Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.66%; H, 9.53%; N, 6.96%. Found: C, 59.63%; H, 9.86%; N, 7.39%.

(−)-3-Morpholino-1,2-propanediol (XI).—(+)-3-Morpholino-1,2-*O*-isopropylidene-1,2-propanediol (63.2 g., 0.31 mole), 4060 ml. of water and concentrated sulfuric acid (16.5 ml., 30.4 g., 0.30 mole) were heated at reflux for 3 hr. then cooled. Barium hydroxide octahydrate (98 g., 031 mole) was added to the solution and the white precipitate filtered.

The filtrate was evaporated under vacuum then re-evaporated twice with 100 ml. of absolute ethanol to 51.5 g. of pale yellow oil.

This pale yellow oil was distilled under vacuum and a colorless liquid (39.3 g.) was collected, b.p. 124–127° at 1.1 mm.

A redistilled sample was used for the physical data, b.p. 120–121° at 0.9 mm., $[\alpha]^{26}D$ −19.4°, 10.04% in water.

Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.16%; H, 9.38%; N, 8.69%; Found: C, 52.07%; H, 9.50%; N, 8.68%.

(+)-3-Morpholino-1-*O*-(*p*-toluenesulfonyl)-1,2-propanediol (XII).—To (−)-3-morpholino-1,2-propanediol (19 g., 0.15 mole) dissolved in 60 ml. of dry pyridine was added *p*-toluenesulfonyl chloride (28 g., 0.15 mole) with ice-bath cooling. The reaction mixture was allowed to stand at room temperature for 2 days. Water (100 ml.) was added and the mixture was extracted with ether.

The ether extract was washed with water then dried and the ether was evaporated under vacuum. The crude residual solid was recrystallized twice from 2-propanol to recover 6.7 g. of white solid, m.p. 134–143°. Two recrystallizations from benzene–absolute ethanol elevated the melting point to 146–147°, $[\alpha]^{23}D$ +0.80°, 5% in 95% EtOH.

Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.31%; H, 6.71%; N, 4.44%; S, 10.17%. Found: C, 53.50%; H, 6.61%; N, 4.17%; S, 10.24%.

(−)-N-Glycidylmorpholine (XIII).—To (−)-3-morpholino-1,2-propanediol (47 g., 0.29 mole) dissolved in 100 ml. of dry pyridine was added, with cooling, *p*-toluenesulfonyl chloride (57 g., 0.30 mole). The reaction mixture was allowed to stand at room temperature 2 days.

Methanol (100 ml.) was added to the reaction mixture and, at 0°, added sodium (14.8 g., 0.64 g.-atom) dissolved in 370 ml. of methanol. After 14 hr. at 0–6°, the mixture was filtered and the filtrate was evaporated under vacuum. Carbon tetrachloride was added to the residue and the mixture was filtered. The carbon tetrachloride was distilled under vacuum and the residue was fractionated under vacuum. A colorless liquid (10.3 g.) was collected, b.p. 77–86° at 2.0–2.3 mm. Redistillation of an aliquot gave a colorless liquid, b.p. 65° at 1.8 mm., for determination of the physical data, $[\alpha]^{24}D$ −20.56°, 5.012% in water.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72%; H, 9.15%; N, 9.78%. Found: C, 58.86%; H, 9.01%; N, 9.70%.

(−)-3-(5-Nitrofurfurylideneamino)-5-morpholinomethyl-2-oxazolidinone (XVI).—To *N*-(−)-glycidylmorpholine, b.p. 71–75° at 2.1–2.2 mm., (2 g., 0.014 mole) was added 85% hydrazine hydrate (9 g., 0.15 mole) with ice-bath cooling. The mixture was kept at ice bath temperature an additional hour and allowed to stand at room temperature for 24 hr. The solution was heated to 50° for 0.5 hr. and the excess hydrazine and water were removed under vacuum.

Diethyl carbonate (5 g., 0.042 mole) and sodium methoxide (0.2 g., 3.7 mmoles) dissolved in 0.7 ml. of methanol were added to the residue (2.3 g.) and the mixture was heated at reflux 30 min.

The reaction mixture was cooled and 2 ml. of 2-propanol, 10 ml. of water, 5 *N* sulfuric acid to pH 2 and 5-nitro-2-furfural (3 g., 0.02 mole) dissolved in 10 ml. of 2-propanol were added. The mixture was heated on the steam bath 15 min., cooled, and filtered.

The filtrate was extracted with ether and the aqueous layer was neutralized with concentrated aqueous ammonia. The solid which precipitated was collected (1.5 g.), m.p. 208–209°C., $[\alpha]^{27}D$ −54.50°, 2% in 25% aqueous acetic acid.

After three recrystallizations an isopropyl alcohol-nitromethane mixture there was recovered 0.39 g. of solid, m.p. 208–209°. No change in the specific rotation was observed, $[\alpha]^{24}D$ −56.0°, 2% in 25% aqueous acetic acid, since the 1-1/2° difference in the specific rotation is within the experimental error of the determination.

Anal. Calcd. for $C_{13}H_{16}N_4O_6$: C, 48.15%; H, 4.97%; N, 17.28%. Found: C, 48.24%; H, 5.09%; N, 17.24%.

Acknowledgment.—The author gratefully acknowledges the invaluable services of Dr. Julian G. Michels, Messrs. Gordon B. Ginther and Grant Gustin, and associates of the Eaton Laboratories Physical and Analytical Section who obtained the elementary analyses and the ultraviolet and infrared curves. The author also wishes to thank Mr. Frank F. Ebetino and Dr. Edward Watson for the many helpful discussions during the course of this work.

An Approach to the Total Synthesis of Steroids[1a]

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The construction of 1-carbomethoxy-8β-methyl-$\Delta^{4(9)}$-tetrahydroindanone-5 (15) is described and its conversion to a tricyclic steroid intermediate was investigated.

Since the mythical barrier to the synthesis of the nonaromatic steroids was first breached independently by Robinson[2] and Woodward,[3] this once formidable obstacle has been overcome by numerous scientists with more or less finesse. In general, this effort has not only led to highly stereoselective and short syntheses of these complex molecules, but also to a much more thorough understanding of polycyclic systems and their construction.[4] While the former result may, in the final analysis, be quite temporal in character, the latter information transcends the immediate goal at hand and is of incalculable value to the science as a whole. It is with the hope that some small portion of the work we record here may fall into this latter category that prompts the description of yet another approach to the synthesis of the steroid nucleus.

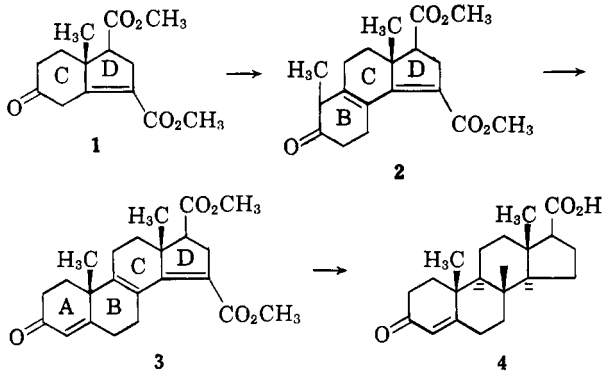
The plan that was envisaged for this work was the CD → B → A approach, whereby the keto ester **1** could be condensed with ethyl vinyl ketone to form ring B and the resulting tricyclic keto ester **2** with methyl vinyl ketone to add ring A and form the steroid nucleus **3**. By a sequence of hydrolysis, decarboxyla-

(1) (a) Taken from the Ph.D. dissertation of M. Chaykovsky, University of Michigan, 1961. (b) National Institutes of Health Predoctoral Research Fellow, 1959–1961.

