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Derivatives of Hydroxylamine: Central Nervous System Stimulants

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The value of the drug, iproniazid, 1-isonicotinoyl-2-isopropylhydrazine, in the treatment of certain types of apathy and depression has led to the study of a number of other derivatives of hydrazine for that purpose.[1-3] It was postulated that iproniazid owed its antidepressive properties to the fact that it is a monoamine oxidase inhibitor.[4] It has been found that most, if not all, of the new antidepressive hydrazine derivatives were monoamine oxidase inhibitors.[4]

In view of the rather close chemical similarity between hydrazine, H_2NNH_2, and hydroxylamine, H_2NOH, a number of hydroxylamine derivatives which were related chemically to certain hydrazine derivatives have been synthesized. The effect of these compounds on the behaviour of animals and on monoamine oxidase, *in vitro*, has then been tested.

Analogues of Iproniazid

N-Alkoxynicotinamide hydrochlorides were prepared by the interaction of a suspension of one molar equivalent of nicotinoyl chloride hydrochloride[5] in dry ether with three molar equivalents of the appropriate alkoxyamine. The *N*-alkoxynicotinamide hydrochlorides, in which the alkoxy group was methoxy, ethoxy and isopropoxy, were colourless crystals, which were insoluble in ether. The *N*-alkoxynicotinamides themselves were also only moderately soluble in ether, but were quite insoluble in water.

N-Alkoxyisonicotinamides were prepared by the interaction of isonicotinoyl chloride with alkoxyamines, where the alkoxy groups were methoxy,[7] ethoxy[8] and isopropoxy.[9] The amides were extracted in an extractor with ether. Due to their relatively low solubility in ether, they precipitated from the ether extract as

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oils, which eventually solidified. The hydrochlorides of the *N*-alkoxyisonicotinamides were formed by the addition of a solution of hydrogen chloride in ether to a solution of the base in alcohol.

Analogues of β-Phenylisopropylhydrazine

β-Phenylisopropylhydrazine, known also as JB 516,[3] was one of the better known psychic energizers. Analogous *N*-alkoxy-*N*-(2-phenyl)isopropylamines, $C_6H_5CH_2CH(CH_3)NHOR$, have been prepared, in which R = methyl, ethyl or isopropyl, by the catalytic reduction of the corresponding *O*-alkyl-oxime by the method of Jones and Major.[10] The *O*-alkyl benzyl methylketoximes, $C_6H_5CH_2C(CH_3)=NOR$, were formed by the interaction of 1-phenyl-2-propanone with the appropriate alkoxyamine in boiling alcohol. The *N*-alkoxy-*N*-(2-phenyl)isopropylamines were distillable oils which were soluble in the usual organic solvents, but relatively insoluble in water. They behaved as quite weak bases.

A lower homologue of the above compounds, namely *N*-methoxy-*N*-2-(phenyl)ethylamine, was prepared by the interaction of phenethylamine with two molar proportions of methoxyamine. This compound was a weakly basic oil, which was relatively insoluble in water.

In order to increase the basicity of the compounds, the pyridine nucleus was substituted for the phenyl nucleus in some of the above analogues of β-phenylisopropylhydrazine. 1-(β-Pyridyl)-2-methoxyaminopropane, 3-Py-$CH_2CH(CH_3)NHOCH_3$, was produced by the catalytic reduction of *O*-methyl-β-picolyl methyl ketoxime, 3-Py-$CH_2C(CH_3)=NOCH_3$, in two molar proportions of hydrogen chloride in alcohol. The *O*-methyl ketoxime was produced by refluxing an absolute alcoholic solution of methoxyamine with 3-acetonylpyridine, prepared by the method of Raynolds and Levine.[11] Both the *O*-methyl-oxime and the 1-(β-pyridyl)-2-methoxyaminopropane were oils which showed strong absorption in the infrared at 9·5 μ, which seems characteristic of the lower *O*-alkyl derivatives of hydroxylamine. A monopicrate of the *O*-methyloxime was a crystalline solid.

