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Hydroxylamine Analogues Pheniramine*

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Introduction

It is well known that many of the synthetic antihistaminic agents possess some sedative and depressant effects in man.[1] Relatively slight changes in the chemical structures of some of the antihistaminics has led to powerful central nervous system depressants: an example of this relationship is found in the antihistaminic drug, promethazine, 10-(2-dimethylaminopropyl)-phenothiazine, and the central nervous system depressant, promazine, 10-(3-dimethylaminopropyl)-phenothiazine.[2]

While some *O*,*N*-substituted hydroxylamine analogues of pharmacologically active amines are similarly active,[3] this is not true of all such compounds.[4] One of the better antihistaminic drugs is pheniramine.[5] It seemed possible that some hydroxylamine analogues of pheniramine, having the general structures (I) to (IV) below, might be central nervous system depressants. Compounds, in which $n = 2$ and 3, and $R = CH_3$ and C_2H_5, were prepared. The new compounds were prepared by the condensation of 2-benzylpyridine|| with *N*-chloroalkyl-*N*-alkoxy-*N*-alkyl-

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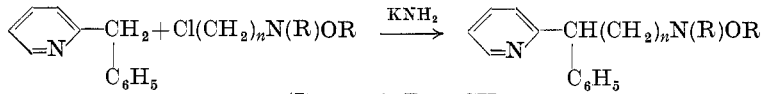
|| Eastman Kodak Company.

amine in liquid ammonia in the presence of potassium amide, according to the following equations:



(I) $n = 2$, R = CH_3
(II) $n = 2$, R = C_2H_5
(III) $n = 3$, R = CH_3
(IV) $n = 3$, R = C_2H_5

The chloroalkylamines used in the preparation of (I), (II), (III) and (IV) were prepared from the corresponding alcohols by interaction with thionyl chloride in benzene.[4]

N-2-Hydroxyethyl-*N*-methoxy-*N*-methylamine and *N*-2-hydroxyethyl-*N*-ethoxy-*N*-ethylamine[6] were prepared by the procedure used by Major and Peterson for the preparation of the former compound, namely *N*-2-hydroxyethyl-*N*-methoxy-*N*-methylamine,[4] or, the condensation of *N*-alkoxy-*N*-alkylamine with ethylene oxide in methanol.

N-3-Hydroxypropyl-*N*-methoxy-*N*-methylamine was produced by heating a solution of *N*-methoxy-*N*-methylamine and 3-chloropropanol-1 in benzene at 100° for 48 h.

N-3-Hydroxypropyl-*N*-ethoxy-*N*-ethylamine was prepared by heating a mixture of *N*-ethoxy-*N*-ethylamine and sodium allyloxide in allyl alcohol at 100–120° for 9 h.[7]

Experimental

N-*Hydroxyethyl*-N-*ethoxy*-N-*ethylamine.* To 42 g (0·47 mole) of *N*-ethoxy-*N*-ethylamine[8] in 30 ml of methanol was added a cold solution of 30 g (0·68 mole) of ethylene oxide in 90 ml of methanol. The mixture was refluxed for 7 h on a steam bath with stirring (condenser temperature less than 10°). During that time the temperature of the reaction mixture rose to 65°. The reaction mixture was cooled, concentrated under reduced pressure and the residue was distilled; the fraction of b.p. 85–90° (38 mm) was collected, yield 42 g (66 per cent); re-distilled, b.p. 65–66° (11 mm). Jones and Burns[6] reported b.p. 63° (10 mm).

