was introduced into 300 cc. of ice-cold water, and a yellowish precipitate settled out. It was filtered by suction, washed and allowed to dry, m. p. 117–118°, and the substance was redissolved in water containing a little alcohol and allowed to recrystallize. After having been dried, its melting point was found to be 120°. Inasmuch as a qualitative test revealed no nitrogen we concluded that it was unchanged benzoic acid. No nitration took place in this case.

The same experiment was then repeated at temperatures of 50°, 60° and 100° with the same result. We may, therefore, conclude that benzoic acid cannot be nitrated by this method.

Action of Cupric Nitrate on Benzaldehyde and Nitrobenzene.—The experiments outlined above in the case of benzoic acid were repeated with benzaldehyde and nitrobenzene and in every case we could distil off an almost quantitative amount of unchanged substance.

Summary

As a result of the foregoing experiments we may draw the following conclusions.

1. The nitrating action of metallic nitrates is a selective one.
2. This action seems to favor those aromatic compounds which contain groups of the first class, while compounds with second class groups apparently remain unaffected. It is interesting to note the difference between this and the action of nitric acid, with which compounds like nitrobenzene, benzoic acid, etc., can be nitrated into their respective *m*-nitro derivatives.
3. The "nature" of a particular nitrate apparently has an influence on the structure of the resulting nitro compound as exemplified by the formation of the *ortho* derivative with heavy metallic nitrates and to a certain extent also bismuth nitrate, and the *para* isomer with lithium nitrate in the nitration of acetanilide. This, however, seems not to be a general attitude, since all the nitrates gave with *p*-toluidine the same nitro derivative.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

SUBSTITUTED O-ALKYL HYDROXYLAMINES CHEMICALLY RELATED TO MEDICINALLY VALUABLE AMINES[1]

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One of the most important chemical groups found in alkaloids and in a great many other drugs is the amino group. Except for their greater ease of oxidation, reduction and reaction with the carbonyl group, hydroxylamine and substituted hydroxylamines react chemically very much as do ammonia and the amines. However, in the past, probably be-

[1] This paper is based upon a thesis submitted by Randolph Thomas Major to the Faculty of the Graduate School of Princeton University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

cause of this greater reactivity, very little success has attended attempts to introduce hydroxylamine and its derivatives into medicine. Hydroxylamine, itself, is extremely poisonous.[2] Loew attributes its toxicity to its interaction with compounds containing the aldehyde group.[3] Binz found that it was partially oxidized in the body to a toxic nitrite.[3] N-phenylhydroxylamine is a violent poison;[4] according to Lewin it is partially oxidized to toxic azoxybenzene.[5]

It is strange that O-substituted hydroxylamines have not been investigated to determine their value in medicine. They are known to be much less active chemically than their nitrogen isomers. The N-alkyl and N,N-dialkyl hydroxylamines are readily oxidized by ammoniacal silver nitrate and also by Fehling's solution.[6] The isomeric O-alkyl hydroxylamines reduce ammoniacal silver nitrate and Fehling's solution much less readily,[7] and most O,N-dialkyl hydroxylamines reduce neither ammoniacal silver nitrate nor Fehling's solution.[8] Because of these differences in reactivity, it was thought that O-alkyl hydroxylamines might be introduced into the animal body and produce effects similar to those obtained by the use of corresponding amines.

Accordingly, a number of substituted O-alkyl hydroxylamines have been prepared in which the substituted amino groups of several known drugs have been replaced by analogous hydroxylamino radicals. We are indebted to the Department of Pharmacology of the University of Wisconsin for a pharmacological study of some of these substances; the study is being continued with other compounds.

The compounds synthesized will be classified under the therapeutically active amine to which they are related.

Choline-Like Substances

Choline (I), its salts and esters are vasomotor dilators and depressants.[9] A corresponding hydroxylammonium compound, dimethylmethoxy-ammonium hydroxide (II) has been synthesized.

(I) $(CH_3)_3\equiv N(OH)-CH_2-CH_2.OH$ (II) $(CH_3)_2(CH_3O)\equiv N(OH)-CH_2-CH_2.OH$

The iodide (m. p., 57–58°) of this base was formed by the action of methyl iodide upon O,N-dimethyl-N-hydroxy-ethylhydroxylamine, a compound

[2] Raimondi and Bertoni, *Gazz. chim. ital.*, **12**, 199 (1882).

[3] Frankel, "Arzneimittel-Synthese," Julius Springer, Berlin, **1921**, p. 74.

[4] Ref. 3, p. 83.

[5] Ref. 3, p. 78.

[6] Behrend and Leuchs, *Ann.*, **257**, 218, 239 (1890).

[7] (a) Gürke, *Ann.*, **205**, 277 (1880). (b) Hecker, *Am. Chem. J.*, **50**, 462 (1913).

[8] (a) Lossen, *Ann.*, **252**, 235 (1889). (b) Jones, *Am. Chem. J.*, **20**, 45 (1898). (c) Ref. 7 b, p. 459.

[9] Ref. 3, p. 327.

obtained by the addition of O,N-dimethylhydroxylamine to ethylene oxide, according to the method of Jones and Burns.[10]

When an aqueous solution of the free base, prepared from the iodide by the action of moist silver oxide, was subjected to distillation, formaldehyde was produced and identified. A solution of the base was distilled and the distillate passed into hydrochloric acid; it gave a chloride which yielded a chloroplatinate whose platinum content lay between that required by the chloroplatinate of dimethylamino-ethanol and that of dimethylamine.