Similarly, 1-(γ-pyridyl)-2-methoxyaminopropane and 1-(γ-pyridyl)-2-isopropoxyaminopropane,

$$4\text{-Py-}CH_2CH(CH_3)NHOCH(CH_3)_2,$$

were prepared by the catalytic reduction of *O*-methyl and *O*-isopropyl-γ-picolyl methyl ketoxime, 4-Py-$CH_2C(CH_3)=NOR$,

in two molar proportions of hydrogen chloride in alcohol. The *O*-alkyl ketoximes were produced by refluxing a solution of the *O*-alkylhydroxylamine with 4-acetonylpyridine.[11] Both the *O*-methyloxime and the 1-(γ-pyridyl)-2-methoxyaminopropane were oils which showed strong absorption in the infrared at 9·5 μ. The corresponding *O*-isopropoxy derivatives are oils which show practically no absorption at 9·5 μ in the infrared. It is not known why substituted *O*-isopropoxyamines do not show absorption at this point since substituted *O*-methoxy and *O*-ethoxyamines quite generally do show this absorption. Solid picrates of the *O*-alkyloximes were prepared.

The analogous β-arylethoxyamines, $ArCH_2CH_2ONH_2$ and their hydrochlorides, in which the aryl groups were phenyl or 3,4,5-trimethoxyphenyl, were prepared. The latter compound was of particular interest because of its chemical relation not only to the psychic energizer, JB 516,[3] but also to the hallucinogenic agent, mescaline,[12] 3,4,5-trimethoxyphenethylamine. In order to prepare β-phenylethoxyamine, a solution of phenethyl bromide and the sodium salt of hydroxyurethane in dimethylformamide were heated for several hours on a steam bath. This gave *N*-(β-phenylethoxy)urethane, $C_6H_5CH_2CH_2ONHCOOC_2H_5$. Saponification of this compound with sodium hydroxide in 50 per cent alcohol gave β-phenylethoxyamine, as an oil. The hydrochloride was an unstable colourless crystalline solid.

Similarly, 3,4,5-trimethoxy-β-phenylethoxyamine was prepared by a series of reactions from 3,4,5-trimethoxyphenylacetic acid, which in turn was obtained by the method of Slotta and Muller;[13] the intermediate, 3,4,5-trimethoxybenzoyl chloride which was used by Slotta and Muller, was prepared by the method of Späth.[14] From 3,4,5-trimethoxyphenylacetic acid the sequence of reactions was as follows:

$$(CH_3O)_3C_6H_2CH_2COOH \longrightarrow (CH_3O)_3C_6H_2CH_2COOC_2H_5$$
(I) (II)

$$\xrightarrow{LiAlH_4} (CH_3O)_3C_6H_2CH_2CH_2OH \xrightarrow{SOCl_2} (CH_3O)_3C_6H_2CH_2CH_2Cl$$
(III) (IV)

$$\xrightarrow{C_2H_5OCNHONa} (CH_3O)_3C_6H_2CH_2CH_2ONHCOOC_2H_5$$
(V)

$$\xrightarrow[alc.]{NaOH} (CH_3O)_3C_6H_2CH_2CH_2ONH_2$$
(VI)

Compound II was formed by the esterification of I with a mixture of ethyl alcohol and sulphuric acid. Compound III was obtained by the reduction of II with lithium aluminium hydride in ether. Compound IV formed when III was treated with thionyl chloride in pyridine. Preliminary experiments, directed towards the preparation of the corresponding bromide, were unsuccessful. Compound V was produced by the interaction of IV with hydroxyurethane in sodium ethoxide solution. Saponification of V with a solution of sodium hydroxide in 50 per cent alcohol gave VI. The hydrochloride of VI was obtained by the addition of hydrogen chloride in ether to an ethereal solution of VI in ether. It was an unstable colourless crystalline solid and darkened readily when it was stored at room temperature.

Pharmacological Activity

The Merck Institute for Therapeutic Research, West Point, Pennsylvania has kindly given us the information shown in Tables I and II on the toxicity and biological activity of these new compounds.