(2) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(3) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

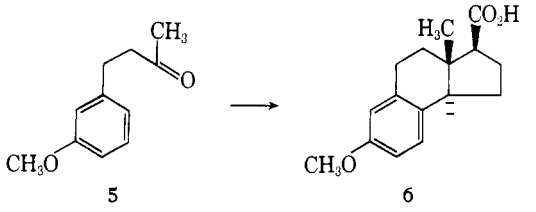
(4) W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen, and R. Pappo, *ibid.*, **84**, 2181 (1962); L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, and J. M. Constantin, *ibid.*, **74**, 4974 (1952).



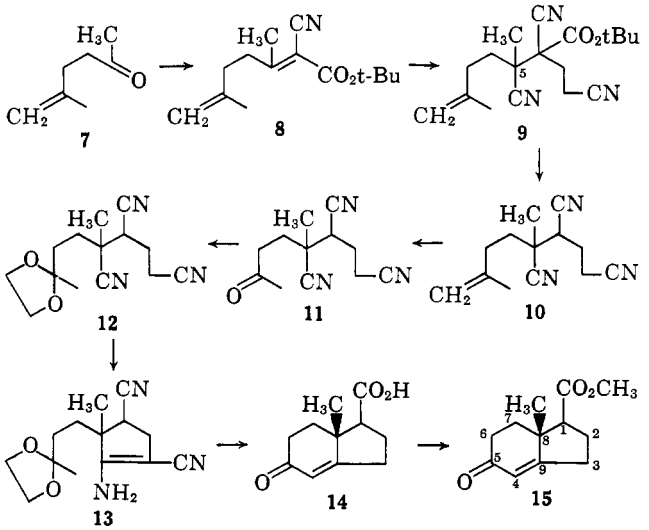
tion and reduction, it would then be possible to prepare the steroidal acid **4**.

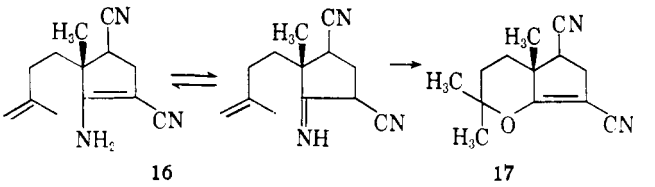
This scheme was considered to have two attractive characteristics: first, both of the keto esters **1** and **2** are vinylogous β-keto esters and hence the homoannulation reactions should not only proceed in good yield but also in the desired sense without the necessity of a blocking group; and second, the tetracyclic nucleus **3** possesses only two of the potential five asymmetric centers of the steroid and thus affords the opportunity of introducing the remaining three centers under controlled conditions. With this over-all plan at hand, we embarked on a study of methods for the synthesis of the keto ester **1**.

The construction of ring D followed the same reaction sequence recently reported by Banerjee, Johnson, and co-workers[5] for the conversion of *m*-methoxybenzylacetone (**5**) to the tricyclic acid **6**.



However, rather than employing the benzylacetone **5**, we used methallylacetone **7**, prepared by hydrolysis and decarboxylation of the readily available ethyl methallylacetoacetate.[6] Condensation of ketone **7** with *t*-butyl cyanoacetate[7] afforded a 75% yield of the alkylidene cyanoacetate **8**. Addition of the elements of hydrogen cyanide generated a dicyanoester, which was not purified but treated directly with acrylonitrile in the presence of Triton B. In this manner we were able to isolate an 81% over-all yield of the tricyano ester **9** in two diastereoisomeric modifications. The production of two diastereomers at this point was expected, and inasmuch as only one of the asymmetric centers present was not epimerizable—*i.e.*, the quaternary carbon at C-5—the production of a mixture of the two at this stage had no importance to the over-all scheme. While the mixture was separated by fractional crystallization from ethanol for the purposes of identification, the synthesis was carried further by pyrolysis of the mixture at 165°, whereby isobutylene and carbon dioxide were lost with the production of a quantitative yield of the trinitrile **10** as a viscous, yellow oil. Treatment of the nitrile **10** with potassium *t*-butoxide in benzene solution afforded a 67% yield of the expected cyclic dinitrile **16** as a mixture of the ketimine and eneamine forms, as judged from the infrared spectrums.





Unfortunately, this effort went for naught when it was found that the dinitrile **16** could not be hydrolyzed to the corresponding β-ketonitrile or derivative without affecting the terminal methylene grouping. Thus on treatment of mixture **16** with aqueous ethanolic hydrochloric acid there resulted a solid for which structure **17** is suggested on the basis of the spectral properties and analytical data obtained.

By way of circumventing this difficulty, the methylene grouping was ozonized and the resulting ketotrinitrile **11** converted to the ketal **12** in 69% over-all yield. Again a mixture of diastereoisomeric ketals was encountered, from which one isomer was purified for identification purposes; the mixture was used in further experiments. When the ketal trinitrile **12** was cyclized with potassium *t*-butoxide in benzene solution, a 75–81% yield resulted of the corresponding cyclic dinitrile **13** as a mixture of eneamine and ketimine tautomers.

While several attempts were made to hydrolyze and cyclize the dinitrile **13** to obtain the desired diester **1**, all went to no avail. The dinitrile **13** could be hydrolyzed to what appeared to be a diketodinitrile, but after base treatment, the same material was re-isolated. Cyclization could, however, be effected by heating a solution of the dinitrile in a mixture of sulfuric and acetic acids. The solid acid **14** obtained in this manner was difficult to purify but on esterification by the method of Clinton and Laskowski,[8] there resulted a 59% over-all of the keto ester (**15**). Thus, to effect cyclization of the dinitrile **13**, we had to resort to such vigorous acid treatment that hydrolysis and decarbox-

(5) D. K. Banerjee, H. N. Khastigir, J. Dutta, E. J. Jacob, W. S. Johnson, C. F. Allen, B. K. Bhattacharyya, J. C. Collins, Jr., A. L. McClaskey, W. T. Tsatsos, W. A. Vredinburgh, and K. L. Williamson, *Tetrahedron Letters*, 76 (1961).

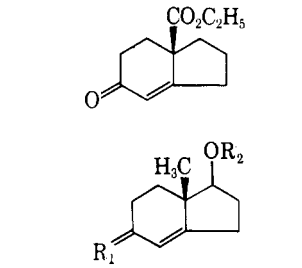
(6) G. R. Clemo and B. K. Davison, *J. Chem. Soc.*, 447 (1951).

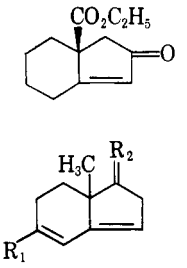
(7) R. E. Ireland and M. Chaykovsky, *Org. Syn.*, **41**, 5 (1961).

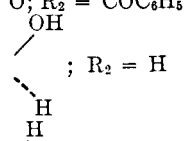
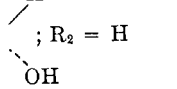
(8) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

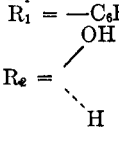
ylation of the sensitive β-ketonitrile was unavoidable. While a dicyclic analog of the desired diester **1** was obtained, the absence of the C-3 carbomethoxyl grouping necessitated a change in the proposed plan for further synthesis. Now we could not rely on activation of the 4-position by the vinylogous β-keto ester system to orient attachment of ring B. Therefore, in spite of the relative ease with which the keto ester **15** (20% over-all yield) could be obtained, the synthesis from this point lacked much of the luster of the original scheme.

