1574 and 1553 cm.$^{-1}$. In the ultraviolet (0.02 *N* sodium hydroxide), *6a* had λ_{max} 252 (ϵ 132,000), 317 (ϵ 6800), 331 (ϵ 7400), 347 (ϵ 9300), 365 (ϵ 11,200), and 384 mμ (ϵ 9400), and λ_{min} 226 (ϵ 24,000), 279 (ϵ 4000), 322 (ϵ 6800), 338 (ϵ 6800), 355 (ϵ 6700), and 375 mμ (ϵ 5100).

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17. Found: C, 78.03; H, 4.35.

1-(9-Anthryl)-1,2-dihydro-3,6-pyridazinedione (6b) by rearrangement of 6,11-dihydro-6,11-o-benzenopyridazino[1,2-b]phthalazine-1,4-dione (4b). A solution of *4b*, (1.33 g.), glacial acetic acid (50 ml.), and concd. hydrochloric acid (3 ml.) was stirred at room temperature for 4 hr. The yellow precipitate which formed was removed by filtration, and washed with acetic acid and water. It amounted to 1.24 g. (93%) of *6b* which was obtained pure, as yellow cubes, m.p. > 300°, after a single crystallization from dimethylformamide–water. In the infrared, *6b* exhibited H-stretching absorption (broad, weak, ambiguous) at 2960–2340 cm.$^{-1}$, acyl absorption at 1661 cm.$^{-1}$, and intense absorption at 1563 and 1497 cm.$^{-1}$. In the ultraviolet (0.02 *N* sodium hydroxide), *6b* had λ_{max} 252 (ϵ 148,000), 333 (ϵ 5300), 348 (ϵ 7800), 365 (ϵ 10,700), and 385 mμ (ϵ 9100) and λ_{min} 226 (ϵ 23,300), 282 (ϵ 1300), 336 (ϵ 5300), 355 (ϵ 6400), and 375 mμ (ϵ 5100). It was soluble in 0.01 *N* sodium hydroxide.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20. Found: C, 75.12; H, 4.42.

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CHICAGO 37, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF MICHIGAN]

Experiments Directed toward the Total Synthesis of Terpenes. II. The Synthesis of *dl*-6-Keto-5,5,9-trimethyl-2-methylene-*trans*-decalyl-1α-acetic Acid and Derivatives[1]

ROBERT F. CHURCH,[2] ROBERT E. IRELAND, AND JAMES A. MARSHALL[3]

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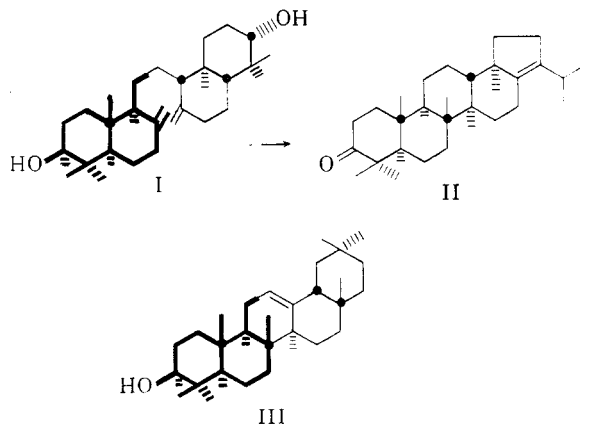
Utilization of the alkoxymethylene grouping allowed the conversion of 6,6-ethylenedioxy-5,5,9-trimethyl-*trans*-decalone-1 (*2*) to the corresponding keto alcohol (*7*). Pyrolysis of the vinyl ether prepared from this alcohol generated an acetaldehyde derivative that was readily oxidized to the title compound (*10*), a potentially useful intermediate in triterpene total synthesis. The acid (*10*) was converted into the keto acid (*12*), a key intermediate in the total synthesis of α-onocerin. Studies in the 6-desoxydecalone-1 series demonstrated the axial character of the acetaldehyde residue introduced by the Claisen rearrangement.

One approach to the total synthesis of pentacyclic triterpenes that has been under investigation in these laboratories[4] is the coupling of two dicyclic moieties, followed by acid-catalyzed cyclization of the resulting tetracyclic system—*i.e.*, the ABDEC scheme. The success of such a plan has recently been amply demonstrated by the construction of such model pentacyclic systems as pentacyclosqualene by Corey[5] and Eschenmoser[6] and olean-11,12; 13,18-diene by Corey.[7] The most notable result of this plan has been the total synthesis of α-onocerin (I)[26] announced by Stork and coworkers.[8] In view of the earlier conversion[9] of α-onocerin (I) to hopenone-I(II), this latter total synthesis represents the first total synthesis of a naturally occurring pentacyclic triterpene.



The symmetry of the α-onocerin molecule makes the task of constructing the appropriate dicyclic moieties somewhat easier, and it is not surprising that it has been the first of the polycyclic triterpenes to be conquered by the synthetic organic chemist. Indeed, it is possible that an appro-

(1) A preliminary account of this work has appeared in *Tetrahedron Letters*, 34 (1961); taken in part from the Ph.D. thesis of R. F. Church, University of Michigan, 1961.

(2) Dow Chemical Company Fellow, 1958–1959; Sun Oil Company Fellow, 1959–1960.

(3) Public Health Service Research Fellow of the National Heart Institute, 1958–1960.

(4) R. E. Ireland and J. A. Marshall, *J. Org. Chem., in press.*

(5) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 81, 1739 (1959).

(6) A. Eschenmoser, P. A. Stadler, A. Nechvatal, and A. J. Frey, *Helv. Chim. Acta*, 40, 1900 (1957).

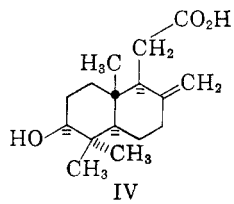
(7) E. J. Corey, H. Hess, and S. Proskow, *J. Am. Chem. Soc.*, 81, 5258 (1959).

(8) G. Stork, J. E. Davies, and A. Meisels, *ibid.*, 81, 5516 (1959).

