Prostaglandins. IV. Total Syntheses of *dl*-11-Deoxy PGE_1 and 13,14-Dihydro Derivatives of 11-Deoxy PGE_1, $PGF_{1\alpha}$, and $PGF_{1\beta}$

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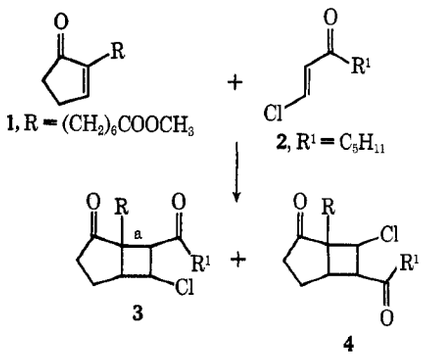
A photoannelation reaction between two α,β-unsaturated ketones 1 and 2 is described. The photoadduct 5 was isolated and characterized by spectral analysis and was transformed into methoxy and acetoxy derivatives 6 and 7. A minor product 9 was also isolated from the reaction and its structure elucidated. Some data on the effect of the concentration of the substrates and the temperature and on the photoannelation reaction are reported. Treatment of photoadduct 5 with zinc–acetic acid led to the cyclobutane dione 13 and the cleaved diketone 14. These products were also obtained from a similar treatment of 7. Under the same conditions, methoxy compound 6 yielded a rearrangement product. Some mechanistic implications of (a) photoannelation and (b) the rearrangement product 16 are discussed. Finally, the transformation of diketone 14 to other prostanoic acid derivatives is described.

In recent years prostaglandins, a class of naturally occurring 20-carbon fatty acids, have occupied the attention of several research groups.[1-6]

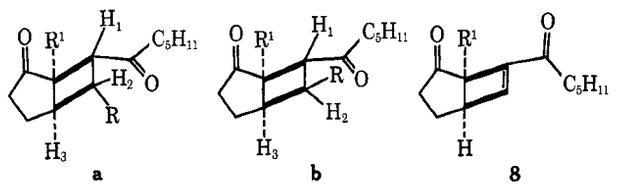
In an earlier communication[7] we reported a novel method of constructing the prostanoic acid skeleton. This article describes further studies of the photoannelation reaction involved, and the chemical transformation of several of the intermediates.

It was conceived that photoannelation of a suitably substituted acyclic ketone such as 2 with 2-(6-carbomethoxyhexyl)-cyclopent-2-en-1-one (1) can give rise to two possible head-to-head (HH) and head-to-tail (HT) products, 3 and 4. The cleavage of the C–C bond (a) of 3 can then generate the prostanoic acid derivatives.



Photoannelation.—Photoannelation of the α,β-unsaturated ketones between two molecules of the same ketone[8] or between a ketone and an olefin[9] has proven of great synthetic utility.[10] The first example of photoannelation of a substituted vinyl ketone and an α,β-unsaturated ketone was recently reported[11] when our work was in progress.

In our initial studies we irradiated cyclopentenone 1 and 1-chlorooct-1-en-3-one (2) (1:5 molar ratio) with a 550-W Hanovia burner at 35–40° for about 40 hr and obtained after purification a homogeneous product having empirical formula $C_{21}H_{33}ClO_4$ in ~35% yield, based on recovered starting materials. The adduct was assigned HH structure 5, based on its spectroscopic data and its chemical transformations.



5, R = Cl
6, R = OCH3
7, R = OCOCH3

R1 = (CH2)6COOCH3

The cis stereochemistry at the ring junction is assumed from the earlier analogies.[9] That it is an HH adduct follows from its nmr spectrum. The spectrum exhibited a quartet at δ 4.5 and a triplet at δ 4.9. The two together integrated for one proton. These signals were assigned to protons H_2 in 5a and 5b, respectively. These assignments are based on the long-range deshielding caused by the ketone function located between the cyclobutane ring and the $-C_5H_{11}$ chain.[12a] The

(1) (a) For a review of recent chemical literature, see J. F. Bagli, *Annu Rep. Med. Chem.*, 170 (1970); (b) G. Bundy, *ibid.*, 137 (1971).

(2) D. Taub, R. D. Hoffsommer, C. H. Duo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Chem. Commun.*, 1258 (1970).

(3) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970).

(4) M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970).

(5) R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **89**, 1043 (1970).

(6) (a) E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, **93**, 1489 (1971); (b) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); (c) E. J. Corey, S. M. Albonico, U. Koeliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (d) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7318 (1971); (e) J. Fried, M. M. Mehra, and W. L. Kao, *J. Amer. Chem. Soc.*, **93**, 5594 (1971), and references cited therein.

(7) J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 1639 (1969).

(8) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968).

(9) (a) P. de Mayo, *ibid.*, **4**, 41 (1971); (b) P. G. Banslaugh, *Synthesis*, 290 (1970).

(10) (a) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, **86**, 485 (1964); (b) J. D. White and D. N. Gupta, *ibid.*, **88**, 5364 (1966); (c) *ibid.*, **90**, 6171 (1968); (d) Z. Koblicova and K. Wiesner, *Tetrahedron Lett.*, 2563 (1967); (e) E. J. Corey and S. Nazoe, *J. Amer. Chem. Soc.*, **86**, 1652 (1964); (f) B. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. Mayo, *J. Org. Chem.*, **34**, 794 (1969).

(11) P. Sunder-Plassmann, P. H. Nelson, L. Durham, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 653 (1967).

(12) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 100. For a case in cyclobutanes, see V. Georgian, L. Georgian, A. V. Robertson, and L. F. Johnson, *Tetrahedron*, **19**, 1219 (1963). (b) When the reaction was carried out without solvent the mixture of cis and trans isomers varied from batch to batch. Conversely, in the presence of solvent the major component was consistently trans isomer **5b** (80%). (c) Each of the signals of the doublet had a shoulder, indicating the slight differences in the chemical shift due to the difference in structure of **5a** and **5b**. (d) In both cases the singlet was not sharp. This may be attributed (i) to the presence of two isomers, and (ii) to 1,3 splitting in cyclobutane series [K. B. Wiberg, *et al.*, *J. Amer. Chem. Soc.*, **84**, 1594 (1962)].

proportion of the *cis*-**5a** and *trans*-**5b** isomers varied with the reaction conditions.[12b] The nmr spectrum also showed a doublet[12c] at δ 3.17, attributable to H_1. The signals at δ 4.9 and 4.5 collapsed to doublets (J = 7.5 and 6.5 Hz, respectively) during the irradiation at resonance frequency of H_1. Conversely, the doublet of H_1 collapsed to a singlet[12d] when observed during irradiation at resonance frequency of H_2.