N-*3-Hydroxypropyl*-N-*methoxy*-N-*methylamine.* A solution of 50 g (0·53 mole) of 3-chlorpropanol-1 and 65 g (1·06 moles) of *N*-methoxy-*N*-methylamine in 60 ml of benzene was heated in a pressure bottle in a boiling water bath for 48 h. As the reaction mixture was cooled, 35 g of *N*-ethoxy-*N*-ethylammonium chloride precipitated. The filtrate from this was concentrated *in vacuo*, the residue acidified with hydrochloric acid while cooling the reaction mixture and then extracted with five 50 ml portions of ether. The aqueous layer was made alkaline with dilute sodium hydroxide and extracted with ether. This latter ether extract was dried with sodium sulphate; the ether was then evaporated and the residue was distilled, b.p. 94–96° (34–37 mm); yield, 47 g (74 per cent). Re-distilled, b.p., 95–97° (39 mm).

Anal. Calcd. for $C_5H_{13}NO_2$: C, 50·39; H, 10·99. Found: C, 50·02; H. 11·13.

N-*3-Hydroxypropyl*-N-*ethoxy*-N-*ethylamine.* To a solution of 46 g (2 g atoms) of sodium in 348 g (6 moles) of allyl alcohol was added 188 g (2 moles) of *N*-ethoxy-*N*-ethylamine. The mixture was placed in an autoclave and heated carefully to 100°; it was heated at 100–120° for 9 h with shaking. It was then cooled and the semi-solid mass in the bottle was dissolved in water; the aqueous solution was acidified with hydrochloric acid and then extracted several times with ether. The acid solution was made basic with sodium hydroxide and extracted with ether. This ether solution was dried with sodium sulphate and then distilled. The fraction b.p. 97–125° (22 mm) was collected (110 g). An additional 35 g was distilled, b.p. 125–160° (22 mm) but was not further investigated. The lower boiling fraction was re-distilled, b.p. 88–92° (11 mm) as a colourless oil; yield 79 g (27 per cent).

Anal. Calcd. for $C_7H_{17}NO_2$: C, 57·11; H, 11·64. Found: C, 57·10; H, 11·43.

Picrate. Prepared in ether and re-crystallized from *n*-butanol, m.p. 61–64°.

Anal. Calcd. for $C_{13}H_{20}N_4O_9$: C, 41·49; H, 5·36. Found: C, 41·44; H, 5·26.

N-*Chloroalkyl*-N-*alkoxy*-N-*alkylamine.* To a solution of 0·55 mole of *N*-hydroxyalkyl-*N*-alkoxy-*N*-alkylamine in 300 ml of dry benzene was added 1·26 moles of thionyl chloride in 200 ml of dry benzene; the dark mixture was heated for 5 h under reflux

until the evolution of gas ceased. The reaction mixture was cooled and the benzene and excess thionyl chloride were removed *in vacuo*. The tarry residue was made basic by the addition with cooling of a cold 30 per cent solution of potassium hydroxide. This was extracted with four 100 ml portions of ether. After the ether solution had been dried with sodium sulphate the ether was evaporated and the remaining oil was distilled *in vacuo*. It was then re-distilled.

N-*3-Chloropropyl*-N-*methoxy*-N-*methylamine*, b.p. 60° (31 mm); yield, 65 per cent.

Anal. Calcd. for $C_5H_{12}ClNO$: C, 43·64; H, 8·79. Found: C, 43·22; H, 8·83.

N-*3-Chloropropyl*-N-*ethoxy*-N-*ethylamine*, b.p. 80° (32 mm); yield, 47 per cent.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50·75; H, 9·74. Found: C, 50·91; H, 9·63.

N-*2-Chloroethyl*-N-*ethoxy*-N-*ethylamine*, b.p. 81° (57 mm); yield 50 per cent.

Anal. Calcd. for $C_6H_{14}ClNO$: C, 47·50; H, 9·31. Found: C, 47·39; H, 9·52.

