hands may possibly be accounted for by the different medium we employed for the transformation. This same effect has been noted previously by us in the action of *Cornynebacterium simplex* on I from which either II or III may be produced as the major product by appropriate choice of medium.[2]

We also observed that an unidentified species of the genus *Alcaligenes*, family Achromobacteriaceae, (Schering ON No. 1–42) converted I into III. In this instance it was possible to isolate III by chromatography without subsequent acetylation.

EXPERIMENTAL[3]

Myocobacterium lacticola. To each of ten 300-ml. Erlenmeyer flasks was added 100 ml. of a broth made from 10 g. of yeast extract (Difco), 10 g. of cerelose, 4.4 g. of potassium dihydrogen phosphate, and 8.84 g. of disodium hydrogen phosphate heptahydrate made up to 1 l. with tap water. The flasks and their contents were sterilized, inoculated with a loopful of *Mycobacterium lacticola* (A.T.C.C. 9626), and incubated, with rotary shaking at 220 cycles/min., for 48 hr. at 30°. Then, to each flask was added 0.025 g. of I in 0.5 ml. of 80% aqueous ethanol. Shaking was continued for 48 hr. at which time extraction of an aliquot of the reaction mixture with chloroform followed by chromatography on Whatman No. 4 paper by the method of Shull[4] indicated complete transformation of I. A single, more polar, spot absorbing in the ultraviolet, was observed, which did not stain with red tetrazolium. The total reaction mixture was extracted with chloroform and the extracts were concentrated to a small volume which was chromatographed over 20 g. of Florisil prepared with hexane. Elution with methylene chloride containing 0.5%, 1.0%, and 2.0% of methanol afforded a series of glassy residues which appeared to be paper chromatographically homogeneous. They were pooled and acetylated with 2 ml. of acetic anhydride in 2 ml. of pyridine. After 16 hr. at room temperature, 50 ml. of water was added and the oily precipitate was allowed to stand in contact with the solvent until crystallization ensued (*ca.* 1 month). The resulting prisms were removed by hand and washed with cold ether. A total of 0.040 g. of solid, m.p. 175–177°, was collected. Bands were observed in the infrared spectrum of this compound at 2.87μ (OH), 5.75μ (acetate carbonyl), 6.01, 6.14 and 6.22μ (1,4-diene-3-one) and 8.16μ (C—O—C of acetate). The spectrum was identical with that from the 20,21-diacetate of III.[2] Admixture with an authentic sample did not depress the melting point.

Alcaligenes sp. (ON No. 1–42). To each of ten 300-ml. Erlenmeyer flasks was added a broth made from 3 g. of yeast extract (Difco), 10 g. of cerelose, and 1 g. of corn steep liquor per liter of tap water. The *p*H was adjusted to 7.0 and the sterile medium was inoculated with a 5% charge of *Alcaligenes sp.* (ON No. 1–42) (20-hr. growth culture). After 24 hr. of incubation, under the conditions described previously, 0.025 g. of I in 2 ml. of 95% ethanol was added to each flask and incubation with shaking was continued for 72 hr. The reaction mixture was extracted with chloroform, washed with water, dried, and concentrated, and the residues were chromatographed on 15 g. of Florisil in the usual way. Crystalline III was obtained from the 1% methanol in methylene chloride eluates. Recrystallization from acetone-hexane afforded 65 mg. of III, m.p. 190–193°, λ_{max}^{Nujol} 3.02μ (OH), 6.02, 6.19, and 6.24μ ($\Delta^{1,4}$-diene-3-one). The infrared spectrum was identical with that from an authentic sample.[2]

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(2) H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik, E. B. Hershberg, A. Nobile, W. Charney, C. Federbush, D. Sutter, and P. L. Perlman, unpublished results; also H. L. Herzog, Gordon Conference on Steroids and Natural Products, August 1955.

(3) Infrared measurements were made and interpreted by the Physical Chemistry Laboratory of the Schering Corp.

(4) G. M. Shull, Abstracts of the 126th Meeting of ACS, New York, 1954, p. 9A.

