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STEROID TOTAL SYNTHESIS--BENZHYDRINDANE APPROACH

PRELIMINARY SURVEY

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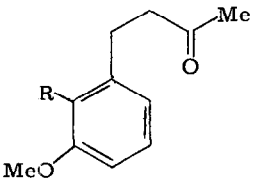
IN view of the recent report of Barnes and Miller[1] on a synthesis of desoxyequilenin, we are prompted to disclose some of the results of a long-range Indian-American collaborative study on steroid synthesis that involves a similar basic approach.



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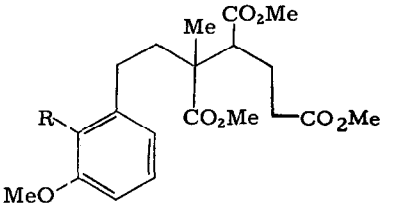
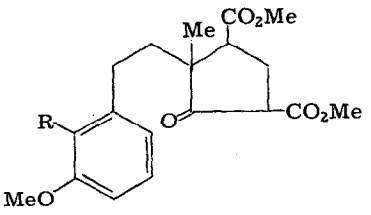


II

[1] R. A. Barnes and R. Miller, J. Am. Chem. Soc. 82, 4960 (1960).



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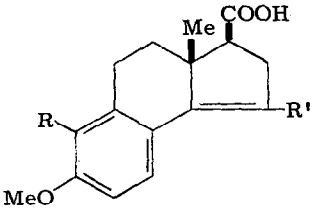

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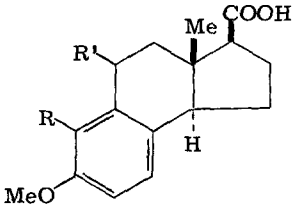

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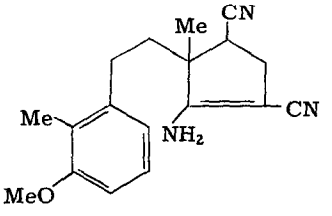

VI

m-Methoxybenzylacetone, I (R = H), was converted into the triester II (R = H) in 63% yield by the following reaction sequence: condensation with ethyl cyanoacetate, addition of hydrogen cyanide, cyanoethylation, hydrolysis, and esterification. Dieckmann cyclization gave the keto diester III (R = H) which on acid-catalyzed ring closure, followed by hydrolysis and decarboxylation, afforded the acid IV (R = R' = H), m.p. 227-228°. Catalytic hydrogenation of this acid proceeded stereoselectively to give (see below) the trans-benzhydrindane derivative V (R = R' = H).

A similar study was carried out with the ketone I (R = Me), which was best obtained, among other ways, by the Stobbe condensation of the isobutyl enol ether of 2-methyldihydroresorcinol[2] with di-t-butylsuccinate,

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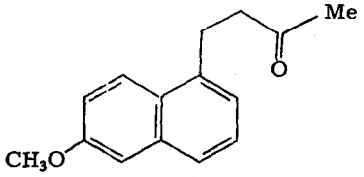
[2] A. Eschenmoser, J. Schreiber and S. A. Julia, Helv. Chim. Acta 36, 482 (1953).

followed by heating with palladium-on-carbon to effect removal of the carbo-t-butoxyl group, and aromatization. The resulting 3-methoxy-2-methyl-β-phenylpropionic acid, m. p. 170. 5-172. 5°, was converted via the acid chloride, into the methyl ketone I (R = Me), b. p. 112-114° (0. 1 mm); 2,4-dinitrophenylhydrazone, m. p. 126-128°.

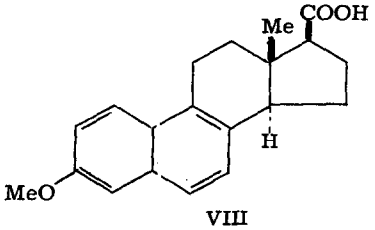
The ketone I (R = Me) was converted, by a sequence similar to that outlined above for the nor series, into the acid IV (R = Me, R' = H), m. p. 267. 5-269 (methyl ester, m. p. 136-137°), thence to the reduced substance V (R = Me, R' = H), m. p. 248. 5-249° (methyl ester, m. p. 115-116°).

The best method for preparing V (R = Me, R' = H) involved condensation of I (R = Me) with t-butyl cyanoacetate (product, m. p. 78-78. 5°), addition of hydrogen cyanide (product, m. p. 81. 5-82°), and cyanoethylation to give a mixture of diastereomers, m. p. 145-146°. Pyrolysis at 175° removed the carbo-t-butoxyl group to give the trinitrile corresponding to II (R = Me) which on t-butoxide-catalyzed Thorpe cyclization yielded two isomeric forms of VI, m. p. 167-168° and 148. 5-149°. The mixture of isomers was submitted to acid hydrolysis followed by cyclization with hydrogen fluoride (two isomers, m. p. 242. 5-243. 5° and 183-184°), then, without separation of isomers, alkaline hydrolysis to yield IV (R = Me, R' = COOH), m. p. 247-250°. Decarboxylation and hydrogenation yielded V (R = Me, R' = H) in 41% over-all yield from the ketone I (R = Me).

