Anal. Caled. for C<sub>25</sub>H<sub>35</sub>N<sub>7</sub>O<sub>4</sub>:2HCl+3.33H<sub>2</sub>O; C, 47.62; H, 6.98; Cl, 11.25; N, 15.55; H<sub>2</sub>O, 9.51. Found: C, 47.72; H, 7.08; Cl, 11.80; N, 15.53; H<sub>2</sub>O, 9.58.

5-[8-(4-Amino-1-methylbutylamino)-6-methoxy-5-quinolylazo|uracil (IIIc).-5-Aminouracil (12.7 g., 0.1 mole) was diazotized and coupled with 45.5 g. (0.1 mole) of primaquine diphosphate utilizing the procedure described for IIIa. The crude dye was crystallized from dimethylacetamide-water to give 6.0 g.  $(15^{C}_{C})$  of reddish brown crystals, m.p. 254-256°

Anal. Caled. for  $C_{19}H_{23}N_7O_3$ : C, 57.42; H, 5.83; N, 24.67. Found: C, 57.03; H, 5.67; N, 24.16.

5-[4-(2-Diethylaminoethylamino)-1-naphthylazo]-8-(2-diisobutylaminoethylamino)-6-methoxyquinoline (V).-To a solution of 9.8 g. (0.025 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide hydrochloride<sup>3,4</sup> in 100 ml. of ice-water and 4.5 ml, of concentrated hydrochloric acid was added 25 ml, of a 1 M sodium nitrite solution over a period of 2 min. The resulting red solution was stirred for 4 min. and added in one portion at  $0-5^{\circ}$  to a solution of 10.5 g. (0.025 mole) of 8-(2-diisobutylaminoethylamino)-6-methoxyquinoline dihydrochloride monohydrate in a mixture of 100 ml. of water, 10 ml. of concentrated hydrochloric acid, and 100 g. of ice. The reaction mixture was stirred at  $0-5^{\circ}$  for 2 hr., 15 ml. of concentrated ammonium hydroxide was added, and the crude intermediate trifluoroacetamide IV that separated was collected by filtration, washed with water, and dried in racuo. The maroon solid weighed 16.7 g. (96%), m.p. 50~70°

The crude amide was dissolved in 400 ml. of methanol, 15 ml. of 6 N aqueous sodium hydroxide was added, and the mixture was stirred at 40° under nitrogen for 5 days. The mixture was cooled and the deep maroon crystals that separated were collected by filtration and washed successively with cold methanol and water. Crystallization from 95% ethanol gave 7.9 g. (53% over-all) of maroon crystals, m.p. 92–94° dec.

Anal. Caled. for C36H31N7O: C, 72.32; H, 8.60; N, 16.40. Found: C, 72.54; H, 8.60; N, 16.80.

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## Hypocholesteremic Agents. II. The Hydrogenation of Some Pyridinesulfonic and Pyridinealkanesulfonic Acids

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Our interest in some aminosulfonic acids as cholesterollowering agents prompted us to attempt hydrogenation of available pyridine and pyridinealkanesulfonic acids and test the activity of the resultant products in this program.

2-(2-Pvridine)ethanesulfonic acid (I) and the corresponding 4-pyridine derivative (III) were readily converted to the piperidine acids II and IV by a method used for the reduction of pyridinealkanoic acids.<sup>1</sup> It is of interest that this method failed in attempting to convert pyridine-3-sulfonic acid (V) to piperidine-3sulfonic acid (VI). However, in the absence of ammonia, VI was obtained when enough platinum catalyst was used.<sup>2</sup> 3-Pyridinehydroxymethanesulfonic acid (VII) could not be reduced under any conditions. The compound can be viewed as an aldehyde addition product. It apparently undergoes reversal during attempted reduction with the release of sulfur dioxide. This is reduced to hydrogen sulfide, poisoning the catalyst immediately.

$$\bigcirc \overset{CH(OH)SO_3H}{\longrightarrow} ~ \rightleftarrows ~ \bigcirc \overset{CHO}{\longrightarrow} \overset{CHO}{\longrightarrow} \overset{H_2O}{\longrightarrow}$$

Pharmacology.-The test method used was described by Wright.<sup>3</sup> Compounds I, II, and V were found inactive. The general lack of activity discouraged further testing among this group. The toxicity of IV and VI, however, was determined. One delayed death (48 hr.) was noted in a dose of 1500 mg./kg. and none at 2000 mg./kg. when IV was administered orally as a 5% solution in water (pH 5.0). Intermittent convulsions were noted at the higher doses. Compound VI, administered as a 5% solution in water (pH 7.0), was well tolerated intraperitoneally and orally in doses up to 1500 mg./kg., but appeared to have no physiological activity.

#### Experimental

All melting points taken on a Thomas-Hoover apparatus are corrected.