2-[(2-*N*-methyl-*N*-methoxyaminoethyl)-(*p*-methoxybenzyl)Amino]Pyridine. An Hydroxylamine Analog of Pyrilamine

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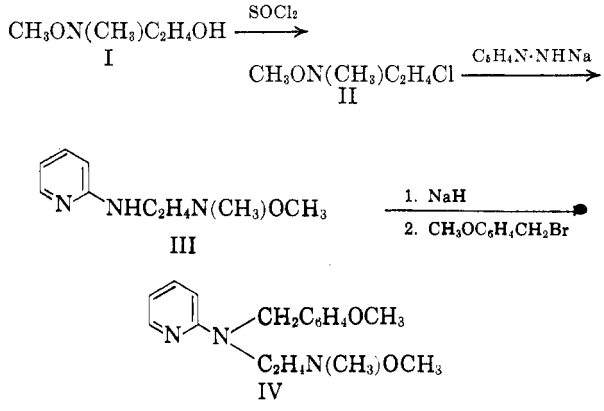
Some *O,N*-substituted hydroxylamines which are chemically related to pharmacologically active amines have pharmacological action similar to the corresponding amines.[1–3] It became of interest to determine whether the hydroxylamine analog of pyrilamine would have pharmacological properties similar to the well known antihistamine. Therefore, a sample of 2-[(2-*N*-methyl-*N*-methoxyaminoethyl)(*p*-methoxybenzyl)amino]pyridine was prepared, according to the following series of reactions:



N-2-Hydroxyethyl-*O,N*-dimethylhydroxylamine (I) was converted into *N*-2-chloroethyl-*O,N*-dimethylhydroxylamine (II) with thionyl chloride through the hydrochloride. *N*-2-Choloroethyl-*O,N*-dimethylhydroxylamine was then interacted with the reaction product of 2-aminopyridine and sodium hydride in 1,4-dioxane. The resulting product, 2-[(2-*N*-methyl-*N*-methoxyaminoethyl)amino]pyridine (III) was then treated with a suspension of sodium hydride in 1,4-dioxane. The solution, which resulted from this reaction, was treated with *p*-

(1) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, 49, 1527 (1927).

(2) E. F. Rogers, G. Bovet, V. G. Longo, and G. B. Marini-Bettolo, *Experientia*, 9, 260 (1953).

(3) G. Palazzo, E. F. Rogers, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, 84, 915 (1954).

methoxybenzyl bromide[4] at a temperature not over 50°. 2-[(2-*N*-Methyl-*N*-methoxyaminoethyl) (*p*-methoxybenzyl)amino]pyridine (IV) was obtained in high yield. The simple salts which could be obtained with various acids were either oily or very hygroscopic. Crystalline chloroplatinates and a chloroaurate were obtained. Paper strip chromatography of the base, as well as other criteria, indicated that the product was pure.

N-2-Chloroethyl-*O*,*N*-dimethylhydroxylamine (II) was quite unreactive and was very stable when compared with 2-chloroethyldimethylamine. It was hydrolyzed only under rather drastic conditions and failed to react with sodium iodide in acetone. 2-Chloroethyldimethylamine quickly forms precipitates with either alcoholic silver nitrate or with sodium iodide in acetone.

The investigation of the stability of II was made because of its failure to react with the sodium salt of 2-(*p*-methoxybenzylamino)pyridine in refluxing toluene, triethylamine, or tri-*n*-butylamine. It also failed to react with the sodium salt of 2-aminopyridine in refluxing toluene or tri-*n*-butylamine.

When 1,4-dioxane was employed as the solvent, both 2-aminopyridine and 2-(*p*-methoxybenzylamino)pyridine reacted vigorously with sodium hydride to form soluble sodium salts. The condensations with *N*-2-chloroethyl-*O*,*N*-dimethylhydroxylamine (II) could then be carried out in a homogeneous system. The reaction with 2-aminopyridine went smoothly, yielding up to 30% of 2-[(2-*N*-methyl-*N*-methoxyaminoethyl)amino]pyridine (III). The sodium salt of 2-(*p*-methoxybenzylamino)pyridine and the chloro compound (II) failed to give any condensation product even though a theoretical yield of sodium chloride was obtained. A 78% yield of 2-(*p*-methoxybenzylamino)pyridine was recovered.

Dr. C. A. Winter of the Merck Institute for Therapeutic Research has compared the antihistamine effects of pyrilamine maleate and IV, neutralized with dilute HCl, on guinea pigs exposed to an histamine aerosol. Subcutaneous doses of 0.1 mg. pyrilamine maleate per kilogram injected 30 min. prior to exposure protected the animals against shock, while doses of 10 mg. of IV per kilogram were ineffective in preventing histamine shock.