1-Phenyl-1-(2-pyridyl)-N-*alkoxy*-N-*alkylaminoalkane*. Into a three-necked round-bottom flask, equipped with stirrer, dropping funnel and air condenser, was run 1·5 l. of liquid ammonia; a spatula of ferric oxide was then added as a catalyst for the formation of potassium amide. While stirring, 9·5 g (0·243 g atm) of potassium, in small pieces, was added. After 20 to 30 min, when the dark blue colour of the dissolved potassium had disappeared, the solution turned grey. Through the dropping funnel 41·2 g (0·243 mole) of 2-benzylpyridine was then added. The mixture was stirred for 20 min. To the intensely reddish solution was added 0·243 mole of *N*-chloroalkyl-*N*-alkoxy-*N*-alkylamine. After 3 h 300 ml of absolute ether was added. The reaction mixture was stirred for 20 h at room temperature, when alcohol was added in order to decompose traces of potassium amide. After the addition of water the solution was extracted with ether. The ether solution was dried over sodium sulphate, the ether evaporated and the residual oil distilled *in vacuo* and then re-distilled.

The dipicrates of these bases were prepared in the usual way in

ether and were re-crystallized from methanol, except number (I) which was re-crystallized from ethanol.

The dihydrochlorides of (II), (III) and (IV) were prepared by the addition of a solution of hydrogen chloride in dry ether to an ethereal solution of the base.

1-Phenyl-1-(2-pyridyl)-N-methoxy-N-methyl-3-aminopropane, (I), b.p. 113° (0·06 mm); yield, 40 per cent.

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74·95; H, 7·88; N, 10·93. Found: C, 74·73; H, 7·65; N, 10·87.

Dipicrate: m.p. 159–161°.

Anal. Calcd. for $C_{28}H_{26}N_8O_{15}$: C, 47·24; H, 3·66; N, 15·63. Found: C, 47·08; H. 3·56; N, 15·45.

1-Phenyl-1-(2-pyridyl)-N-ethoxy-N-ethyl-3-aminopropane, (II), b.p. 123–125° (0·06 mm); yield, 44 per cent.

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76·02; H, 8·51; N, 9·85. Found: C, 75·62; H, 8·61; N, 10·35.

Dipicrate: m.p. 164–166°.

Anal. Calcd. for $C_{30}H_{30}N_8O_{15}$: C, 48·48; H, 4·07; N, 15·15. Found: C, 48·66; H, 4·19; N, 15·56.

Dihydrochloride: Re-crystallized by dissolving in acetone and re-precipitating with ether, followed by re-precipitation twice from alcohol solutions with dry ether, m.p. 177–180°.

Anal. Calcd. for $C_{18}H_{25}Cl_2N_2O$: C, 60·22; H, 7·33; Cl, 19·84; N, 7·88. Found: C, 60·22; H, 7·48; Cl, 20·18; N, 8·06.

1-Phenyl-1-(2-pyridyl)-N-methoxy-N-methyl-4-aminobutane,(III), b.p. 145–150° (0·5 mm); yield 89 per cent.

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75·52; H, 8·20; N, 10·36. Found: C, 75·18; H, 8·06; N, 9·92.

Dipicrate: m.p. 149–150°.

Anal. Calcd. for $C_{29}H_{28}N_8O_{15}$: C, 47·80; H, 3·87; N, 15·39. Found: C, 48·04; H, 4·06; N, 15·36.

Dihydrochloride: was very hygroscopic, m.p. 80–85° (uncertain) with foaming.

Anal. Calcd. for $C_{17}H_{24}Cl_2N_2O$: C, 59·48; H, 7·05; N, 8·16. Found: C, 59·37; H, 7·19; N, 8·20.

1-Phenyl-1-(2-pyridyl)-N-ethoxy-N-ethyl-4-aminobutane, (IV), b.p. 148–153° (0·05 mm); yield, 58 per cent.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76·49; H, 8·78; N, 9·39. Found: C, 75·98; H, 8·71; N, 9·49.

Dipicrate: m.p. 150–151°.

Anal. Calcd. for $C_{31}H_{32}N_8O_{15}$: C, 49·21; H, 4·26; N, 14·82. Found: C, 49·24; H, 4·54; N, 14·58.

Dihydrochloride: re-crystallized by dissolving in acetone and re-precipitating with ether.