These results suggest that decomposition occurs in two different ways. The first reaction is similar to that shown by trimethylmethoxy-ammonium hydroxide which, according to Meisenheimer,[11] gave trimethylamine and formaldehyde. The second reaction resembles the decomposition by heat of choline itself, which yields trimethylamine and ethylene glycol,[12] except that in the case of the hydroxylamine derivative, formaldehyde and dimethylamine appear instead of trimethylamine. The following equations represent these changes.

$$(CH_3)_2(CH_3O)\equiv N(OH)-C_2H_4OH \begin{cases} \rightarrow CH_2O + (CH_3)_2{=}N-C_2H_4OH + H_2O \\ \rightarrow CH_2O + HOC_2H_4OH + (CH_3)_2NH \end{cases}$$

The corresponding diethylethoxy-hydroxy-ethylammonium hydroxide, $(C_2H_5)_2(C_2H_5O)(C_2H_4OH)N.OH$, and its acetyl and benzoyl esters offer interesting compounds for study and comparison with the closely related triethylhydroxy-ethylammonium hydroxide, which has been known for some time.[13] Acetyl choline is physiologically more active than choline itself.[14] Triethylacetoxy-ethylammonium iodide was prepared by the action of ethyl iodide on diethylamino-ethyl acetate, according to the equation

$$C_2H_5I + CH_3C(=O)-OC_2H_4-N(C_2H_5)_2 \longrightarrow CH_3-C(=O)-O-C_2H_4-N\equiv(C_2H_5)_3\,I$$

Diethylamino-ethyl acetate is described in German patent 290,522.[15] In our experiments this compound was prepared also by the action of acetyl chloride on diethylamino-ethanol. Similarly, the benzoyl ester of the triethyl homolog of choline iodide was prepared by the action of ethyl iodide on diethylamino-ethyl benzoate.

[10] Jones and Burns, THIS JOURNAL, **47**, 2972 (1925).

[11] Meisenheimer, *Ann.*, **397**, 292 (1913).

[12] (a) Ref. 11, p. 284. (b) Dunstan and Goulding, *J. Chem. Soc.*, **75**, 799 (1899).

[13] Wurtz, *Ann. Suppl.*, **7**, 88 (1870). Stoermer and Prall, *Ber.*, **30**, 1509 (1897). Johnson, Brit. pat. 8031; *C. A.*, **14**, 1411 (1920).

[14] Ewins, *Biochem. J.*, **8**, 44 (1914).

[15] Friedländer, **12**, 693 (1914–1916).

A pharmacological study of the chloride of the latter compound was made by Hunt and Taveau.[16]

As a start in the investigation of the corresponding hydroxylamine analogs, hydroxy-ethyldiethylamine oxide was obtained by the oxidation of diethylamino-ethanol[10,17] with hydrogen peroxide; $(C_2H_5)_2NCH_2CH_2OH + H_2O_2 \longrightarrow (C_2H_5)_2N(=O)CH_2CH_2OH + H_2O$. A continuation of this study is planned.

Procaine-Like Substances

Procaine, diethylamino-ethyl *p*-aminobenzoate hydrochloride,[18] has proved an extremely useful local anesthetic. The corresponding hydroxylamine derivative, ethylethoxy-amino-ethyl *p*-aminobenzoate, has been prepared by heating chloro-ethyl *p*-aminobenzoate with O,N-diethylhydroxylamine; $NH_2C_6H_4COOC_2H_4Cl + 2C_2H_5ONH(C_2H_5) \longrightarrow NH_2C_6H_4COOC_2H_4N(OC_2H_5)(C_2H_5) + H_2N{\equiv}(C_2H_5)(OC_2H_5)Cl$.

Diethylamino-ethyl benzoate[19] has the properties of a local anesthetic. Ethylethoxy-amino-ethyl benzoate was made by treating O,N-diethyl-N-hydroxy-ethylhydroxylamine[10] with benzoyl chloride, as shown in the equation

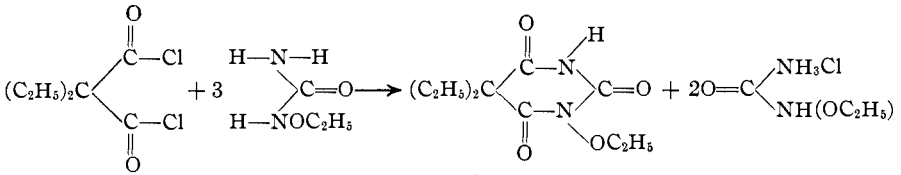
$$C_6H_5COCl + 2HOC_2H_4{-}N(OC_2H_5)(C_2H_5) \longrightarrow C_6H_5COOC_2H_4N(OC_2H_5)(C_2H_5) + HOC_2H_4N(OC_2H_5)(C_2H_5)\cdot HCl$$

The nitrobenzoates of O,N-dimethyl-N-hydroxy-ethylhydroxylamine and O,N-diethyl-N-hydroxy-ethylhydroxylamine were also prepared by the action of *p*-nitrobenzoyl chloride on the respective hydroxylamines. An attempt was made to synthesize ethylethoxy-amino-ethyl benzoate and ethylethoxy-amino-ethyl *p*-nitrobenzoate by the method used in preparing ethylethoxy-amino-ethyl *p*-aminobenzoate, namely, by heating the chloro- or iodo-ethyl ester with O,N-diethylhydroxylamine. However, there was no reaction with the nitrobenzoate and little, if any, with the benzoate.

Veronal-Like Substances

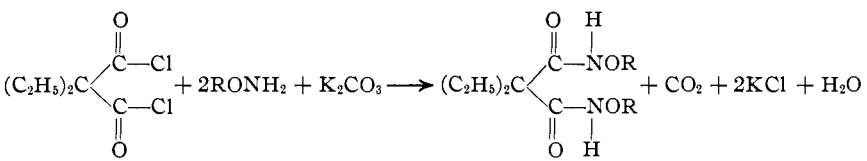
Veronal, C,C-diethylbarbituric acid, has powerful hypnotic properties.[20] The related hydroxylamine derivative, C,C-diethyl-N-ethoxy-barbituric acid, has been synthesized by us by the action of diethylmalonyl chloride on ethoxy-urea, according to the equation

[16] Hunt and Taveau, *J. Pharmacol.*, **1**, 308 (1909).
[17] Ref. 12 b, p. 1005.
[18] Einhorn and Uhlfelder, *Ann.*, **371**, 134 (1909).
[19] Ger. pat. 17,580, 187,209, 190,688.
[20] Ref. 3, p. 493.