EXPERIMENTAL

N-2-Hydroxyethyl-O,N-dimethylhydroxylamine (I)[1,5,6] *O*,*N*-Dimethylhydroxylamine[7] (50 g., 0.82 mole) in 50 ml. methanol was added slowly to a cold solution of 52 g. (1.18 moles) ethylene oxide in 150 ml. methanol. The resulting solution was refluxed (condenser temperature <10°) with stirring for 5 hr. During that time the reaction temperature rose from 37° to 56°. The reaction was cooled and concentrated under reduced pressure. The residue which weighed 70 g. was distilled. After a forerun of 5.8 g., b.p. 25–52° (21 mm.), n_D^{25} 1.4133, a distillate was collected which weighed 46.5 g., b.p. 52.5–56.5° (19–20 mm.), n_D^{25} 1.4180–1.4209,[8] (54%).

N-2-Chloroethyl-O,N-dimethylhydroxylamine (II). A solution of 60 g. I (0.57 mole) in 50 ml. dry benzene was added with heating to a solution of thionyl chloride (102 g., 0.85 mole) in 250 ml. of dry benzene. When the temperature reached 50°, the heater was removed. During the remainder of the addition, the temperature rose to 65° and a gas was evolved. The solution was refluxed with stirring until the evolution of gas stopped (1.5 hr.). The final temperature was 82°. The reaction was permitted to cool until precipitation started. Four hundred ml. of ether was added and the mixture was cooled to 5°. The product was filtered and washed with ether. The crystalline product, which weighed 82 g., was dissolved in hot ethyl acetate, decolorized with Darco G-60, filtered, and crystallized, m.p. 98.5–100°, 61.5 g. Concentration of the filtrate gave a second crop of 3.5 g., m.p. 85–92°. The product is quite volatile.

A solution of this hydrochloride (19.1 g.) in 20 ml. of water was cooled in ice. To this solution 150 ml. of 10% $NaHCO_3$ (30% NaOH is more satisfactory) was added slowly. The solution was extracted thrice with 100 ml. of ether. The dried ether solution was concentrated under reduced pressure. The residue was distilled, b.p. 52–53° (58 mm.), redistilled b.p. 53° (58 mm.) n_D^{25} 1.4192; b.p. 122–123° (760 mm.) n_D^{25} 1.4182.

Anal. Calcd. for $C_4H_{10}ClNO$: C, 38.87; H, 8.16; Cl, 28.69. Found: C, 38.93; H, 7.93; Cl, 28.88.

Stability of N-2-chloroethyl-O,N-dimethylhydroxylamine (II). Studies carried out on II demonstrated the rather considerable stability of this molecule. The following experiments show this: (A) One g. of II was refluxed for 2 hr. in toluene containing one equivalent of NaH. The toluene was decanted. The residue was decomposed with methanol and tested for Cl^- ion with silver nitrate. Only a slight precipitate formed. The toluene was treated with dry HCl and diluted with ether. II Hydrochloride, (0.87 g., 67%), m.p. 98–99.5° was obtained. (B) A suspension of a few drops of II in 30% NaOH was heated on a steam cone for 15 min. A subsequent test for chloride ion with $AgNO_3$ was negative. (C) a few drops of II were heated to 70° for 0.5 hr. in an alcoholic solution of sodium ethoxide. A sample taken at this stage gave only a slight test for chloride ion with $AgNO_3$. When the same suspension was heated at 90° for an additional 0.5 hr. in a closed tube, a strong test for chloride ion was obtained. (D) No precipitate of NaCl was obtained after refluxing II with a solution of NaI in acetone.

2-[(2-N-Methyl-N-methoxyaminoethyl)amino]pyridine (III). A 41% emulsion of sodium hydride (4.7 g., 0.08 mole) in mineral oil was suspended in 35 ml. purified dioxane. To this mixture 7.5 g. (0.08 mole) of 2-aminopyridine in 15 ml. of dioxane was added slowly. Gas evolved at once and the temperature rose to 37° at which time all insoluble matter dissolved. To this solution 9.9 g. *N*-2-chloroethyl-*O*,*N*-dimethylhydroxylamine (0.08 mole) in 10 ml. of dioxane was added. The solution which resulted was heated to 100° with stirring. At 80–85° a precipitate began to form. Heating at 100° was continued for 2 hr. and then the mixture was cooled and filtered. The precipitate weighed 3.3 g. The filtrate was diluted with 200 ml. of ether and washed twice with water. The aqueous extract was in turn washed with ether. The combined ether solutions were dried over $MgSO_4$ and concentrated under reduced pressure. The resi-

(4) Lapworth and Shoesmith, *J. Chem. Soc.*, **121**, 1391 (1922).

