Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 1 (1961)

Note

N-Allyl-noratropine

K. NÁDOR, L. GYÖRGY and MRS. M. M. DODA, with the technical assistance of MISS M. GAÁL, *Department of Drug-Research, Institute for Experimental Medical Research of the Hungarian Academy of Sciences, Budapest 9, Pfiok 87*

In recent years, research concerned with compounds with a tropane structure has been greatly intensified, because such compounds have outstanding pharmacological actions.[1-3] However, in these compounds it is the N–CH_3 group that is of importance, as this group features in the alkaloids of natural tropane structure, and the readily accessible tropine has been the starting point for the synthetic substances. Very little is known about the chemistry and pharmacology of *N*-alkyl-nortropine derivatives.[4-6]

We have found the tertiary *N*-alkyl-nortropeines to be invariably much less active than their otherwise analogous *N*-methyl derivatives.[7] For example, *N*-ethyl-noratropine is 25 times less active as a parasympathetic blocking agent than is atropine, and *N*-isopropyl-norhomatropine is from 7 to 10 times less potent than its *N*-methyl analogue, homatropine. Nevertheless, both we and other workers[8] have devoted increased attention to *N*-allyl-noratropine and the related tropeines, owing to the special pharmacodynamic actions of *N*-allyl-normorphine.

Although methods for preparing related compounds are known, the synthesis of *N*-allyl-noratropine presented some difficulties. A variety of attempts at acylating *N*-allyl-nortropine, by analogy with the synthesis of atropine, have failed; we have almost invariably obtained a resinous substance. For this reason other routes were investigated. Noratropine, needed as the starting material, has been produced by two methods, both of which constitute the first total syntheses of this substance, which has previously only been obtainable from plants. Treatment of

noratropine in excess with allyl bromide yielded *N*-allyl-noratropine.

The *N*-allyl-noratropine was found to be a very weak parasympathetic blocking agent, being 25 times weaker than atropine against the effect of acetylcholine on the cat's blood pressure. As determined by Pulevka's method on the rat's pupil, its activity relative to that of atropine was 13 per cent (30 min) and 5·1 per cent (90 min), respectively. It did not antagonize atropine. It was found to be adrenolytic on the nictitating membrane of the cat but this effect was less marked on the blood pressure, therefore its ganglionic blocking action could not be studied on the superior cervical ganglion. It inhibited the action of TMA on the blood pressure, its activity being about 0·15 to 0·2 TEA. No other marked central nervous symptoms were produced. Toxicity: LD_{50} = 500 mg/kg in the mouse, subcutaneously.

Experimental

Noratropine

Method 1. *N*-Benzyl-nortropan-3α-ol which melted at 92° was used as the starting material.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77·38; H, 8·81; N, 6·45. Found: C, 77·35; H, 8·82; N, 6·64.

The hydrochloride melted at 213°.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66·28; H, 7·95; Cl, 13·97; N, 5·52. Found: C, 66·53; H, 7·79; N, 5·69.

The hydrochloride was melted with *O*-acetyltropic acid chloride at a temperature of 85°, and the reaction product when processed in the usual way yielded *N*-benzyl-noratropine, which melted at 115°.

Anal. Calcd. for $C_{23}H_{27}NO_3$: C, 75·58; H, 7·45; N, 3·83. Found: C, 75·52; H, 7·48; N, 3·96.

On catalytic hydrogenation in the presence of 10 per cent Pd–charcoal this substance yielded noratropine which melted at 114° (literature value[9] also 114°). The method may also be employed with other analogues.

Method 2. This route is also applicable to other analogues. Nortropan-3α-ol was treated with carbobenzoxy chloride to give *N*-carbobenzoxy-nortropan-3α-ol, which melted at 124°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68·95; H, 7·33; N, 5·36. Found: C, 69·25; H, 7·40; N, 5·23.

This substance was readily acylated in pyridine solution by means of *O*-acetyltropic acid chloride and gave *N*-carbobenzoxy-noratropine, which melted at 113°.

Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70·39; H, 6·65; N, 3·42. Found: C, 70·36; H, 6·77; N, 3·32.

Catalytic removal of the carbobenzoxy group gave noratropine as above. N-*Allyl-noratropine,* which melted at 77°, was obtained in good yield by treatment of noratropine with allyl bromide, the noratropine being present in sufficient excess to bind the HBr formed.

Anal. Calcd. for $C_{19}H_{25}NO_3$: C, 72·35; H, 7·99; N, 4·44. Found: C, 72·15; H, 8·14; N, 4·55.

Several times recrystallized from alcohol, the picrate melts with decomposition at 102°.

Anal. Calcd. for $C_{25}H_{28}N_4O_{10}$: C, 55·14; H, 5·18; N, 10·29. Found: C, 55·28; H, 5·34; N, 10·44.

(*Received 19 April, 1960*)

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