Tetrahedron Letters No.2, pp.72-75, 1961. Pergamon Press, Inc. Printed in the United States of America.

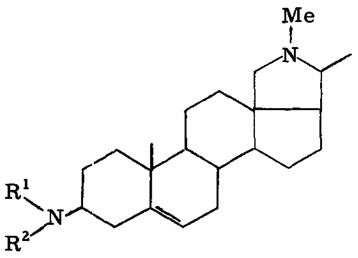
THE SYNTHESIS OF CONESSINE FROM THE CORRESPONDING 3-KETO-Δ^4-UNSATURATED SYSTEM

William S. Johnson, Victor J. Bauer and Richard W. Franck

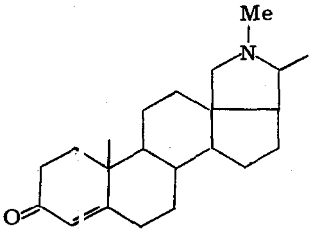
Department of Chemistry, University of Wisconsin, Madison, Wisconsin
and Department of Chemistry, Stanford University, Stanford, California

(Received 12 January 1961)

IN connection with studies directed toward the total synthesis of conessine, I ($R^1 = R^2 = Me$), we have been in search of a facile method for its production from a 3-oxygenated derivative. The results of previous studies[1] toward this objective were not promising, e.g. reaction of dimethylamine with a 3β-p-toluenesulfonate-Δ^5-unsaturated steroid gave, at best, very poor yields of the desired product.



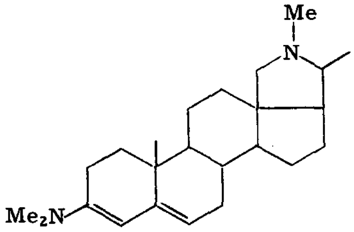
I



II

---

[1] E. J. Corey and W. R. Hertler, J. Am. Chem. Soc. 81, 5209 (1959).



III

The selective reduction of an enamine like III to yield I ($R^1 = R^2 =$ Me) was considered an attractive possibility, because the former substance promised to be readily accessible[2] from Δ^4-conanene-3-one (II).[3] In the present work a new direct approach to the latter ketone was developed. Conessine was converted, by the action of cyanogen bromide, into cyano-iso-conessimine, I (R^1 = Me, R^2 = CN), which, on alkaline hydrolysis, was transformed into iso-conessimine, I (R^1 = Me, R^2 = H), as previously described.[4] This product, on treatment with N-chlorosuccinimide or t-butyl hypochlorite (to produce I, R^1 = Me, R^2 = Cl) followed by dehydrohalogenation with sodium ethoxide, then hydrolysis,[5] afforded in 62% yield

---

[2] Cf. F. W. Heyl and M. E. Herr, J.Am. Chem. Soc. 75, 1918 (1953).

[3] R. Pappo, U. S. Patent No. 2,913,455, Nov. 17, 1959; Chem. Abst. 54, 3527 (1960). In our hands the method of A. Bertho and M. Goetz, Ann. 619, 96 (1958) failed.

[4] S. Siddiqui and R. H. Siddiqui, J. Indian Chem. Soc. 11, 787 (1934).

[5] Cf. W. E. Bachmann, M. P. Cava and A. S. Dreiding, J. Am. Chem. Soc. 76, 5554 (1954).

Δ^4-conanene-3-one (II), m.p. after purification 108.5-110°, $\lambda^{95\%\ \mathrm{EtOH}}_{\mathrm{max}}$ 241 mμ (ϵ 16,000) (Found: C, 80.5%; H, 10.2%; N, 4.3%). Mixed m.p. determinations and infrared spectroscopy demonstrated the identity of this material with that of Pappo.[3]

Treatment of II with anhydrous dimethylamine in the presence of magnesium sulfate and a trace of p-toluenesulfonic acid in a sealed tube (exclusion of air) readily gave the enamine III, m.p. 151-152°, (after recrystallization from acetone) $\lambda^{\mathrm{Et_2O}}_{\mathrm{max}}$ 271 mμ (ϵ 18,400) (Found: C, 81.0%; H, 10.8%; N, 8.0%). Despite the known resistance of such enamine systems to reduction by lithium aluminum hydride[6] we tried the reaction of III with sodium borohydride and, to our pleasure, found that reduction occurred smoothly and selectively to give conessine, I (R^1 = R^2 = Me), as the major and only isolable product.

Prior to the experiments described above we carried out a study with Δ^4-cholestene-3-one which, under the conditions already mentioned, was converted readily into 3-dimethylamino-3,5-cholestadiene, m.p. 97-99°, $\lambda^{\mathrm{ether}}_{\mathrm{max}}$ 272 mμ (ϵ 19,000) (Found: C, 84.1%; H, 11.8%; N, 3.9%). Reduction with sodium borohydride afforded 3β-dimethylamino-Δ^5-cholestene, m.p. 151-151.5° (reported,[7] 151°). The new synthetic

---

[6] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, J. A. Hogg, J. Am. Chem. Soc. 78, 6213 (1956).

[7] D. P. Dodgson and R. D. Haworth, J. Chem. Soc. 67 (1952).

sequence for converting a Δ^4-3-keto-steroid into the 3β-dialkylamino-Δ^5-unsaturated derivative thus promises to be generally applicable.

Acknowledgement. We are most grateful to Dr. Raphael Pappo of G. D. Searle Co. for a gift of conessine and for supplying us with a specimen of Δ^4-conanene-3-one for comparison purposes. We also wish to thank the U. S. Public Health Service and the National Science Foundation for grants which have supported this work in part.