(5) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, **52**, 1078 (1930).

(6) W. H. Horne and R. G. Shriner, *J. Am. Chem. Soc.*, **54**, 2925 (1932).

(7) R. T. Major and E. E. Fleck, *J. Am. Chem. Soc.*, **50**, 1479 (1928).

(8) L. W. Jones and R. T. Major, ref. 1, p. 1532 reported *N*-2-hydroxyethyl-*O*,*N*-dimethylhydroxylamine b.p. 57–58° (23 mm.).

due, weighing 12.4 g. was in two phases, one of which was undoubtedly mineral oil. The second phase was separated from the mineral oil by dissolving it in a small amount of methanol in which the mineral oil was not very soluble.[9] The crude product was distilled *in vacuo*. The initial distillate contained 2-aminopyridine. The desired product boiled at 73–74° at 0.004 mm. n^{25}_D 1.5323, yield 1.95 g., 13%.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.92; H, 8.16; N, 22.88.

2-[2-N-Methyl-N-methoxyaminoethyl)(p-methoxybenzyl)-amino]pyridine (IV). A 41% emulsion of sodium hydride (4.25 g., 0.073 mole) in mineral oil was suspended in 30 ml. purified dioxane. To this mixture 11.5 g. III (0.063 mole) in 30 ml. purified dioxane was added. This mixture was heated with stirring. At 75° a vigorous reaction took place with a temperature rise and foaming. When the reaction ceased, the preparation was cooled to 30°. A solution of 13.4 g. *p*-methoxybenzyl bromide[4] (0.067 mole, b.p. 80.5–81.5° at 1 mm.) in 20 ml. dry dioxane was added at such a rate that the temperature of reaction did not exceed 50°. The reaction product was stirred for a short time after the addition was complete and then the product was diluted with 100 ml. of ether, and the mixture which formed was filtered. The filtrate was extracted with 2.5*N* HCl in four portions of 25 ml. each. The extracts were combined, washed with ether, and then made alkaline with 2.5*N* NaOH.The alkaline solution was extracted thrice with 100 ml. ether. The ether extracts were combined, washed with water, dried and concentrated under reduced pressure. The residue, after the removal of solvent *in vacuo* weighed 18.1 g. (95%) n^{25}_D 1.5688.

Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.74; H, 7.69; N, 13.95. Found: C, 67.59; H, 7.76; N, 13.79.

The ultraviolet spectrum was identical with that of pyrilamine with maxima at 311 mμ, ε 4,540; 285 mμ, ε 2,890; 278 mμ, ε 2,740; 251 mμ, ε 19,280; 227 mμ, ε 12,400.

The infrared spectrum was very similar to that of pyrilamine except for an intensification of absorption in 9.6μ region and the absence of a band at 3.6μ. This band was also absent in the infrared spectrum of 2-[(2-*N*-methyl-*N*-methoxyaminoethyl)amino]pyridine (III).

A portion of the above analyzed residue was distilled, b.p. 150–152° (20 mm.), n^{25}_D 1.5683.

Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.74; H, 7.69. Found: C, 67.81; H, 7.45.

Investigations of the purity of the 2-[(2-N-methyl-N-methoxyaminoethyl)(p-methoxybenzyl)amino]pyridine (IV). (1) *Distribution:* Distilled IV (31.6 mg.) was added to 10 ml. of isooctane and 10 ml. of 90% methanol. After shaking the mixture for a few minutes, 1 cc. of each phase was removed and diluted to 50 ml. with spectrographically pure methanol. The ultraviolet spectra of the two phases were identical. The absorbance of the isooctane sample at 311 mμ was 0.332 and the absorbance of the methanol sample at 311 mμ was 0.729. The distribution ratio was 0.46.

(2) *Paper strip analysis.* Distilled IV (185 μg.) was chromatographed on paper in an isooctane–90% methanol solvent system. When the paper was viewed in ultraviolet light through a phosphor screen, one spot was visible which had an R_f value of 0.75. Assay by ultraviolet spectrum showed that 95% of the original material was in this spot.

