$ Hz or *vice versa*). Thus **10a** is the *dl* isomer. Under conditions in which **4** smoothly formed **8**, **10a** apparently isomerized but did not decarboxylate. The 100 MHz spectrum of the equilibrated mixture, **10a**–**10c**, clearly showed the separate resonances of the *dl* and two *meso* isomers. The *dl* isomer **10a** was predominant (58 ± 5%), and the two *meso* isomers occurred in lesser amounts (27 and 15%). Although fur-

ther assignments are extremely difficult, Stuart-Briegleb molecular models suggest that the C-2 phenyl-benzoyl interactions would destabilize **10c**, and this *meso* isomer would probably be the minor product.

A second model compound, **11**, was prepared which

11
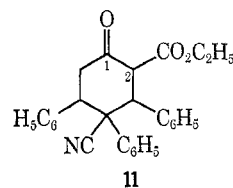
differed from **4–6** in the lack of the hydroxyl function. Again this model compound does not readily lose the carboethoxy function under conditions in which **4** reacts smoothly. Indeed the severe conditions necessary to condense phenylacetonitrile with ethyl cinnamate to form **11** (ethoxide catalyst at 140°) obviously do not involve the loss of the C-2 carboethoxy group. The literature reveals no examples of a decarboalkoxylation under the conditions in which **4** reacts.[28]

An attractive mechanism for the **4** → **8** conversion is shown in eq 3.

$$(3)$$

12

8
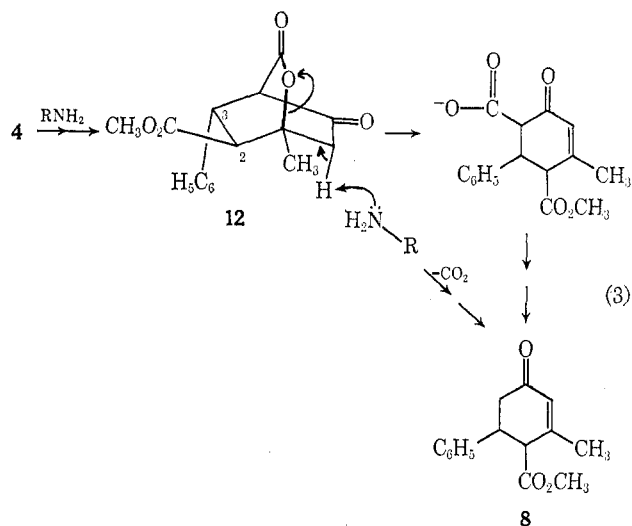
Formation of the bicyclic intermediate **12** has precedent from the work of Newman and coworkers.[29] A number of stable bicyclic lactones are known from the work of Perkin,[30] but the present intermediate, **12**, must be short lived, since no sizable resonance which could be assigned to **12** was visible in the nmr spectrum.

In an attempt to isolate a bicyclic lactone similar to **12**, **13** was subjected to the reaction conditions used for

13
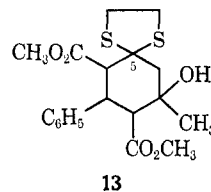
(28) (a) F. Elsinger, *Org. Syn.*, **45**, 7 (1964). (b) P. Bavin, *Can. J. Chem.*, **38**, 882 (1960). (c) F. Bohlmann, *Chem. Ber.*, **89**, 792 (1956). (d) K. Campbell, J. Corrigan, and B. Campbell, *J. Org. Chem.*, **16**, 1712 (1951).

(29) (a) M. S. Newman and S. Mladenoric, *J. Amer. Chem. Soc.*, **88**, 4523 (1966), and many related papers. (b) See also D. S. Noyce and H. J. Weingarten, *ibid.*, **79**, 3093 (1957).

(30) W. Perkin, Jr., *J. Chem. Soc.*, **85**, 654 (1904).

the **4 → 8** conversion. Only starting material was recovered. The increased steric bulk at C-5 may prevent closure to the bicyclic lactone.