(9) K. Schaffner, O. Jeger, L. Caglioti, and D. Arigoni, *Helv. Chim. Acta*, 41, 152 (1958).

priately substituted dicyclic system could serve both as an α-onocerin intermediate through electrolytic coupling[6] and as a β-amyrin (III) intermediate in conjunction with a different decalin derivative.[7] With such an intermediate in mind, we embarked on a synthetic scheme that has succeeded in elaborating the keto acid (*10*) which was converted to the hydroxy keto acid (*12*). The latter acid is identical to that prepared earlier by Stork and thus in a formal sense represents an alternative route to the total synthesis of α-onocerin (I).

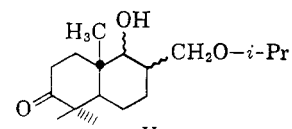
Consideration of the α-onocerin (I) and β-amyrin (III) molecules reveals that the most suitable dicyclic structure that could represent the A and B rings [outlined in bold face in formulas (I) and (III)] is the acid IV. The difficulties encountered in



IV

the construction of this acid are associated with the introduction of the C-1 acetic acid residue and the C-2 exocyclic methylene. The synthesis reported by Stork[8] employed the degradation of a phenanthrene derivative as the means to generate the C-1 acetic acid group, but in turn this made impossible the incorporation of the C-2 exocyclic methylene at the dicyclic stage. The very recently reported work of Sondheimer and co-workers[10] that led to the synthesis of the keto acid (IV) also sacrifices the introduction of the C-2 exocyclic methylene group at the dicyclic stage in favor of introduction of a C-1 acetic acid residue. As a result of the satisfactory results[4] obtained in the application of the Claisen rearrangement to a similar problem under investigation in these laboratories, it was felt that this method could be used to introduce both the C-1 acetic acid and the C-2 exocyclic methylene into the hydroxy ketone (*1*),[11] and thereby achieve the synthesis of the intermediate acid (IV).

The first problem to overcome in this transformation was the conversion of the hydroxy ketone (*1*) go the appropriate allylic alcohol (*7*). In order to mask the C-6 ketone while affecting this transformation on the C-1 hydroxyl, the hydroxy ketone (*1*), prepared by the method of Sondheimer,[11] was first ketalized in the usual manner with ethylene glycol. The crude hydroxy ketal that resulted from this treatment was then oxidized with Jones reagent,[12] whereupon the ketal ketone (*2*) was isolated in 58% over-all yield. The stage was now set for the preparation of the desired allylic alcohol system and experience gained earlier[4] with the reduction and acid rearrangement of a similar 2-*n*-butylthiomethylene ketone[13] made this sequence appear to be most appropriate. However, it was found that the acid-catalyzed etherification procedure necessary for the introduction of the *n*-butylthiomethylene group destroyed the ketal and only dark oils were produced. The solution to this problem was found by using the isopropoxymethylene group,[14] which can be introduced under basic reaction conditions. Thus, by first hydroxymethylation of the ketal ketone (*2*) and then treatment of the resulting derivative with isopropyl iodide and potassium carbonate in acetone solution, there resulted an 85% over-all yield of the desired isopropoxymethylene derivative (*3*). The fact that this type of compound will serve almost as well as the *n*-butylthiomethylene derivative in the reduction–acid rearrangement sequence is documented.[15] However, the reduction of this oxygen analog is complicated by a significant amount of 1,4-reduction. Thus, the infrared spectrum of the reduction product of the ketone (*3*) with lithium aluminum hydride indicated the presence of a saturated ketone. In view of the basic work-up used in this reaction, this ketone could not have arisen from ketal hydrolysis. While the product obtained from reduction with sodium borohydride in aqueous methanol showed only O—H absorption in the infrared, a portion of this alcoholic material could have resulted from 1,4-reduction, followed by further reduction of the saturated ketone so generated. That this was indeed the case was shown by acid-catalyzed rearrangement of this crude alcohol (*4*) and then oxidation of the resulting keto aldehyde with silver oxide.[16] In this fashion the keto acid (*5*) was obtained in a 62% over-all of yield from the isopropoxymethylene ketone (*3*), together with a 20% yield of a neutral, oily keto alcohol, for which the structure V appears most likely. The presence of the hydroxyl (2.83 μ), the ketone (5.88 μ), and the



V

(10) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron Letters*, 310 (1961).

(11) F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **79**, 5542 (1957); **80**, 1967 (1958).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(13) R. E. Ireland and J. A. Marshall, *ibid., in press.*

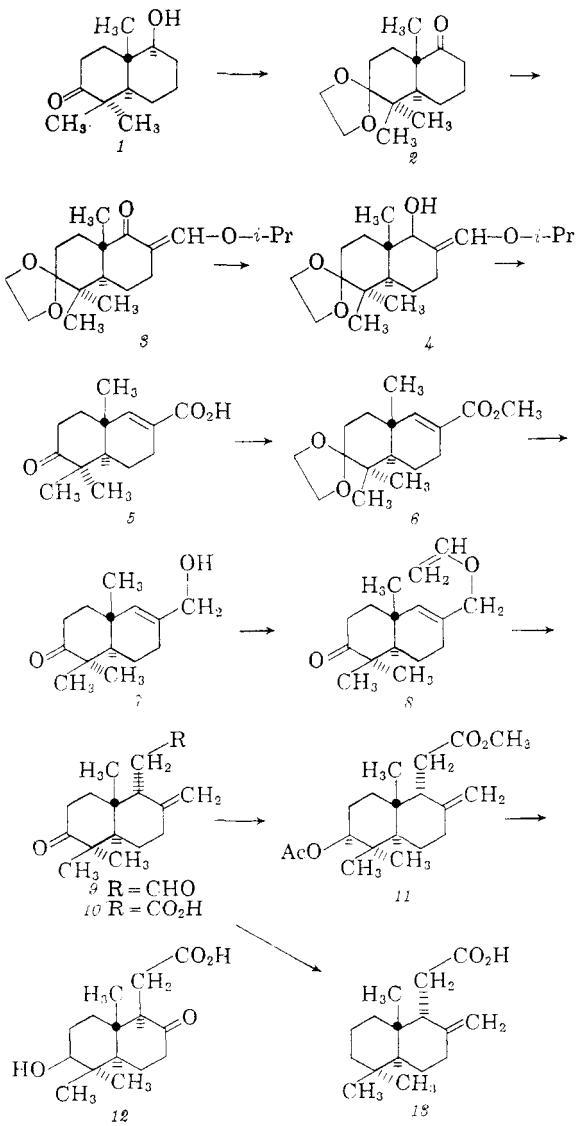
(14) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

(15) P. Seifert and H. Schinz, *Helv. Chim. Acta*, **34**, 728 (1951); O. P. Viq, T. R. Sharma, and S. M. Mukherji, *Chem. and Ind.*, 381 (1956).