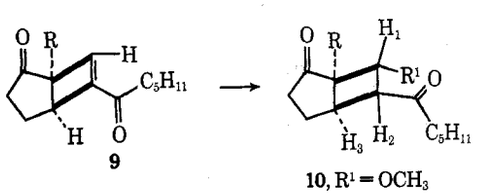
Refluxing the adduct **5** in collidine yielded the olefin **8**. This was characterized by a new olefinic proton in the nmr at δ 6.92 (J = 2 Hz). The photoadduct **5** was readily transformed with methanolic sodium methoxide at room temperature to the methoxy derivative **6**. The corresponding acetate **7** was also obtained from silver acetate–acetic acid treatment of **5**. The nmr spectral data (Table I) of these compounds were in accordance with the assigned structures.

TABLE I

Compd	H_1, δ	H_2, δ
5a	3.19 (d, J = 7 Hz)	4.5 (t, $J_{1,2} = J_{2,3}$ = 7.5 Hz)
5b		4.9 (q, $J_{1,2}$ = 7, $J_{2,3}$ = 6.5 Hz)
6	2.95 (d, J = 7 Hz)	4.04[a] (q, $J_{1,2}$ = 7, $J_{2,3}$ = 5 Hz)
7	3.17 (d, J = 6 Hz)	5.07 (q, $J_{1,2}$ = 7, $J_{2,3}$ = 5 Hz)
10	4.03 (d, J = 6 Hz)	2.93 (m)
11	5.00 (d, J = 7 Hz)	3.00 (t, $J_{1,2} = J_{2,3}$ = 7 Hz)

[a] It is assumed that methoxy compound is formed by an elimination addition pathway, and therefore should lead predominantly to isomer **6b**. However, in the nmr of the pure product there were very small signals present (q) centered at δ 3.5 (partially buried under methoxyl) which might be due to the presence of the methoxy isomer **6a**.

A second product isolated (8% yield) from the chromatogram of the crude photoannelation product showed in its infrared spectrum bands at 1670 and 1590 cm^{-1}, attributable to an α,β-unsaturated ketone. The nmr spectrum exhibited a signal at δ 6.54 (1 H) as a sharp singlet and the ultraviolet had maxima at 229 and 249[13] mμ (ϵ 4000 and 3800, respectively). Based on the above evidence the enone was assigned structure **9**. The generation of the enone **9** must involve dehydrochlorination of the HT adduct **4**, formed as a minor product in the photoannelation. The confirmation of the above structural assignment was afforded by the following chemical transformation. Treatment of **9** with methanolic sodium methoxide readily gave a methoxy derivative **10**. The corresponding acetate



9

10, $R^1 = OCH_3$

11, $R^1 = OCOCH_3$

$R = (CH_2)_6COOCH_3$

11 was obtained with sodium acetate–acetic acid treatment. When the doublet of H_1 in acetate **11** was observed while irradiating with the resonance frequency of H_2, the doublet collapsed to a singlet. Conversely, the quartet of H_2 collapsed to a doublet when irradiated with the resonance frequency of H_1.

The influence of solvents and concentration of the substrate in photodimerization[14] and photoannelation[15] has been a subject of study by various groups. Recently, a report on the role of temperature[16] in photoannelation has also been published.

Hexane was chosen as a solvent for the study of the influence of the temperature and concentration of the substrates on the course of the reaction. The results of this study are recorded in Table II. It was noted that

TABLE II

Expt[b]	Concn of 1,[f] mol	Mol ratio, 1:2	Temp, °C	Yield[a] of 3, %
1	0.15	1:5	35–40	19
2	0.15	1:5	−10 to −20	16.5
3	0.15	1:1	35–40	41.2
4	0.15	1:1	−10 to −20	47
5	0.015	1:1	35–40	4.5
6	0.03	1:1	35–40	*e*
7	0.045	1:1	35–40	*e*
8[c]	0.15	1:1	35–40	82
9[d]	0.3	1:1	35–40	88

[a] Yields are calculated based on recovered starting materials from chromatography. [b] Unless otherwise mentioned, the irradiations were carried out for 7 hr in a nitrogen atmosphere. [c] Irradiation time 15 hr. [d] Irradiation time 40 hr. [e] No pure product could be isolated by chromatography. [f] The solutions were made up to 1 l. with reagent grade hexane.

temperature had little influence on the yield of the desired product **5** (expt 1, 2 and 3, 4). Reducing the concentration of chlorovinyl ketone from 5 mol to 1 mol resulted in approximately threefold improvement of the yield of the HH adduct (expt 1, 3 and 2, 4). At lower concentrations of the substrates (expt 6, 0.03 mol, and expt 7, 0.045 mol) a significant amount of polymeric materials was formed. The desired product was indeed present in the reaction mixture, as noted by tlc, but could not be isolated in pure form. In photodimerization a marked increase in the formation of the HT adduct has been observed at the lower concentration.[14] It was apparent that at lower concentrations the photodimerization reaction predominated. When the experiment was performed as in expt 3 and the irradiation time was doubled (expt 8) the yield of the HH adduct **5** was essentially doubled. Further doubling the concentration of the substrates and the time of irradiation (expt 9) had no detrimental effect on the yield of the product.

The predominant formation of HH adduct may be partly accounted for by invoking the interaction between the excited species of cyclopentenone (a) with the ground state species (b) of acyclic ketone shown below.

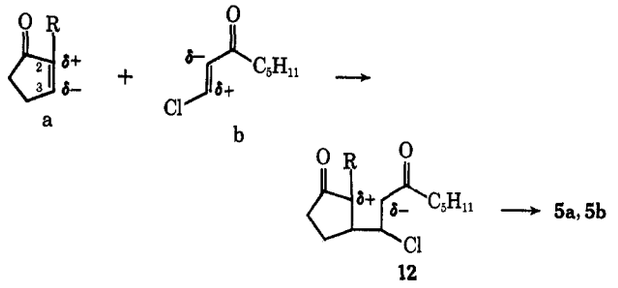
The formation of **5a** and **5b** could result from equilibration of stabilized anion radical **12**, or by direct formation of the C–C bond with the cis isomer of ketone **2**. The presence of the cis isomer of **2** in the reaction

(13) This band may be attributed to a charge transfer transition observed in unsaturated carbonyl compounds [see J. F. Bagli, *et al.*, *J. Org. Chem.*, **28**, 1207 (1963)].

(14) (a) P. C. Eaton and W. S. Hurt, *J. Amer. Chem. Soc.*, **88**, 5038 (1966); (b) J. L. Ruhlen and P. A. Leermakers, *ibid.*, **89**, 4944 (1967).

(15) P. de Mayo, J. P. Pete, and M. Tachir, *Can. J. Chem.*, **46**, 2535 (1968).