The intermediates, ethoxy-urea and methoxy-urea, were obtained by the action of potassium isocyanate on a solution of the hydrochlorides of O-ethylhydroxylamine and O-methylhydroxylamine, respectively, thus: $KNCO + RONH_3.Cl \longrightarrow RO{-}NH.CO.NH_2 + KCl$.

Compounds not so closely related to veronal as C,C-diethyl-N-ethoxy-barbituric acid, namely, C,C-diethyl-N,N′-diethoxy-malonamide and C,C-diethyl-N,N′-dimethoxy-malonamide, were synthesized by the action of diethylmalonyl chloride on O-ethylhydroxylamine and O-methylhydroxylamine, respectively.



Although O-methylhydroxylammonium chloride has been known for some time,[21] the properties of the free base have not been described. It has now been isolated for use in this work, and some of its properties have been determined.

Derivatives of Phenyl-urea

Phenyl-urea is a strong antiseptic.[22] Four derivatives of this compound have been synthesized which have the following structural formulas: $C_6H_5NH.NH(OC_2H_5)$, *sym.*-phenylethoxy-urea; $C_6H_5NH.CO.NH(OCH_3)$, *sym.*-phenylmethoxy-urea; $C_6H_5NH.CO.NC_2H_5(OC_2H_5)$, α-phenyl-, β,β'-ethylethoxy-urea; $C_6H_5NH.CO.NCH_3(OCH_3)$, α-phenyl-, β,β'-methylmethoxy-urea. These compounds were formed according to the method of Beckmann,[23] by the action of phenyl isocyanate on O-ethylhydroxylamine, O-methylhydroxylamine, O,N-diethylhydroxylamine and O,N-dimethylhydroxylamine, respectively. It is probable that these ureas may prove valuable as a means of identification of these hydroxylamines.

Thiosinamine-Like Substance

Thiosinamine, allyl-thiourea, has been used as an antiseptic.[24] The

[21] Lossen and Zanni, *Ann.*, **182**, 225 (1876).

[22] Ref. 3, p. 53.

[23] Beckmann, *J. prakt. chem.*, **56**, 75 (1897).

[24] Fourneau, "Organic Medicaments," translated by Silvester, P. Blakiston's Son, Philadelphia, **1925**, p. 77.

closely related *sym.*-methoxy-allylthio-urea has been prepared by the method used by Kjellin and Kuylenstjerna to prepare its isomer, α-allyl-β-methyl-β'-hydroxythio-urea.[25] Mustard oil dissolved in ether was treated with O-methylhydroxylamine, as shown in the equation $C_3H_5NCS + CH_3ONH_2 \longrightarrow C_3H_5—NH—CS—NH(OCH_3)$.

Pharmacological Results

The preliminary pharmacological study of some of these substituted O-alkyl hydroxylamines, which is described in the Experimental Part of this paper shows that unlike the O-unsubstituted hydroxylamines, they possess properties which may prove valuable to medicine. Thus, both procaine and diethylamino-ethyl benzoate are very inefficient anesthetics when used on the surface of a mucous membrane, but must be injected beneath its surface to be effective.[26] On the other hand, the corresponding hydroxylamine derivatives, ethylethoxy-amino-ethyl *p*-aminobenzoate and ethylethoxy-amino-ethyl benzoate were found to penetrate mucous membrane when applied to its surface, and to produce pronounced local anesthesia. Unfortunately, ethylethoxy-amino-ethyl *p*-aminobenzoate seems to be rather toxic, but the exact degree of toxicity has not been determined. C,C-Diethyl-N-ethoxy-barbituric acid, which as has been pointed out resembles the hypnotic veronal in chemical structure, was also found to have hypnotic properties. Although a greater concentration of this compound than of veronal is required to produce the same hypnotic effect, it is less toxic than veronal. C,C-Diethyl-N,N-diethoxymalonamide was also found to possess the properties of a sedative and in addition to be only slightly toxic.

Experimental Part

Dimethylmethoxy-hydroxy-ethylammonium hydroxide, $(CH_3)_2(CH_3O)\equiv N(OH)CH_2CH_2OH$

Preparation of O,N-Dimethyl-N-hydroxy-ethylhydroxylamine.—A mixture of 5.5 g. of O,N-dimethylhydroxylamine, obtained by the method of Jones[27] as modified by Hecker,[28] and 4 g. of ethylene oxide was placed in a stoppered bottle and left at room temperature for nine days. Fractional distillation of the reaction mixture gave O,N-dimethyl-N-hydroxy-ethylhydroxylamine; b. p., 57–58°, at 23 mm.; yield, 32%. It was a mobile, colorless liquid, soluble in alcohol, ether and water.

HYDROCHLORIDE.—A solution of the base in absolute alcohol saturated with hydrogen chloride was treated with dry ether. This caused the precipitation of an oil, which solidified slowly to give long, fibrous needles. They were recrystallized from absolute alcohol with addition of ether; m. p., 71–72°.

Anal. Subs., 0.1236: AgCl, 0.1244. Calcd. for $C_4H_{12}O_2NCl$: Cl, 25.07. Found: 24.90.

[25] Kjellin and Kuylenstjerna, *Ann.*, **298**, 127 (1897).

[26] Sollmann, *J. Am. Med. Assoc.*, **70**, 218 (1918). Ref. 21, p. 63.