The first obstacle to be overcome in considering the transformation of the keto ester **15** further along the path to the steroid nucleus was the establishment of a *trans* ring fusion. While this result can readily be accomplished by lithium-ammonia reduction of an octalone system such as 9-methyl-Δ^4-octalone-3,[9] the stability relationship between the *cis*- and *trans*-hydrindane skeleton[10] would be so as to favor the undesired *cis* isomer under similar reducing conditions. The geometry of cyclohexenone ring of the keto ester **15** should be quite similar to that of the corresponding 9-methyl-Δ^4-octalone-3 and hence catalytic hydrogenation of the double bond should give the same result—*i.e.*, formation of the undesired *cis*-fused system. In fact, Dauben[11] found that both the unsaturated esters **18** and **19** afforded *cis*-fused products on catalytic reduction and was prompted to conclude that "neither the position of the unsaturation nor the type of angular substituent can be utilized to control the steric course of catalytic hydrogenation." Boyce and Whitehurst[12] also drew the same conclusion when they found that hydrogenation of a variety of indane derivatives **20** and **21** led exclusively to the *cis*-fused ring system. The latter work more closely parallels the situation at hand, and yet we had little choice but to attempt similar catalytic hydrogenations.



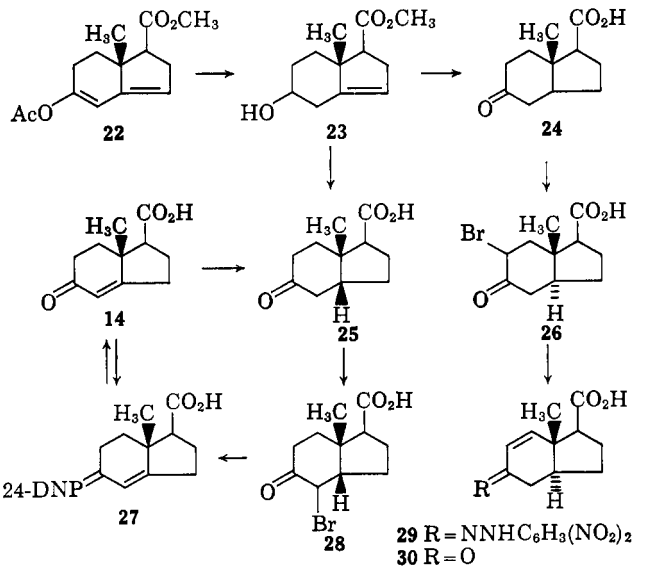


20a. $R_1 = O; R_2 = H$
b. $R_1 = O; R_2 = COC_6H_5$
c. $R_1 =$  $; R_2 = H$
d. $R_1 =$  $; R_2 = H$

21a. $R_1 = -OC_2H_6; R_2 = O$
b. $R_1 = -C_6H_4-OCH_3(p);$ 

The above results of others showed that at least one method of controlling the stereochemistry of the catalytic hydrogenation had to be investigated—namely, the saturation of an isolated 3(9)-double bond. By way of obtaining such a compound, we converted the keto ester **15** into its enol-acetate **22** in 87% yield by treatment with acetic anhydride and acetyl chloride. The presence of a maximum at 241 mμ (log ε = 4.2) in the ultraviolet spectrum of this acetate indicated that the desired heteroannular diene system[13] had been formed. Reduction[14] of the enol-acetate **22** with sodium borohydride in aqueous methanol afforded the unsaturated ester **23** in 60% yield after distillation; however, the crude material, obtained in 88% yield, was sufficiently pure for further use in the synthesis. That this material was a viscous liquid probably resulted from the presence of stereoisomers about both the C-1 carbomethoxyl grouping and the C-5 hydroxyl function; no attempt was made to separate this mixture into its pure components. When the ester **23** was reduced over 10% palladium on carbon in acetic acid, hydrolyzed with methanolic potassium hydroxide, and finally oxidized, there resulted a mixture of saturated keto acids. Fractional crystallization of this mixture from benzene–petroleum ether afforded a 32% yield of the *trans*- acid **24**, m.p. 148–160°, and an 18% yield of the *cis*- acid **25**, m.p. 95–105°. Both acids had wide melting point ranges, probably due again to isomerization about the C-1 carboxyl grouping, and while repeated recrystallization of the *trans*- acid **24** brought its melting point to 166–166.5°, the *cis*- acid still retained the same broad range. It will be shown in the sequel that while this isomerization about the C-1 carboxyl grouping was annoying, it did not hinder the synthetic effort.

The presence of two distinct saturated acids in this reduction mixture was partially satisfying, for one must be the *trans*- acid **24**, but, of course, there was no way of telling which of the acids this was at the outset. We employed two methods to effect this identification. First, catalytic hydrogenation of the α,β-unsaturated keto acid **14** under the same conditions used above led to an 88% yield of a saturated acid, m.p. 91–109°, that was identical to the lower melting acid obtained above. From the precedence[11,12] cited above, we concluded, then, that the lower melting acid obtained from the mixture of saturated acids was indeed that with the *cis*-ring fusion **25**.



29 $R = NNHC_6H_3(NO_2)_2$
30 $R = O$

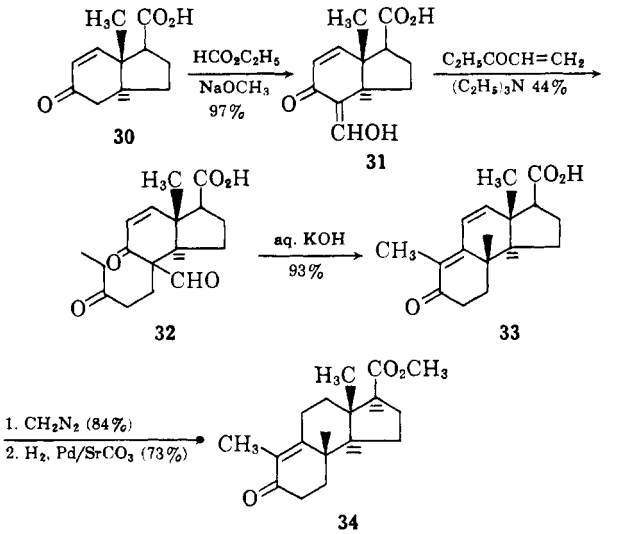
(9) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960).
(10) The evidence is well reviewed by L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 212–216.
(11) W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961).
(12) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 4547 (1960).
(13) L. Dorfman *Chem. Rev.*, **53**, 47 (1953).
(14) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, **73**, 4463 (1951).

The second method was even more definitive and served also in the direct synthetic scheme (p. 750). When the *cis*-(lower melting)-keto acid **25** was treated with one equivalent of bromine in chloroform solution, there resulted the oily bromo derivative **28** which was not purified further but converted directly to its 2,4-dinitrophenylhydrazone by the procedure of Mattox and Kendall.[15] In this fashion there was formed a 97% over-all crude yield of the derivative **27** which was identical with that prepared from the unsaturated keto acid **14** directly. Finally, cleavage of this 2,4-dinitrophenylhydrazone **27** by the method of Demaecker and Martin[16] resulted in a 62% yield of the unsaturated keto acid **14** itself. This result is similar to the behavior of the A/B-*cis*-fused steroids which lead to Δ^4-3-keto steroids on similar treatment, and it is reasonable to argue that these experiments corroborate the *cis*-fusion of the lowering melting keto acid **25**, which brominates preferentially in the 4-position and thus regenerates the starting unsaturated keto acid **14**.

