Hydronopol and Its Derivatives as Possible Sources for New Medicinal Agents

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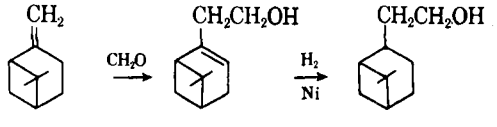
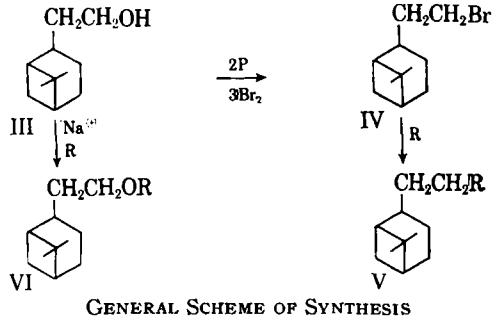
A group of compounds prepared from nopol has been synthesized for pharmacological evaluation. Preliminary studies indicate that they have only a very limited potential in this area, but further studies are in process.

HYDRONOPOL was first prepared (1) by condensing (−) β-pinene (I), a constituent of turpentine, with paraformaldehyde, thus obtaining an alcohol (II), which was named nopol. Hydrogenating nopol over Raney nickel yielded a saturated alcohol (III), the hydronopol.



I II III

Reviewing the literature for new avenues, we found that some nopol and hydronopol derivatives have been made (2, 3), but these were not screened for physiological activity; an exploratory study was thus begun.



GENERAL SCHEME OF SYNTHESIS

In this study compounds 1, 2, and 3 (Table I) had been previously reported (1, 2); the compounds of Type V were prepared by reacting hydronopol bromide with hydrazine in xylene. The compounds of Type VI were prepared by reacting compound III with a corresponding chloro derivative in the presence of sodium.

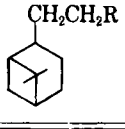
1. Spontaneous Motor Activity in Mice and Rats.—Animals receiving intraperitoneal injections of these derivatives exhibited a biphasic motor response which was characterized by a brief stimulatory phase preceding a period of depression. During the latter stage, the animals exhibited varying degrees of ataxia and sedation, but loss of the righting reflex did not occur. Derivatives III and VII appeared to produce the most profound degree of depression, although none of the hydronopol compounds exerted a significant hypothermic effect.

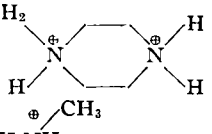
2. Effect of Barbiturate or Ethanol Hypnosis.—Among the various derivatives examined, only V was found to potentiate hexobarbital hypnosis, to effect reinduction of hexobarbital-induced sleep, and to augment ethanol narcosis. The remaining derivatives were inconsistent with regard to the ability to alter the depressant effects of either evipal or ethanol. Derivatives IV, VI, and VII produced varying degrees of mydriasis at high dose levels, but this response was unrelated to their actions on barbiturate or ethanol-induced sleep.

3. Anticonvulsant Action in Mice.—The ability of these compounds to antagonize strychnine-induced convulsions in mice was studied. At the high dose levels employed, only compound II exerted a definite protective effect against strychnine.

4. Analgesic Activity.—The analgesic activity of the hydronopol derivatives was assessed through the use of the following tests: (*a*) phenylquinone-induced writhing, and (*b*) rat tail-flick. Possible analgesic activity was detected in the phenylquinone writhing test for derivatives IV, V, and VI, although none of the compounds was active at the levels used

TABLE I.—HYDRONOPOL AND ITS DERIVATIVES SYNTHESIZED AND TESTED



Compd. No.	R	
1	OH	
2	Br	
3	OCH_2CH_2OH	
4	$OCH_2CH_2\overset{\oplus}{N}(CH_3)_2CH_3$	$I^{\ominus}$
5	$\overset{\oplus}{N}H_2\,\overset{\oplus}{N}H_3$	$2\,Br^{\ominus}$
6		$2\,Cl^{\ominus}$
7	$OCH_2CH_2\overset{\oplus}{N}H(CH_3)CH_3$	$Cl^{\ominus}$

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in the rat tail-flick test. Further, none of the derivatives appeared to possess either antipyretic or anti-inflammatory activity.

5. Anticholinergic Action, In Vitro.—Compounds IV, VI, and VII effectively antagonized the ileal contractures induced by acetylcholine. Compounds III and V were less active, while II was without anticholinergic action even at high concentrations.

