usually hydrolyzed the oxime and the salt separately. Thus steam distillation of 29.2 g. of the salt in 370 ml. of 10% sulfuric acid gave by collection of about a liter and half of distillate, salting out with sodium sulfate, extracting four times with ether, treating with solid sodium bicarbonate, washing three times with saturated sodium chloride solution, drying and removing the ether, 6.68 g. (54%) of 1-methylcyclopenten-5-one, b. p. 158–161° (760 mm.), $n^{20}D$ 1.4771.

**Ketones, $C_{19}H_{26}O$ (Dimethylsteradienones?).**—Hydrocarbon, containing 10% of 10-methyl-1-vinyl-1,7?-naphthitadiene, b. p. 61–63° (0.1 mm.), $n^{20}D$ 1.5270, 6.24 g., 3.61 g. (10 moles) of 1-methylcyclopenten-5-one and a few crystals of hydroquinone were sealed in a Pyrex tube in an atmosphere of nitrogen and held at 200° for forty-eight hours. The viscous product was transferred with ether and distilled. Fifty per cent. of the methylcyclopentenone, 70% of the hydrocarbon, and 3 g. of nonvolatile product were recovered. This last was dissolved in 40 ml. of ethanol and refluxed for six hours with 3 g. of semicarbazide hydrochloride and 4.5 g. of sodium acetate in 15 ml. of water and 50 ml. of ethanol. Removal of solvents and keeping in vacuum overnight with calcium chloride and soda-lime gave a residue which was thoroughly extracted with ether. Concentration of the solution gave 121 mg. of semicarbazone, m. p. 230–254° (dec.). The ether was removed from the mother liquor and the residue was taken up in ethanol. Concentration of this solution gave 72 mg., m. p. 242–251°. The semicarbazone appears to form very slowly from some products of the triene-methylcyclopentenone reaction for removal of the ethanol, which gave 1.7 g. of material which did not crystallize, and refluxing the residue for six hours with 1.7 g. of semicarbazide hydrochloride, 6 ml. of dry pyridine and 54 ml. of methanol gave 181 mg. more of semicarbazone, m. p. 254–257° (dec.). Filtration, continued refluxing of the filtrate for eleven hours more, and concentration gave still more semicarbazone (80 mg.); total 454 mg.; 39%, calculated on reactive triene (according to reaction with *p*-benzoquinone); 13%, calculated on the hydrocarbon consumed. A portion of the semicarbazone was recrystallized from ethanol for analysis, m. p. 254.6–256.6°, cor.

*Anal.*[5] Calcd. for $C_{20}H_{29}N_3O$: C, 73.35; H, 8.9; N, 12.80. Found: C, 73.7; H, 8.55; N, 12.7.

In another experiment, material which did not react with semicarbazide hydrochloride and sodium acetate under the conditions specified, gave some carbonyl derivative with Girard's T reagent. The yield of ketones $C_{19}H_{26}O$ is probably considerably higher than is indicated by the weight of semicarbazones. Distillation of the ketones in high vacuum gave no crystalline material of the composition $C_{19}H_{28}O$.

**Hydrolysis of the Semicarbazones.**—The semicarbazones employed melted from 239–254°. They had been precipitated from ether, recrystallized from ethanol, and then washed with ethanol and ether. In one experiment, 69.9 mg. was dissolved in 2.89 ml. of warm acetic acid, 0.3 g. of anhydrous oxalic acid was added, and the mixture was refluxed for four hours. Addition of 130 ml. of water, extraction with ether, washing, drying, evaporation of the ether, and purification of the residue gave 53.9 mg. which was sublimed in vacuum. A number of sublimed fractions were taken, two of which appeared crystalline, but these weighed only 2 mg. each. Three other fractions, 11.6 mg., collected at 1.5–3.0 × $10^{-5}$ mm. and bath temperature 44–55°, 11.8 mg., 1.5–5.0 × $10^{-5}$ mm. and 55–69°, and 8.7 mg., 0.2–25 × $10^{-5}$ mm. and 67–151° did not crystallize.

In another experiment, 200.8 mg. of semicarbazones by a similar procedure gave 149 mg. of sublimed ketones. Crystalline material was obtained from some of these sublimates by the use of ethanol, but the amounts separated were small.

It was not found possible to convert this quantity of material to a known steroid.

## Summary

1. A mixture of semicarbazones, $C_{20}H_{29}N_3O$, has been obtained from the reaction products of *cis*?-10-methyl-1-vinyl-1,7?-naphthitadiene and 1-methylcyclopenten-5-one. This material is isomeric with and may contain the semicarbazone of 10,13-dimethyl-2,9(11)-steradien-17-one (2,4b-dimethyl-1,2,3,4b,5,8,8a,9,10,10a-decahydrocyclopenta[a]phenanthren-3'-one).