Reinforcement for this view came when it was found that the bromoketo acid **26**, obtained as a crystalline solid in 91% yield by similar treatment of the *trans* (higher melting) keto acid **24**, was converted to a new 2,4-dinitrophenylhydrazone **29** in 96% yield on heating with 2,4-dinitrophenylhydrazine in acetic acid. Cleavage of the hydrazone derivative **29** by the Demaecker–Martin procedure[16] then afforded an 89% yield of the new unsaturated keto acid **30**, the ultraviolet spectrum of which was in complete accord[13] with the structure proposed [λ_{max}^{alc} 228 mμ (ϵ 9800)]. These results closely parallel the behavior of the A/B-*trans*-3-keto steroids which are brominated in the 2-position and ultimately afford a Δ^1-3-keto steroid by the procedures employed here. Since both of the saturated keto acids prepared here closely parallel their corresponding steroidal counterparts, we felt quite confident of the structural assignments made above. In this connection it is interesting to note the reported[17] lack of such a correspondence between the behavior of the *cis*- and *trans*-9-methyl-3-decalones on bromination, even though the formal resemblance is even greater.

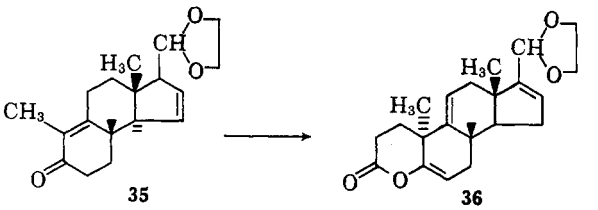
The formation of the 6-bromoketo acid **26** demonstrates the next obstacle to be overcome, for it means that the 5-ketone function in the *trans*-keto acid **24** enolizes preferentially toward the 6-position. This result means that in order to add the rudiments of ring B to this acid, the 6-position must be blocked if we are to realize the desired angular relationship of the three B, C, and D rings.

Therefore, the bromination–dehydrobromination sequence served not only to differentiate the two keto acids but also to introduce the necessary "blocking group" into the *trans*-keto acid **24**. Available in 78% over-all yield from the *trans*-keto acid **24** in three steps, the unsaturated keto acid **30** was admirably suited for the construction of ring B, for the ketone can only enolize to the desired 4-position. A similar system was employed by Woodward and his collaborators[3] in their steroid synthesis referred to earlier. By employing the same procedures as described by these workers, we were able to construct the tricyclic ester **34** in 25% over-all yield as shown below and found it to be identical with that prepared previously in connection with the Harvard group's synthesis.[18] The correlation firmly establishes the *trans*-character of the hydrindane ring fusion, as the Woodward synthesis has been successfully related to the natural occurring steroids.



30 **31** **32** **33** **34**

While at first sight it might seem that the independent construction of the ester **34** establishes another route to the non-aromatic steroids by employing the Woodward method[3] for the addition of ring A, there is reason to believe that this analogy might not be valid. First of all, Woodward's synthesis was carried out on a phenanthrene derivative and led to a mixture of C-10-epimers.[19] Secondly, an even more closely related analog of the ester **34** has been studied in the Monsanto laboratories[20] where it was found that the acetal **35** led *solely* to the 10-*epi*-enol-lactone (**36**)[19] *via* a similar cyanoethylation sequence to that used in Woodward's synthesis. Therefore, it would not be unreasonable to expect that application of this method to the ester **34** would lead again to a steroid that was epimeric with the natural series at C-10.[19]



35 **36**

Barkley,[20] however, developed a very satisfactory alternative to this cyanoethylation scheme whereby the sequence of the addition of the C-10 substituents[19] were reversed, and the methyl group introduced last. In this manner they were able to convert the ketone **37** stereoselectively to the desired enol-lactone **39** through the acetal **38** by substituting methyl 5-exo-6-heptanoate for the ethyl vinyl ketone used in the earlier work.

Since we have now related our dicyclic keto acid **24** to the *trans*-series by the above correlation with the suc-

(15) V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948); **72**, 2290 (1952).

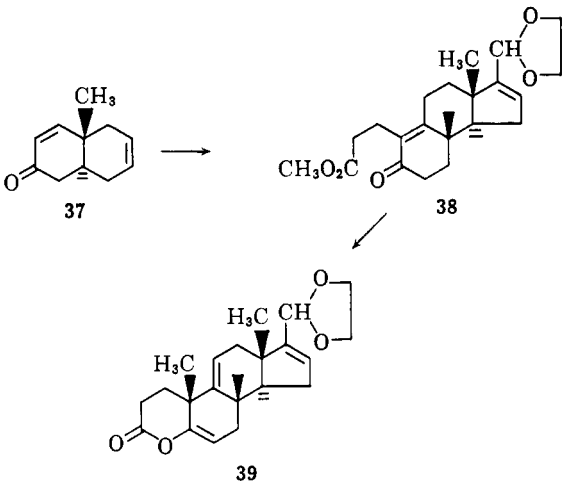
(16) J. Demaecker and R. H. Martin, *Nature*, **173**, 266 (1954).

(17) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956); **22**, 291 (1957).

(18) The authors express their deep appreciation to Professor R. B. Woodward for making available a generous supply of the acid corresponding to the ester **34** and from which this ester was readily obtained.

(19) Steroid numbering is used here.

(20) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).



cessful Woodward synthesis,[3] the obvious solution to the completion of this approach is then the substitution of the Barkley procedure for Woodward's route whereby we could expect to add rings A and B stereoselectively to our intermediate. However, in view of the close similarity between the two approaches at this stage and the obvious superiority of the Harvard–Monsanto approach to the problem, there seemed to be little to be gained by such a *tour de force* and no further efforts in this direction are planned.

Experimental[21]

***t*-Butyl (1-Methallylisopropylidene)cyanoacetate (8).**—A solution of 353 g. (3.15 moles) of methallylacetone (**7**),[6] 324 g. (3.0 moles) of *t*-butyl cyanoacetate,[7] 36 g. (0.6 mole) of glacial acetic acid, and 23.1 g. (0.3 mole) of ammonium acetate in 1200 ml. of benzene was heated under reflux for 24 hr. with a Dean–Stark water separator to remove the water produced. After cooling the benzene solution was washed successively with water, 10% aqueous sodium carbonate, water, and dried (Na_2SO_4). Removal of the benzene at reduced pressure and then distillation of the residue afforded 530 g. (75%), b.p. 115°–117° (0.8 mm.), of the adduct **8**.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.28; H, 8.99; N, 5.96.

4-Carbo-*t*-butoxy-4,5-dicyano-5,8-dimethyl-8-nonenonitrile (9).—A solution of 390 g. (1.66 moles) of the cyano ester **8** in 1200 ml. of ethyl alcohol was cooled to 0° and treated with a solution of 216 g. (3.32 moles) of potassium cyanide in 970 ml. of water with stirring and cooling such that the temperature of the reaction mixture remained between 0–5°. After stirring for an additional 30 min. following completion of the cyanide addition, a 1:1 aqueous hydrochloric acid solution (1.85 moles) was added while maintaining the temperature between 0–5°. An oil separated, and the whole was stirred for an additional 30 min. at 0°. The reaction mixture was made acidic by another addition of 1:1 aqueous hydrochloric acid solution (1.85 moles) and the oil that separated isolated by chloroform extraction. Removal of the chloroform at reduced pressure left a yellow oil which was not further purified but used directly in the following cyanoethylation.

A solution of the above dicyano ester in 1450 ml. of benzene containing 177 g. (3.34 moles) of acrylonitrile and 6 ml. of 38% aqueous Triton B was allowed to stand at room temperature, with occasional shaking, for 24 hr. Another 4 ml. of Triton B solution was added, and the mixture allowed to stand for an additional 24 hr. After the reaction mixture was washed with water and dried over anhydrous sodium carbonate, removal of the solvent left a tan, solid residue which was combined with the product from two other runs of equal size, and the whole crystallized from 3 l. of ethyl alcohol. The first crop amounted to 880 g. and melted at 118–123°. Two further crystallizations of a small sample from the same solvent afforded the analytical sample of isomer A of the tricyano ester (**9**) as soft, long white needles, m.p. 128–130°.

Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.65; H, 8.03; N, 13.35.

Concentration of the mother liquors from the first crop to 1300 ml., and cooling, afforded a second crop of crystals which amounted to 390 g., m.p. 62–65°. The analytical sample of isomer B of the tricyano ester (**9**) obtained after two further crystallizations from the same solvent, melted at 66–69°.

Anal. Found: C, 68.39; H, 7.81; N, 13.44.

The total yield of solid product was thus 1270 g. (81%). When the mother liquors from the second crop were evaporated at reduced pressure, 239 g. of a red oil remained. Pyrolysis and distillation of this oil as described in the following experiment afforded 73 g. of the trinitrile **10**, b.p. 174–182° (0.4 mm.). This represents an additional 7% yield and raises the over-all yield of the cyanoethylation experiment to 88%.

4,5-Dicyano-5,8-dimethyl-8-nonenonitrile (10).—A 500-ml. round bottom flask, charged with 76 g. (0.24 mole) of the tricyano ester **9**, m.p. 119–123° (isomer A), was connected to the vacuum pump through an air condenser and heated in an oil bath at 165° under reduced pressure. The pressure, initially at 0.5 mm., rose as the pyrolysis proceeded to liberate carbon dioxide and isobutylene, and then fell to its original value when the reaction was finished (about 45 min.). The yield of the viscous, yellow trinitrile **10** was quantitative and the product was sufficiently pure for use in succeeding steps. The same results were obtained when isomer B or a mixture of the two isomers was used. The analytical sample, obtained by distillation of this material, boiled at 164–165° (0.3 mm).

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.45; H, 7.86; N, 19.65.

Cyclization of the Trinitrile (10).—To a suspension of potassium *t*-butoxide (from 25.4 g. (0.65 g.-atom) of potassium) in approximately 1 l. of benzene contained in a nitrogen atmosphere was added a solution of 45 g. (0.209 mole) of the trinitrile **10** in 125 ml. of benzene, and the reaction mixture stirred at room temperature for 18 hr. After cooling and acidifying the reaction mixture with aqueous acetic acid, the product was isolated in the usual manner by ether extraction. Crystallization of the solid residue, obtained after removal of the ether, from ethyl alcohol afforded 29.7 g. (67%) of the cyclized dinitrile mixture **16** in two crops of 14.6 g., m.p. 115–118°, and 15.1 g., m.p. 96–106°. Both crops were a mixture of immio and eneamine tautomers as shown by their infrared spectra, and also diastereoisomeric forms were probably present as well. The analytical sample, obtained by three further crystallizations of a sample from the first crop, melted at 119.5–120°.

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.38; H, 7.74; N, 19.62.

Infrared: $\nu_{max}^{Nujol\ mull}$ 3240 cm.$^{-1}$, 3340 cm.$^{-1}$ and 3400 cm.$^{-1}$ (N—H); 2240 cm.$^{-1}$ (—CN); 2200 cm.$^{-1}$ (conj. —CN); 1665 cm.$^{-1}$ (> C=NH); 1610 cm.$^{-1}$ (conj. > C=C <); 900 cm.$^{-1}$ (> C=CH_2).

Hydrolysis of the Dinitrile (16).—A solution of 1.0 g. (4.6 mmole) of the dinitrile **16** in 10 ml. of ethanol containing 3 ml. of water and 3 ml. of concentrated hydrochloric acid was heated under reflux for 90 min. Crystallization took place on cooling, and collection of the precipitate afforded 750 mg. (75%) of a solid, m.p. 150–153°. The analytical sample, obtained after two further crystallizations from alcohol–water, melted at 153.5–156.5°. While the structure of this material is not known with certainty, formula **17** is suggested on the basis of analytical and spectral data.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.20; H, 7.51; N, 12.83.

Infrared: $\nu_{max}^{Nujol\ mull}$ 2240 cm.$^{-1}$ (—CN); 2220 (conj. —CN); and 1635 cm.$^{-1}$ (conj. > C=C <). There were no bands between 1800 cm.$^{-1}$ and 1650 cm.$^{-1}$.

4,5-Dicyano-8,8-ethylenedioxy-5-methylnonanonitrile (12).—The trinitrile **10** was ozonized at 0° in 50 g. (0.232 mole) batches in 100 ml. of acetic acid and 100 ml. of ethyl acetate and the ozonide decomposed after removal of the ethyl acetate at reduced pressure by heating the acetic acid solution with 200 ml. of water. The ketone was isolated in the usual manner by chloroform ex-

(21) Melting points were taken on a Kofler Hot Stage and are corrected for stem exposure. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The term "petroleum ether" refers to that fraction with a boiling range of 40–60° unless otherwise specified. Where infrared spectral bands are recorded in reciprocal centimeters (cm.$^{-1}$), the spectra were taken on a Perkin–Elmer Model 21 spectrophotometer, and where they are reported in microns (μ), the spectra were taken on a Perkin–Elmer Infracord. Ultraviolet spectra were taken on a Cary, Model 11, recording spectrophotometer.

traction and the crude product from four such runs combined. A solution of the crude ketone **11** in 1250 ml. of benzene containing 115.2 g. (1.86 moles) of ethylene glycol and 4.0 g. of *p*-toluenesulfonic acid monohydrate was heated under reflux with a Dean–Stark water separator for 20 hr. After the usual work-up, evaporation of the benzene at reduced pressure left a yellow oil which afforded 168 g. (69%) of the ketal (**12**), m.p. 60–86°, by crystallization from alcohol. Crystallization of a sample of this material from benzene–alcohol four times afforded the analytical sample of one of the diastereoisomeric ketals (**12**), m.p. 101–103.5°. No attempt was made to separate the other diastereomer.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.28; H, 7.39; N, 16.11.

Cyclization of the Tricyanoketal 12.—In the same fashion as described above for the trinitrile (**10**), 119 g. (0.456 mole) of the diastereoisomeric mixture of the tricyanoketal **11** was cyclized by treatment with potassium *t*-butoxide [from 57.1 g. (1.46 g.-atoms) of potassium] in 2.5 l. of benzene. The solid residue obtained after work-up and evaporation of the solvent was crystallized from 500 ml. of alcohol and afforded a first crop of cream colored crystals that amounted to 81 g., m.p. 142–145° of isomer A of the ketal **13**. The analytical sample, obtained after two further crystallizations from the same solvent, melted at 146–147.5°.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.45; H, 7.34; N, 16.13.

On concentration of the mother liquors from the first crop, there was obtained a second crop of crystalline material that amounted to 13.4 g., m.p. 127–133°, of isomer B of the ketal **13**. Thus the total yield of both diastereoisomers was 94.4 g. (79%). In other runs this total yield varied between 75–81%. The analytical sample of isomer B of the ketal **13** obtained after two further crystallizations from alcohol, melted at 137–138°.

Anal. Found: C, 64.47; H, 7.39; N, 16.28.

The infrared spectra of the two isomers showed slight differences in the 1500–700-cm.$^{-1}$ region but both showed bands characteristic of a tautomeric mixture of the eneamine and ketimine forms of the β-iminonitrile system: $\nu_{max}^{Nujol\ mull}$ 3240 cm.$^{-1}$, 3340 cm.$^{-1}$ and 3400 cm.$^{-1}$ (N—H); 2240 cm.$^{-1}$ (—CN); 2200 cm.$^{-1}$ (conj. —CN); 1670 cm.$^{-1}$ (> C=NH); and 1610 cm.$^{-1}$ (conj. > C=C<).

