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A CONVENIENT SYNTHESIS OF NORTROPINE FROM TROPINE OR TROPINONE

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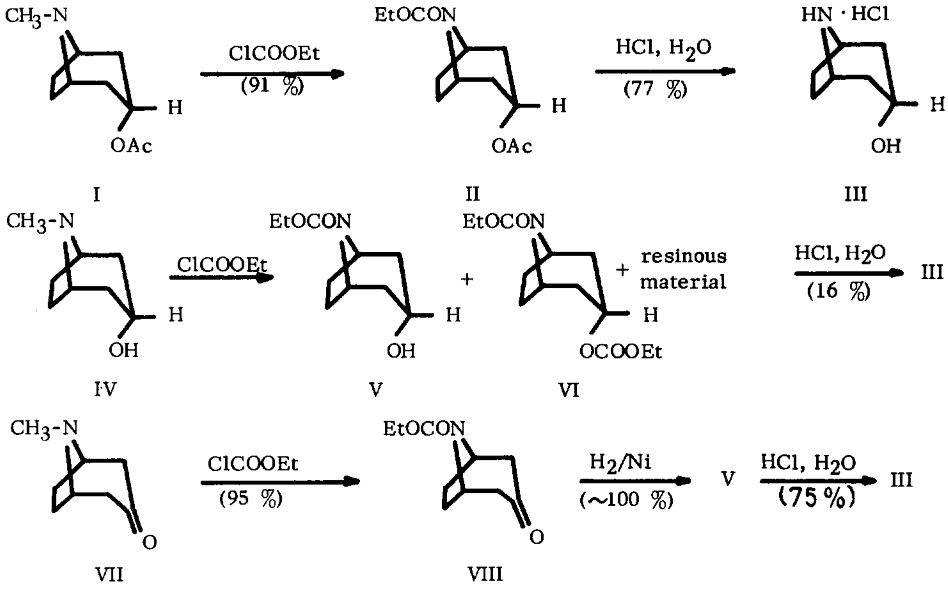
Several methods are known for the preparation of nortropine (III). Oxidation of tropine (IV) and its natural derivatives with potassium permanganate (1) or potassium ferricyanide (2) and treatment of tropine acetate (I) with bromine cyanide (3) after hydrolysis gave nortropine (III) in a very poor yield. However, the conversion of tropane to nortropane via ethyl chloroformate followed by hydrochloric acid hydrolysis has been realised in a good yield (4).

We wish to report a novel convenient synthesis of nortropine in three variations:



Tropine acetate (I) was treated in boiling benzene with three mol of ethyl chloroformate. Evolution of methyl chloride gas was observed. After refluxing for three hours it was extracted with a small amount of water and then concentrated and distilled at reduced pressure to give 91% yield of II, b.p. 110°/0,3 mm, n_D^{25} 1,4771. II was hydrolysed in boiling 20% hydrochloric acid for six hours to nortropine hydrochloride (77%, m.p. 280-282°, dec.).

On the other hand tropine (IV) was treated with an excess of ethyl chloroformate in boiling benzene to give N-carbethoxy nortropine (V, m.p. 87°), a negligable quantity of N-carbethoxy 3 α -tropanyl ethyl carbonate (VI) and a large amount of resinous material. During the reaction generation of methyl chloride and a small amount of hydrogen chloride gas was observed. The crude reaction product was hydrolysed in boiling 20% hydrochloric acid for eight hours to nortropine hydrochloride (16% based on tropine, m.p. 280-281°, dec.).

Recently Fischer and coworkers found (5) that the tropinone (VII) and ethyl chloroformate afforded N-carbethoxy nortropinone (VIII) in a good yield. But VIII showed no ability to undergo a simple hydrolysis.

However, it has been possible to apply the N-carbethoxy nortropinone (VIII) to another synthesis of nortropine. VIII was synthetized from tropinone (VII) with the Fischer's method (5) in 95% yield. The stereospecific hydrogenation was carried out for three hours in ethanolic solution with Raney Ni at 100 atm. and 80°. N-carbethoxy nortropine (V) was formed in nearly quantitative yield, m.p. 87° (6). It was identical with the compound obtained from tropine. V was hydrolysed in the same way as II to nortropine hydrochloride (75%, m.p. 280-282°, dec.).

REFERENCES:

1. R. Willstätter: Ber. **29**, 1575 (1896); G. Werner, R. Hackel, N. Mohammad, N. Seiler and K.-H. Störr: Liebigs Ann. Chem. **708**, 210 (1967)
2. S. P. Findlay: J. Amer. Chem. Soc. **75**, 3204 (1953)
3. A.Nickon and L. F. Fieser: J. Amer. Chem. Soc. **74**, 5566 (1952)
4. E. Jucker and A. Lindenmann: Swiss Patent 442,318 [C.A. **69**, P35974x (1958)]
5. J. Fischer at al.: Acta Chim. Hung. in press.
6. The new compounds (II and V) in this paper showed reasonable analitical and spectroscopic (ir) data.