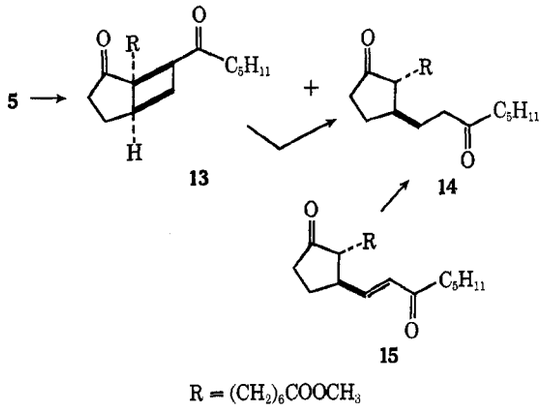
(16) R. O. Loutfy, P. de Mayo, and M. F. Tachir, *J. Amer. Chem. Soc.*, **91**, 3984 (1969).



mixture was confirmed by its isolation and characterization by nmr from recovered chloro vinyl ketone. The formation of the cis ketone **2** is readily explained by the extremely rapid decay of its excited triplet by rotation around the C–C bond.[8]

Reductive Cleavage of Cyclobutane.—Opening of a small ring conjugated to a carbonyl function has been the subject of a recent study.[17] A special case of reductive opening of cyclobutane in a cage system has also been reported.[18]

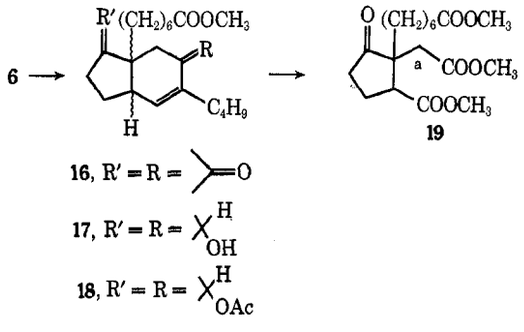
We considered the opening of adduct **5** with the idea that such a reaction would be an extension of a 1,4-enedione → 1,4-diketone transformation (reduction), provided proper σ–π[19] orbital overlap is possible as suggested by Dauben.[17] Zinc–acetic acid treatment at reflux temperature of the photoadduct **5** gave rise to two compounds, to which structures **13** and **14** were assigned based on their spectral properties.



The structure of cyclobutane dione **13** was confirmed by its generation both by chemical (zinc–acetic acid) as well as by catalytic reduction of enone **8**. The structure of compound **14** was confirmed by its obtention from the hydrogenation of enone **15**.[20]

The formation of dechloro ketone **13** in the reductive cleavage is worthy of comment. Loss of a halogen atom β to a ketone function under reductive condition is not very facile except under certain circumstances.[21] The formation of diketone **13** *via* an elimination–reduction mechanism might be preferred, based on the following facts. (1) Whereas 16–20 hr at 115° (bath temperature) was required for all the photoproduct to disappear, the unsaturated ketone **8** was quantitatively consumed in zinc–acetic acid reduction in 10 min at room temperature to yield dione **13**. (2) The treatment of acetate **7** under similar reaction conditions also led to the formation of cyclobutane dione **13** and diketone **14** as identified by tlc and glc. The high propensity of the reduction of the double bond of **8** with zinc–acetic acid must be attributed to the relief of strain in going from the sp^2 to sp^3 state. The above evidence does not, however, preclude a possible direct reductive loss of chlorine under these conditions. The cyclobutane dione **13** can be transformed essentially quantitatively to the diketone **14** by a further treatment with zinc–acetic acid.

Treatment of methoxy diketone **6** with zinc–acetic acid gave in good yield the α,β-unsaturated ketone **16**. This reaction proceeded in the absence of zinc to give the same compound at essentially the same rate. The above structural assignment followed from the spectral analysis of **16** and its derivatives **17** and **18**. Striking evidence of the rearrangement was afforded by the mass spectrum of **16**, which showed no fragments for $-COC_5H_{11}$ (*m/e* 99) and $-C_5H_{11}$ (*m/e* 71) commonly



present in 15-oxygenated prostanoic acid derivatives. Ozonolysis of enone **16** followed by oxidative cleavage and esterification yielded the triester **19**. This compound was characterized in its nmr by the absence of the terminal methyl, and a poorly resolved doublet due to methylene protons at carbon a.

This rearrangement product was also formed when the photoadduct **5** was allowed to remain at room temperature without solvent over a certain length of time. Treatment of the adduct **5** with ethylamine at ice-bath temperature also led to the formation of the ring expansion product **16**. The formation of enone **16** under acidic as well as basic conditions implicates nucleophillic attack by carbon a on the cyclobutane carbon bearing the substituent (–Cl or $-OCH_3$) leading to the ring expansion. A β elimination of the substituent can then generate enone **16**.

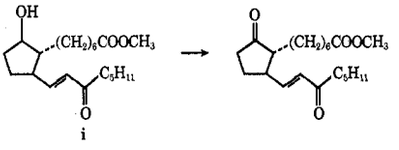
Reduction of ketone **14** with sodium borohydride in methanol led to a mixture of isomeric diols **20** and **21** which were separable by chromatography. When the reduction was conducted in dimethoxyethane at −50° using sodium borohydride, under controlled conditions,

(17) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

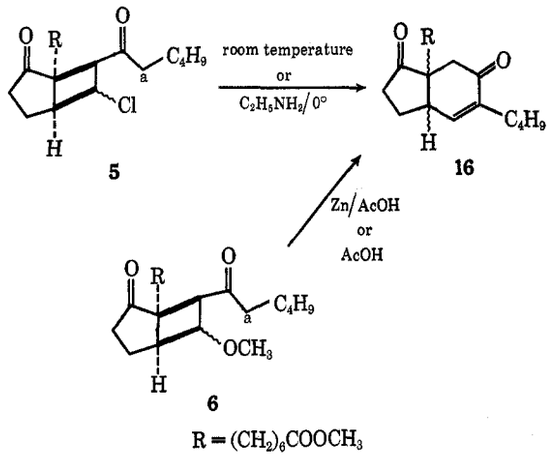
(18) E. Wenkert and J. E. Joder, *ibid.*, **35**, 2986 (1970).

(19) The probability of such σ–π overlap in adduct **3** appeared quite high, in view of a free rotating carbonyl group which can align itself in a desired conformation.

(20) This compound was readily obtained by oxidation of i described earlier [J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 5 (1967)].

