A Ready Total Synthesis of 8,13-Diaza-18-norœstrone Methyl Ethers

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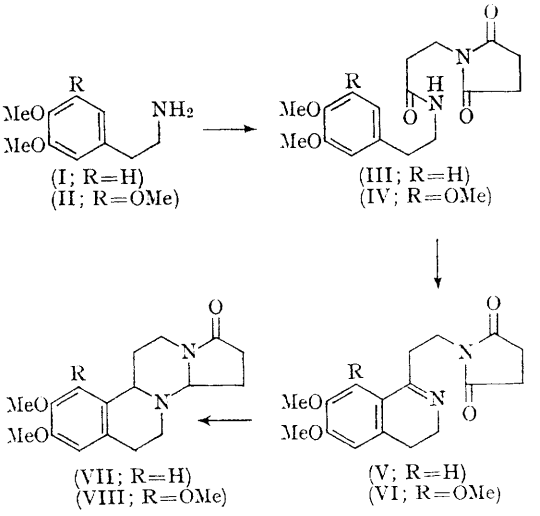
A RECENT report[1,2] on synthetic studies directed towards the total synthesis of 8,13-diaza-steroids prompts us to describe briefly a ready, three-step total synthesis of derivatives of 8,13-diaza-18-norœstrone methyl ether (VII and VIII), starting with homoveratrylamine and mescaline, respectively.

2-Methoxy-8,13-diaza-18-norœstrone methyl ether (VII) was prepared as follows:* succinimidopropionic acid[3] was converted into its acid chloride with thionyl chloride under nitrogen and then condensed with homoveratrylamine (I) in tetrahydrofuran. The resulting amide (III) (m.p. 127—128°, 55% yield) under normal Bischler–Napieralski cyclization conditions ($POCl_3$–benzene) was converted smoothly into the dihydroisoquinoline (V) (m.p. 162—164°, 80% yield). Catalytic reduction in ethanol solution, using platinum oxide as catalyst, resulted in conversion *in a single step* into (VII) (m.p. 166—167°, 70% yield). The success of this reductive cyclization is dependent upon the purity of the dihydroisoquinoline and upon the complete absence of traces of acid; in our hands, attempts to reduce the hydrochloride of (V) resulted only in the formation of the tetrahydroisoquinoline.†

An analogous series of reactions starting with mescaline (II) gave 1,2-dimethoxy-8,13-diaza-18-norœstrone methyl ether (VIII) (m.p. 138—139°, 42·5% overall yield) *via* the intermediate formation of the amide (IV) (m.p. 142—143°) and the dihydroisoquinoline (VI) (m.p. 97—98°).



* All compounds reported gave correct microanalytical results, confirmed by high-resolution mass spectrometry. All n.m.r. spectra were completely in accord with the structures assigned.

† The dihydroisoquinoline (V) was prepared similarly from homoveratrylamine by Burckhalter and Abramson (ref. 1), but their reported melting point (196°) corresponds to an impure sample of the *hydrochloride* of (V) (m.p. 211—212°), not to the free base (m.p. 162—164°) as stated. Their failure to effect reductive cyclization with their preparation of (V) is thus readily apparent.

Preliminary pharmacological evaluation of these compounds, kindly performed by Dr. William J. Novick of the Smith Kline and French Laboratories in Philadelphia, Pa., has shown that both compounds (VII) and (VIII) possess some analgesic activity.

This work was supported by a grant to Princeton University from Smith, Kline and French Laboratories.

(*Received, November 28th,* 1966; *Com.* 931.)

[1] J. H. Burckhalter and H. N. Abramson, *Chem. Comm.*, 1966, 805.
[2] H. N. Abramson and J. H. Burckhalter, Abstracts of the 152nd ACS Meeting, New York City, September, 1966; P43.
[3] T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick, F. T. Fiedorek, R. A. Bankert, J. T. Gregory, and W. L. Beears, *J. Amer. Chem. Soc.*, 1952, **74**, 1323.