2-(2-Piperidine)ethanesulfonic Acid (II).-A solution of 18.7 g. (0.1 mole) of I<sup>4</sup> in 150 ml, of water and 9 ml, of concentrated ammonium hydroxide was hydrogenated in the presence of 5.0 g. of 5% rhodium on alumina<sup>3</sup> under 2 atm. pressure. Uptake was complete in less than 2 hr. The solution was filtered from the catalyst and concentrated to dryness. It was ground to a fine powder, dried to constant weight, and analyzed without further purification: yield, 18.5 g. (95.8%); m.p.  $315^{\circ}$ . Anal. Caled. for C<sub>7</sub>H<sub>13</sub>NO<sub>8</sub>8: C, 43.50; H, 7.82; N, 7.25.

Found: C, 43.60: H, 7.92; N, 7.10.6

The isomeric 2-(4-piperidine)ethanesulfonic acid, melting at  $355^\circ$ , was prepared in 96.8% yield by the same method.<sup>7</sup> The carbon, hydrogen, and nitrogen found, 43.43, 7.84, and 7.47 c respectively, are in excellent agreement with the calculated values shown for II.

II could also be obtained by reduction of I with platinum oxide<sup>5</sup> in the absence of ammonia. Colloid formation occurred which required large amounts of filter aids to remove the catalyst. As a result, much material was adsorbed and the yield was low.

Piperidine-3-sulfonic Acid (VI).-The described method<sup>2</sup> calls for a small quantity of catalyst. When  $7.95 \, g$ ,  $(0.05 \, mole)$  of pyridine-3-sulfonic acid4 (m.p. 331°) in 50 ml. of water was hydrogenated in the presence of 0.5 g, of platinum oxide at  $60\,^\circ$ under 2.7 atm. pressure, uptake of hydrogen was about 50% in 18-20 hr. The solution was filtered and rehydrogenated with an additional 1.0 g. of catalyst. When uptake was complete the reduction solution was filtered from the catalyst and concentrated under reduced pressure to dryness. The solid material was treated with absolute alcohol, filtered, washed, and dried

- (4) Available from Aldrich Chemical Company, Milwaukee, Wis.
- (5) The catalyst was purchased from Engelhard Industries, Newark, N. J.

<sup>(1)</sup> M. Freifelder, J. Org. Chem., 28, 602 (1963).

<sup>(2)</sup> O. Nieodemus and O. Wulff, U. S. Patent 2,008,292 (1935).

<sup>(3)</sup> H. B. Wright, J. Med. Chem., 7, 113 (1964).

<sup>(6)</sup> Microanalyses were carried out by Mr. O. F. Kolsto and his group at this laboratory

<sup>(7)</sup> The starting material, 2-(4-pyridine)ethanesulfonic acid was supplied by Reilly Tar and Chemical Co., Indianapolis, Ind.

thoroughly before submitting for analysis; yield, 7.8 g. (94.7%); m.p.  $340-344^{\circ}$  dec.; lit.<sup>2</sup>  $320-330^{\circ}$  dec.

Anal. Calcd. for  $C_5H_{11}NO_5S$ : C, 36.34; H, 6.71; N, 8.48. Found: C, 36.53; H, 6.82; N, 8.29.<sup>6</sup>

Infrared and ultraviolet spectra<sup>8</sup> showed that no starting material was present. When reduction in aqueous ammonia was attempted in the presence of rhodium on a carrier, complete uptake of hydrogen was never achieved even when a 60% ratio of catalyst to compound was used.

Attempted Hydrogenation of VII.—A solution of 6.3 g. (0.033 mole) of VII<sup>4</sup> in 100 ml. of water and 3 ml. of concentrated ammonium hydroxide was subjected to reduction under 3 atm. pressure in the presence of 2.0 g. of 5% rhodium on alumina. No uptake occurred. The solution was filtered and rehydrogenated with fresh catalyst. This operation was repeated several times. No uptake of hydrogen was ever observed. Attempted reduction in the absence of animonia with the same catalyst or with platinum oxide also failed.

(8) Infrared examination was carried out by Mr. A. Kammer and ultraviolet work by Mr. V. Papendick, both of this laboratory.

# The Synthesis of N-Hydroxycarbanilides and Their Evaluation as Germicides

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Previous workers have shown that substituted carbanilides are a biocidally active group of compounds, but none have investigated the activity of the N-hydroxycarbanilides. The introduction of a hydroxyl group on the nitrogen atom of a carbanilide should give the resulting compound chelating properties and thereby perhaps increase the germicidal activity.

Although the reaction of phenylhydroxylamine and phenylisocyanate to give N-hydroxycarbanilide is known,<sup>1</sup> only a very few N-hydroxycarbanilides are reported in the literature<sup>2</sup> and there are no examples where dihalo- and polyhalo-substituted phenylhydroxylamines are used.