1-Carbomethoxy-8-methyl-$\Delta^{4(9)}$-tetrahydroindanone-5 (15).—A solution of 50 g. (0.191 mole) of the ketal **13** (either isomer could be used with identical results) in 320 ml. of glacial acetic acid containing 160 ml. of water and 80 ml. of concentrated sulfuric acid was heated under reflux in a nitrogen atmosphere for 20 hr. The cooled solution was poured into 800 ml. of cold water, and the product isolated by chloroform extraction in the usual manner. The pasty, tan, semisolid residue obtained after evaporation of the solvent was dissolved in a mixture of 150 ml. of ethylene dichloride, 32 g. (1.0 mole) of methanol, and 1 ml. of concentrated sulfuric acid and the whole heated under reflux in a nitrogen atmosphere for 18 hr. The cooled solution was washed with water, 5% aqueous sodium bicarbonate, water, and then dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration and evaporation of the solvent at reduced pressure, distillation of the residue afforded 23.5 g. (59%) of the keto ester **15**, b.p. 110–112° (0.1 mm). Despite repeated attempts, this material could not be obtained pure enough to afford satisfactory analytical values. However, both of the derivatives reported below gave acceptable analytical results.

Infrared: ν_{max}^{film} 1730 cm.$^{-1}$ (ester > C=O); 1675 cm.$^{-1}$ (unsaturated > C=O).

Ultraviolet: λ_{max}^{alc} 237 mμ (ε 12500).

The 2,4-dinitrophenylhydrazone, prepared by the method of Shriner, Fuson, and Curtin[22] and crystallized twice from ethyl acetate–ethanol, melted at 209–211°.

Anal. Calcd. for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.84; H, 5.34; N, 14.45.

The **semicarbazone**, prepared by the procedure of Fieser[23] and crystallized twice from alcohol, melted at 210–213° dec. (introduced at 205°).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.73; H, 7.04; N, 15.89.

On one occasion, an attempt was made to purify the **acid 14** prior to esterification by trituration in petroleum ether and then ether. However, the solid material obtained, m.p. 170–190°, could not be induced to crystallize from several solvents. An alcoholic solution of this solid material showed a maximum at 237 mμ (ε 12500) in the ultraviolet region and afforded the following derivatives.

The **2,4-dinitrophenylhydrazone (27)**, obtained by the method of Shriner, Fuson, and Curtin[22] and crystallized twice from ethyl acetate: ethanol, melted at 199–200°.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.66; H, 4.78; N, 15.01.

The **semicarbazone**, prepared by the method of Fieser[23] and crystallized several times from ethanol, carbonized between 230–240° (introduced at 225°), but did not show a sharp melting point.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.13; H, 6.73; N, 16.60.

5-Acetoxy-1-carbomethoxy-8-methyl-$\Delta^{3(9);4}$-dihydroindane (22).—A solution of 49 g. (0.236 mole) of the bicyclic keto ester **15** in 160 ml. of acetic anhydride and 160 ml. of acetyl chloride was heated under reflux in a nitrogen atmosphere for 6 hr. After removal of excess reagents at reduced pressure, distillation of the residue afforded 51 g. (87%) of colorless enol acetate (**22**), b.p. 102–106° (0.03 mm); $n^{20}D$ 1.5050. This compound was quite sensitive to hydrolysis by atmospheric moisture, and no satisfactory analytical data could be obtained.

Infrared: λ_{max}^{film} 5.65 μ (vinyl ester > C=O); 5.75 (ester > C=O); 6.02 μ and 6.18 μ (> C=C <).

Ultraviolet: λ_{max}^{alc} 241 mμ (log ε 4.2).

1-Carbomethoxy-5-hydroxy-8-methyl-$\Delta^{3(9)}$-tetrahydroindane (23).—Over a period of 30 min. a solution of 31 g. (0.82 mole) of sodium borohydride in 110 ml. of water was added to a cooled, stirred solution of 51 g. (0.204 mole) of the enol acetate **22** in 400 ml. of methanol. After stirring for 16 hr., the reaction mixture was refluxed for 20 min., most of the methanol removed at reduced pressure, and the aqueous residue diluted with 280 ml. of water. After the customary ethereal work-up and removal of the ether at reduced pressure, there remained 37.7 g. (88%) of the crude alcohol **23**, which was used directly in the next experiment without further purification. In other runs, the pure alcohol **23** was isolated as a viscous, colorless liquid, b.p. 105–110° (0.03 mm.) in yields of 55–60%. The analytical sample was obtained by evaporative distillation of a specimen at 110° (bath temp.) 0.03 mm.).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.68; H, 8.72.

Hydrolysis of the ester **23** was effected in 21% yield (the remainder was an oily α lactone probably formed on acidification of the hydrolysis mixture) when it was heated under reflux for 5 hr. with 20% methanolic potassium hydroxide. The analytical sample of the hydroxy acid, obtained after four crystallizations from ethylene dichloride, melted at 181–182.5°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.19. Found: C, 67.42; H, 8.15.

1-Carboxy-8β-methyl-*trans*-hexahydroindanone-5 (24) and 1-Carboxy-8β-methyl-*cis*-hexahydroindanone-5 (25).—A solution of 9.9 g. (0.0471 mole) of the hydroxy ester **23** in 50 ml. of glacial acetic acid in which was suspended 1.0 g. of 10% palladium on carbon was shaken in a hydrogen atmosphere for 3 hr. The residue, obtained after removal of the catalyst by filtration and evaporation of the solvent at reduced pressure, was treated with 50 ml. of 20% methanolic potassium hydroxide, and the mixture heated under reflux in a nitrogen atmosphere for 6 hr. Most of the methanol was removed at reduced pressure, the residue diluted with 50 ml. of water and extracted once with ether. The aqueous layer was cooled in an ice bath, acidified to congo red with concentrated hydrochloric acid, and the precipitated acid isolated by chloroform extraction in the usual manner. The resulting hydroxy acid (a viscous yellow oil) was dissolved in 40 ml. of acetone, cooled to 5° in an ice bath, and titrated with Jones reagent[24] until a permanent red-brown coloration had been imparted to the solution (approximately 12 ml. of the reagent was required). The reaction was diluted with 60 ml. of cold water, and the keto acid mixture isolated by chloroform extraction. After removal of the chloroform at reduced pressure and crystallization of the

(22) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, New York, N. Y., 1956, p. 219.

(23) L. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 85.

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

residual, yellow oil from 15 ml. of benzene, there resulted 2.9 g. (32%) of the *trans* isomer **24**, m.p. 148–160°. Evaporation of the benzene from the filtrates left an oil which on crystallization from 12 ml. of diisopropyl ether afforded 1.7 g. (18%) of the *cis*-isomer (25), m.p. 90–110°. The oil (2.5 g.) obtained on evaporation of the diisopropyl ether from these filtrates resisted further attempts at crystallization.

The analytical sample of the *trans* isomer **24**, obtained after two further crystallizations from benzene, melted at 166–166.5°, while that of the *cis* isomer **25**, obtained after two further crystallizations from benzene–petroleum ether (60–75°), melted at 95–105°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.19. Found: *trans:* C, 67.24; H, 8.15. *cis*: C, 67.54; H, 8.17.

The same *cis*-keto acid **25**, m.p. 91–104° was obtained in 88% yield when 2.0 g. (0.0103 mole) of the crude, unsaturated keto-acid (14), m.p. 170–190°, was reduced over 0.3 g. of 10% palladium on carbon in 60 ml. of glacial acetic acid in the same manner as described above. After two crystallizations of a sample of this material from diisopropyl ether, the melting points was raised to 98–110°, and the mixture melting point of this material and that prepared above (m.p. 95–105°) was 95–110°.