2. Hydrolysis of the semicarbazones and fractional distillation of the products did not give a crystalline compound.

3. A salt, $CH_3C_5H_5NOH \cdot C_5H_5N \cdot HCl$, has been prepared from pyridine and the nitrosochloride of 1-methylcyclopentene.

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(5) By Dr. T. S. Ma, University of Chicago.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PYRIDIUM CORPORATION]

# Tuberculostatic Compounds. I. Ethers of 2-Hydroxy-5-aminopyridine

BY HARRIS L. FRIEDMAN, LEO D. BRAITBERG, ALEXANDER V. TOLSTOOUHOV AND EDMOND T. TISZA

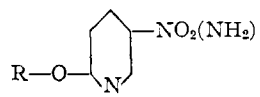
Ethers of 2-hydroxy-5-aminopyridine have been found in these laboratories to have an *in vitro* tuberculostatic activity.[1] In an effort to select the most active and the least toxic compound of this type a series of ethers was prepared.[2] This paper describes the preparation of these compounds.

The nitro ethers were prepared from 2-chloro-5-nitropyridine by interaction with the appropriate sodium alcoholate or phenolate. The nitro ethers were then reduced with iron and acetic acid in aqueous methanol and the corresponding amino ethers were isolated as the dihydrochlorides. Details of the procedures are included in the experimental part and the results are given in Table I. Most of the compounds are new. A few have been reported but the physical constants are not given in the literature. Our physical constants of known compounds are included for comparative purposes. It was not possible to prepare the ethers from *t*-butyl alcohol and dipropylcarbinol because the nitro compounds exploded during vacuum distillation. The products from *s*-butyl alcohol and diethylcarbinol were successfully isolated although mild explosions were often encountered during vacuum distillation of the nitro ethers.

(1) W. H. Feinstone, *Proc. Soc. Exp. Biol. Med.*, **63**, 153 (1946).

(2) W. H. Feinstone, H. L. Friedman, M. Rothlauf, A. Kelly, R. Williams, *J. Pharm. Exp. Therapy*, **89**, 153 (1947).