The second cyclohexanone isomer, **5**, also undergoes the dehydration–decarbomethoxylation reaction, although more slowly than **4**. The formation of a bicyclic lactone would be hindered by the eclipsing of the C-2 carbomethoxy and the C-3 phenyl groups. Under mild conditions, the olefin **8** is again the predominant product. The stereochemistry at C-2 in **8** (pseudo-equatorial) is the opposite of that in **5** (axial); thus an isomerization must have occurred. Under the reaction conditions (*t*-butylamine catalyst in deuteriochloroform at 57°) **5** did not isomerize to **4**. Monitoring the course of the reaction by thin layer chromatography showed that the precursors of **8** were other probable olefins of similar general structure.

The minor product, **6**, did not undergo the dehydration–decarboxylation reaction under conditions in which **4** reacted smoothly. The *trans* C-1 hydroxyl and C-4 carbomethoxy groups are incapable of reacting to form a bicyclic lactone.

Experimental Section

Preparation of β_1 and β_2.—These materials were prepared by the method of Rabe. The product mixture was separated by crystallization and by chromatography on silica gel (Baker). The intramolecularly hydrogen bonded isomer, β_1, was eluted first with a few per cent ether in benzene solution. The isomer, β_1, was recrystallized twice from ethanol–methylene chloride yielding needles: mp 156.0–156.5°, lit.[8] 149–150°; ir (CH₂Cl₂) 3580 (weak) and 3480 (OH), 1745, 1720, 1455, 1375, 1345, 1205, 1185, 1160, 1035, 1025, 990, and 910 cm⁻¹. The hydroxyl absorptions changed very slightly on dilution. The nmr spectrum was very similar to that of **4** (Figure 1). The second isomer, β_2, was eluted immediately after β_1, and was recrystallized twice from ethanol: mp 154.3–156.8°, lit.[8] 150°; ir (CH₂Cl₂) 3580 and 3470 (OH), 1740, 1720, 1450, 1370, 1345, 1330, 1185, 1160, 1140, 1035, 925, and 910 cm⁻¹. The second hydroxyl absorption diminished in intensity upon dilution. The nmr spectrum was very similar to that of **5** (Table I). In several runs, although Rabe's procedure was followed as closely as possible, β_3 could not be separated.

Preparation of 4, 5, and 6.—These materials were prepared similarly to β_1 and β_2. To 137 g of methyl acetoacetate (1.18 mol) plus 58 g of benzaldehyde (0.55 mol), 1.0 ml of piperidine was added and the solution allowed to stand overnight. The resulting dense solid was broken up and triturated with two 200-ml portions of ether, and filtered. The solid was triturated again with two 200-ml portions of warm ethanol and filtered. A portion of the remaining solid, **4**, 216 g, mp 186–189°, was recrystallized twice from chloroform–ethanol: mp 189.5–190.5° lit.[9] 183°; ir (CH₂Cl₂) 3600 (w) and 3515 (OH), 1755, 1725, 1435, 1370, 1355, 1210, 1160, 1075, 1030, 990, and 950 cm⁻¹. A slight change occurred in relative intensity of the hydroxyl absorptions upon dilution. The ethanol filtrate yielded additional **4** upon evaporation. The ether filtrate produced **5** on evaporation, mp 172–173°. This material was recrystallized twice from ethanol: mp 175.5–176.1°; 7.8 g; ir (CH₂Cl₂) 3600 (OH), 1745, 1720, 1430, 1350, 1335, 1190, 1155, 1135, 1055, 1025, 990, and 970. The hydroxyl absorption was unchanged upon dilution.

Anal. Calcd for C₁₇H₂₀O₆: C, 63.70; H, 6.25. Found: C, 63.75; H, 6.27.

Upon further evaporation, **8** was deposited: mp 85.0–85.7°, lit.[9] 87°; 7.0 g.