(16) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

ether linkage (8.32 μ) can be inferred from the infrared spectrum. In later experiments it was found possible to isolate the alcohol (*4*) in 70% yield in pure condition by crystallization from petroleum ether. When this pure material was rearranged with mineral acid and then oxidized, the acid (*5*) was obtained in 90% yield and no neutral material was detected.

The mineral acid necessary for the rearrangement of the alcohol (*4*) precluded the retention of the C-6 ketal. Inasmuch as it was felt that the ethyl vinyl ether equilibration experiment would be more likely to succeed with the keto alcohol (*7*) than the corresponding C-6 hydroxyallyl alcohol, it was now necessary to reketalize the C-6 ketone prior to hydride reduction of the carboxyl group. To this end, the acid (*5*) was esterified with diazomethane, and the resulting keto ester treated with ethylene glycol in the usual manner. The ketal ester (*6*), obtained in this way in 93% over-all yield, was reduced with lithium aluminum hydride and then the ketal removed with 3 *N* aqueous hydrochloric acid. The desired keto alcohol (*7*) that resulted from this sequence in 84% yield had thus been prepared from the starting ketal ketone (*2*) in a 41% over-all yield in nine steps with five isolations.



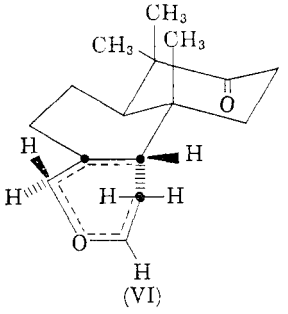
Further modification of this keto alcohol (*7*) proceeded in a manner similar to that previously described.[4] Thus, equilibration[17] of this alcohol with ethyl vinyl ether in the presence of mercuric acetate led to an oily vinyl ether (*8*). Due to the oily nature of this vinyl ether and its susceptibility to hydrolysis by moisture, it was not characterized further than inspection of the infrared spectrum for the absence of O—H absorption and the presence of the vinyl ether bands at 6.05 μ and 8.40 μ. On pyrolysis[18] in a sealed tube under a nitrogen atmosphere the vinyl ether (*8*) rearranged smoothly (75% yield based on crude vinyl ether) to the corresponding acetaldehyde derivative (*9*) in a 53% over-all yield. Examination of the infrared spectrum of this aldehyde (*9*) revealed bands at 3.20 μ, 6.08 μ, and 11.20 μ due to the exocyclic methylene, 3.62 μ and 5.83 μ due to the aldehyde function and 5.89 μ due to the ketone. That the acetaldehyde grouping had been introduced at C-1 can be inferred from the known structure of the allylic alcohol (*7*) and the mechanism of the Claisen rearrangement. As might be expected this aldehyde was quite susceptible to air oxidation, and it was found more expedient to oxidize it directly with silver oxide[16] to the acid (*10*). This acid was thus available in 85% yield from the aldehyde or 45% over-all yield from the allylic alcohol (*7*).

While a compound known to have the structure of the desired dicyclic intermediate (IV) had been obtained, the problem of the stereochemistry about C-1 remained. The asymmetry at this point was introduced as a result of the Claisen rearrangement and could possess either the 1α-(axial)- or 1β-(equatorial)-acetaldehyde system. Since there was no obvious path available to this aldehyde (*9*) or the resulting acid (*10*) for equilibration to the more stable $C_1\beta$-(equatorial) group, it was felt that if the $C_1\alpha$-(axial)-acetaldehyde (*9*) had resulted from the Claisen rearrangement, this unstable configuration would remain. Furthermore, it appeared more likely that this $C_1\alpha$-(axial)-acetaldehyde derivative (*9*) would be the preferred product based on the hindrance to attack of the β-face of the vinyl ether (*8*) offered by the two axial C-5 and C-9 methyl groups. Augmenting this steric factor is the stereoelectronic control that might be exerted by the formation of the C-2 exocyclic methylene grouping. The analogy between

(17) W. H. Watenabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(18) A. W. Burgstahler and I. C. Nordin, *ibid.*, **83**, 198 (1961).

this process and the ketonization of an enol is formally obvious, and the preferred axial attack in the latter reaction is well documented.[19] Thus, the most reasonable representation of the transition state (VI) for the Claisen rearrangement would be that of a helix oriented on the $C_1\alpha$-(axial)-side of the molecule. This rationale coupled with the observation that only one isomer could be isolated from the pyrolysis reaction made it seem

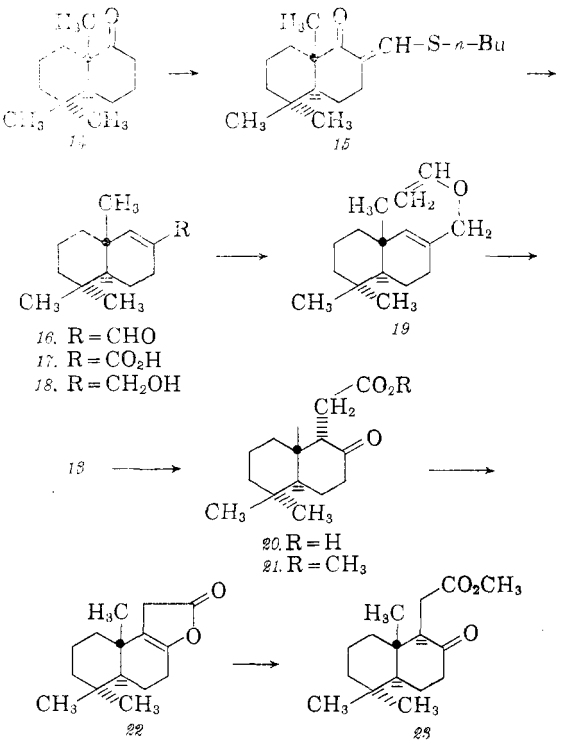


(VI)

reasonable that the Claisen rearrangement had proceeded stereospecifically to generate the $C_1\alpha$-(axial)-acetaldehyde derivative (*9*).