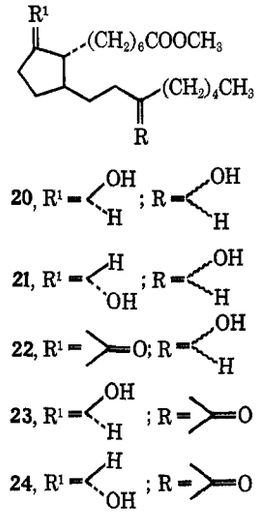


(21) (a) A. Nickon and N. Werstuik, *J. Amer. Chem. Soc.*, **89**, 3914 (1967); (b) D. P. G. Hamon and R. W. Sinclair, *Chem. Commun.*, 890 (1968).



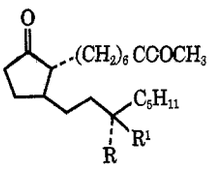
a mixture of monoalcohols was obtained together with some unchanged starting material.

The chromatographic separation yielded a faster moving product homogeneous by tlc and glc, and structure **24** (11.2%) was assigned to it based on analytical data. Further elution led to the isolation of a major

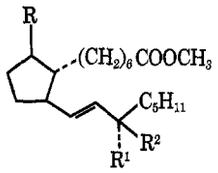


component homogeneous by tlc. Gas chromatography, however, showed it to be a mixture of a major and a minor component (3:1). This mixture was converted to the corresponding tetrahydropyranyl ether, followed by chromatographic separation, and the acid hydrolysis yielded the two compounds in pure form. The minor component was characterized by a carbonyl absorption at 1710 and 1730 cm^{-1} indicating an acyclic ketone and an ester carbonyl. In contrast, the major product showed carbonyl absorption at 1730 cm^{-1}. The former was assigned structure **23** (7.5%) and the latter **22** (56.5%). It must be noted that the above method of preparation of 13,14-dihydro derivatives gives the mixture of two C-15 hydroxy epimers. These epimers are not separable either by tlc or glc. In order to obtain the pure epimeric alcohol the following synthetic route was followed. Enone **25**[22] could be transformed *via* (1) THP ether, (2) borohydride reduction, (3) acetylation, (4) hydrolysis of ether, (5) Jones oxidation, (6) selective hydrolysis of the acetoxy group in an overall yield of 52–54%, into a mixture of epimeric

(22) J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 5 (1967).



32, R = OH; R^1 = H
33, R = H; R^1 = OH



25, R = OH; R^1, R^2 = =O
26, R = OTHP; R^1, R^2 = =O
27, R = OTHP; R^1, R^2 = OH, H
28, R = OTHP; R^1, R^2 = OAc, H
29, R = —OH; R^1, R^2 = OAc, H
30, R = =O; R^1 = OH; R^2 = H
31, R = =O; R^1 = H; R^2 = OH

alcohols[23] **30** and **31**. It was possible to separate the alcohol **30** and **31** by silicic acid chromatography. Subsequent reduction of the double bond catalytically led to the isolation of 13,14-dihydro epimers **32** and **33** in pure form.

Although detailed accounts of pharmacology of these compounds will appear elsewhere, suffice it to say that some derivatives of prostanoic acid described above possess a profile closely similar to that of natural prostaglandins.

Experimental Section[24]

5-Oxo-1-cyclopentene-1-heptanoic Acid Methyl Ester (1).—To a suspension of the potassium salt[25] of cyclopentanone ethyl carboxylate[26] (31.04 g) in dry toluene (160 ml) was added methyl ω-bromoheptanoate[27] (37.92 g). The mixture was refluxed overnight, cooled, and acidified with 10% H_2SO_4 (120 ml). The aqueous layer was separated, saturated with sodium chloride, and extracted several times with ether. The organic extract was washed with sodium bicarbonate and water and dried, and the solvent was removed. The residue (46.3 g) was distilled to yield **1-carbomethoxy-2-oxocyclopentaneheptanoic acid methyl ester** (24.9 g, 50%): bp 146–148° (0.07–0.05 mm); $n^{22}D$ 1.4557; ν_{max} 1718, 1740 cm^{-1} (carbonyl absorptions).

The diester (10 g) obtained above was decarboxylated by refluxing with 10% sulfuric acid (45 ml) overnight. The usual work-up gave **2-oxocyclopentaneheptanoic acid** (4.5 g, 69%), ν_{max} 1710, 1725 cm^{-1}. Its 2,4-dinitrophenylhydrazone was crystallized from ethanol, mp 74–76°.

Anal. Calcd for $C_{18}H_{24}O_6N_4$ (420): C, 57.13; H, 6.71; N, 13.33. Found: C, 57.06; H, 6.57; N, 13.1.

The keto diester (105.6 g) obtained above was taken in chloroform (300 ml) and was brominated with bromine (53.9 g) in chloroform (200 ml) at 0° over a period of 1 hr. The crude product (135 g) was isolated in the usual way, suspended in 20% sulfuric acid (1000 ml), and refluxed for 48 hr. The reaction mixture was cooled, saturated with sodium chloride, and extracted with ether. The acidic compound was isolated *via* alkaline extract followed by acidification to yield a crude product

(23) The assignments of the stereochemistry of the hydroxyl at C-15 are based solely on certain physical behavior and pharmacological data, and is therefore tentative. Absolute proof will be forthcoming in a later publication.

(24) The Varian spectrometer was used for 60-Mc nmr, whereas the Jeolco machine was used for 100-Mc nmr, and for all spin decoupling studies. Unless otherwise mentioned all infrareds were done on film, nmr in chloroform, and uv in ethanol. Merck silica gel (mesh 0.05–0.2 mm) was used for column chromatography. Organic extracts were dried over anhydrous magnesium sulfate, and the solvents were always removed under vacuum. Mass spectra were recorded on a Hitachi RMU-6D spectrometer. Double resonance studies were all carried out on the 100-Mc machine.

(25) R. Mayer, "Newer Methods of Preparative Organic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 122.

(26) Commercial Aldrich sample is a mixture of methyl and ethyl esters (1:1).

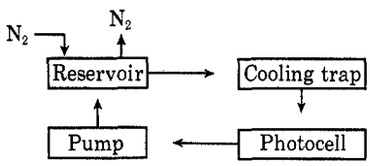
(27) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).

(53.2 g). This was passed through a silica gel (1 kg) column and the product was eluted with 1% methanol in chloroform to give crystalline 5-oxo-1-cyclopentene-1-heptanoic acid (26.3 g, 37%): mp 40–42°; ν_{max} 3000, 1700, 1630 cm^{-1}; λ_{max} 228 nm; nmr (CCl_4) δ 7.27 (1 H, vinylic).

Anal. Calcd for $C_{12}H_{18}O_3$ (210.2): C, 68.57; H, 8.57. Found: C, 68.42; H, 8.65.