Table I. Certain biological properties of *N*-alkoxypyridine carboxylic acid amide salts

Compound no.		LD_{50} mouse, i.p. mg/kg	Effect on serotonin content of mouse brains after i.p. injection[a]
I	*N*-Methoxynicotinamide hydrochloride	597	100 mg/kg (3 days): increase
II	*N*-Ethoxynicotinamide hydrochloride	> 640	100 mg/kg: negligible increase
III	*N*-Isopropoxynicotinamide hydrochloride	> 640	—
IV	*N*-Methoxyisonicotinamide hydrochloride	362	—
V	*N*-Ethoxynicotinamide hydrochloride	394	100 mg/kg: negligible increase
VI	*N*-Isopropoxyisonicotinamide hydrochloride	> 640	100 mg/kg: slight increase
VII	Iproniazide phosphate	—	100 mg/kg: increase

[a] Dr. C. C. Porter, of the Merck Institute for Therapeutic Research, reports that groups of five mice each were injected intraperitoneally with two doses of the compound under test. The first dose was given 24 h prior to the second, which was administered 1 h prior to sacrificing. The brains of these mice were pooled and the serotonin was assayed by the method of Udenfriend, Weisbach and Brodie.[15] A concurrent group of control mice received the vehicle employed to dissolve or suspend the test drugs.

Table II. Biological activity of some *N*-alkoxy-*N*-(2-aryl)-alkylamines

Compound no.		LD_{50} mouse, i.p. mg/kg	Amphetamine-like activity[a]
VIII	*N*-Methoxy-*N*-(2-phenyl)-isopropylamine	> 640	Marked
IX	*N*-Ethoxy-*N*-(2-phenyl)-isopropylamine	> 640	Marked
X	*N*-Isopropoxy-*N*-(2-phenyl)-isopropylamine	65	Marked
XI	*N*-Methoxy-*N*-(2-phenyl)-ethylamine hydrochloride	452	Inactive
XII	1-(3-Pyridyl)-2-methoxy-aminopropane	> 324	—
XIII	β-Phenylethoxyamine hydrochloride	> 640	Inactive
XIV	3,4,5-Trimethoxy-β-phenyl-ethoxyamine hydrochloride	> 640	Inactive

[a] Amphetamine-like activity was shown by hyperactivity in mice receiving the compound, increasing lever pressing rates by rats under operant conditions and increasing blood pressure in anaesthetized dogs. None of the compounds tested were quite as active as amphetamine itself.

Dr. Barbara Blair, of the Department of Neurology and Psychiatry of the University of Virginia, has found that in concentrations as high as 10^{-4} compounds II, III, V, VI, VIII, IX, X, and XIV in Tables I and II showed no or only negligible inhibition of monoamine oxidase in liver or brain homogenates, based on the amount of serotonin that is utilized. The methods of Horita[16] were used. Under similar conditions and at a concentration of 10^{-4}, phenyl-β-isopropylhydrazine (JB 516) decreased the activity of the amine oxidase in a liver homogenate to zero and in a brain homogenate to 12 per cent of normal.

Experimental

Iproniazid Analogues

N-*Alkoxynicotinamide hydrochlorides.* A suspension of nicotinoyl chloride hydrochloride[5] in dry ether was placed in a 500-ml three-necked flask, fitted with a stirrer, reflux-condenser, drying tube and dropping funnel. At least 0·3 mole of the *N*-alkoxyamine in dry ether[6, 7, 8] was added slowly with stirring. After

stirring and refluxing for 1 h, 150 ml of water was added to the reaction mixture. The aqueous solution was made basic with sodium carbonate, and then extracted with ether in an extraction apparatus for at least 48 h.

The free amides are not easily soluble in ether and form an oily layer under the ether during the extraction. This oil generally crystallized and could be transformed directly into the hydrochloride by dissolving it in ethanol and precipitating it, under cooling, with a dry ethereal solution of hydrogen chloride. The original ether extract was dried (Na_2SO_4 anhyd.); evaporation left additional amide which was converted as above into the hydrochloride. The hydrochloride was recrystallized from ethanol or ethanol–ether.