The most logical method to prove this postulate was by ozonization to the C-2 ketone group and then epimerization of the C-1 two carbon residue to the more stable β(equatorial) configuration. However, in order to remove the complications possible with a polycarbonyl derivative, this epimerization sequence was carried out using the 6-desoxy acid (*13*). This acid was obtained in 92% yield by applying the Huang-Minlon modification[20] of the Wolff-Kishner reduction to the keto acid (*10*). Rather than expend supplies of the keto acid (*10*) in this degradation, it was found more expedient to prepare the 6-desoxy acid (*13*) from 5,5,9-trimethyl-*trans*-decalone-1 (*14*), readily available from the hydroxy ketone (*1*) by previously described procedures.[11]

In the case of the decalone (*14*) it was possible to employ the *n*-butylthiomethylene grouping[13] to introduce the requisite alyllic alcohol system; this derivative was prepared from the decalone (*14*) in 86% yield. Reduction of the *n*-butylthiomethylene ketone (*15*) with sodium borohydride, followed by steam distillation of the resulting alcohol from 10% aqueous ethylene glycolic sulfuric acid afforded a quantitative *crude* yield of the aldehyde (*16*). This aldehyde was again quite susceptible to air oxidation and was characterized by its infrared spectrum and by conversion to the corresponding acid (*17*) with silver oxide.[16] Further reduction of the aldehyde (*16*) with sodium borohydride afforded the desired allylic alcohol (*18*) in 81% over-all yield from the thioenol ether (*15*). A comparison of the yield obtained here with the thioenol ether and that obtained above from the



oxygen analog attests to the general superiority of the sulfur derivative, when it can be used. This is probably due to the lack of any 1,4-hydride addition in the initial reduction of the thioenol ether.

Equilibration[17] of the allylic alcohol (*18*) with ethyl vinyl ether resulted in a 91% yield of chromatographed vinyl ether (*19*), which was directly pyrolyzed[18] to the corresponding aldehyde. This aldehyde, obtained in 91% yield, was then oxidized with silver oxide[16] in 77% yield to the same acid (*13*) that had been obtained by Wolff-Kishner reduction of the keto acid (*10*).

When the acid (*13*) was ozonized at −78° and the ozonide reduced immediately at −20°, there resulted an 80% yield of the keto acid (*20*). That these ozonization conditions were not vigorous enough to affect epimerization of the $C_1\alpha$-(axial) acetic acid residue was shown by conversion of the acid (*20*) to the enol-lactone (*22*) (acetic anhydride–sodium acetate[21]) in 78% yield and subsequent cleavage of this enol-lactone to the keto ester (*23*) in 66% yield with methanolic sodium methoxide. The keto ester (*23*) so obtained was *not* the same as the ester (*21*) afforded by the original keto acid (*20*) by treatment with diazomethane. Inasmuch as the methoxide treatment of the enol-lactone (*22*) would most certainly generate the more stable $C_1\beta$-(equatorial) acetate derivative (*23*), the above experiments confirm the prediction that the substituted acetic acids (*10*) and (*13*) obtained *via* the Claisen rearrangement must possess $C_1\alpha$-(axial)-oriented acetic acid residues.

(19) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.* **77**, 2505 (1955).

(20) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(21) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

As has been pointed out earlier,[4] this result should not interfere with the plan to utilize the acids (*10*) and (*13*) for further synthetic efforts in the pentacyclic field due to the eventual isomerization of the C-1 position during acid-catalyzed cyclization of a tetracyclic derivative. Moreover, this Claisen rearrangement represents the best method[22] to date for introducing an α(axial) substituent and is being utilized at present for the total synthesis of both the diterpenoid acid eperuic acid[23] and perhydrophenanthrenes with the *trans-syn-cis* backbone.[24] However, the keto acid (*10*) could not served as an intermediate in an α-onocerin (I) total synthesis without epimerization of the C-1 acetic acid residue.

Unaesthetic as it may be, the best way to modify the keto acid (*10*) so that it might serve in the α-onocerin synthesis was to replace the C-2 exocyclic methylene by a ketone, in spite of the fact that this carbon would have to be replaced at a later stage. To affect this transformation the keto acid (*10*) was successively esterified with diazomethane, reduced with sodium borohydride and acetylated with acetic anhydride in pyridine solution. In this fashion the acetoxy ester (*11*) was obtained in 69% yield. Finally, the keto acid (*12*) was obtained in 51% yield by ozonolysis of the ester (*11*) and then alkaline hydrolysis of the resulting keto ester. That the required epimerization at C-1 had taken place during the alkaline treatment was shown by the identity (mixture melting point and infrared) of this keto acid (*12*) and a sample of the *dl*-keto acid prepared by Stork and co-workers[8] in their total synthesis of α-onocerin. This identity provides the link between this work and that of Professor Stork and fulfills the requirements for a formal total synthesis of α-onocerin(I).

The use of the keto acid (*10*) in further triterpene syntheses and the interesting possibility of obtaining 9,9′-isoonocerin by electrolytic coupling of this acid are being investigated at present.

EXPERIMENTAL[25]

6,6-Ethylenedioxy-5,5,9-trimethyl-trans-decal-1β-ol. A solution of 30.3 g. (0.144 mole) of the ketal (*1*),[11] 25 ml. of ethylene glycol, and 100 mg. of *p*-toluenesulfonic acid in 300 ml. of benzene was refluxed under a Dean-Stark water separator for 3 hr. After this period, 2.1 ml. of water had collected and the reaction mixture was cooled, diluted with ether, and washed successively with 10% aqueous potassium bicarbonate, water, and saturated salt solution. After drying (Na_2SO_4) the solvents were removed at reduced pressure and the residue crystallized from petroleum ether (b.p. 30–60°). In this manner there was collected 30.3 g. (83%) of the hydroxy ketal, m.p. 106–108°. The analytical sample, obtained after three further crystallizations from the same solvent, melted at 108.5–109°; $\lambda_{max}^{HCCl_3}$; 2.70 μ and 2.82 μ (O—H), 9.05 μ and 9.21 μ (ketal).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.08; H, 10.20.