Methyl ester of 5-oxo-1-cyclopentene-1-heptanoic acid (1) was prepared in the usual manner with methanol and *p*-toluenesulfonic acid: ν_{max} 1730, 1694, 1630, 1220 cm^{-1}; λ_{max} 228 (10,250) nm.

6-Chloro-7-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-hexanoic Acid Methyl Ester (5).—A solution of 1-chlorooct-1-en-3-one (2) (48 g, 0.3 mol) and cyclopentenoneheptanoic acid methyl ester (1) (67.2 g, 0.3 mol), made up to 1 l. with reagent grade hexane, was irradiated with a 550-W mercury arc Hanovia lamp in a Pyrex vessel. The apparatus used is shown schematically below.



The solution was continuously circulated under a nitrogen atmosphere through a photocell equipped with a water-cooled condenser. The irradiation was continued for 30–32 hr. After this time the solution was removed from the apparatus and the solvent was evaporated. The resulting residue (120 g) was filtered through a column of silica gel (2 kg) in benzene. The elution with benzene yielded first the unchanged chlorovinyl ketone 2[28] (31.3 g). Changing the solvent to 5% ethyl acetate–benzene yielded the photoadduct **5** (23.3 g, *ca.* 88%), and finally the column was washed with 50% ethyl acetate–benzene to elute the unchanged cyclopentenone **1** (49.37 g). The photoadduct thus obtained was essentially homogeneous by tlc and was used for subsequent reactions. A sample was rechromatographed to yield an analytically pure sample: ν_{max} 1730, 1712 cm^{-1}; nmr δ 3.65 (3 H, s, methoxy), 0.88 (4 H, t, methyl) (also see Table I); *m/e* 348 ($M^+ - 36$).

Anal. Calcd for $C_{21}H_{33}O_4Cl$ (384): C, 65.60; H, 8.58; Cl, 9.24. Found: C, 65.25; H, 8.44; Cl, 9.26.

Methyl 6-Hexanoyl-2-oxobicyclo[3.2.0]hept-6-ene-1-heptanoate (9).—When the irradiation was conducted without a solvent, it was possible to isolate a compound having an R_f slightly above that of the HH photoadduct. This product was obtained in *ca.* 8% yield. An analytical sample purified chromatographically gave a pure sample of enone **9**: ν_{max} 1727, 1670, 1590 cm^{-1}; λ_{max} 227 nm (ϵ 4000), 249 (3800);[18] nmr δ 6.54 (1 H, s, vinylic), 3.59 (3 H, s, carbomethoxy), 0.92 (3 H, t, terminal methyl); mass spectrum M^+ (*m/e* 348), $M^+ - 31$ (*m/e* 317), $M^+ - 71$ (*m/e* 277), $M^+ - 99$ (*m/e* 249).

Anal. Calcd for $C_{21}H_{32}O_4$ (348): C, 72.38; H, 9.26. Found: C, 72.45; H, 9.39.

Methyl 7-Hexanoyl-2-oxobicyclo[3.2.0]hept-6-ene-1-heptanoate (8).—A solution of the photoadduct **5** (0.603 g) in redistilled collidine (25 ml) was refluxed for 4.5 hr. The solvent was then removed, the residue was taken up in ether, washed with water, and dried, and the solvent was evaporated. The residue was purified by chromatography to yield pure enone **8** (0.442 g, 81%): ν_{max} 1730, 1672, 1590 cm^{-1}; λ_{max} 225 nm (ϵ 5000); nmr δ 6.92 (1 H, d, J = 2 Hz, vinylic), 3.65 (3 H, s, carbomethoxy), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for $C_{21}H_{32}O_4$ (348): C, 72.38; H, 9.26. Found: C, 72.45; H, 9.39.

Methyl 7-Hexanoyl-6-methoxy-2-oxobicyclo[3.2.0]heptane-1-heptanoate (6).—To a solution of photoadduct **5** (1.4 g) in methanol (21 ml) was added sodium (0.174 g) and the mixture was stirred at room temperature for 30 min. The mixture was then diluted with ether, washed with dilute hydrochloric acid followed by water, and dried and the solvent was removed. The residue was purified through a column of silica gel (35 g). The compound **6** (0.806 g, 81.5%) was eluted with 10% ethyl acetate–benzene: ν_{max} 1725, 1700 cm^{-1}; nmr δ 4.04 (1 H, q, carbinolic), 3.64 (3 H, s, carbomethoxy), 3.11 (3 H, s, methoxyl), 2.95 (1 H, d, α-keto methine), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for $C_{22}H_{36}O_5$ (380.5): C, 69.44; H, 9.54. Found: C, 69.47; H, 9.57.

Methyl 6-Acetoxy-7-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (7).—To a solution of photoadduct **5** (1 g) in acetic acid (45 ml) was added silver acetate (1.4 g) and the mixture was refluxed overnight. The mixture was cooled, diluted with ether, and filtered. The solvent was evaporated, the residue was taken up in ether, washed with water, and dried, and the solvent was removed. Residue was purified by chromatography to yield pure acetoxy derivatives **7** (0.9 g, 68.2%): $M^+ - 60$ (*m/e* 348), $M^+ - (60 + 31)$ (*m/e* 317); ν_{max} 1725, 1228, 1220 cm^{-1}; nmr δ 5.07 (1 H, q, carbinolic), 3.67 (3 H, s, carbomethoxy), 3.17 (1 H, d, α-keto methine), 2.05 (3 H, s, acetoxy methyl), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for $C_{23}H_{36}O_6$ (408.5): C, 67.62; H, 8.88. Found: C, 68.02; H, 8.97.

Methyl 6-Hexanoyl-7-methoxy-2-oxobicyclo[3.2.0]heptane-1-heptanoate (10).—To a solution of the enone **9** (0.397 g) in methanol (3 ml) was added a solution of sodium (0.112 g) in methanol (6 ml). The mixture was stirred for 1 hr, diluted with ether, and washed with water. The ether extract was worked up in the usual manner to yield the crude product (0.518 g). The chromatographic purification gave the methoxy compound **10** (0.360 g, 83.1%): ν_{max} 1737, 1712 cm^{-1}; nmr δ 4.04 (1 H, d, J = 6 Hz, carbinolic), 3.68 (3 H, s, carbomethoxy), 3.28 (3 H, s, methoxyl), 2.93 (1 H, m, α-keto methine).

Anal. Calcd for $C_{22}H_{36}O_5$ (380.0): C, 69.44; H, 9.54. Found: C, 69.16; H, 9.27.