Anal. Calcd. for $C_{19}H_{28}Cl_2N_2O$: C, 61·45; H, 7·60; Cl, 19·12; N, 7·54. Found: C, 61·20; H, 7·41; Cl, 19·25; N, 7·30.

Biological Activity

As is well known, many of the antihistaminic agents which are clearly sedative in man fail to produce observable signs of depression when used alone in various species of animals. Winter,[9] however, has demonstrated that various antihistaminics are capable of potentiating barbiturate-induced depression in animals and suggested that such activity was correlated with their sedative properties in man. In view of this, the various hydroxylamine analogues of pheniramine were studied with respect to their barbiturate potentiating action. Each compound was inactive with respect to blocking histamine vasodepressor response in dogs after doses of 10 and 20 mg/kg I.V.

Method

The effect of the various agents on the duration of action of hexobarbital in mice was determined as follows: Mice were pretreated intraperitoneally with the agent under study 30 min prior to the intraperitoneal injection of an effective anaesthetic dose of hexobarbital (100 mg/kg). The duration of the subsequent anaesthetic effect, as indicated by loss of the righting reflex, was measured and compared to the similar effect of the barbiturate in a concurrent control group of mice which had received only the vehicle. Groups of 10 mice were employed. The end-point or recovery from the anaesthetic was always taken at the time the mice spontaneously rolled to the supine position. To obviate observer bias, the experiments were conducted by the 'blind' technique.

The effect of the various agents on the potency of hexobarbital was determined by measuring its anaesthetic dose 50 (AD50) after the administration of the potentiator as compared to the

AD50 in the absence of the potentiator. Several groups (4 to 6) of 10 mice each were treated with the same dose of potentiator 30 min prior to the intravenous injection of hexobarbital. The dose of hexobarbital was varied so that the proportion of the mice responding with loss of the righting reflex within 1 to 2 min increased from 0 to 100 per cent as the dose of the anaesthetic was raised. The AD50 was thus calculated from the dose response line, relating log dose of anaesthetic and the proportion of mice losing the righting reflexes, by the moving average procedure of Thompson.[10] This experiment was also conducted by the blind technique.

Female mice of the CF‡‡1 strain were employed in all experiments. The doses of all drugs used herein were calculated as the base.

Results and Discussion

The four hydroxylamine analogues of pheniramine were found capable of markedly prolonging the depressant properties of hexobarbital in mice, as is shown by the data in Table I. In this respect, each of the four compounds was considerably more active than pheniramine, which exerted only minimal prolongation and then required a convulsive dose. The new agents were also more active than iproniazid, but less active than either chlorpromazine or SKF–525A (β-diethylaminoethyl-α,α-diphenylvalerate hydrochloride) (Table I).

The data in Table I also reveal some of the structural requirements for activity within the limited series of hydroxylamine analogues. A comparison between compounds (I) and (II) and (III) and (IV) suggests that the methoxy analogue was more active than the ethoxy derivative. In the latter pair, however, there was no significant increase in activity with methoxy substitution, as compared to its corresponding ethoxy derivative. It may be seen, however, that both compounds (III) and (IV) are more active than either (I) or (II). This finding suggests that the nature of the alkyl side-chain may be more important than the alkoxy substitution in determining maximal activity.

The experiments outlined in Table I do not reveal the mechanism by which the hydroxylamine derivatives of pheniramine prolong the action of hexobarbital. Brodie *et al.*[11,12] have shown

Table I. Effect of various hydroxylamine analogues of pheniramine on the duration of action of hexobarbital in mice