Table III. *N*-Alkoxynicotinamide hydrochloride

Alkoxy group	Yield, %	m.p., °C	Analysis, %					
			Calcd.			Found		
			C	H	N	C	H	N
CH_3O	20	142	44·44	4·67	14·99	44·57	4·81	14·85
C_2H_5O	57	161–163	47·41	5·47	13·86	47·29	5·31	13·71
$(CH_3)_2CHO$	51	141–143	49·89	6·05		50·09	6·19	

N-*Alkoxyisonicotinamide hydrochlorides.* A solution of at least 0·2 mole of the *N*-alkoxyamine in dry ether was added slowly with stirring to a solution of isonicotinoyl chloride[9] (b.p. 75°/12 mm) in dry ether. After having stirred the mixture, with refluxing, for 1 h, 150 ml of water was added. The aqueous solution was made basic with sodium carbonate. The free amides were not readily soluble in ether but were extracted with ether continuously for 48 h. An oil separated in the ether extract during the extraction which crystallized on standing. Evaporation of the ether gave additional crystals. The amide was recrystallized from ethanol or ethanol–ether.

The hydrochlorides of *N*-alkoxy isonicotinamides were prepared by the addition of a solution of hydrogen chloride in dry ether to an alcoholic solution of the free amide. The colourless crystals were recrystallized from ethanol or ethanol–ether.

Table IV. *N*-Alkoxyisonicotinamides

Alkoxy group	Yield, %	m.p., °C	Analysis, %					
			Calcd.			Found		
			C	H	N	C	H	N
CH_3O	22	101–102	55·26	5·30		54·86	5·30	
C_2H_5O	69	116–118	57·82	6·07	16·94	57·65	5·90	16·85
$(CH_3)_2CHO$	64	132–133·5	59·98	6·72	15·55	59·95	6·54	15·77

Table V. *N*-Alkoxyisonicotinamide hydrochloride

Alkoxy group	m.p., °C	Analysis, %					
		Calcd.			Found		
		C	H	N	C	H	N
CH_3O	184–185	44·66	4·67		44·38	4·67	
C_2H_5O	186–187	47·41	5·47	13·86	47·38	5·45	14·07
$(CH_3)_2CHO$	187–189	49·89	6·05	12·94	50·08	6·19	12·55

N-*Alkoxy*-N-(*2-phenyl*)-*isopropylamines*

O-*Alkyl benzyl methyl ketoximes.* Equimolar proportions of phenyl-2-propanone (Eastman) and the appropriate *O*-alkylhydroxylamine[6–8] were dissolved in at least two molar equivalents of absolute ethanol. After the solution had been refluxed for 4 h, the alcohol was distilled off and the residue was distilled *in vacuo*. Colourless liquids were obtained.

Table VI. *O*-Alkyl benzyl methyl ketoximes

Alkyl group	Yield, %	b.p., °C/mm	Analysis, %			
			Calcd.		Found	
			C	H	C	H
CH_3—	97·3	73/0·35				
C_2H_5—	98·5	96/4·5	74·55	8·51	74·08	8·81
$(CH_3)_2CH$—	94·1	124/14	75·35	8·96	75·23	8·93

N-*Alkoxy*-N-(*2-phenyl*)-*isopropylamines.* To a solution of the *O*-alkyl benzyl methyl ketoxime (0·2 mole) in absolute ethanol (100 ml) was added 12N hydrochloric acid (0·22 mole), and this solution was hydrogenated in an Adams–Parr apparatus[17] with 0·5 g of platinum oxide until 0·2 mole of hydrogen had been absorbed. After filtration and evaporation of the alcohol, the residue was dissolved in a small amount of water, the solution made alkaline with sodium hydroxide, and the base was extracted with ether. The combined ether extracts were washed twice with water and then dried (Na_2SO_4 anhyd.). After evaporation of the ether, the residual oil was distilled *in vacuo*. The colourless oils which were obtained on distillation were weak bases which required an excess of dilute hydrochloric acid in order to form clear solutions in water.