[27] Ref. 8b, p. 44.

[28] Ref. 8c, p. 459.

CHLOROPLATINATE.—Chloroplatinic acid in absolute alcohol was added to an alcohol solution of this chloride. Absolute ether precipitated a reddish oil which solidified finally to yield yellow crystals. Recrystallized from hot absolute alcohol, the melting point was 112–113°.

Anal. Subs., 0.1014: Pt, 0.0314. Calcd. for $C_5H_{24}O_4N_2Cl_6Pt$: Pt, 31.47. Found: 30.90.

Preparation of Dimethylmethoxy-hydroxy-ethylammonium Iodide.—To 1.8 g. of O,N-dimethyl-N-hydroxy-ethylhydroxylamine, 2.4 g. of methyl iodide was added. After 15 hours in the dark, a heavy, red oil was formed which solidified to give yellow, plate-like crystals. These were recrystallized from absolute alcohol; metallic mercury was added to remove free iodine and the compound was precipitated by absolute ether. It was a white, deliquescent, crystalline solid which darkened rapidly in the light; m. p., 57–58°; yield, practically quantitative.

Anal. Subs., 0.1976: AgI, 0.1863. Calcd. for $C_5H_{14}O_2NI$: I, 51.42. Found: 50.96.

Preparation of Dimethylmethoxy-hydroxy-ethylammonium Hydroxide in Aqueous Solution.—One g. of this iodide was dissolved in 200 cc. of ice water. A little more than the calculated amount of silver oxide was shaken with this solution, kept quite cold, until there was no test for iodide ion with silver nitrate. The filtered solution was clear and colorless, and reacted alkaline to litmus paper. If, however, the solution was allowed to stand and come to room temperature before it was filtered, the base was rapidly oxidized by the excess of silver oxide, and a silver mirror was formed.

Decomposition of Dimethylmethoxy-hydroxy-ethylammonium Hydroxide.—When 0.2648 g. of the iodide, dissolved in 50% alcohol in order to have a lower boiling solvent, was converted to its hydroxide as described above, and the solution was distilled into a solution of an excess of *p*-nitrophenylhydrazine hydrochloride, a red, crystalline precipitate appeared; m. p., about 175°; yield, 0.0183 g. Pure formyl-*p*-nitrophenylhydrazone forms red crystals; m. p., 181–182°.[29] The odor of formaldehyde became pronounced as soon as the solution was boiled. Assuming complete change of the methoxy group to formaldehyde, 19% of the calculated amount was obtained.

The hydroxide was formed in the same way from 0.3183 g. of the iodide. The solution was all distilled in a current of nitrogen and the distillate caught in dil. hydrochloric acid. This acid solution, evaporated to dryness on the water-bath, gave a heavy oil which was dissolved in absolute alcohol. To the alcoholic solution a slight excess of chloroplatinic acid dissolved in absolute alcohol was added. An orange-colored chloroplatinate was precipitated by dry ether; it weighed 0.1627 g., and upon ignition yielded 0.0595 g. of platinum.

Calcd. for $[(CH_3)_2NCH_2CH_2OH]_2H_2PtCl_6$: Pt, 33.2. Calcd. for $[(CH_3)_2NH]_2$-H_2PtCl_6: Pt, 39.03. Found: 36.5.

Assuming one molecule of dimethylamino-ethanol formed for each molecule of dimethylmethoxy-hydroxy-ethylammonium iodide, there was obtained a yield of 21.5% of the calculated amount of dimethylamino-ethanol, or assuming one molecule of dimethylamine formed for each molecule of the parent substance, there was obtained a yield of 43% of the calculated amount.

HYDROCHLORIDE.—The hydrochloride was obtained by acidifying a solution of the base with hydrochloric acid and evaporating the solution to dryness on a water-bath. After lengthy drying it remained an oil.

CHLOROPLATINATE.—The chloroplatinate produced in absolute alcohol formed

[29] Bamberger, *Ber.*, **32**, 1807 (1899).

a yellow, crystalline precipitate. It was recrystallized from water by the addition of alcohol; m. p., 183°, with decomposition.

Anal. Subs., 0.2322: Pt, 0.0705. Calcd. for $C_{10}H_{28}O_4N_2Cl_6Pt$: Pt, 30.12. Found: 30.36.

Triethylacyloxy-ethylammonium Iodide, $R—CO.OC_2H_4.N\equiv(C_2H_5)_3.I$

Preparation of Acyl Ester of Diethylamino-ethanol.—A solution of 11.7 g. of diethylamino-ethanol in dry benzene was cooled by ice, and an equivalent molecular portion of acyl chloride was added in small portions. A white solid appeared. This was dissolved in water and the solution was washed with ether. The solution was then made alkaline with potassium carbonate; an oil separated which was extracted with ether. After the ether solution had been dried with sodium sulfate, the ether was distilled, and then the ester. The acetyl ester boiled at 80°, at 20 mm.; yield, 44%. The benzoyl ester boiled at 156–158°, at 19 mm.; yield, 82%.

CHLOROPLATINATES.—Chloroplatinic acid added to a sample of the acetyl ester dissolved in absolute alcohol gave a yellow, crystalline chloroplatinate. The benzoyl ester reacted similarly. Both chloroplatinates were only slightly soluble in alcohol and insoluble in ether, but the benzoate was much less soluble in water than the acetate. The acetate melted at 147°, the benzoate at 161°.

Anal. Subs., 0.1997: Pt, 0.0535. Calcd. for $C_{16}H_{36}O_4N_2Cl_6Pt$: Pt, 26.80. Found: 26.79. Subs., 0.3089: Pt, 0.0699. Calcd. for $C_{26}H_{40}O_4N_2Cl_6Pt$: Pt, 22.99. Found: 22.63.