6,6-Ethylenedioxy-5,5,9-trimethyl-trans-decalone-1 (*2*). To a solution of 27.8 g. (0.11 mole) of the above hydroxy ketal in 300 ml. of dry acetone was added dropwise 26 ml. of Jones reagent[12] while maintaining the temperature below 20°. The clear acetone solution was decanted from the chromium salts and concentrated at reduced pressure to approximately 50 ml. Ice water was added to dissolve the chromium salts. This solution was combined with the acetone concentrate, and the whole extracted three times with 100-ml. portions of ether. The combined ethereal extracts were washed with 10% aqueous potassium bicarbonate, water, and saturated salt solution and dried over sodium sulfate. After filtration and evaporation of the ether, the solid residue was crystallized from petroleum ether (b.p. 30–60°). In this manner there was collected 20.5 g. (75%) of the ketal ketone (*2*), m.p. 126–128°, in two crops of 19.5 g. and 1.0 g. The analytical sample, m.p. 126.5–128° was obtained as hard sugar-like prisms after two further crystallizations from the same solvent; $\lambda_{max}^{HCCl_3}$ 5.89 μ (> C=O), 9.00 μ and 9.09 μ (ketal).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.38; H, 9.59. Found: C, 71.29; H, 9.46.

6,6-Ethylenedioxy-5,5,9-trimethyl-2-hydroxymethylene-trans-decalone-1. A modification of the procedure of Johnson and Posvic[14] was employed. A solution of 4.5 g. (0.02 mole) of the ketal ketone (*2*) and 20 ml. (0.2 mole) of purified ethyl formate in 20 ml. of dry benzene was added dropwise to an ice-cooled suspension of 11 g. (0.2 mole) of commercial sodium methoxide in 100 ml. of dry benzene in a nitrogen atmosphere. After stirring overnight at room temperature the reaction mixture was cooled in an ice bath and treated with 100 ml. of cold 2.5 *M* aqueous sodium dihydrogen phosphate. The product was isolated from the benzene solution after dilution with ether and the usual washing and drying procedure. Crystallization of the solid residue from petroleum ether (b.p. 60–75°) afforded 4.1 g. (81%) of the hydroxy-methylene derivative as white plates, m.p. 129–131°. The analytical sample, obtained after one further crystallization from the same solvent, melted at 132–133°. This material gave a dark green color when treated with 1% alcoholic ferric chloride solution.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.56.

6,6-Ethylenedioxy-5,5,9-trimethyl-2-isopropoxymethylene-trans-decalone-1 (*3*). Following the procedure of Johnson and Posvic,[14] 2.1 g. (7.5 mmoles) of the above hydroxymethylene derivative in 40 ml. of dry acetone was treated with 1.1 g. (7.5 mmoles) of anhydrous powdered potassium carbonate and 1.3 g. (7.5 mmoles) of freshly distilled isopropyl iodide. After the prescribed work-up the solid residue was crystallized from petroleum ether (b.p. 60–75°). In this manner there was obtained 2.1 g. (87%) of the isopropoxymethylene derivative (*3*), m.p. 84–86°. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 85–86°. This material was particularly sensitive to atmospheric moisture and had to be stored in a desiccator over calcium chloride.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.85; H, 9.42.

In another experiment when 20.5 g. (0.0815 mole) of the ketal ketone (*2*) was hydroxymethylated as above and the crude product etherified by the same procedure, there re-

(22) Compare, S. K. Balasubramanian, *Tetrahedron*, **12**, 196 (1961) and E. Wenkert, V. I. Stenberg, and P. Beak, *J. Am. Chem. Soc.*, **83**, 2320 (1961).

(23) F. E. King and G. Jones, *J. Chem. Soc.*, 658 (1955); C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957).

(24) R. F. Church and R. E. Ireland, *Tetrahedron Letters*, 493 (1961).

(25) Melting points were determined on a Kofler hot stage and are corrected for stem exposure. Infrared spectra were taken on a Perkin-Elmer Infracord Model 137, except where noted. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

sulted 22.3 g. (85%) of the isopropoxymethylene derivative, m.p. 84–86°.

6,6-Ethylenedioxy-5,5,9-trimethyl-2-isopropoxymethylene-trans-decalol-1 (*4*). A solution of 6.55 g. (0.0204 mole) of the isopropoxymethylene derivative (*3*) in 150 ml. of methanol was reduced with a solution of 0.80 g. (0.021 mole) of sodium borohydride in 10 ml. of 0.1 *N* aqueous sodium hydroxide. After standing for 6 hr. at room temperature, the solvent was removed at reduced pressure and the residue taken up in ether, washed with 10% aqueous sodium hydroxide, water, and saturated salt solution, and dried (Na_2SO_4). When the solid that remained after evaporation of the ether was crystallized from petroleum ether (b.p. 60–75°), there was obtained 4.60 g. (70%) of the alcohol (*4*), m.p. 124–126°. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 125.5–127°; λ_{max}^{film} 2.83 μ (OH), 5.98 μ (> C=C—O—).

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.38; H, 9.94.

2-Carboxy-5,5,9-trimethyl-trans-Δ¹-octalone-6 (*5*). A solution of 4.60 g. (0.0142 mole) of alcohol (*4*) in 150 ml. of ether was stirred for 2 hr. at room temperature with 100 ml. of 3 *N* aqueous hydrochloric acid. The aqueous layer was separated, and the ethereal solution washed and dried (Na_2SO_4) in the usual manner. Evaporation of the ether afforded a corresponding α,β-unsaturated aldehyde [infrared: λ_{max}^{film} 3.66 μ, 5.95 μ (—CHO); 6.10 μ (conj. C=C); 5.87 μ (> C=O)] which was dissolved[16] in 110 ml. of ethanol, treated with a solution of 2.48 g. (0.0146 mole) of silver nitrate in 26 ml. of water. To this well stirred solution was added dropwise a solution of 2.48 g. (0.062 mole) of sodium hydroxide in 100 ml. of water, and the suspension stirred overnight at room temperature. After filtration to remove the precipitated silver, the aqueous liquor was extracted with 50 ml. of ether (no residue was detected on evaporation of this ethereal extract) and then made acidic with excess concd. hydrochloric acid. The precipitated acid was extracted with ether, and after the usual washing and drying (Na_2SO_4) sequence, the ether was evaporated at reduced pressure. The solid that remained was crystallized from aqueous ethanol and amounted to 3.02 g. (90%) of the acid (*5*), m.p. 199–202°. The analytical sample, obtained after two further crystallizations from methylene chloride, melted at 202–204°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.11; H, 8.53. Found: C, 71.38; H, 8.60.

