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Some pharmacological effects and chemical properties of *N*-propargylnoratropine

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N-Propargylnoratropine has been prepared from noratropine, and its structure proved by hydrogenation followed by alkaline hydrolysis. Some pharmacological effects of this compound have been compared with atropine. The central and peripheral cholinolytic activity is some 50% lower than that of atropine. There is a fourfold increase in the analgesic-disorientating action of atropine.

SUBSTITUTION of the *N*-methyl group of atropine by other alkyl groupings may lead to marked alterations in the pharmacological properties of the parent compound (György, Dóda & Nádor, 1965). *N*-Allyl-noratropine (N-728) (Nádor, György & Dóda, 1961; Decsi & Nádor, 1963) had a preferential inhibitory effect on cholinergic receptors in the central nervous system with only a very slight influence on those in peripheral structures (Soyka & Unna, 1961; Dal Ri & Schmidt, 1961). On continuing these experiments we thought it worthwhile to investigate the pharmacological properties of noratropine with an *N*-acetylenic substituent, namely propargyl ($CH{\equiv}C{-}CH_2$).

Experimental

The pharmacological methods have been described elsewhere (Decsi & Nádor, 1963; Decsi, Várszegi & Méhes, 1961, 1963) and a comparison of *N*-propargylnoratropine (N-1084) with atropine is made in Table 1.

TABLE 1. PHARMACOLOGICAL PROPERTIES OF *N*-PROPARGYLNORATROPINE

Compound	Cholinolytic activity		Anti-tremorine effect, ED50 mg/kg	Analgesic disorientating effect ED50 mg/kg	Acetylcholine-depleting effect, ED50* mg/kg
	Central ED50 mg/kg	Peripheral Relative activity			
Atropine	0·92	1·0	1·51	2·06	11·2
N-Propargylnoratropine (N-1084)	1·80	0·64	4·10	0·55	14·1

* An intraperitoneal dose causing 50% decrease of the cerebral acetylcholine level in the mouse.

The LD50 of N-1084 in the mouse was 150 mg/kg when given by the intraperitoneal route and 60 mg/kg in the rat when administered intravenously. In addition to the effects demonstrated in the Table, the compound had a central excitatory action shown by slightly increased spontaneous motility of mice. On the isolated intestine, it showed a musculotropic spasmolytic action about half that of papaverine.

The potencies of the central and peripheral cholinolytic effects of N-1084 were about one half of those of atropine. On the other hand, there was a fourfold increase in the analgesic-disorientating action,

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probably a manifestation of the psychotomimetic action of anticholinergic drugs (Decsi, Várszegi & Nádor, 1966), but also the depletion of cerebral acetylcholine was less than that due to atropine.

The exchange of the *N*-methyl group of atropine for the triple bond-containing propargyl radical produces only slight alteration in the pharmacological properties of the parent compound. Of these changes, the increase in disorientating effect may deserve attention, in view of the psychotomimetic activity of some cholinolytic drugs.

Preparation of N-*propargylnoratropine.* A solution of propargyl bromide (9·3 g, 0·078 mole) in benzene (90 ml) was added dropwise over 30 min to a solution of noratropine (43 g = 0·156 mole) in ten volumes of benzene at 60°. After stirring for 1 hr at this temperature the solution was cooled and the benzene extracted with 5 × 50 ml of water. The benzene was extracted with 4 × 25 ml of dilute hydrochloric acid and *N*-propargylnoratropine base liberated by concentrated ammonia. The base was extracted by methylene chloride. Yield: 21 g (86%). *N*-Propargylnoratropine was obtained in colourless crystals, m.p. 116–117°, after two recrystallizations from light petroleum (b.p. 100–120°). (Found, C, 72·9; H, 7·5; N, 4·3%. $C_{19}H_{23}NO_3$ requires C, 72·9; H, 7·3; N, 4·5%.)

Thin-layer chromatography (silica gel with a 1 : 1 mixture of ethanol and hydrochloric acid as solvent and with Dragendorff reagent as developer) showed the compound to be homogeneous. The picrate salt prepared in the usual way melted at 168°. (Found: C, 55·5; H, 4·8; N, 10·5%. $C_{25}H_{26}N_4O_{10}$ requires C, 55·35; H, 4·8; N, 10·3%.)

Transformation into N-*n-propyl-noratropine.* *N*-Propargylnoratropine (1 g) in methanol (25 ml) was hydrogenated at atmospheric pressure in the presence of a small amount of 9·6% Pd-charcoal. Hydrogenation was complete in 80 min. After filtration, the methanol solution was evaporated. The residue (0·983 g) of *N*-n-propyl-noratropine was dissolved in a small amount of ethanol and transformed into the hydrochloride by dry HCl in ether. Recrystallization from ethanol-ether gave a product m.p. 168–169°. The mixed melting point with an authentic sample (Nádor & Gaál, 1962) was 168–169°.

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