6. Cardiovascular Effects.—Hydronopol derivatives IV and VII elicited an immediate, transient, dose-dependent hypotensive response in the chloralosed cat. Both compounds potentiated the pressor response consequent on the intravenous injection of epinephrine, but neither compound altered the depressor responses following the administration of either acetylcholine or histamine. Other studies indicated that these actions reflected the ganglionic-blocking property of these derivatives.

Compounds V and VI also elicited a weak, transient hypotensive response in the anesthetized cat. Like IV, compound V caused relaxation of the nictitating membrane and mydriasis. Neither V nor VI altered the cardiovascular changes after acetylcholine or histamine.

The hypotensive actions of these compounds were not altered when studied in the bilaterally vagotomized, atropinized cat.

7. Local Anesthetic Action.—Derivative IV exerted a local anesthetic effect when applied to the cornea of the rabbit. Associated with this effect, however, was a marked irritation of the ocular mucosal membrane. No attempt was made to titrate these responses.

EXPERIMENTAL[1]

2-Hydronopoxy-1-ethyldimethylamino Methiodide.—Seven grams (0.03 mole) of 2-hydroxy-1-ethylmethylamino hydrochloride was converted to the corresponding base by dissolving it in 15 ml. of water and made basic with sodium carbonate. After salting with sodium chloride, the mixture was extracted twice with 50 ml. of ether. Ether extracts were combined and dried over sodium carbonate. The ether was then evaporated; 15 ml. of dry acetone was added with 5 ml. of methyliodide and refluxed for 5 minutes. The acetone was evaporated and 15 ml. of dry ether added. The formed crystalline product was separated by filtration and washed twice with 10 ml. of ether, m.p. 169–170°, yield 85%.

Anal.—Calcd. for $C_{16}H_{32}INO$: C, 50.04; H, 8.48; I, 33.03. Found: C, 49.89; H, 8.41; I, 33.24.

[1] Analyses performed by G. Robertson, Florham Park, N. J. All melting points are uncorrected.

Hydronopolhydrazide Dihydrobromide.—A 22.99-Gm. (0.1 mole) quantity of hydronopol bromide and 3.7 Gm. (0.1 mole) of hydrazine (85%) in 100 ml. of ethanol were refluxed for 20 hours; then the reaction mixture was evaporated to 1/5 volume and 100 ml. of ether added. Then the mixture was cooled, and the formed crystals were separated by filtration and washed twice with 15 ml. of ether, m.p. 200°, yield 12%.

Anal.—Calcd. for $C_{11}H_{24}Br_2N_2$: C, 38.39; H, 7.02; N, 8.10. Found: C, 38.21; H, 7.17; N, 7.88.

2-Hydronopoxy-1-ethylpiperazine Dihydrochloride.—A 6.5-Gm. (0.05 mole) quantity of hydroxyethylpiperazine was refluxed with 1.14 Gm. (0.05 mole) of sodium in 35 ml. of xylene for 30 minutes. To the formed sodium salt was then added 11.45 Gm. (0.05 mole) of hydronopol bromide; the mixture was refluxed for 20 hours. The reaction mixture was then filtered and the filtrate evaporated to dryness in high vacuum. Seventy milliliters of dry ether was added and acidified with dry HCl. The formed crude product was collected by filtration and recrystallized from the ethanol-ether mixture, m.p. 169°, yield 78%.

Anal.—Calcd. for $C_{17}H_{34}ClN_2O$: C, 64.22; H, 10.77; N, 7.99. Found: C, 64.01; H, 10.69; N, 8.25.

2-Hydronopoxy-1-ethyldimethylamino Hydrochloride.—A 8.9 Gm. (0.1 mole) portion of dimethylaminoethanol was refluxed with 2.29 Gm. (0.1 mole) of sodium in 100 ml. of xylene. After the salt formation was complete, 22.99 Gm. (0.1 mole) of hydronopol bromide was added; the mixture was refluxed for 18 hours. The formed sodium bromide was filtered off and the filtrate evaporated to dryness. To the residue was then added 100 ml. of dry ether, and it was acidified with dry HCl. The formed product was separated by filtration and washed twice with 15 ml. of ether, m.p. 113°, yield 82%.

Anal.—Calcd. for $C_{15}H_{23}NO$: C, 67.17; H, 8.64; N, 5.14. Found: C, 67.02; H, 8.59; N, 5.13.

SUMMARY

A brief, preliminary evaluation of the pharmacologic activity of several hydronopol derivatives indicates that the compounds studied in the reported series have only limited potential in this area.

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