Bromination and Dehydrobromination of 1-Carboxy-8β-methyl-*cis*-hexahydroindanone-5 (25).—Over a 15-min. period a solution of 1.73 g. (0.0108 mole) of bromine in 8 ml. of chloroform was added to a cold, stirred solution of 2.11 g. (0.0108 mole) of the *cis*-keto acid **25** (m.p. 95–105°) in 15 ml. of chloroform. After standing at room temperature for 40 min., evaporation of the chloroform at reduced pressure left a greenish yellow oil which could not be induced to crystallize.

To a solution of the crude bromo ketone **28** in 20 ml. of glacial acetic acid was added 2.36 g. (0.0119 mole) of 2,4-dinitrophenylhydrazine, and the mixture was warmed on the steam bath for 10 min. and then allowed to stand at room temperature for 2 hr. The reaction mixture was poured into 60 ml. of water, cooled in the refrigerator for 2 hr., filtered, and air dried. In this manner there was obtained 3.9 g. (97%) of crude 2,4-dinitrophenylhydrazone (27) as a dark red crystalline solid, m.p. 175–190°. The analytical sample, obtained after three crystallizations from ethyl acetate, melted at 198–199° and the melting point of a mixture of this material and that prepared directly from the keto acid **14** (m.p. 199–200°) was 198–200°.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.60; H, 5.04; N, 14.68.

Cleavage of the 2,4-Dinitrophenylhydrazone (27).—A solution of 0.65 g. (1.74 mmoles) of the 2,4-dinitrophenylhydrazone (27) in 200 ml. of acetone containing 5 ml. of concentrated hydrochloric acid was heated under reflux for 45 min., cooled, treated with a solution of 5.0 g. of stannous chloride in 20 ml. of concentrated hydrochloric acid and then 30 ml. of water, and this mixture reheated under reflux in a nitrogen atmosphere for an additional 45 min. Most of the acetone was removed at reduced pressure at room temperature and the product isolated by chloroform extraction in the usual manner. Evaporation of the chloroform at reduced pressure, then, afforded 0.21 g. (62%) of the keto acid **14** as a tan solid, m.p. 165–185°. The melting point of a mixture of this material and that prepared above (m.p. 170–190°) was 165–187°.

6-Bromo-1-carboxy-8β-methyl-*trans*-hexahydroindanone-5 (26).—In a fashion similar to that described above for the *cis* isomer **25**, 1.37 g. (7 mmoles) of the *trans*-keto acid **24** afforded 1.75 g. (91%) of the bromoketo acid **26**, m.p. 150–163°, on treatment with 1.12 g. (7 mmoles) in 12 ml. of chloroform. The analytical sample, obtained after treatment with Norite and crystallization twice from chloroform, melted at 176–178° (dec.).

Anal. Calcd. for $C_{11}H_{15}O_3Br$: C, 48.01; H, 5.50; Br, 29.04. Found: C, 47.91; H, 5.59; Br, 29.27.

The 2,4-Dinitrophenylhydrazone of 1-Carboxy-8β-methyl-*trans*-Δ⁶-tetrahydroindanone-5 (29).—A solution of 1.0 g. (3.64 moles) of the *trans*-bromo keto acid (26) in 10 ml. of glacial acetic acid was treated with 0.79 g. (4.0 mmoles) of 2,4-dinitrophenylhydrazine, and the reaction mixture warmed on the steam bath for 10 min. and then allowed to stand at room temperature for 2 hr., during which time orange needle-like crystals separated. The solution was heated again on a steam bath, 30 ml. of water added, and the mixture allowed to cool to room temperature. After cooling in an ice bath for 30 min., the precipitated 2,4-dinitrophenylhydrazone (29) was separated by filtration and dried. In this fashion there was obtained 1.30 g. (96%) of material, m.p. 170–180°, of sufficient purity to be used directly in the next experiment. The analytical sample was obtained after three crystallizations from ethyl acetate as flat, needle-like prisms and showed a double melting point of 194° and 216–217.5°. The melting point of the mixture of this material and the 2,4-dinitrophenylhydrazone (27) (m.p. 198–199°) prepared above was depressed to 178–186°.

Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.63; H, 4.87; N, 15.02.

1-Carboxy-8β-methyl-*trans*-Δ⁶-tetrahydroindanone-5 (30).—By employing the same procedure as well as the same quantities of reagents as described above for the cleavage of the 2,4-dinitrophenylhydrazone (27), 1.0 g. (2.7 mmoles) of the corresponding derivative **29** afforded 427–466 mg. (81–89%) of the keto acid **30**, m.p. 180–195°. The analytical sample was prepared by crystallization of a small quantity of this material two times from benzene and melted at 199–200°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.15.

Ultraviolet: λ_{max}^{alc} 228 mμ (ε 9800).

1-Carboxy-4-formyl-4-(3-ketophenyl)-8β-methyl-*trans*-Δ⁶-tetrahydroindanone-5 (32).—To a suspension of 0.97 g. (0.018 mole) of sodium methoxide in 15 ml. of dry benzene was added 1.91 g. (0.0258 mole) of purified ethyl formamate and the whole stirred in a nitrogen atmosphere at room temperature for 15 min. After cooling in an ice bath, 1.0 g. (5.15 mmoles) of the keto acid (30) was added all at once, and the reaction mixture allowed to stir overnight at room temperature. The mixture was diluted with 15 ml. of chloroform, 5 ml. of water was added, and then the system made acidic with 10% aqueous sulfuric acid. The aqueous layer was separated, washed with chloroform, and the combined chloroform extracts washed and dried in the usual fashion. Evaporation of the solvents and reduced pressure left 1.11 g. (97%) of the crude, yellow hydroxymethylene derivative **31**. This material was not further purified but dissolved in 15 ml. of methanol and treated with 0.63 g. (7.5 mmoles) of ethyl vinyl ketone and 1.0 g. (0.01 mole) of triethylamine. After this solution had been allowed to stand at room temperature for 2 days in a nitrogen atmosphere, the methanol was removed at reduced pressure and sufficient dilute aqueous sulfuric acid added to render the mixture acidic to congo red paper. When the product, isolated by chloroform extraction in the usual manner, was crystallized from 30 ml. of ethyl acetate, there resulted 708 mg. (44% over-all yield) of the adduct **32** in two crops of 437 mg., m.p. 169–174°, and 271 mg., m.p. 145–158°. The analytical sample was prepared by two crystallizations from ethyl acetate of a specimen of the first crop and melted at 176–181° (dec.).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.77; H, 7.18.

1-Carboxy-3a,6β-dimethyl-*trans*-3a,7,8,9a,9b-hexahydrobenz[e]-indanone-7 (33).—To a solution of 224 mg. (4.0 mmoles) of potassium hydroxide in 5 ml. of water was added 160 mg. (0.523 mmole) of the adduct **32**, and the mixture allowed to stand 5 hr. in a nitrogen atmosphere at room temperature. After acidification of the solution with 10% aqueous, sulfuric acid, the product was isolated by chloroform extraction in the usual fashion. Removal of the chloroform at reduced pressure left 126 mg. (93%) of the tricyclic acid **33**, m.p. 204–213°, as a pale yellow solid. The analytical sample, obtained after two crystallizations from ethyl acetate, melted at 225–230° (dec.).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.85; H, 7.83.

Infrared: $\lambda_{max}^{Nujol\ mull}$ 5.80 μ (—COOH); 6.18 μ (> C=O); 6.29 μ and 6.38 μ (> C=C<).

Ultraviolet: λ_{max}^{alc} 290 mμ (ε 24600).

The **methyl ester** was prepared by treatment of a chloroform solution of 43 mg. (0.165 mmole) of the crude keto acid **33** with excess ethereal diazomethane and then chromatography of the product on 4 g. of Florisil. Elution with 70 ml. of chloroform afforded a yellow solid which on crystallization from 1.5 ml. of petroleum ether (60–75°) gave 38 mg. (84%) of the ester, m.p. 106–106.5°, as long, colorless needles.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 74.42; H, 8.08. Found: C, 74.44; H, 8.13.

