Tetrahedron Letters No. 4, pp. 193-196, 1963. Pergamon Press Ltd.
Printed in Great Britain.

RACEMIC PROGESTERONE

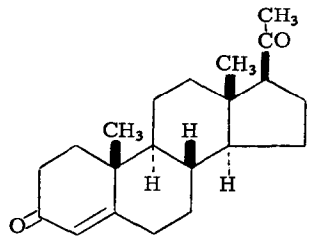
William S. Johnson, John F. W. Keana and William S. Johnson

Department of Chemistry, Stanford University,

Stanford, California

(Received 5 November 1962)

ALL of the synthetic pathways from coal tar products to progesterone (I) that have been reported up to now depend on relays involving one or more naturally derived intermediates.[1] We are disclosing herewith a new approach to the hormone which has been carried through to completion to yield racemic progesterone.



I

The stereoselective total synthesis of the cyano hydroxy ketone II (probably the 17β-epimeric form) has already been described in connection

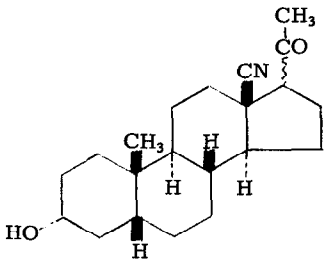
[1] Cf. inter alia J. W. Cornforth in "Progess in Organic Chemistry" Vol 3 (Edited by J. W. Cook), p. 1, Butterworths, London (1955).

with the total synthesis of conessine.[2] We have also described[2] the conversion of this substance II into the cyano ketal III (R = CN) which, although crystalline, appeared to be a mixture of C-17 epimers which we have not yet been able to separate. In the present study this cyano ketal III (R = CN) was selectively reduced by treatment for 5 hr. in refluxing tetrahydrofuran with a five-fold molar excess of lithium aluminum hydride to give the imino compound III (R = CH=NH).[3] The crude imino ketal, after a pretreatment with excess hydrazine hydrate and potassium hydroxide in triethylene glycol at 130° for 17 hr. to form the hydrazone, was submitted to the Huang-Minlon modification of the Wolff-Kishner reduction to give the ketal III ($R = CH_3$).[3] After chromatography the product (from which a form melting at 121.5-124° (Found: C, 76.1; H, 10.5) could be isolated by crystallization) was treated with Sarett's reagent in order to oxidize the hydroxyl at C-3 to the keto group. A pure form of the ketone IV melting at 168.5-170.5° (Found: C, 76.5; H, 9.9) could be isolated by chromatography and crystallization. Treatment of the crude chromatographed keto ketal IV with dilute acid effected hydrolysis of the ketal residue (and presumably also equilibration of the C-17 side chain) to give DL-3,20-pregnanedione (V), m.p. 111-112° (Found: C, 79.5; H, 10.3). The solution infrared spectrum of this substance was identical with that of natural D-V. Treatment of a solution of the crude chromatographed keto ketal IV in acetic acid with bromine effected bromination at C-4 as well as hydrolysis of the ketal

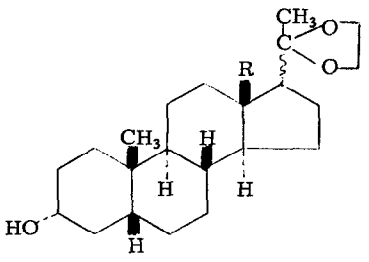
---

[2] J. A. Marshall and W. S. Johnson, J. Amer. Chem. Soc. 84, 1485 (1962).

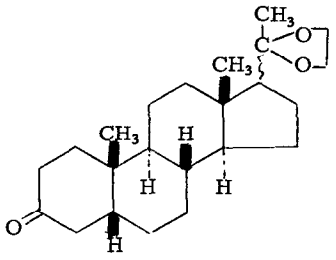
[3] Cf. the similar case of W. Nagata, I. Kikkawa and K. Takeda, Chem. and Pharm Bull. (Tokyo) 9, 79 (1961).



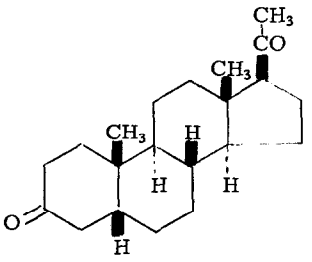
II



III



IV



V

residue. Dehydrobromination was effected by heating a solution of the crude bromo diketone in acetone containing 2 mole-equivalents of trimethylbenzylammonium mesitoate at reflux temperature for 1 hr.[4] The product was DL-progesterone, m.p. 183.5-185.5° (Found: C, 80.2; H, 9.7). The solution infrared spectrum of this material was indistinguishable from that of the natural hormone, and the high temperature mass spectral fragmentation patterns of the two substances were identical.

---

[4] This is an unpublished method of W. S. Johnson, P. J. Kropp and K. O. Gelotte for effecting the dehydrohalogenation of α-halo ketones under mild conditions. By treatment with tetramethylammonium mesitoate in acetone, 4β-bromocoprostanone was thus converted to cholestenone in 69-78% yield.

Acknowledgements. We wish to express our appreciation to Dr. H. Budzikiewicz for the mass spectrometric analyses. We also thank the National Science Foundation and the U. S. Public Health Service for providing support for this study.