Compound	Dose,* mg/kg I.P.	Mean duration of loss of the righting reflexes,† min.		Ratio, $\frac{\text{Treated}}{\text{control}}$	Dose, mg/kg I.P. required for ratio = 6·0‡
		control	treated		
(I)	3·125	38·8	77·2	2·0	18
	6·25		127·0	3·3	
	12·5		172·4	4·4	
	25·0		279·8	7·2	
	50·0		>335·0	>8·6	
(II)	3·125	48·0	90·2	1·9	48
	6·25		105·3	2·2	
	12·5		127·9	2·7	
	25·0		205·7	4·3	
	50·0		314·2	6·5	
	100·0		364·8	7·6	
(III)	3·125	32·2	175·9	5·5	7·2
	6·25		176·9	5·5	
	12·5		221·9	6·9	
	25·0		225·5	7·0	
	50·0		>305·4	>9·5	
(IV)	3·125	34·7	148·3	4·3	9·0
	6·25		182·8	5·3	
	12·5		213·5	6·2	
	25·0		283·0	8·2	
	50·		>290·5	>8·4	
Pheniramine	25·0	36·9	35·5	0·9	—
	50·0		52·3	1·4 (conv.)	
	100·0		lethal		
Chlorpromazine	2·5	30·6	88·4	2·7	7·0
	5·0		127·2	5·5	
	10·0		213·1	7·0	
SKF-525A	2·5	27·6	101·3	3·7	10·0
	5·0		126·6	4·6	
	10·0		166·4	6·0	
	20·0		207·2	7·6	
Iproniazid	12·5	20·0	55·2	2·8	76
	25·0		68·7	3·4	
	50·0		107·3	5·4	
	100·0		118·2	5·9	
	200·0		166·2	8·3	

* Administered 30 minutes before hexobarbital. The latter was given to all mice at a level of 100 mg/kg, also intraperitoneally.

† Groups of 10 mice were employed at each dose level. See text for details of method.

‡ Estimated graphically.

that at least two types of agents may produce a similar result. The first of these are the metabolic prolonging agents, which act by decreasing the rate of destruction of hexobarbital through enzymatic interference. This type is best exemplified by SKF–525A.[13,14] The second category of agents which may prolong the depressant properties of barbiturates are the tranquillizing agents, of which chloropromazine is the most widely studied. According to Brodie *et al.*[11,12] these latter act by increasing the sensitivity of the central nervous system to barbiturates.

In an effort to determine the nature of the action of the hydroxylamine derivatives, their action on the anaesthetic potency of hexobarbital was determined. SKF–525A and chlorpromazine were studied in comparison. The data in Table II demonstrate

Table II. Effect of various agents on the anaesthetic doses of hexobarbital in mice

Compound	Dose,* mg/kg I.P.	Anaesthetic potency of hexobarbital AD 50: mg/kg I.V.	
		Treated	Concurrent control†
(I)	18	35·9	35·3
SKF–525A	10	28·5	28·1
Chlorpromazine	10	11·0	28·1

* Administered 30 min before determining the AD50 of hexobarbital. The dose used with each agent was one which produced a six (or more) fold increase on the duration of action of hexobarbital (see Table I).

† Determined on the same day as the treated group.

that compound (I) was incapable of lowering (potentiating) the anaesthetic dose of hexobarbital. In this respect the agent resembled SKF–525A and was unlike chlorpromazine which increased the anaesthetic potency of hexobarbital, as indicated by the lower anaesthetic dose 50. Such evidence suggests that the hydroxylamine derivatives are probably SKF–525A-like in mode of action and that they are not true depressants. This conclusion is supported by the observation that none of the new agents produced observable signs of depression in mice in the

dose range listed in Table I and, moreover, did not reveal depressant actions in rats studied by operant behavioural techniques (J. J. Boren and H. M. Hanson, personal communication).

Summary. Certain chemical analogues of the antihistaminic drug, pheniramine, namely, 1-phenyl-1-(2-pyridyl)-3-*N*-alkoxy-*N*-alkylamino propane and 1-phenyl-1-(2-pyridyl)-4-*N*-alkoxy-*N*-alkylaminobutane, have been made in which the alkoxy and alkyl groups were methoxy and methyl, or ethoxy and ethyl. All of these compounds markedly potentiated the length of hypnosis produced in animals by barbiturates, probably by a mechanism of action similar to that demonstrated by SKF–525A.

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