Preparation of Triethylacyloxy-ethylammonium Iodides.—Five g. of the acyl ester of diethylamino-ethanol was added to a molecular equivalent of ethyl iodide and the mixture was allowed to stand in the dark for 15 hours. At the end of this time there was a solid mass of white crystals which was recrystallized from absolute alcohol by the addition of ether; the salt was soluble in water. The acetyl ester melted at 113°; yield, 50%; the benzoyl ester at 134°; yield, 28%.

Anal. Subs., 0.1893: AgI, 0.1417. Calcd. for $C_{10}H_{22}O_2NI$: I, 40.27. Found: 40.45. Subs., 0.1999: AgI, 0.1235. Calcd. for $C_{15}H_{24}O_2NI$: I, 33.21. Found: 33.39.

Diethylhydroxy-ethylamine Oxide, $(C_2H_5)_2(HOC_2H_4)\equiv N=O$

To 10 g. of diethylamino-ethanol an excess of a 3% solution of commercial hydrogen peroxide was added.[30] Considerable heat was generated in the reaction. The solution was allowed to stand for five hours, and the excess of hydrogen peroxide and water was removed by distillation. A greenish-yellow, heavy oil was left which was dried thoroughly in a vacuum over sulfuric acid. In order to remove a trace of barium carbonate, the oil was dissolved in absolute alcohol, the solution filtered and the alcohol evaporated. This gave an oil which did not solidify. It was very soluble in water and in alcohol, but insoluble in ether.

CHLOROPLATINATE.—Diethylhydroxy-ethylamine oxide dissolved in absolute alcohol was saturated with dry hydrogen chloride. Chloroplatinic acid, dissolved in absolute alcohol and added to this solution, gave an orange-colored chloroplatinate; m. p., 191°, with decomposition. It was soluble in water, slightly soluble in alcohol and insoluble in ether.

Anal. Subs., 0.2694: Pt, 0.0774. Calcd. for $C_{12}H_{32}O_4N_2Cl_6Pt$: Pt, 28.86. Found: 28.73.

[30] The solution of hydrogen peroxide had been freed from sulfuric acid by shaking it with solid barium carbonate.

Ethylethoxy-amino-ethyl *p*-Aminobenzoate, $H_2NC_6H_4COOC_2H_4N=(OC_2H_5)(C_2H_5)$

Nine g. of dry O,N-diethylhydroxylamine prepared by the method of Hecker and of Lossen[31] was heated in a sealed tube for 24 hours at 100° with 9 g. of dry chloro-ethyl *p*-aminobenzoate.[32] When the tube was cooled, a yellow oil and white precipitate were observed. A dilute solution of sodium carbonate was added to make the mixture slightly alkaline. The white solid dissolved and the oil was extracted with ether. The ether solution was dried with sodium sulfate, the ether distilled and the oil finally distilled in a vacuum. There was some decomposition.

In order to remove a small amount of hydroxy-ethyl *p*-aminobenzoate[33] and amino-benzoic acid, which also were carried over, absolute ether was added to the oil in order to precipitate most of the hydroxy-ethyl *p*-aminobenzoate, which is only very slightly soluble in ether. The ether solution was washed with a dilute solution of sodium carbonate and then with water to remove a trace of aminobenzoic acid. The ether, dried with sodium sulfate, was evaporated. This gave a heavy oil which was treated with dry carbon tetrachloride in order to remove the last of the hydroxy-ethyl *p*-aminobenzoate, which is quite insoluble in carbon tetrachloride. The solution was shaken with animal charcoal and filtered. Cold, dilute hydrochloric acid extracted ethylethoxy-amino-ethyl *p*-aminobenzoate from it. The acid solution was made alkaline with a solution of sodium carbonate. This caused the oil to separate. It was extracted with ether, the ether solution dried with sodium sulfate, and the ether distilled. Finally, the residual oil was distilled in a vacuum; b. p. 217°, at 11 mm.; yield, 17%.

The compound was a colorless, heavy oil very soluble in ether, alcohol, carbon tetrachloride and dilute acids, but insoluble in water.

Anal. Subs., 0.2331: N_2, 22.15 cc. (21.6°, 738.3 mm.). Calcd. for $C_{13}H_{20}O_3N_2$: N, 11.10. Found: 10.76.

When the compound was heated with a concentrated solution of potassium hydroxide, *p*-aminobenzoic acid was isolated.

Ethylethoxy-amino-ethyl Benzoate, $C_6H_5CO.OC_2H_4N(OC_2H_5)(C_2H_5)$

Preparation from O,N-Diethyl-N-hydroxy-ethylhydroxylamine and Benzoyl Chloride.—Four g. of O,N-diethyl-N-hydroxy-ethylhydroxylamine[10] and 4.2 g. of benzoyl chloride were heated together on a water-bath for an hour. A viscous oil was formed which was cooled, washed with a dilute solution of sodium carbonate and then dissolved in ether. The ether was dried with anhydrous sodium sulfate and distilled; a heavy oil remained which was distilled in a vacuum. In order to purify the product it was redistilled; b. p., 152–153°, at 10 mm.; yield, 59%. It was an almost colorless oil, soluble in benzene, ether and alcohol, soluble with difficulty in dil. hydrochloric acid and insoluble in water.

Anal. Subs., 0.2134: N_2, 11.9 cc. (21°, 738.2 mm.). Calcd. for $C_{13}H_{19}O_3N$: N, 5.91. Found: 6.28.

Attempted Preparation from Chloro-ethyl Benzoate and O,N-Diethyl-hydroxylamine

Preparation of Chloro-ethyl Benzoate.—Seventy g. of benzoyl chloride was heated on a water-bath with ethylene chlorohydrin until evolution of hydrogen chloride ceased. The solution was fractionated. The fraction boiling at about 254° was dissolved in

[31] Ref. 7 b, p. 451. Ref. 8 a, p. 234.