Methyl 7-Acetoxy-6-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (11).—A mixture of enone **9** (0.3 g), sodium acetate (0.08 g), and acetic acid (16 ml) was stirred overnight at 120° (bath temperature). After the solvent was removed, the residue was taken in ether, washed with water, and dried and the solvent was evaporated. The residue was purified through a silica gel column to yield acetoxy ketone **11** (0.097 g, 36.6%): ν_{max} 1730, 1708 cm^{-1}; nmr δ 5.0 (1 H, d, J = 7 Hz, carbinolic), 3.64 (3 H, s, carbomethoxyl), 3.00 (1 H, t, α-keto methine), 2.03 (3 H, s, acetoxy methyl).

Anal. Calcd for $C_{23}H_{36}O_6$ (408.5): C, 67.62; H, 8.88. Found: C, 67.64; H, 8.95.

Methyl 7-Hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (13). A.—A solution of photoadduct **5** (0.454 g) in glacial acetic acid (30 ml) was stirred overnight at reflux temperature in the presence of zinc (2.76 g). The reaction mixture was filtered and the acetic acid was removed. The residue was taken in ether, washed with water, and dried and the solvent was removed to yield crude product (0.45 g). Chromatographic separation gave pure diketone **13** (0.233 g, 54.4%): ν_{max} 1700, 1725 cm^{-1}; nmr δ 3.65 (3 H, s, methoxyl), 3.05 (1 H, α-keto methine), 0.88 (3 H, terminal methyl); mass spectrum M^+ (*m/e* 350), $M^+ - 31$ (*m/e* 319, $M^+ - 99$ (*m/e* 251), and $M^+ - 71$ (*m/e* 279).

Anal. Calcd for $C_{21}H_{34}O_4$ (350): C, 71.96; H, 9.78. Found: C, 72.07; H, 9.76.

B.—Hydrogenation of the cyclobutenone **8** (0.1 g) in methanol (5 ml) and 5% palladium/charcoal gave, after chromatography, a product (0.06 g) identical in all respects with diketone **13**.

C.—To a solution of cyclobutenone **8** (0.2 g) in acetic acid (6 ml) was added zinc dust (2.2 g). The reaction was followed by uv and tlc. An aliquot after stirring for *10 min at room temperature* showed complete absence of uv. The reaction mixture was filtered, the acetic acid was removed, and the product (0.1 g) was isolated by extraction with ether, followed by chromatography. The product was shown to be identical in all respects (gc, tlc, mass spectrum) with the dione **13**.

Methyl 2-Oxo-5-(3-oxo-1-octyl)cyclopentaneheptanoate (14). A.—A solution of diketone **13** (20 g) in acetic acid (600 ml) was heated to 120° (bath temperature). To the hot solution was added zinc (70 g), and the heating was continued. A further 70, 60, and 60 g of zinc were added after 7, 24, and 31 hr, respectively. The heating was stopped after 37 hr. The mixture was cooled and filtered. The acetic acid was evaporated, the residue was worked up with ether, washed with water, and dried, and the solvent was removed to yield crude product (21 g). Chromatography on a silica gel column and elution with 10% ethyl acetate–benzene gave pure ketone **14** (14.32 g, 75%): ν_{max} 1726, 1708 cm^{-1}; nmr δ 3.67 (3 H, s, carbomethoxyl); mass spectrum M^+ (*m/e* 352), $M^+ - 31$ (*m/e* 321).

(28) The recovered chlorovinyl ketone showed on a tlc plate as two spots which were separated and shown to be cis and trans isomers (*vide infra*).

Anal. Calcd for $C_{21}H_{36}O_4$ (352.5): C, 71.55; H, 10.30. Found: C, 71.27; H, 10.00.

B.—A solution of enedione **15** (0.101 g) was hydrogenated in methanol with 5% palladium on charcoal (0.1 g) overnight. The reaction mixture was filtered and the product was isolated in the usual manner to yield pure compound (0.07 g) identical in all respects with the diketone **14**.

C.—A solution of photoadduct **5** (50 g) in acetic acid (1520 ml) was brought to gentle reflux. Zinc (228 g) was added to the solution. After 6, 22, 28, and 42 hr, 104, 104, 100, and 100 g of zinc were added, respectively, with vigorous stirring. The reaction was monitored by tlc and was stopped after 48 hr. Most of the acetic acid was carefully removed under vacuum, the mixture was filtered, and the residue was washed well with ether. After removal of all the solvent the residue was taken up in ether, washed with water, and dried and the solvent was removed. The residue (37.1 g) was chromatographed to yield the diketone **13** (4.1 g, *ca.* 10%) and diketone **14** (18.2 g, *ca.* 40%).

Methyl 6-Butyl-2,3,3a,4,5,7a-hexahydro-3,5-dioxo-3a-indanheptanoate (**16**).—A solution of methoxy ketone **6** (0.47 g) in acetic acid (35 ml) was refluxed for 4 hr. The acetic acid was removed, the residue was diluted with ether, washed with water, and dried, and the solvent was removed to yield the crude product (0.366 g). Purification by chromatography gave pure enone **16** (0.202 g, 47%): ν_{max} 1674, 1737 cm^{-1}; λ_{max} 235 nm (ϵ 8000); nmr δ 6.52 (1 H, d, vinylic), 3.65 (3 H, s, carbomethoxy); mass spectrum M^+ (*m/e* 348), $M^+ - 31$ (*m/e* 317), $M^+ - 56$ (*m/e* 292).

Anal. Calcd for $C_{21}H_{32}O_4$ (348): C, 72.38; H, 9.26. Found: C, 72.62; H, 9.38.

Sodium borohydride reduction of the above diketone in methanol led to the isolation of diol **17**. The diol showed in its infrared absorptions at 3400, 1730, 1715 cm^{-1}; nmr 5.44 (1 H, m, vinylic), 3.8–4.4 (2 H, m, carbinolic), and 3.69 (1 H, s, carbomethoxy). Acetylation of the diol led to the diacetate **18**: ν_{max} 1730, 1240 cm^{-1}; nmr δ 5.6 (1 H, vinylic), 4.95 (1 H, m, carbinolic), 3.69 (1 H, s, carbomethoxy), 2.08 (6 H, two acetoxy methyls).

Anal. Calcd for $C_{25}H_{38}O_6$ (436): C, 68.78; H, 9.23. Found: C, 68.71; H, 9.42.