A similar experiment using a ligroin-Carbitol solvent system also failed to produce any separation.

Salts of 2-[(2-N-methyl-N-methoxyaminoethyl)(p-methoxybenzyl)amino]pyridine (IV). *Hydrochloride.* Gaseous HCl produced an amorphous white solid when bubbled into a solution of IV in dry ether. The solid was very hygroscopic. Chloride analysis of 17.3% indicated that the hydrochloride was largely the dihydrochloride mixed with some monohydrochloride. *Hydrobromide.* Gaseous HBr precipitated an amorphous white hydroscopic solid when bubbled into a solution of IV in ether.

Picric acid, maleic acid, sulfuric acid, nitric acid, and perchloric acid gave oily salts with IV which did not crystallize or solidify.

Chloroplatinates. Two chloroplatinates of IV were obtained, depending on whether IV was added to a solution of chloroplatinic acid or the reverse. (1) Compound IV (102 mg., 0.00034 mole) was dissolved in ethanol. To this solution was slowly added 4.25 ml. of a 0.04 molar solution of chloroplatinic acid (0.17 mole) in ethanol. The precipitate which formed was recrystallized by adding water dropwise to the hot alcoholic suspension of the salt until a solution occurred. Cooling precipitated 105 mg. of a chloroplatinate of IV; m.p. 146–148° with decomposition.

Anal. Calcd. for $(C_{17}H_{23}N_3O_2)_2H_2PtCl_6$: C, 40.32; H, 4.78; Cl, 21.01; Pt, 19.28. Found: C, 40.14; H, 4.85; Cl, 20.92; Pt, 20.11; 20.17.

(2) A solution of IV (85 mg., 0.00028 mole) in ethanol was added to 9.0 ml. of 0.04 molar H_2PtCl_6 (0.00036 mole) in ethanol. The precipitate which formed was recrystallized from hot ethanol containing a very small amount of water. The salt which was obtained had no definite melting point but slowly sintered above 140°.

Anal. Calcd. for $C_{17}H_{23}N_3O_2.H_2PtCl_6$: C, 28.70; H, 3.54; Cl, 29.91; Pt, 27.44. Found: C, 28.95; H, 3.40; Cl, 29.76; Pt, 26.91, 27.31.

Chloroaurate. A solution of IV (86 mg., 0.00029 mole) in ethanol was added to 6.0 ml. of 0.05*M* $HAuCl_4$ (0.0003 mole). The solution which was obtained yielded a precipitate when diluted with 200 ml. ether. It was recrystallized from butanol; yield, 106 mg., m.p. 100–101°.

Anal. Calcd. for $C_{17}H_{23}N_3O_2.HAuCl_4$: C, 31.83; H, 3.77; Cl, 22.11; Au, 30.75. Found: C, 31.94; H, 3.72; Cl, 21.84; Au, 30.93, 31.06.

Acknowledgments. We are indebted to Mr. F. A. Bacher and associates for ultraviolet spectra; to Mr. R. N. Boos and associates for microanalysis; to Dr. N. R. Trenner and Mr. R. N. Walker for infrared spectra; and to Dr. R. E. Harmon and Mr. H. R. Barkemeyer for advice and assistance on the paper strip chromatography.

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(9) In later preparations the separation was effected more easily by extracting the combined ether solutions with dilute hydrochloric acid, adding NaOH solution to the acid fraction and then reextracting the base with ether.

Note on the Structure of Certain Nitrobenzene Addition Compounds

R. F. GROSSMAN

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Several addition compounds of nitrobenzene with inorganic halides have previously been recorded. The compound $C_6H_5NO_2 \cdot TiCl_4$ was reported by Pushin and coworkers,[1] who studied the nitrobenzene–titanium tetrachloride system cryoscopically. The addition compound $C_6H_5NO_2 \cdot AlCl_3$ is well known[2]; an adduct of nitrobenzene with antimony pentachloride, $2C_6H_5NO_2 \cdot SbCl_5$, has also been re-

(1) N. A. Pushin, L. Nikolic, A. Radojcin, and T. Voroponova, *Ann.*, **551**, 259 (1942).

(2) B. Menschutkin, *Chem. Zentr.*, **I**, 1240 (1910).