Infrared: $\lambda_{max}^{Nujol\ mull}$ 5.78 μ (—$COOCH_3$); 6.05 μ (> C=O); 6.25 μ and 6.38 μ (>C=C>).

Ultraviolet: λ_{max}^{alc} 289 mμ (ε 24800).

1-Carbomethoxy-3a,6β-dimethyl-*trans*-3a,4,5,7,8,9,9a,9b-octahydrobenz[e]-indanone-7 (34).—A solution of 116 mg. (0.424 mmole) of the tricyclic keto ester above in 8 ml. of benzene was added to a prereduced suspension of 80 mg. of 2% palladium-on-

strontium carbonate[3] in 6 ml. of benzene and the mixture stirred in a hydrogen atmosphere at room temperature until absorption of the gas ceased (11-ml. uptake). After removal of the catalyst filtration and the benzene by distillation at reduced pressure, the residue was boiled with 2 ml. of petroleum ether for 1 min., cooled, and filtered free of 15 mg. of a white, insoluble solid. After cooling the petroleum ether filtrate in the refrigerator overnight, there was deposited 85 mg. (73%) of the ester **34**, m.p. 89–90°, as thick, colorless prisms. The melting point of a mixture of this material and that (m.p. 89–90°) prepared (diazomethane) from the corresponding tricyclic keto acid supplied by Professor R. B. Woodward was also 89–90°. The infrared and ultraviolet spectra of the two samples were also identical.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.00; H, 8.84.

Infrared: $\lambda_{max}^{Nujol\ mull}$ 5.78 μ (—$COOCH_3$); 6.0 μ (> C=O); 6.22 μ (> C=C <).

Ultraviolet: λ_{max}^{alc} 248 mμ (ϵ 15500).

11-Oxygenated Pregnenolones. II. Synthesis of 11α-Hydroxy-, 11β-Hydroxy-, and 11-Ketopregnenolones and 11-Keto-17α-pregnenolone

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6β-Hydroxy-3,5α-cyclopregnan-20-one has been hydroxylated microbially in high yield to 6β,11α-dihydroxy-3,5α-cyclopregnan-20-one. From this intermediate are synthesized 11α-hydroxy-, 11β-hydroxy-, and 11-ketopregnenolones and 11-keto-17α-pregnenolone. 6β,11β-Dihydroxy-3,5α-cyclopregnenolone has also been prepared by microbial hydroxylation of *i*-pregnenolone. The configuration of the side chain of steroid 20-ketals has been rigorously established.

While 3β-hydroxy-Δ^5-steroids such as pregnenolone and dehydroepiandrosterone occur widely in nature, their 11-hydroxy derivatives have only recently been described.[1,2] In a preliminary communication[2] we described the high yielding microbiological conversion of 6β-hydroxy-3,5α-cyclopregnan-20-one (I) to 6β,11α-dihydroxy-3,5α-cyclopregnan-23-one[1b,2] (II) and the subsequent conversion of this compound to 11α-hydroxypregnenolone[1-3] (III).

We now wish to report the experimental details of the microbial 11α- and 11β-hydroxylations of *i*-pregnenolone (I) as well as the synthesis of some simple 11-oxygenated pregnenolones. 6β-Hydroxy-3,5α-cyclopregnan-20-one[4] (I), prepared from pregnenolone (readily available from diosgenin) by the *i*-steroid rearrangement is hydroxylated by the mold *Rhizopus nigricans* (ATCC 6227b) in high yield to give the 6β,11α-diol (II).[5] The structure of this product was confirmed[6] by acid-catalyzed rearrangement to 11α-hydroxypregnenolone (IIIa) followed by Oppenauer oxidation of this diol to the microbial metabolite 11α-hydroxyprogesterone.[7] To synthesize the remaining 11-oxygenated pregnenolones, a method was required for differentiating the oxygen functions at C-11 and C-3 (or C-6). Three sequences, namely selective esterification, selective oxidation, and homoallylic displacement with chloride ion, were investigated in order to block chemically the C-3 oxygen function so that the C-11 oxygen might be both oxidized and reduced selectively.

Initially selective esterifications at C-3 were attempted. Reaction of the diol (II) with formic acid at low temperature resulted in the formation of the diformate (IIIb), which was hydrolyzed to the diol (IIIa). Treatment of the diol (II) with hot glacial acetic acid resulted in the isolation of a small amount of the desired 3-monoacetate (IIIc); however, the diacetate was the major product. The structure of the monoacetate (IIIc) was established by oxidation to 11-ketopregnenolone acetate (IXa, *vide infra*). Acetylation of the diol (IIIa) with a single mole of acetic anhydride was also unselective.

A second approach involved the Oppenauer oxidation of the 6,11-diol (II). This reaction was selective in producing in good yield the 11α-hydroxy-6,20-dione (V). However, the reactivities of the 6- and 23-ketonic functions are similar; consequently, this sequence offered little opportunity for the synthesis of the desired intermediates.

Lastly, treatment of the 6,11-diol (II) with concentrated hydrohalic acid under heterogeneous conditions provided the requisite protection of the "3-hydroxyl group" to allow further synthetic elaborations. Treatment with hydrochloric acid provided a mixture of chloro compounds (VIa) epimeric at C-17. The composition of this mixture was established by n.m.r.[8] which indicated approximately 97% of the 17β- and 3% of the 17α-isomer were present. Hydrobromic acid gave similar results.

Oxidation of the isomeric chlorides (VIa) gave a separable mixture of diones VIIa (17β) and VIII (17α). The configurations of the side chains of VIIa and VIII were established by the chemical shifts of the C-18 protons in their n.m.r. spectra.[6] Treatment of the

(1) (a) I. Chuma, Japanese Patent Specification 17231 (1960); (b) Y. Kurosawa, *J. Agr. Chem. Soc., Japan*, **32**, 515 (1958).

(2) W. J. Wechter and H. C. Murray, *Chem. Ind.* (London), 411 (1962).

(3) E. S. Rothman and M. S. Wall, *J. Am. Chem. Soc.*, **81**, 411 (1959), reported the synthesis of this compound from 3β-hydroxypregna-5,16-diene-11,20-dione (*via* synthetic 11-ketodiosgenin) by catalytic reduction. While the melting point of the material prepared by Y. Kurosawa[1b] and that prepared in our laboratory agree with that reported by Rothman and Wall, the specific rotation does not ($[\alpha]^{CHCL_3}D$ +70° *vs.* $[\alpha]^{CHCL_3}D$ +15°).

(4) V. Petrow, I. A. Stewart-Webb, and D. K. Patel, U. S. Patent 2,816,901 (1959).

(5) Earlier efforts to hydroxylate pregnenolone selectively at C-11 proceeded only in poor yield, if at all, owing to a competing facile oxidation at C-7 under aerobic conditions. *Cf.* A. Kramli and J. Horvath, *Nature*, **163**, 219 (1949) and D. H. Peterson, *Record Chem. Progr.*, **17**, 211 (1956).

(6) The configuration of the pregnane side chain was established in all cases by n.m.r. G. Slomp (private communication) has found by the examination of model compounds of known configuration (see ref. 12 for examples) that the C-18 proton absorption appears at about 36 to 40 c.p.s. (measured downfield from tetramethylsilane) in 17β isomers, while it is shifted downfield to 51 to 54 c.p.s. in the corresponding 17α isomers.

(7) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 1933 (1952).

(8) The quantitative constitution of the mixture was determined by integration of the area of the C-18 proton absorptions characteristic of the 17α and 17β compounds.