2-Carboxy-1-(carboxymethyl)-5-oxocyclopentaneheptanoic Acid Trimethyl Ester (**19**).—A solution of enone **16** (0.45 g) in chloroform (45 ml) was cooled to −20 to −30° and the ozone was passed through the solution for 1 hr; when dark blue color persisted, ozone was stopped and the mixture was warmed to room temperature. The solvent was removed to yield crude ozonide (0.554 g). The above ozonide was dissolved in acetic acid (24 ml) and oxidized with 30% hydrogen peroxide (6 ml). The reaction mixture was stirred at 50° (bath temperature) for 48 hr. The solvent was evaporated, the residue was taken up in ether, washed with water followed by saturated saline, and dried, and the solvent was removed to yield crude acidic product (0.533 g). The acidic residue was esterified with diazomethane to yield crude ester (0.62 g). Chromatographic separation yielded the pure product **19** (0.16 g): ν_{max} 1725, 1200–1150 cm^{-1}; nmr showed no terminal methyl, δ 2.6 (2 H, s) attributable to the methylene α to the newly created carbomethoxyl group, 3.65 (9 H, methoxyl); mass spectrum M^+ (*m/e* 356), $M^+ - 31$ (*m/e* 325), $M^+ - (31 + 74)$ (*m/e* 251), $M^+ - (31 + 143)$ (*m/e* 182, base peak).

Borohydride Reduction of 2-Oxo-5-(3-oxooctyl)cyclopentaneheptanoic Acid Ester. A.—To a solution of diketone **14** (0.42 g) in MeOH (6 ml) was added sodium borohydride (0.157 g). The reaction mixture was stirred at room temperature for 30 min. After diluting with ether, the mixture was washed with dilute hydrochloric acid, water, and saline. The organic liquor was dried and the solvent was removed. The residual oil (0.32 g) was chromatographed on silica gel to yield diol **20** (0.16 g) and **21** (0.06 g). The ir of both the products showed bands at 3400 and 1725 cm^{-1}. The nmr spectrum of the diol **20** showed a carbinolic proton (C-9)[22] at δ 3.94 (m), and that of **21** was located at δ 4.29 (m). Both the spectra showed 4 H signals at δ 3.71–3.52. The mass spectrum of the diol **20** showed peaks at $M^+ - 18$ (*m/e* 338), $M^+ - 18 \times 2$ (*m/e* 320), $M^+ - (18 + 31)$ (*m/e* 307), $M^+ - (36 + 71)$ (*m/e* 249). The alkaline hydrolysis of the methyl esters yielded the corresponding acids. The acid obtained from diol **21** was crystallized from acetone–hexane, mp 97–99°.

Anal. Calcd for $C_{20}H_{38}O_4$ (342): C, 70.13; H, 11.18. Found: C, 69.76; H, 11.13.

B.—A solution of diketone (3 g) in dimethoxyethane (18 ml) was cooled to −50°. Sodium borohydride (0.32 g) was added gradually to the solution. The reaction mixture was stirred for 1 hr, diluted with ether, washed with saturated ammonium chloride solution followed by water, and dried. The solvent was removed to yield crude product (3.21 g). Chromatography of the above residue on silicic acid (245 g) in ethyl acetate–benzene (2:8) yielded unchanged starting material (1.7 g). Further elution yielded **2α-hydroxy-5-(3-oxooctyl)cyclopentaneheptanoic acid methyl ester** (**24**) (0.18 g): ν_{max} 3475, 1730, 1710 cm^{-1}; nmr δ 4.20 (1 H, carbinolic),[22] 3.68 (3 H, carbomethoxy), and 0.91 (3 H, t, terminal methyl); mass spectrum $M^+ - (31 + 18)$ (*m/e* 305), $M^+ - (18 + 143)$ (*m/e* 193). Continued elution led to the isolation of 1 g of a product homogeneous by tlc but found to be a mixture of a major and a minor component by glc.[29] The latter mixture (1.05 g) was treated with dihydropyran (1.2 g) in chloroform (18 ml) containing *p*-toluenesulfonic acid overnight. The tetrahydropyranyl ethers (2.6 g) were isolated in the usual manner. This was chromatographed on silica gel to separate the two derivatives. Subsequent hydrolysis of the faster moving (tlc) THP ether in methanol and Dowex 50W-X4 (1 g) yielded **2β-hydroxy-5-(3-oxooctyl)cyclopentaneheptanoic acid methyl ester** (**23**) (0.115 g): ν_{max} 3425, 1730, 1710 cm^{-1}; nmr δ 3.89 (1 H, carbinolic),[27] 3.68 (3 H, carbomethoxyl), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.15; H, 10.8. Found: C, 71.14; H, 11.10.

The slower moving (tlc) pyranyl ether was eluted in later fractions and yielded upon hydrolysis in a similar manner as described above **2-oxo-5-(3-hydroxyoctyl)cyclopentaneheptanoic acid methyl ester** (**22**) (0.84 g): ν_{max} 3425, 1730 cm^{-1}; nmr δ 3.68 (4 H, carbomethoxyl and carbinolic), 0.88 (3H, t, terminal methyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.15; H, 10.8. Found: C, 71.12; H, 10.85.

Methyl 2-Oxo-5-(3-hydroxy-1-octenyl)cyclopentaneheptanoate. Isomer A (**31**) **and Isomer B** (**30**).—Unsaturated ketone **25** described earlier[27] was transformed to its THP ether by standard procedure. To a solution of enone **26** (30 g) in methanol (127 ml), cooled in ice bath, was added sodium borohydride (2.55 g) gradually. The mixture was stirred for 30 min and allowed to reach room temperature. Acetic acid (3 ml) was added and the solvent was evaporated. The residue was taken up in ether and washed with water until neutral, and the solvent was removed. The alcohol **27** (29.5 g) showed no absorption in ir or uv due to α,β-unsaturated ketone: ν_{max} 3460 cm^{-1}; nmr δ 5.5 (2 H, m, vinylic), 4.63 (1 H, doubly carbinolic).

Acetylation.—The above product was acetylated with acetic anhydride (85 ml) in dry pyridine (46 ml). After the usual work-up the crude acetate **28** (30.2 g) showed no OH absorption in the ir, ν_{max} 1735, 1240 cm^{-1}.

Hydrolysis.—The acetate was dissolved in acetic acid (288 ml) and mixed with water (144 ml) and tetrahydrofuran (24 ml). The solution was stirred at 55° overnight. The solvent was removed and the residue was taken up in ether and processed as usual to yield crude product (29.5 g). Chromatographic purification gave the pure mixture of isomeric hydroxy acetate **29** (21 g).

Oxidation.—The acetoxy alcohol **29** (23.27 g) was dissolved in acetone (250 ml) and the solution was cooled to 0°. The Jones reagent was added dropwise until the faint orange color persisted (22 ml). The stirring was continued until all starting material disappeared (tlc). Methanol was added to destroy the excess of the reagent. The solvent was removed, the residue was taken in ether, washed with water, and dried, and the solvent was removed to yield crude keto acetate (20.8 g).