All remaining solutions were recombined and chromatographed on a 2 × 30 cm silica gel column. The hexane eluents were unreacted starting materials and methyl benzalacetoacetate (**14**). With increasing quantities of benzene in hexane, other oils were eluted, probably the mixed isomers of **1** (methyl esters), which could not be separated. Small amounts of additional **8** were then eluted. In this particular run, *ca.* 0.1 g of an unknown material, mp 124.0–124.7°, was eluted (5% ether in benzene) originally thought to be **6**. However, this material

was analyzed for C₁₅H₁₆O₄ and showed a mass spectrometric molecular ion at *m/e* 260.

Anal. Calcd for C₁₅H₁₆O₄: C, 69.30; H, 6.19. Found: C, 69.24; H, 6.29.

The nmr of this compound showed a vinyl multiplet at δ 6.07, coupled to a methyl doublet at δ 1.91. An ABX pattern was observed with J_{AB} = 15.5 Hz and chemical shifts of *ca.* δ 3.63, δ 3.32, and δ 2.62. The latter was also coupled to the vinyl proton with J = *ca.* 1.2 Hz. The preparation of this material could not be repeated.

The elusive material **6** was finally prepared by condensing carefully purified benzaldehyde and methyl acetoacetate with a trace of piperidine. In this case the condensation was only partially complete after a period of 10 days. The solid material was filtered off and triturated with slightly acidic ethanol as before. The combined filtrates were allowed to stand and several other crops of high melting products (**4** and **5**) were filtered off and checked by nmr (no **6**). After no more solid could be obtained, the ethanol was evaporated, the solution (about 30 ml) was dried (MgSO₄) and chromatographed on a 36 × 2 in. column of Florisil. The petroleum ether eluent contained starting materials and the olefins, **14**. With increasing quantities of benzene in petroleum ether, materials, very likely the open-chain isomers, **1** (methyl esters) were eluted, as well as **8**. Finally several oily fractions were obtained, whose nmr spectra, however, indicated bad mixtures of materials of the general structure as shown in eq 1. From these combined oils, only **4** could be crystallized, probably from conversion of the enol **4a** to **4** itself. The remaining oils were rechromatographed on 1 × 18 in. column of silica gel. The fractions generally were similar to the previous attempts, however, the fractions eluted immediately prior to **4** (70% benzene in petroleum ether to 100% benzene) again showed methyls in the nmr spectrum at δ *ca.* 1, possibly indicative of **6** plus at least three other components. On long standing (1–2 weeks) crystals of **6** were deposited: mp 133–135°, mp 141.4–142.4° recrystallized from ether–hexane; 0.08 g; ir (0.5%, CH₂Cl₂) 3590, 1745, 1715, 1405, 1225, 1150, 1095, 1030, and 990 cm⁻¹.

Anal. Calcd for C₁₇H₂₀O₆: C, 63.70; H, 6.25. Found: C, 63.71; H, 6.31.

Preparation of 7.—This material was prepared by the method of Schiff,[23] mp 170.2–170.7° (lit. 168°). No attempt was made to isolate additional isomers. This material also readily enolized on addition of pyridine.

Preparation of 8 (R = CH₃).—Treatment of **4** or **5** with any of a number of bases (*e.g.*, piperidine, *t*-butylamine, or sodium methoxide) smoothly produced **8**, which was separated from starting materials by chromatography on silica gel (**8** was eluted with about 60% benzene in petroleum ether), mp 85.0–85.7°, lit.[13] mp 87°. This material was also formed in the condensation to form **4** or **5**, or by treatment of β_1 or β_2 with sodium methoxide. The latter reaction involved a transesterification.

Preparation of 9.—To a solution of 10 g of **4** in 100 ml of benzene was added 1 g of toluenesulfonic acid and the mixture refluxed overnight. Solvent was removed by rotary evaporation and the solution was chromatographed on silica gel. The benzene in hexane fractions were a mixture of **8** and **9**, which were separated by crystallization, **9**, mp 134.5–135.2°, 0.4 g.

Anal. Calcd for C₁₇H₁₈O₅: C, 67.55; H, 5.99. Found: C, 67.54; H, 6.00.