The preparation of dihalo- and polyhalo-substituted phenylhydroxylamines, by reduction with zinc dust in the presence of ammonium chloride, proceeds quite smoothly. However, the isolation of the product is difficult since it will oxidize rapidly in air in a matter of seconds to the azoxybenzene derivative. It was found that the phenylhydroxylamine could be used without isolation; care had to be taken however to remove all alcohol and water used in the reduction step before proceeding to the reaction with the isocyanate.

The monohalo phenylhydroxylamines having a methyl group in the *ortho* position were found to be more stable than the monohalo phenylhydroxylamines and could be isolated and recrystallized in good yields without undue oxidation.

The N-hydroxycarbanilides were screened, by the agar dilution method,<sup>3</sup> and were found to be a biocidally

active class of compounds. In general, they were more active than the corresponding carbanilides. Table I compares the relative activity of several carbanilides with that of the corresponding N-hydroxycarbanilides.

Notes

 TABLE I

 Comparison of Activity of Carbanilides and

 N-Hydroxycarbanilides against Staphylococcus aureus

$R$ $N$ $CO$ $N$ $R^1$				
	ñ	n Minimum inhibitory		
		$R^2 =$	$R^2 = OH$	$R^2 = H.$
R	$\mathbb{R}^1$	$R^{3} = H$	$R^{3} = H$	$R^{2} = OH$
3-Cl	$3-CF_3$	125	31	31
4-Cl	4-Cl		15	
4-Cl	3-CF <sub>3</sub> -4-Cl	31	2	
$3,4$ - $Cl_2$	$3,4$ - $Cl_2$		4	
$3,5-\mathrm{Cl}_2$	$3-NO_2$	• - •	8	
$3,5-Cl_2$	$3-CF_3-4-Cl$	8	0.5	
3,4,5-Cl <sub>3</sub>	$3-CF_3$	31	0.5	8

The physical data and germicidal activity against *Staphylococcus aureus* of the N-hydroxycarbanilides are shown in Table II.

### Experimental

The N-hydroxycarbanilides isolated were found to be white or off-white solids which could be recrystallized from aqueous methanol. They melted with decomposition, readily formed sodium salts, and gave blue or green colorations with ferric chloride solution indicative of chelate formation. They were soluble in alcohol, dimethylformamide, and ether; partially soluble in benzene and chloroform; and insoluble in water and petroleum ether. Exposure to sunlight for 2–3 days gave changes in the melting points and additional peaks in the infrared curves of the compounds, indicating instability under these conditions.

Method A.—This procedure was suitable for the fairly stable monohalo phenylhydroxylamines which were isolated and purified before reacting with the isocyanates.

Method B.—Procedure A was modified by not isolating the freshly prepared phenylhydroxylamine. This method was used for the very unstable dihalo and polyhalo phenylhydroxylamines. Any oxidized phenylhydroxylamine that was formed could be removed readily by washing the N-hydroxycarbanilide with petroleum ether (b.p.  $40-60^{\circ}$ ). The isocyanates used, with the exception of the monohalo derivatives which were commercially available, were prepared by the phosgenation of the amine.<sup>4</sup>

3',4,5'-Trichloro-N-hydroxycarbanilide (Method A).—To a solution of 1.91 g. (0.0133 mole) of 4-chlorophenylhydroxylamine in 50 ml. of chloroform was added a solution of 2.5 g. (0.0133 mole) of 3,5-dichlorophenyl isocyanate in 50 ml. of chloroform. After stirring for a few min. a white precipitate was formed. The mixture was stirred for 1 hr., then filtered, the white solid vacuum dried, and then recrystallized from aqueous methanol to give white crystals, m.p. 155–156°, in 75% yield.

**3,3',4,4'-Tetrachloro-N-hydroxycarbanilide** (Method B).— A mixture of 21.9 g. (0.114 mole) of 3,4-dichloronitrobenzene in 240 ml. of 2B alcohol and 4.8 g. of ammonium chloride in 60 ml. of water was stirred well and heated to reflux. At reflux small portions of pure zinc dust were carefully added over approximately a 1-hr. period until the mixture became colorless. Approximately 43 g. of zinc dust were necessary. The mixture was then cooled slightly, quickly vacuum stripped to dryness, then slurried with 500 ml. of chloroform, filtered, the filtrate quickly was dried with anhydrous sodium sulfate and then filtered into a solution of 12.68 g. (0.068 mole) of 3,4-dichlorophenyl isocyanate in 100 ml. of chloroform. The mixture was stirred for 1-2 hr. The white precipitate, which formed almost immediately, was removed by filtration and washed with a little petroleum ether (to remove oxidized

<sup>(1)</sup> E. Beckmann, J. prakt. Chem., [2]56, 71 (1897).

<sup>(2)</sup> B. Hirsch, ibid., 284, 264 (1961).

<sup>(3)</sup> S. A. Waksman and H. C. Reilley, Ind. Eng. Chem. Anal. Ed., 17, 556 (1945).

<sup>(4)</sup> D. J. Beaver, D. P. Roman, and P. J. Stoffel, J. Am. Chem. Soc., 79, 1236 (1957).