Table VII. *N*-Alkoxy-*N*-(2-phenyl)-isopropylamines

Alkoxy group	Yield, %	b.p., °C/mm	Analysis, %			
			Calcd.		Found	
			C	H	C	H
CH_3O—	68·7	75/1·2	72·69	9·15	73·09	9·11
C_2H_5O—	70	81/1·7	73·71	9·54	74·02	9·66
$(CH_3)_2CHO$—	68·1	124/18	74·56	9·90	74·49	9·90

N-*Methoxy*-N-*2-phenylethylamine.* A solution of methoxyamine[6] (7·6 g, 0·16 mole) in dry ether was added to phenethyl bromide (Eastman) (15 g, 0·08 mole). An oily solid precipitated slowly. After the mixture had stood at room temperature for 7·5 months, the odour of phenethyl bromide, on evaporation of the ether filtrate, had almost entirely disappeared. The oily solid was separated from the ether solution by decantation. The solid was separated from the oil by pressing the mixture on to a porous plate. A white solid was obtained which melted at 91–165°. It was added to a slight excess of cold 5N sodium hydroxide until alkaline to phenolphthalein. The alkaline solution was extracted with ether; after the addition of anhydrous potassium carbonate it was further extracted with ether. The combined ether extracts were dried with potassium carbonate and then distilled. All but a trace distilled at a temperature below 50°. Dry hydrogen chloride was passed into the distillate. A white solid precipitate

formed which was recrystallized from butanol as colourless, shiny plates, m.p. 153°. Lossen gives 149° as the melting point of methoxyammonium chloride.[18]

Anal. Calcd. for CH_6ClNO: C, 14·42; H, 7·24. Found: C, 14·43; H, 7·02.

Dry hydrogen was passed into the original ethereal solution from which the oily solid was removed by decantation. A white precipitate, m.p. 92–144°, formed. This was dissolved in sufficient 5N potassium hydroxide to give an alkaline reaction to phenolphthalein. An oil separated and was extracted with ether. Additional oil was extracted with ether after dry potassium carbonate had been added to the aqueous layer. The combined ether extracts were dried with potassium carbonate, and distilled. An ethereal smelling oil was obtained, b.p. 129–130°/43 mm; yield, 3 g (25 per cent).

Anal. Calcd. for $C_9H_{13}NO$: C, 71·49; H, 8·65. Found: C, 71·45; H, 8·86.

1-Pyridyl-2-alkoxyaminopropanes

O-*Alkyl pyridylmethyl methyl ketoxime.* The appropriate ketone (0·1 mole), either 3-acetonylpyridine[12] or 4-acetonylpyridine,[11] was mixed with a slight excess of a molar equivalent of the alkoxyamine. Heat was evolved, the reaction mixture was diluted with absolute ethanol and the solution was refluxed for 4 h. The alcohol was removed by distillation and the residual oil was distilled *in vacuo*. The *O*-methylketoximes showed strong absorption in the infrared at 9·5 μ, which was not shown by the *O*-isopropyl derivative.

The picrates of the *O*-alkyl picolyl methyl ketoximes were prepared in ether and then recrystallized from ethanol.

Table VIII. *O*-Alkyl picolyl methyl ketoxime picrates

Alkyl group	Position of pyridyl side chain	m.p., °C	Analysis, %			
			Calcd.		Found	
			C	H	C	H
CH_3	β	158	45·80	3·84	45·77	3·77
CH_3	γ	112–113	45·80	3·84	45·87	3·90
$(CH_3)_2CH$	γ	125	48·46	4·55	48·23	4·32