Base-Catalyzed Reactions of 4, 5, 6, and 9.—In parallel experiments about 100 mg of **4** and **5** were placed in 1 ml of methanol and 20 drops of 1.6 *N* solution of sodium methoxide was added. On standing markedly yellow solutions were formed owing to enolization of the above. The progress of the reaction at room temperature was followed by thin layer chromatography; **4** rapidly produced **8** with only a hint of an intermediate being observed. The substrate **5** also formed **8**, though somewhat more slowly, and other olefinic materials of generally the same constitution as **8** were observed. On a preparative scale, these olefins were separated from **8**, but their nmr spectrum was not indicative of a pure compound. The spectrum did exhibit a large vinyl multiplet δ *ca.* 6, coupled to a doublet methyl, δ *ca.* 2, similar to but slightly different from that of **8**.

In other experiments **4** and **5** were treated with about 25 mol % *t*-butylamine in deuteriochloroform at *ca.* 55° over a period of 1 week. The reaction was followed by nmr. The absorptions of **4** were cleanly replaced by those of **8**. With **5**, a second material of almost identical resonances as **8** was evident.

On the other hand, **6** did not form any **8** when treated under

identical conditions. The enol of 6 appeared to form, similar to the reaction of 4, but not of 5; no other products were observed.

The substrate 9, in the same period of time, isomerized to other materials of a larger R_f, but no 8 was evident by tlc. The product mixture was worked up by extraction into ether, and dried (MgSO$_4$). The nmr spectrum did not show the characteristic absorptions of 8.

Preparation and Reaction of 10.—This material was prepared by the procedure of Ruheman:[31] mp 129–130°, lit. 131°; nmr (100 MHz, pyridine) δ *ca.* 7.5 (m, 15, aromatic protons), 5.86 (d, 1, J = 8.6 Hz, H$_1$ or H$_3$), 5.67 (d, 1, J = 9.3 Hz, H$_3$ or H$_1$), δ 5.30 (doublet of doublets, 1, H$_2$), *ca.* 3.9 (interspersed quartets, 4, O—CH$_2$—CH$_3$), *ca.* 0.9 (superposed triplets, 6, O-CH$_2$-CH$_3$). Treatment with *t*-butylamine in deuteriochloroform this material rapidly changes in part to two other materials with nmr absorptions in the same general regions as starting material. However no change in integration was evident during the period which 4 readily formed 8. Upon work-up by adding to ether, extracting three times with H$_2$O, drying (MgSO$_4$), and evaporating, the same materials were evident, in the same proportions. Thus ethanol was not formed and no decarboxylation had occurred.

In pyridine at 100 MHz, the resonances of the three isomers were well separated: nmr of the major *meso* isomer, δ 5.72 (superposed d, 2, J = 7.8 Hz, H$_1$ and H$_3$), δ 5.18 (d of d, 1, H$_2$); minor *meso* isomer, δ 5.88 (superposed d, 2, J = 9.2 Hz, H$_1$ and H$_3$), 5.17 (d of d, 1, H$_2$).

Preparation of 11.—This material was prepared by the method of Erlenmeyer:[32] mp 205–206°, lit. 206°; nmr (60 MHz, CDCl$_3$) δ 7.09 (m, 15, aromatic protons), 4.57 (d, 1, J = 12.5 Hz, H$_1$),

4.08 (d, 1, J = 13.5 Hz, H$_2$), 4.02 (9, 2, J = 7.0 Hz, OCH$_2$-CH$_3$), *ca.* 3.87 (m, 1, H$_{4e}$), 3.53 (d of d, 1, $J_{4e,4a}$ = 14 Hz, H$_{3a}$), 3.92 (d of d, 1, $J_{3,4e}$ = 1.5 Hz, $J_{3,4a}$ = 12.5 Hz, H$_3$), 0.98 (t, 3, J = 7 Hz, O-CH$_3$-CH$_3$). Upon treatment of 0.25 g of 11 with 0.1 g of *t*-butylamine in chloroform at 69° for 3 weeks, followed by evaporation to dryness and very slow crystallization, 0.203 g of starting material was recovered. The remainder was a tar.