[32] Ref. 18, p. 133.

[33] Cretcher and Pittenger, THIS JOURNAL, **47**, 2561 (1925).

ether and washed with a solution of sodium carbonate. The ether solution was dried with calcium chloride and fractionated again; b. p., 256–257°, at 752 mm.; yield, 55%.

Results Obtained by Heating Chloro-ethyl Benzoate with O,N-Diethylhydroxylamine.—Ten g. of chloro-ethyl benzoate was heated for 24 hours at 105° in a sealed tube with 8.5 g. of dry O,N-diethylhydroxylamine. After cooling, the tube was opened and the solution made acid with dil. hydrochloric acid. An oil remained which was extracted with ether. From the ether solution 7 g. of pure chloro-ethyl benzoate was recovered, b. p. 256–257°, and a small amount of tarry material. The acid solution was made alkaline with sodium carbonate and extracted with ether, but not enough material was obtained to work with.

Ethylethoxy-amino-ethyl *p*-Nitrobenzoate, $O_2N—C_6H_4CO.OC_2H_4—N(OC_2H_5)(C_2H_5)$

Preparation from O,N-Diethyl-N-hydroxy-ethylhydroxylamine and *p*-Nitrobenzoyl Chloride.—A solution of 2 g. of O,N-diethyl-N-hydroxy-ethylhydroxylamine and 1.4 g. of *p*-nitrobenzoyl chloride in benzene was allowed to stand at room temperature for 24 hours. A solid, crystalline, almost white precipitate was obtained. The benzene was evaporated and the oil and solid left were washed with a solution of sodium carbonate in order to remove *p*-nitrobenzoic acid. The solid was recrystallized by dissolving it in hot benzene and precipitating it with ligroin. It was again recrystallized from hot absolute alcohol; m. p., 189–190°; yield, 43%. The compound formed faintly yellow crystals, soluble in chloroform, hot benzene and hot alcohol. They were less soluble in ether, insoluble in water and dil. or concd. hydrochloric acid.

Anal. Subs., 0.0688: N_2, 6.40 cc. (22.8°, 732 mm.). Calcd. for $C_{13}H_{18}O_5N_2$: N, 9.93. Found: 10.33.

This compound hydrolyzed on being heated with concd. potassium hydroxide solution. Sulfuric acid added to the solution precipitated *p*-nitrobenzoic acid; m. p., 236°.

Preparation of Iodo-ethyl *p*-Nitrobenzoate.—Twelve g. of ethylene iodohydrin was heated on a water-bath with 10 g. of *p*-nitrobenzoyl chloride until evolution of hydrogen chloride ceased. A cream-colored solid formed when the mixture became cool. It was washed with a small amount of alcohol, recrystallized from hot ligroin, and finally from hot alcohol; m. p., 68–69°. The crystals were readily soluble in benzene and chloroform, less so in ether and only slightly soluble in water. Concd. nitric acid decomposed the compound; a strong qualitative test for iodide ion was subsequently obtained with silver nitrate.

Anal. Subs., 0.6247: N_2, 27.30 cc. (22°, 739 mm.). Calcd. for $C_9H_9O_4NI$: N, 4.36. Found: 4.91.

Preparation of Hydroxy-ethyl *p*-Nitrobenzoate.—Ten g. of potassium *p*-nitrobenzoate was heated in a sealed tube at 100° with an equivalent of ethylene chlorohydrin dissolved in benzene. The tube was cooled and opened; its contents were made alkaline with sodium carbonate, and the undissolved solid was collected on a filter. This solid was purified by dissolving it in absolute ether and precipitating it with ligroin. It was recrystallized from hot benzene; m. p., 77–78°; yield, 60%. It was very soluble in alcohol and ether, less so in benzene and in water, and almost insoluble in ligroin.

Anal. Subs., 0.5380: N_2, 34.22 cc. (21.7°, 732 mm.). Calcd. for $C_9H_9O_5N$: N, 6.64. Found: 7.09.

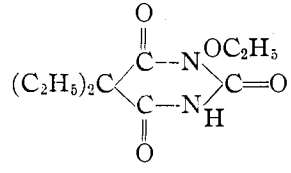
Methylmethoxy-amino-ethyl *p*-Nitrobenzoate

To a solution of 2.5 g. of O,N-dimethyl-N-hydroxy-ethylhydroxylamine dissolved in dry benzene was added 2.5 g. of *p*-nitrobenzoyl chloride. The mixture was allowed

to stand for 15 hours and the benzene was then allowed to evaporate in a stream of air. A white solid mixed with some oil was obtained, and was washed with a solution of sodium carbonate and dissolved in ether; the ether was evaporated. This gave a heavy oil which solidified as it dried in a vacuum. It was recrystallized by dissolving it in alcohol and precipitating it with water. It was then recrystallized from hot 50% methyl alcohol. Finally, it was dissolved in dil. acetic acid and precipitated by water made slightly alkaline with sodium carbonate; m. p., 51.4°; yield, 41%. It formed white crystals, soluble in ether, alcohol and benzene, but insoluble in water.

Anal. Subs., 0.1200: N_2, 12.00 cc. (23°, 749 mm.). Calcd. for $C_{11}H_{14}O_3N_2$: N, 11.52. Found: 11.36.

C,C-Diethyl-N-ethoxy-barbituric Acid



Preparation of Alkyl Oxy-ureas.—Five g. of O-alkyl hydroxylamine hydrochloride, prepared by the method of Jones as modified by Hecker[34] was dissolved in ice water. To this solution an equivalent amount of potassium isocyanate dissolved in water was added gradually. The solution, evaporated to dryness on the water-bath, gave a white solid which was extracted with hot chloroform, and the compound was precipitated from the chloroform by the addition of ligroin. It was recrystallized from hot benzene; yield, 50%. The methoxy-urea melted at 84.5°, the ethoxy-urea at 91.5°.