The same acid (*5*) [0.460 g. (62%)], m.p. 196–199°, was obtained when 1.0 g. (3.1 mmoles) of the isopropoxymethylene derivative (*3*) was reduced, rearranged and oxidized as above, but without isolation of the alcohol (*4*). However, in this case the neutral ethereal extract of the basic oxidation solution contained 170 mg. [20% based on structure V] of an oil, the infrared spectrum of which showed bands at 2.83 μ (O—H), 5.88 μ (> C=O), and 8.32 μ (C—O—C) on a liquid film.

Methyl 6,6-ethylenedioxy-5,5,9-trimethyl-trans-Δ¹-octalin-2-carboxylate (*6*). A solution of 3.35 g. (14.2 mmoles) of the acid (*5*) in 150 ml. of benzene was treated with excess ethereal diazomethane and then concentrated by boiling on the steam bath to approximately 130 ml. To this solution was added 0.85 ml. (930 mg.; 15 mmoles) of ethylene glycol and a trace of *p*-toluenesulfonic acid, and the mixture was refluxed overnight under a Dean-Stark water separator filled with Drierite. After the usual work-up the residue was chromatographed on 130 g. of Florisil. Elution with 5 l. of benzene afforded 4.20 g. of material which on crystallization from petroleum ether (b.p. 30–60°) gave 3.85 g. (93%) of the ketal ester (*6*), m.p. 71–73°. The melting point was not raised by further crystallization; infrared: λ_{max}^{film} 5.85 μ and 8.00 μ (=C(CH₃); 6.05 μ (conj. C=C), 9.00 μ (ketal).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.30; H, 8.97.

2-Hydroxymethyl-5,5,9-trimethyl-trans-Δ¹-octalone-6 (*7*). A solution of 2.43 g. (8.26 mmoles) of the ketal ester (*6*) in 25 ml. of dry ether was added dropwise to an ice-cooled suspension of 0.5 g. (13.18 mmoles) of lithium aluminum hydride in 50 ml. of dry ether. After stirring for 1 hr. in the cold, 1 ml. of water was added, followed by 0.8 ml. of 10% aqueous sodium hydroxide, and the mixture stirred at room temperature for 3 hr. After filtration, the ethereal filtrate was stirred for 2 hr. with 50 ml. of 3 *N* aqueous hydrochloric acid. The aqueous acid was separated, and after the usual washing and drying (Na_2SO_4) sequence, the residue obtained on evaporation of the ether was crystallized from petroleum ether (b.p. 60–75°). In this manner, there was obtained 1.54 g. (84%) of the alcohol (*7*), m.p. 64–66°, in two crops of 1.35 g. and 0.19 g. The analytical sample, obtained by one further crystallization from ether–petroleum ether (b.p. 60–75°), melted at 65–66°; infrared: λ_{max}^{film} 2.85 μ (O—H), 5.88 μ (> C=O).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.78; H, 9.93.

6-Keto-2-methylene-5,5,9-trimethyl-trans-decal-1α-ylacetaldehyde (*9*). According to the procedure of Watenabe[17] a solution of 800 mg. (3.78 mmoles) of the alcohol (*7*) and 150 mg. of mercuric acetate in 15 ml. of freshly distilled ethyl vinyl ether was stirred under reflux in a nitrogen atmosphere for 5 hr. and then quenched with excess solid potassium carbonate. After decantation, the solid was washed several times with ether and the combined ethereal solution evaporated on the steam bath in a stream of nitrogen. The oily residue was chromatographed on 40 g. of alumina (Merck), elution with 200 ml. of benzene affording 655 mg. (70%) of the vinyl ether (*8*) as a colorless, mobile liquid; infrared: λ_{max}^{film} 6.05 μ and 8.40 μ (O—CH=CH₂). The vinyl ether (*8*) [650 mg. (2.62 mmoles)] was sealed in a heavy-walled Pyrex tube under nitrogen and heated for 4 hr. in a boiling ethylene glycol bath. Chromatography of the pyrolysate on 50 g. of Florisil afforded 486 mg. [75%; 53% from the alcohol (*7*)] of the aldehyde (*9*), m.p. 77–79°, by elution with 5% ether–benzene. The analytical sample, obtained by crystallization from petroleum ether (b.p. 30–60°), had the same melting range; infrared: λ_{max}^{film} 3.20 μ, 6.08 μ, and 11.20 μ (> C=CH₂), 3.62 μ and 5.83 μ (—CHO), 5.89 μ (> C=O).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.32; H, 9.72.

6-Keto-2-methylene-5,5,9-trimethyl-trans-decal-1α-ylacetic acid (*10*). The aldehyde (*9*) [537 mg. (2.16 mmoles)] in 12 ml. of ethanol was oxidized according to the procedure of Robinson[16] with 4 ml. of a solution of 1.24 g. of silver nitrate in 13 ml. of water and 15 ml. of a solution of 1.24 g. of sodium hydroxide in 50 ml. of water. After the same work-up described above for the acid (*5*), there was obtained 480 mg. (85%) of the acid (*10*), m.p. 143–145°, after crystallization from ethyl acetate–petroleum ether (b.p. 60–75°). The analytical sample, obtained after one further crystallization from the same solvent pair, melted at 144–146°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.70; H, 9.15. Found: C, 72.75; H, 9.03.

Methyl 6β-acetoxy-2-methylene-5,5,9-trimethyl-trans-decal-1α-ylacetate (*11*). When the keto acid (*10*) [99 mg. (0.375 mmole)] was esterified with excess ethereal diazomethane and the ester crystallized from petroleum ether (b.p. 30–60°), 88 mg. (85%) of the corresponding ester was obtained. This material was reduced with 15 mg. (0.4 mmole) of sodium borohydride in 3 ml. of methanol containing 0.5 ml. of 0.1 *N* aqueous sodium hydroxide. After 1 hr. at 20° the reaction mixture was diluted with water, and the product isolated with ether in the usual manner. This crude hydroxy ester in 2 ml. of dry pyridine was treated with 0.1 ml. of acetic anhydride and allowed to stand at room temperature overnight. The solution was then diluted with ice and water and the precipitate isolated by ether extraction. After the usual washing and drying (Na_2SO_4) sequence, crystallization of the residue obtained on evaporation of the ether from petroleum ether (b.p. 60–75°) afforded 70 mg. [69%; 59% over-all from the keto acid (*10*)] of the acetoxy ester (*11*), m.p. 121–122°; infrared: $\lambda_{max}^{HCCl_3}$ 3.22 μ, 6.10 μ, and 11.20 μ (> C=CH₂), 5.79 μ (ester).