Table IX. *O*-Alkyl picolyl methyl ketoxime

Alkyl group	Position of pyridyl side chain	b.p., °C/mm	Yield, %	Analysis, %					
				Calcd.			Found		
				C	H	N	C	H	N
CH_3	β	102/14	89	65·82	7·37	17·06	64·83	7·37	16·79
CH_3	γ	110/14	59·5	65·82	7·37		65·30	7·41	
$(CH_3)_2CH$	γ	118–120/14	93·7	68·71	8·39		68·56	8·08	

1-Pyridyl-2-alkoxyaminopropane. To a solution of an *O*-alkyl picolyl methyl ketoxime (0·1 mole) in absolute ethanol (200 ml) was added 12N hydrochloric acid (0·2 mole) and then platinum oxide (200 mg). The mixture was hydrogenated in an Adams–Parr apparatus. When the theoretical amount of hydrogen had been absorbed, the mixture was filtered and the filtrate was evaporated *in vacuo* in order to remove most of the alcohol. The residue was diluted with water. After the aqueous solution had been made alkaline with sodium carbonate, it was extracted four to six times with ether and the ether solution dried (Na_2SO_4 anhyd.). Evaporation left oils which were distilled and redistilled *in vacuo*. In order to remove a yellow impurity, it was necessary to treat the β-pyridyl derivative with charcoal. The infrared spectrum of the *O*-alkoxy derivatives showed strong absorption at 9·5 μ but there was practically no absorption at this wave length by the *O*-isopropyl derivative.

Table X. 1-Pyridyl-2-alkoxyaminopropane

Alkoxy group	Position of pyridyl side chain	b.p., °C/mm	Yield, %	Analysis, %					
				Calcd.			Found		
				C	H	N	C	H	N
CH_3	β	107–108 /14	22	65·03	8·49	16·85	64·52	8·64	16·80
CH_3	γ	115–117 /14	63	65·03	8·49	16·85	64·70	7·81	16·50
$(CH_3)_2CH$	γ	125/14	73	68·00	9·35	14·42	67·80	9·11	14·27

β-Arylethoxyamines

Ethyl 3,4,5-trimethoxyphenylacetate. A solution of 3,4,5-trimethoxyphenylacetic acid[13,14] (5·6 g, 0·25 mole) in a cold mixture of concentrated sulphuric acid (50 ml) and absolute ethanol (300 ml) was refluxed for 2 h. The reaction mixture was cooled and poured into 1 l. of water. An oil separated which was extracted four times with ether. The combined ether extracts were washed with water and sodium carbonate solution and then dried with sodium sulphate. Evaporation left an oil, which was

distilled, b.p. 170°/0·7 mm. A practically colourless oil was obtained; yield, 85·8 per cent. It crystallized as large prisms, m.p. 30°.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61·40; H, 7·13. Found: C, 61·25; H, 7·07.

3,4,5-Trimethoxyphenethyl alcohol. A solution of ethyl 3,4,5-trimethoxyphenylacetate (23 g, 0·94 mole) in dry ether (100 ml) was dropped slowly, with stirring, into a refluxing solution of lithium aluminium hydride (3·4 g, 0·86 mole) in dry ether (300 ml). A tough precipitate formed. Refluxing was continued for 2 h; the reaction mixture stood at room temperature overnight, excess lithium aluminium hydride was decomposed with ethyl acetate, and dilute hydrochloric acid was added until solution had taken place. The ether layer was separated; the aqueous layer was extracted repeatedly with ether. The combined ether extracts were washed with water and sodium bicarbonate solution and then dried (Na_2SO_4 anhyd.). Evaporation of the ether gave 14–16 g (72–83 per cent) of the crude alcohol. Distillation was not necessary before proceeding with the next step. However, distillation of a portion of the oil gave a very viscous, colourless oil, which finally crystallized; b.p. 155–157°/0·5 mm; m.p. 40°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62·24; H, 7·60. Found: C, 61·50; H, 7·60.