Hydrolysis.—The keto acetate was dissolved in methanol (295 ml). A solution of sodium (1.35 g) in methanol (75 ml) was added to it, and the reaction mixture was stirred for 1 hr. The solution was neutralized with acetic acid (3 ml) and the solvent was removed. The residue was worked up in the usual manner to yield the mixture of crude alcohols **30** and **31** (18.9 g). Chromatography on silicic acid and elution with 20% ethyl acetate–benzene gave isomer A, **31**[23] (7.6 g): ν_{max} 3455, 1730 cm^{-1}; nmr δ 5.63 (2 H, m, vinylic), 4.13 (1 H, m, carbinolic), and 3.67 (3 H, s, carbomethoxyl).

(29) Gas chromatograms were done as TMS ethers, on XE-60 column (4.6%) at 215°. The retention times for **22**, **23**, and **24** were 20.5, 16.6, and 17.6 min, respectively.

Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.40; H, 10.35.

Further elution yielded a mixture of alcohols of **30** and **31** (2.13 g) followed by isomer B, **30**[23] (4.84 g). The ir and nmr of this isomer were essentially identical with that of isomer A.

Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.39; H, 10.04.

Methyl 5-(3-Hydroxyoctyl)-2-oxocyclopentaneheptanoate (32 and 33).—A solution of keto alcohol **30** (1.06 g) in methanol (25 ml) was hydrogenated with 10% palladium/charcoal (0.360 g). The catalyst was filtered and washed with hot methanol. The crude product was chromatographed to yield alcohol **32** (0.75 g): ν_{max} 3450, 1735 cm^{-1}; nmr δ 3.65 (4 H, s, carbomethoxyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.11; H, 10.85.

In a similar manner as described above, alcohol **31** (2.5 g) was hydrogenated to yield keto alcohol **33** (1.32 g). The infrared and the nmr spectra were essentially identical with those of alcohol **32**.

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.13; H, 10.85.

The two alcohols **32** and **33** were indistinguishable by gc or by tlc in at least two different systems.

Hydrolysis of Alcohols 30, 31, 32, and 33.—Pure samples of the esters **30–33** were hydrolyzed in methanolic sodium hydroxide to yield the corresponding acids. The acids obtained from alcohols **31**, **32**, and **33** were oils, whereas that from alcohol **30** was a solid and crystallized from ether–hexane to yield an analytical sample, mp 85–86°. The ir showed characteristic acid absorption: nmr δ 5.62 (2 H, m, vinylic), 4.3 (1 H, m, carbinolic), 0.92 (3 H, t, terminal methyl).

Anal. Calcd for $C_{20}H_{34}O_4$ (338.47): C, 70.97; H, 10.13. Found: C, 70.72; H, 10.19.

Registry No.—**1**, 34546-57-1; **5a**, 34603-59-3; **5b**, 34603-60-6; **6a**, 34603-61-7; **6b**, 34603-62-8; **7a**, 34603-63-9; **7b**, 34603-64-0; **8**, 22973-15-5; **9**, 34603-66-2; **10**, 34603-67-3; **11**, 34603-68-4; **13**, 28764-52-5; **14**, 22973-16-6; **16**, 34546-58-2; **17**, 34546-59-3; **18**, 34647-02-4; **19**, 34546-60-6; **20**, 28764-72-9; **21**, 28764-73-0; **21** free acid, 16887-10-8; **22**, 28764-56-9; **23**, 22973-17-7; **24**, 28764-75-2; **27**, 34603-78-6; **30**, 34603-79-7; **30** free acid, 34603-80-0; **31**, 34603-81-1; **32**, 20592-62-5; **33**, 34603-77-5; 1-carbomethoxy-2-oxocyclopentaneheptanoic acid Me ester, 34546-61-7; 2-oxocyclopentaneheptanoic acid 2,4-DNP, 34546-62-8; 5-oxo-1-cyclopentene-1-heptanoic acid, 5239-43-0.

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General Methods of Alkaloid Synthesis. X. The Total Synthesis of the Sceletium Alkaloids (±)-Joubertiamine, (±)-*O*-Methyljoubertiamine, and (±)-Dihydrojoubertiamine

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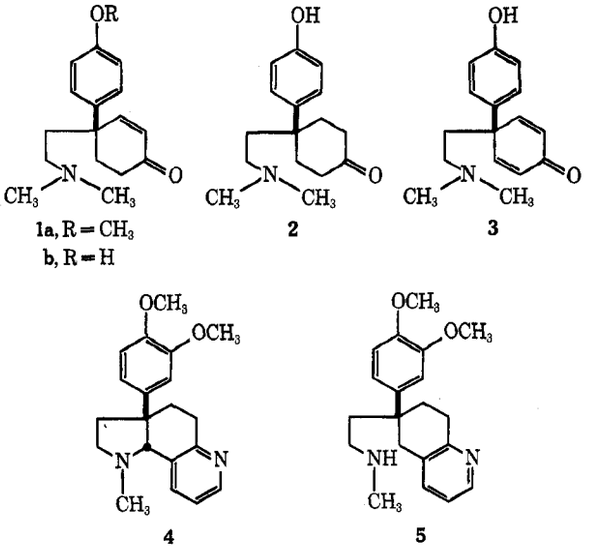
An efficient synthesis of the pharmacologically interesting Sceletium alkaloid (±)-*O*-methyljoubertiamine (**1a**) and its conversion into (±)-joubertiamine (**1b**) and (±)-dihydrojoubertiamine (**2**) is described.

Renewed interest in the mesembrine alkaloids[2,3] has been catalyzed by the recent characterization[4–7] of several new bases found in various Sceletium species which are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed." These include the seco-mesembrine alkaloids joubertiamine (**1b**),[4] dihydrojoubertiamine (**2**),[4] and dehydrojoubertiamine (**3**)[4] and the fused pyridine bases Alkaloid A_4 (**4**)[6,7] and tortuosamine (**5**).[7]

Inspection of the structural features of these new Sceletium alkaloids coupled with their potential physiological activity prompted the present investigation designed to test further two fundamental principles of alkaloid synthesis which have found application in the synthesis of mesembrine (**6**) itself,[8] the closely related



(1) A. P. Sloan Fellow, 1969–1971.

(2) For a review see A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 467.

(3) In the older literature reference is made to the isolation of many of these alkaloids from the genus *Mesembryanthemum* Dill from which the names of several of these bases were derived. However, recently this classification has been revised to the genus *Sceletium* N. E. Brown (Ficoidaceae or Aizoaceae). Therefore, reference to these bases as mesembrine alkaloids is technically a misnomer.

(4) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970).

(5) P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970).

(6) P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Commun.*, 1466 (1971).

(7) F. O. Snyckers, F. Strelow, and A. Wiechers, *ibid.*, 1467 (1971).

(8) (a) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); (b) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (c) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).