Anal. Subs., 0.0518: N_2, 14.7 cc. (19.5°, 726.1 mm.). Calcd. for $C_2H_6O_2N_2$: N, 31.11. Found: 31.55. Subs., 0.0866: N_2, 21.35 cc. (24°, 727 mm.). Calcd. for $C_3H_8O_2N_2$: N, 26.91. Found: 27.10.

Preparation of C,C-Diethyl-N-ethoxy-barbituric Acid.—When 6.2 g. of diethylmalonyl chloride was heated in a sealed tube at 110° for 30 hours with 10 g. of ethoxy-urea dissolved in 50 cc. of dry benzene, a solid was formed which was collected on a filter and dissolved in water. The solution, which reacted acid and gave a strong test for chloride ion, was made neutral with ammonium hydroxide. This neutral solution was evaporated to dryness on the water-bath. The white solid which remained was extracted repeatedly with chloroform, and from the chloroform solution a white solid, m. p. 90–91°, was precipitated by ligroin. Pure ethoxy-urea melts at 91.5°.

The benzene filtrate was distilled in a vacuum. A heavy oil remained in the distilling flask. It was washed with water and then dried over sulfuric acid in a vacuum. It was occasionally scratched during the course of about a month, at the end of which time it suddenly started to crystallize. It was dissolved in carbon disulfide. Slow evaporation of the carbon disulfide gave crystals which were collected on a filter and washed with a little carbon disulfide. It was recrystallized by dissolving it in alcohol and adding water to the solution; m. p., 70°; yield, 25%.

It was a white crystalline solid, very soluble in ether, alcohol and alkalies, less soluble in ligroin, and insoluble in water and in acids. A white silver salt precipitated when silver nitrate was added to an ammonium hydroxide solution of the compound. This salt darkened rapidly in the light.

Anal. Subs., 0.1618: N_2, 18.20 cc. (23.5°, 737.5 mm.). Calcd. for $C_{10}H_{16}O_4N_2$: N, 12.28. Found: 12.53.

[34] (a) Ref. 27, pp. 41, 46. (b) Ref. 7b, p. 447.

Hydrolysis of this substance gave the required amount of malonic acid, O-ethylhydroxylamine, ammonia and carbon dioxide.

C,C-Diethyl-N,N'-dialkyloxy-malonamide, $(C_2H_5)_2C[C(=O)NHOR]_2$

Preparation of O-Methylhydroxylamine.—Eight g. of O-methylhydroxylamine hydrochloride was treated with 10 g. of potassium hydroxide dissolved in 10 cc. of water. The amine was distilled through hot potassium hydroxide sticks, to absorb moisture. It was then dried with potassium hydroxide and redistilled; b. p., 49–50° (at 759 mm.);. yield, 87%.

Preparation of C,C-Diethyl-N,N'-dialkyloxy-malonamide.—To a cold mixture of 28 g. of anhydrous potassium carbonate and slightly more than two molecular equivalents of O-alkyl hydroxylamine dissolved in considerable ether, 18.8 g. of diethylmalonyl chloride was slowly added. There was a vigorous evolution of carbon dioxide. After 15 hours the mixture was filtered from potassium chloride and the excess of potassium carbonate. The ether solution was dried with calcium chloride and distilled to remove ether. A white, crystalline solid was left in the distilling flask. It was dissolved in hot benzene, the solution was treated with animal charcoal, filtered and the compound precipitated by ligroin. It formed white crystals, very soluble in water, less so in ether and insoluble in ligroin; yield, 40%. The methoxymalonamide melted at 130°, the ethoxymalonamide at 117–118°.

Anal. Subs., 0.0563: N_2, 6.75 cc. (23°, 733 mm.). Calcd. for $C_9H_{18}O_4N_2$: N, 12.83. Found: 13.32. Subs., 0.1193: N_2, 13.1 cc. (18°, 731.3 mm.). Calcd. for $C_{11}H_{22}O_4N_2$: N, 11.87. Found: 12.39.

α-Phenyl β-Alkyloxy Ureas, $RONH.CO.NH(C_6H_5)$

One g. of dry O-alkyl hydroxylamine was added to an equivalent amount of phenyl isocyanate dissolved in dry benzene. Considerable heat was generated. A white precipitate formed which, in the case of α-phenyl-β-ethoxy-urea, was increased by the addition of ligroin. The white solid was recrystallized from hot benzene with the addition of ligroin in the case of α-phenyl-β-methoxy-urea; yield, 90%. It was soluble in alcohol, ether and chloroform, and only slightly soluble in water. The methoxy-urea melted at 115°, the ethoxy-urea at 106–108°.

Anal. Subs., 0.1116: N_2, 16.82 cc. (19.2°, 736.1 mm.). Calcd. for $C_8H_{10}O_2N_2$: N, 16.87. Found: 17.05. Subs., 0.1224: N_2, 17.30 cc. (23.8°, 733.8 mm.). Calcd. for $C_9H_{12}O_2N_2$: N, 15.55. Found: 15.65.

α-Phenyl β,β'-Alkyl-alkyloxy Urea, $RONR.CO.NH(C_6H_5)$

One g. of O,N-dialkyl hydroxylamine was added to an equivalent molecular portion of phenyl isocyanate dissolved in benzene. Heat was produced in the reaction. After 12 hours, the benzene was evaporated. The white, crystalline solid (an oil first appeared in the case of α-phenyl-β,β'-methylmethoxy-urea which distilled at 164°, at 20 mm., and finally solidified) was recrystallized by dissolving it in alcohol and precipitating it with water; yield, 30%. The compounds were soluble in alcohol, ether, benzene and ligroin, but only slightly soluble in water. The methylmethoxy-urea melted at 61°, the ethylethoxy-urea at 63°.