3,4,5-Trimethoxyphenethyl chloride. Thionyl chloride (26 g, 0·22 mole) was added slowly, with stirring, to a solution of 3,4,5-trimethoxyphenethyl alcohol (44 g, 0·21 mole) in pyridine (20 g, 0·25 mole). The temperature of the mixture rose. After the mixture had stood overnight, water was added and it was extracted efficiently with ether. The combined ether extracts were washed with water and dried (Na_2SO_4 anhyd.). Evaporation of the ether left an oil which was distilled *in vacuo*. A colourless, not very viscous oil was obtained, b.p. 140°/0·06 mm; yield, 55·7 per cent.

Anal. Calcd. for $C_{11}H_{15}ClO_3$: C, 57·27; H, 6·55. Found: C, 57·95; H, 6·44.

N-(β-Arylethoxy)urethanes. A mixture of 0·05 to 0·1 molar equivalents of phenethyl bromide (Eastman) or 3,4,5-trimethoxyphenethyl chloride with a slight excess of a molar equivalent of the sodium salt of hydroxyurethane[19] in dimethylformamide

was heated on a water bath with occasional shaking for several hours until the precipitation of sodium halide ceased. The sodium salt was filtered, washed with alcohol and carefully dried in a desiccator.

After completion of the reaction in dimethylformamide, the sodium halide was removed by filtration, the filtrate was diluted with water and extracted three times with ether; the combined ether extracts were washed with water and then dried (Na_2SO_4 anhyd.). Evaporation of the ether left an oily residue which was distilled.

N-(*β-Phenylethoxy)urethane* boiled at 149–150°/0·3 mm; yield, 19·8 per cent. The infrared spectrum showed an NH band at 3·05 μ, a CO band at 5·8 μ and a strong band at 8·95 μ.

N-(*β-3,4,5-Trimethoxyphenylethoxy)urethane* boiled at 180–200°/0·1 mm; yield, 23 per cent. The infrared spectrum showed an NH band at 3·05 μ, a CH band at 3·4 μ, a CO band at 5·8 μ and a COC band at 8·9 μ.

β-Arylethoxyamine hydrochloride. A solution of the preceding *N*-(β-arylethoxy)urethane (0·01 mole) in sodium hydroxide (0·03 mole) in 50 per cent ethanol was refluxed for 4 h. The mixture was then diluted with water and extracted four times with ether. The combined ether extracts were washed with water and dried (Na_2SO_4 anhyd.). A solution of hydrogen chloride in dry ether was added to this solution. Colourless crystals were obtained.

β-Phenylethoxyamine hydrochloride was recrystallized from ethanol–ether as needles, m.p. 101° (d.); yield, 87 per cent.

Anal. Calcd. for $C_8H_{12}ClNO$: C, 55·33; H, 6·97. Found: C, 55·18; H, 7·02.

The compound decomposed within a few days at room temperature, but decomposition did not occur at −17°.

3,4,5-Trimethoxy-β-phenylethoxyamine hydrochloride was recrystallized three times from absolute ethanol with charcoaling in order to remove some colour; colourless needles were obtained; m.p. 117° (d.); yield, 28 per cent.

Anal. Calcd. for $C_{11}H_{18}ClNO_4$: C, 50·12; H, 6·88; N, 5·13. Found: C, 49·75; H, 6·67; N, 5·32.

This compound formed a reddish brown material within a few days' storage at room temperature.

Summary. A number of *O*-alkyl substituted hydroxylamine derivatives have been made which are chemically related to the antidepressive agents, iproniazid and β-phenylisopropylhydrazine. These hydroxylamine derivatives, except *N*-methoxynicotinamide, are not monoamine oxidase inhibitors as are the corresponding hydrazine derivatives. The *N*-alkoxy-*N*-(2-phenyl)-isopropylamines acted as stimulants of activity, in both mice and rats, as do amphetamine and β-phenylisopropylhydrazine.[3,4] Unlike the corresponding hydrazine derivative, phenethylhydrazine,[4] the hydroxylamine derivatives, *N*-methoxy-*N*-(2-phenyl)-ethylamine, β-phenylethoxyamine and 3,4,5-trimethoxy-β-phenylethoxyamine, did not appear to stimulate the central nervous system of either mice or rats.

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