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.67; H, 9.33.

6β-Hydroxy-2-keto-5,5,9-trimethyl-trans-decal-1β-ylacetic acid (*12*). The procedure used is a modification of that described by Barton.[26] A solution of 156 mg. (0.48 mmole) of the acetoxy ester (*11*) in 25 ml. of dry methylene chloride was cooled in a Dry Ice–acetone bath and treated for 3 min. with a stream of ozonized oxygen that generated 0.1 mole of ozone per hour. After warming to −20°, 12.5 ml. of glacial acetic acid in 5 ml. of dry methylene chloride was added and then 5 g. of zinc dust was added with stirring over a 1.5-hour period. The reaction mixture was then filtered; the zinc washed with methylene chloride and the combined methylene chloride filtrates washed with 10% aqueous potassium bicarbonate and water and dried (Na_2SO_4). After filtration and evaporation of the methylene chloride, the residue was dissolved in 10.5 ml. of methanol and treated with 1.5 ml. of 40% aqueous potassium hydroxide solution. The reaction mixture was refluxed for 3 hr. in a nitrogen atmosphere, diluted with water, and washed with ether. The aqueous, basic solution was acidified with concd. hydrochloric acid and concentrated until potassium chloride began to separate. This saturated salt solution was extracted three times with 25-ml. portions of ether; the combined ethereal solution was dried (Na_2SO_4) and evaporated. The residue, on crystallization from acetone–petroleum ether (b.p. 30–60°), afforded 64 mg. (51%) of the acid (*12*), m.p. 186–187°. A mixture of this material and an authentic sample (m.p. 186–187°) kindly provided by Dr. Meisels melted at 186–188°. The infrared spectra of this acid (*12*) and the authentic sample were determined using a Beckman IR-7 spectrophotometer and were identical.

2-n-Butylthiomethylene-5,5,9-trimethyl-trans-decalone-1 (*15*). Following the procedure of Johnson and Posvic,[14] 23.7 g. (0.123 mole) of 5,5,9-trimethyl-*trans*-decalone-1 (*14*)[11] was hydroxymethylated in benzene solution using 27 g. (0.5 mole) of commercial sodium methoxide and 40 ml. (37 g., 0.5 mole) of purified ethyl formate. The crude hydroxymethylene derivative was not purified in this instance, but in another experiment an analytical sample, obtained after three crystallizations from petroleum ether (b.p. 30–60°) at −78°, melted at 40–41°.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.68; H, 9.96.

The crude hydroxymethylene ketone above was etherified according to the procedure of Ireland and Marshall[13] with 14.7 ml. (12.3 g., 0.137 mole) of *n*-butyl mercaptan in 300 ml. of benzene containing 50 mg. of *p*-toluenesulfonic acid. The *n*-butylthiomethylene ketone (*15*), m.p. 66–68°, (30.8 g., 86%) was obtained in two crops of 21.0 g. and 9.8 g. by crystallization from petroleum ether (b.p. 60–75°). Two further crystallizations from the same solvent afforded the analytical sample, m.p. 68–69°.

Anal. Calcd. for $C_{18}H_{30}OS$: C, 73.42; H, 10.27; S, 10.88. Found: C, 73.38; H, 10.17; S, 10.62.

5,5,9-Trimethyl-trans-Δ¹-octal-2-ylcarboxyaldehyde (*16*). A solution of 30.9 g. (0.105 mole) of the *n*-butylthiomethylene ketone (*15*) in 500 ml. of methanol was reduced with a solution of 5.0 g. of sodium borohydride in 50 ml. of 0.25 *N* aqueous sodium hydroxide. After the usual work-up, the crude product was steam distilled at 125–140° from a solution of 100 ml. of 10% aqueous sulfuric acid in 200 ml. of diethylene glycol. The aqueous distillate (5 l.) was extracted with ether and the ethereal solution washed with saturated salt solution, dried (Na_2SO_4), and evaporated. The crude aldehyde (*16*) was adsorbed on 450 g. of alumina (Merck) in petroleum ether (b.p. 30–60°). Elution with 4 l. of benzene afforded 22.0 g. (100%) of the aldehyde (*16*) as a colorless liquid. Attempted distillation of this aldehyde led to partial oxidization to the acid (*17*). The infrared spectrum (liquid film) showed bands at 5.92 μ (—CHO) and 6.10 μ (conj. C=C). The *semicarbazone* melted at 224–226° after one crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{25}ON_3$: C, 68.40; H, 9.56; N, 15.96. Found: C, 68.56; H, 9.36; N, 16.09.

The *acid* (*17*), obtained by oxidation with silver oxide according to the procedure of Robinson,[16] melted at 148–149.5° after two crystallizations from methanol.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.66; H, 9.97. Found: C, 75.65; H, 9.95.

2-Hydroxymethyl-5,5,9-trimethyl-trans-Δ¹-octalin (*18*). A solution of 6.0 g. (0.03 mole) of chromatographed aldehyde (*16*) in 100 ml. of methanol was reduced with a solution of 1.0 g. of sodium borohydride in 16 ml. of 0.25 *N* aqueous sodium hydroxide solution. After removal of the methanol at reduced pressure, the product was isolated by ether extraction in the usual manner. Distillation of the residue remaining after evaporation of the ether afforded 4.91 g. (81%) of the alcohol (*18*), b.p. 104° (0.4 mm.). The analytical sample was obtained by evaporative distillation at 100° and 0.05 mm.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.56; H, 11.50.

The 3,5-dinitrobenzoate, crystallized from methanol, melted at 110–111°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.83; H, 6.51; N, 6.96.

2-Methylene-5,5,9-trimethyl-trans-decal-1α-ylacetaldehyde. Following the same procedure described above for the preparation of the vinyl ether (*8*), 1.984 g. (91%) of the vinyl ether (*19*) was obtained by equilibration of 1.94 g. (9.3 mmoles) of the alcohol (*18*) with ethyl vinyl ether (25 ml.) in the presence of 250 mg. of mercuric acetate.