Preparation of 13.—A solution of 5.0 g of 4 and 1.4 g of ethanedithiol in 50 ml of methylene chloride was treated with 0.5 ml of 47% boron trifluoride-ether complex. An immediate precipitate was observed, but the mixture was allowed to stand for 2 wks. The solvent was evaporated and the mixture was mixed with water and methylene chloride. The organic extract was washed with dilute base twice, dilute HCl, and water and dried (MgSO$_4$). Upon evaporation needles of 13 were deposited, mp 180°. These were recrystallized from methylene chloride and from ethanol: mp 202–203°, mmp 180–190° with 4; 2.89 g; nmr (60 MHz, CDCl$_3$) δ 7.18 (s, 5, aromatic protons), 3.87, (d, 1, J = 1.9 Hz, hydroxyl), 3.77 (t, 1, J = 11.7, H$_3$), 3.28 (s, 6, methoxyl), 3.17 (broad s, 4, ethylene bisthioketal protons), 3.16 (d, 1, J = 11.7, H$_4$), 2.66 (d, 1, J = 11.7, H$_2$), 2.62 (d, 1, J = −14.3, H$_{6e}$), 2.35 (d of d, 1, J = −14.3, J = 1.9, H$_{6a}$).

Anal. Calcd for C$_{19}$H$_{24}$O$_5$S$_2$: C, 57.55; H, 6.10. Found: C, 57.51; H, 5.98.

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Proximity Effects. Reactions of Lead Tetraacetate with 4- and 5-Phenylcyclooctanol[1]

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Received October 14, 1969

The reactions of lead tetraacetate with the *cis* and *trans* isomers of 4- and 5-phenylcyclooctanol were examined in order to establish the magnitude of the directive effect of the phenyl substituent on the direction of transannular cyclization leading to bicyclic ethers. As compared with 5-phenylpentanol previously reported, there is observed a marked enhancement in the amount of cyclization at the benzylic position with the *trans* isomers. Thus *trans*-5-phenylcyclooctanol yields 1-phenyl-9-oxabicyclo[3.3.1]nonane in 72% yield. Although cyclization at the benzylic position in the *cis* isomers is not possible, the products obtained with *cis*-4-phenylcyclooctanol suggest that the phenyl group is exerting a directive effect here also. The structures of the new compounds isolated in this study were established by synthesis.

A large amount of data is available on features of the lead tetraacetate oxidation of alcohols such as the effect of solvent and structural variations in the alcohol. One process which has been particularly well examined with acyclic and steroidal substrates involves the formation of cyclic ethers from alcohols containing methyl or methylene groups at the δ and ε positions relative to the hydroxyl group. Indeed this particular reaction has contributed greatly to the solution of certain problems in steroid synthesis such as the introduction of functionality into angular methyl groups.[3] The products are usually five-membered rather than six-membered cyclic ethers, although in some cases mixtures of the two have been isolated. The impor-

tant step in the cyclization process is the transfer of a hydrogen atom from a nonactivated methylene or methyl group to the oxygen atom within an alkoxy radical intermediate *via* a six- or seven-membered transition state. There are some indications that the subsequent steps may involve the oxidation of the resulting carbon radical to a carbonium ion *via* a one-electron transfer to lead followed by a cyclization of the hydroxy group onto the carbonium ion to give the cyclic ethers (Scheme I).[3–5] A competing fragmentation reaction, formulated as proceeding from the same precursor as in the cyclization reaction, gives rise to carbonyl compounds, olefins, and acetates.

The reactions of some medium-ring alcohols with lead tetraacetate have been examined since it was of interest to determine what effect the proximity of the δ and ε methylene groups to the hydroxyl group would

(1) Supported in part by Research Grant GP-1587 from the National Science Foundation.

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