Anal. Subs., 0.1011: N_2, 14.3 cc. (27°, 746.1 mm.). Calcd. for $C_9H_{12}O_2N_2$: N, 15.56. Found: 15.79. Subs., 0.0851: N_2, 10.5 cc. (21.6°, 732.7 mm.). Calcd. for $C_{11}H_{16}O_2N_2$: N, 13.46. Found: 13.76.

A mixture of equal weights of α-phenyl-β,β'-ethylethoxy-urea and of α-phenyl-β,β'-methylmethoxy-urea melted at 43–48°.

Hydrolysis of α-Phenyl-β,β'-ethylethoxy-urea.—The substance was refluxed with dil. hydrochloric acid until evolution of carbon dioxide ceased, as shown by a test with lime water. The liquid in the distilling flask was evaporated to dryness on a water-bath. To the mixture of crystals and oil, solid potassium hydroxide was added and the material fractionated. The first fraction boiled around 80° and had the odor of O,N-diethylhydroxylamine, which boils at 83°.[35] The second fraction boiled around 180°, which is about the boiling point of pure aniline; b. p., 184°.[36]

α-Alkyl β-Methoxy-thio-urea

One g. of alkyl isothiocyanate, dissolved in absolute ether, was aded to 0.5 g. of O-methylhydroxylamine dissolved in absolute ether. After 15 hours ligroin was added to the solution. A heavy oil precipitated which solidified to give white crystals. It was recrystallized by dissolving it in benzene and precipitating it with ligroin; m. p., 37°; yield, almost quantitative. The compound was soluble in alcohol, ether, benzene and carbon tetrachloride, but less so in water. It was quite deliquescent.

Anal. Subs., 0.1333: N_2, 23.8 cc. (21°, 722.1 mm.). Calcd. for $C_5H_{10}ON_2S$: N, 19.15. Found: 19.69.

This preparation was attempted by simply mixing the two reactants in a flask, but it proceeded so violently that the compound charred and there was a violent evolution of gases.

Preliminary Pharmacological Studies of Some of the Compounds[37]

Ethylethoxy-amino-ethyl *p*-Aminobenzoate.—This material, when applied directly to the intact mucous membrane, gave a prompt and deep anesthesia lasting between five and ten minutes. In two rabbits, the anesthesia of the mucous membrane of the nose lasted 7.5 and 11 minutes, respectively. On the mucous membrane of the tongue of man, the anesthesia in one instance came on in 18 seconds and lasted five minutes. In another case it came on in 18 seconds and lasted six minutes. In these experiments, the end of a small glass rod 3 mm. in diameter was immersed in the oil and applied to the mucous membrane; the amount applied was probably not in excess of a cubic millimeter. The material, when injected subcutaneously and intraperitoneally into white mice in 0.1cc. amounts, was found to be slightly irritating and led to a partial necrosis of the tissues. Death followed within 24 hours in the two instances in which the attempt was made.

Ethylethoxy-amino-ethyl Benzoate.—This material, applied as in the case of ethyl-ethoxy-amino-ethyl *p*-aminobenzoate to the mucous membranes of the nose of a rabbit, produced a very slight anesthesia which came on in 30 seconds and lasted three minutes (one experiment). Upon the tongue of man, it had a faintly bitter taste and a fleeting anesthesia.

C,C-Diethyl-N-ethoxy-barbituric Acid.—Ten mg. of C,C-diethyl-N-ethoxy-barbituric acid was injected subcutaneously into a 40g. mouse. Within three minutes there was no response to needle pricking and within four minutes the animal was considerably depressed. The respiration was slowed and the animal lay quiet without response to electrical or mechanical stimulation. There was complete recovery in 12 hours, with the animal perfectly normal. This was 1 mg. per 4 g. of body weight.

The injection of 1 mg. of veronal in 50% alcohol per 2.5 g. of body weight caused death in 24 hours. In this case, the animal was very depressed within five minutes

[35] Ref. 8 a, p. 235.

[36] Perkin, *J. Chem. Soc.*, **69**, 1207 (1896).

[37] The authors are indebted to the Department of Pharmacology of the University of Wisconsin for these studies.

after the injection, the hind legs went into convulsions six minutes after injection, and seven minutes after injection chronic convulsions of the whole animal were noted. After this the animal was extremely depressed and did not respond to any form of stimulation.

Other experiments comparing the action of C,C-diethyl-N-ethoxy-barbituric acid with veronal were made and the results may be tabulated as follows.

	Effect	
Dose per body wt.	Veronal	C,C-Diethyl-N-ethoxy-barbituric acid
1 mg./5 g.	Extreme depression. Dead in 12 hours.	Extreme depression. Recovered.
0.5 mg./5 g.	Excitement followed by extreme depression. Recovered.	Slight loss of equilibrium. No other effect. Recovered.

C,C-Diethyl-N-N′-diethoxy-malonamide.—One mg. of this material per 5 g. of body weight when injected in a mouse, produced extreme depression followed by convulsions. The mouse recovered.

From the pharmacological investigation thus far made, it may be concluded that substituted O-alkyl hydroxylamines have in general the same physiological properties as the substituted amines to which they are related, differing from them in degree only.

Summary

1. Several substituted O-alkyl hydroxylamines related to the medicinally valuable amines, choline, procaine, veronal, phenyl-urea and thiosinamine have been synthesized and studied chemically.

2. The results of a preliminary pharmacological investigation of ethyl-ethoxy-amino-ethyl *p*-aminobenzoate, ethylethoxy-amino-ethyl benzoate, C,C-diethyl-N-ethoxy-barbituric acid and C,C-diethyl-N,N′-diethoxy-malonamide have been given. The substituted O-alkyl hydroxylamines investigated were found to have, in general, the physiological properties of the amines to which they are related, differing from them in degree of activity only.

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