On pyrolysis as above 508 mg. of this vinyl ether afforded 462 mg. (91%) of chromatographed, crystalline aldehyde, m.p. 34–36°. The analytical sample, obtained after several crystallizations from petroleum ether (b.p. 30–60°) at −78°, melted at 37.5–38.5°.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.89; H, 11.21.

The *semicarbazone* melted at 199–200° after crystallization from ethanol.

Anal. Calcd. for $C_{17}H_{29}N_3O$: C, 70.05; H, 10.03; N, 14.43. Found: C, 70.13; H, 10.09; N, 14.52.

In practice this aldehyde was not isolated in a pure state, but the pyrolysate was oxidized directly to the acid (*13*) with silver oxide.[16]

2-Methylene-5,5,9-trimethyl-trans-decal-1α-ylacetic acid (*13*). A. *By oxidation of the aldehyde above.* When 1.78 g. (7.60 mmoles) of the crude aldehyde above was oxidized according to the procedure of Robinson,[16] there resulted 1.47 g. (77%) of the acid (*13*), m.p. 146–148°, after one crystallization from ethyl acetate–petroleum ether (b.p. 30–60°). The analytical sample, obtained after two further crystallizations from the same solvent pair, melted at 147–148°.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.67; H, 10.37.

B. By Wolff-Kishner reduction of the acid (*10*). Following the procedure of Huang-Minlon,[20] 107 mg. (0.405 mmole) of the acid (*10*) was reduced in 3 ml. of diethylene glycol with 0.5 ml. of hydrazine hydrate and 140 mg. of potassium hydroxide. After the usual work-up, crystallization of the acidic product from ethyl acetate–petroleum ether (b.p. 30–60°) afforded 92 mg. (92%) of the acid (*13*), m.p. 147–148° alone or on admixture with that prepared under A above.

2-Keto-5,5,9-trimethyl-trans-decal-1α-ylacetic acid (*20*). When 172 mg. (0.7 mmole) of the acid (*13*) was ozonized and reduced according to the procedure described above for the ester (*11*), there was obtained 138 mg. (80%) of the keto acid (*20*), m.p. 135–138°, after crystallization from ethyl acetate–petroleum ether (b.p. 30–60°). The analytical sample, obtained after another crystallization from the same solvent pair, melted at 136.5–138°.

(26) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.65.

The *methyl ester* (*21*) of this acid, obtained by treatment with diazomethane, melted at 71–72° after crystallization from petroleum ether (b.p. 30–60°) at −78°.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.23; H, 9.91.

Enol-lactone (*22*). Following the procedure of Woodward,[21] a solution of 138 mg. (0.55 mmole) of the keto acid (*20*) in 5 ml. of acetic anhydride was refluxed 1.5 hr. under nitrogen and then 26 mg. of sodium acetate was added. Reflux was continued for 2.5 hr. most of the acetic anhydride removed at reduced pressure, and the residue taken up in 1:1 benzene–ether. The organic solution was washed with 10% aqueous potassium bicarbonate, water, and saturated salt solution and dried (Na_2SO_4). The residue obtained after evaporation of the solvents at reduced pressure was chromatographed on 10 g. of Florisil. Elution with 200 ml. of 1% ether–benzene afforded 100 mg. (78%) of the enol-lactone (*22*), m.p. 90–92°. Crystallization from petroleum ether (b.p. 60–75°) afforded the analytical sample, m.p. 91.5–92.5°; infrared: $\lambda_{max}^{HCCl_3}$ 5.72 μ (>C=O), 8.60 μ (—C—O—C).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46. Found: C, 77.00; H, 9.54.

Methyl 2-keto-5,5,9-trimethyl-trans-decal-1β-ylacetate (*23*). To a stirred solution of 51 mg. (0.22 mmole) of the enol-lactone (*22*) in 2 ml. of dry methanol in a nitrogen atmosphere was added 3 ml. of a solution of 87 mg. (0.45 mg.-atom) of sodium in 25 ml. of dry methanol, and the mixture was refluxed for 2.5 hr. Most of the methanol was removed at reduced pressure, water was added, and the product isolated by ether extraction in the usual manner. The crystalline residue obtained after evaporation of the ether was chromatographed on 10 g. of Florisil. Elution with 200 ml. of 2% ether–benzene and crystallization from petroleum ether (b.p. 30–60°) at −78° afforded 38 mg. (66%) of the keto ester (*23*), m.p. 61–63°. Two further crystallizations from the same solvent afforded the analytical sample, m.p. 63–64°.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.17; H, 9.90.

A mixture of this ester, m.p. 63–64°, and the keto ester (*21*), m.p. 71–72°, softened at 35° and melted over the range 41–55°.

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Steroids. CLXXXI.[1] 11a-Aza- and 11a-Oxa-C-homo Steroidal Hormone Analogs

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The preparation of a number of steroids possessing either 11a-aza or 11a-oxa structures are described. Among these are compounds related to progesterone, prednisone, and certain androgens.

Recently the preparations of 11a-aza-C-homotigogenin and 11a-oxa-C-homotigogenin-11-one 3-acetate (11,12-secotigogenin-11-oic-12-ol 3-acetate (11→12) lactone) were reported.[3] This present paper now describes their conversion to a variety of hormone analogs.

Aside from these modifications other reports have appeared concerning the introduction of nitrogen and oxygen into various positions of the steroid molecule. Mazur,[4] for example, has described the preparation of several 12a-aza-C-homo steroids whereas Jacobs and Brownfield[5] have synthesized steroids containing nitrogen and oxygen in ring B. In addition to these previous reports and the references they contain, the preparation of several 9α-aza-C-homo steroids has also been achieved[6] by means of Beckmann rearrangements of 11-oximino steroids.

For the synthesis of the nitrogen analogs, 11a-aza-C-homotigogenin 3-acetate *N*-acetate[3] (I) was subjected to the usual side chain degradation sequence, with the exception that a 55-minute acetolysis period was employed.[7] The resulting Δ^{16}-pregnene derivative II was epoxidized with *t*-butyl hydroperoxide[8] to provide III which was then transformed to the bromohydrin IVa. In contrast to most 16β-bromo-17α-ols which readily undergo reductive debromination, the removal of bromine from IVa proved initially difficult. For

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