A similar study with I (R = H, and CN β to the keto group) has led to the stereoselective production of the diacid V (R = H, R' = COOH), m. p. 212-213°(dec.), having an additional carboxyl group located at the position (R') corresponding to C_{11} in steroids.

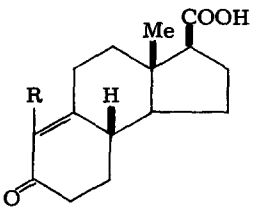


VII

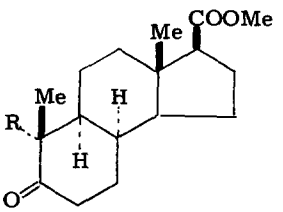


VIII

Evidence for the stereochemical course of the reduction of the substances IV (R' = H, R = H or CH_3) was provided by studying a related series where the configurations were ascertainable. β-(6-Methoxy-1-naphthyl)ethyl bromide[3] on treatment with potassium cyanide in acetone, followed by saponification, yielded β-(6-methoxy-1-naphthyl)propionic acid, m. p. 160-161°, which was converted via the acid chloride (dimethyl cadmium) into the methyl ketone VII, m. p. 48. 5-50°. Condensation of VII with ethyl cyanoacetate, followed by addition of hydrogen cyanide, cyanoethylation (adduct, m. p. 118. 5-120°), hydrolysis and treatment with diazomethane gave a triester, m. p. 94-95. 6°. Dieckmann reaction followed by cyclization with hydrogen fluoride gave the tetracyclic diester, m. p. 174-174. 8°, which was saponified (diacid, m. p. 260-262°), decarboxylated (mono acid, m. p. 260-262. 5°), and hydrogenated to give a single product, m. p. 283. 5-285. 5° (dec.). That this substance was the acid VIII with a trans C/D juncture was proved by establishing its identity with authentic material prepared from dl-equilenin methyl ether[4] via the cyanohydrin which was dehydrated, hydrogenated and finally hydrolyzed.



IX



X

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[3] W. E. Bachmann, W. Cole and A. L. Wilds, J. Am. Chem. Soc. 61, 974 (1939); 62, 824 (1940).

[4] W. S. Johnson, J. W. Petersen, C. D. Gutsche, J. Am. Chem. Soc. 69, 2942 (1947).

Birch reduction of V (R = Me) gave IX (R = Me). The identity of this substance with material prepared in connection with the Woodward steroid synthesis[5] provided conclusive proof of the configuration in our series and established an obvious pathway to completion of the steroid synthesis utilizing the Woodward method of attaching ring A. The yield of IX (R = Me), however, was extremely poor in contrast with that of the lower homolog; the Birch reduction of V (R = H) proceeded readily to give IX (R = H), m. p. 246-248° (vac.). Moreover cyanoethylation of the system IX (R = Me) is known[5] to yield a mixture of epimers at C_{10} (steroid numbering). Therefore we chose to explore a route which promised to be more stereoselective.

Demethylation of V (R = Me, R' = H) afforded the phenolic acid, m. p. 245.5-249° (vac.) which, on hydrogenation in aqueous alkaline solution over ruthenium oxide was converted, in high yield, into a single alcohol, m. p. 203-203.5°. This substance was esterified with diazomethane and oxidized with Sarett reagent to afford the keto ester X (R = H), m. p. 82-82.5°. Cyanoethylation afforded X (R = CH_2CH_2CN), m. p. 142.5-143°, as the exclusive product, which on hydrolysis was converted into the corresponding keto diacid, m. p. 208-211°. The dimethyl ester X (R = $CH_2CH_2CO_2Me$) melted at 80.5-81.5°. Epimerization at C_8 (steroid numbering) would yield a known substance which has been converted to a natural steroid. So far attempts to effect this epimerization have failed. (The bromo diester, m. p. 161-162.5°, could not be converted into the desired 6,7-dehydro X (R = CH_2CH_2COOMe) by the usual methods.) This problem is currently under investigation; also studies on the alkylation of the methyl ester of IX (R = H) are in progress.[6]

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[5] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, J. Am. Chem. Soc. 74, 4223 (1952).

[6] Satisfactory analytical and spectral properties have been obtained for the new substances reported herein.

Acknowledgement: We are indebted to the following agencies for support of this work: The National Institutes of Health, the National Science Foundation, the Wisconsin Alumni Research Foundation, the Allied Chemical and Dye Corporation, and the Sterling-Winthrop Research Institute.