TABLE I




| | R | —NO2— M. p., °C. | B. p. °C. | Mm. | —NH2— M. p., °C. | B. p. °C. | Mm. | Analysis, %HCl (2HCl) Calcd. | Found | Analyses, %N (2HCl) Calcd. | Found | Tbc[l] Stasis, mg. % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Methyl[m] | 107–109[a] | | | | 108–112 | 6[b] | 39.9 | 39.5 | | | 32 |
| 2 | Ethyl[m] | 90–93[a] | | | | 103–107 | 1.5[c] | 34.6 | 34.7 | | | 4 |
| 3 | *n*-Propyl[m] | | 102–105 | 3 | | 124–130 | 1.3[c] | 32.4 | 30.8 | | | 1/4 |
| 4 | Allyl[m] | 48–50 | | | | 112–116 | 1.8[d] | 32.7 | 32.9 | | | 1/4 |
| 5 | *n*-Butyl[n] | | 147–148 | 12[a] | | 148–150 | 12[c] | 30.5 | 30.5 | | | 1/32 |
| 6 | *i*-Butyl[n] | | 125–126 | 1.5 | | 147–151 | 15 | 30.5 | 30.3 | | | 1/2 |
| 7 | *s*-Butyl[n] | | 121–125 | 7 | | 117–128 | 4 | | | 16.9[k] | 17.1 | 2 |
| 8 | *n*-Amyl[n] | | 108–111 | 0.8 | | 117–120 | 2.5 | | | 11.2 | 11.5 | 1/32 |
| 9 | *i*-Amyl[n] | 107–108 | 141–144 | 6 | | 100–107 | 2.5[d] | | | 11.2 | 11.1 | 1 |
| 10 | 3-*n*-Amyl[n] | | 150–160 | 1.5 | | 126–128 | 5 | 28.9 | 28.9 | | | 1/16 |
| 11 | *n*-Hexyl[n] | | 125–135 | 1.5 | | 132–135 | 1 | 27.2 | 27.2 | | | 1/32 |
| 12 | *n*-Heptyl[n] | | 130–140 | 1 | | 134–142 | 1.5 | 26.0 | 25.6 | | | 1/2 |
| 13 | *n*-Octyl[n] | | 175–177 | 1.5 | | 149–152 | 1.5 | 24.7 | 24.5 | | | 4 |
| 14 | *n*-Decyl[n] | 42–43 | 150–155 | 2.5 | | 175–176 | 1 | 22.6 | 22.4 | | | 16 |
| 15 | Hydroxyethyl[m] | 114–115[e] | | | 64–68 | 147–157 | 0.2 | | | 18.2[k] | 18.0 | 64 |
| 16 | Methoxyethyl[m] | 66–67[f] | | | | 119–122 | 0.2 | 30.3 | 30.5 | | | 1 |
| 17 | Ethoxyethyl[m] | 43–44 | | | | 137–138 | 1 | 28.6 | 28.8 | | | 0.5 |
| 18 | Butoxyethyl[m] | 26–27 | 130–138 | 0.2 | | 147–153 | 0.3 | 25.8 | 25.9 | | | 4 |
| 19 | Phenoxyethyl[n] | 90–91 | | | | 187–190 | 2 | | | 12.2[k] | 12.4 | 16 |
| 20 | Benzyloxyethyl[n] | | 189–191 | 1 | | 168–174 | 0.6 | 23.0 | 22.8 | | | 32 |
| 21 | Ethoxy-ethoxyethyl[m] | 42–43 | | | | 168–169 | 1.5 | 24.4 | 23.6 | | | 64 |
| 22 | Diethylaminoethyl[n] | 37–38[e] | | | | [e,g] | | | | 14.9 | 15.0 | >64 |
| 23 | Phenyl[o] | 93–94[a] | | | | 170–175 | 1.7[a] | 28.2 | 28.1 | | | 4 |
| 24 | *o*-Tolyl[o] | 69–71 | | | | 155–160 | 1.5 | 26.2 | 26.2 | | | 16 |
| 25 | β-Naphthyl[o] | 95–96 | | | 91–93 | 188–204 | 1.5 | | | 11.9[k] | 11.6 | 8 |
| 26 | *p*-Nitro-phenyl[o] | 96–98 | | | | | | | | | | .. |
| 27 | *p*-Aminophenyl[o] | | | | [h] | | | | | 26.6 | 27.3 | 0.5 |
| 28 | Benzyl[n] | 106–107[a] | | | | 170–174 | 2.5 | 26.7 | 26.4 | | | 4 |
| 29 | β-Pyridyl[o] | 92–94 | | | 104–105 | | | 28.0 | 27.4 | | | 64 |
| 30 | 2-Pyridylethyl[m] | 114–116 | | | [i] | | | | | 14.6 | 14.3 | 64 |
| 31 | Tetrahydrofurfuryl[m] | 94–95 | | | | 164–166 | 2 | 27.3 | 27.5 | | | 4 |
| 32 | Cyclohexyl[n] | | 145–152 | 2.5 | | 146–154 | 3[j] | 27.6 | 27.4 | | | 4 |

[a] *Cf.* Maier-Bode, "Das Pyridin," Verlag Wilhelm Knappe, Halle (Saale) 1934, pp. 155–156. [b] Our data agree with those of Binz and Schickh, *Ber.*, **68**, 315 (1935), rather than Räth, *Ann.*, **484**, 52 (1930). [c] Binz and Schickh, ref. [b]. [d] Mentioned in Maier-Bode, "Das Pyridin," but not characterized as such. [e] Bremer, *Ann.*, **521**, 286 (1936). [f] German Patent 568,549 (1933). [g] M. p. of dihydrochloride 200.5–201.5°, Bremer (ref. [e]) isolated the Schiff base. [h] Isolated as the dihydrochloride, indeterminate decomposition point. [i] Dihydrochloride, m. p. 187–189°. [j] German Patent 607,662 (1935), gives b. p. 177°. [k] Per cent. of nitrogen of base. [l] Tested against avirulent strain 607 (see ref. 2). [m] Method A. [n] Method B. [o] Method C.

When the tuberculostatic activities of the homologous series of ethers containing normal alkyl radicals were plotted against the number of carbons in the alkyl group, a parabolic type curve was obtained with peak activity at four to six carbons. Those ethers which contained branched chain alkyl and alkoxy-alkyl radicals possessed lowered activity as compared to those with normal butyl and hexyl radicals. Ethers containing hydroxyalkyl and diethylaminoalkyl radicals had no activity. Those containing aryl, aralkyl and heterocyclic radicals were all of low activity.

## Experimental

**Nitro Ethers.**—The following examples indicate the various methods of preparation.

**2-Tetrahydrofurfuryloxy-5-nitro-pyridine (Method A).**—To a solution, cooled to room temperature, of 10 g. of sodium in 270 cc. of tetrahydrofurfuryl alcohol, there was added 64 g. of 2-chloro-5-nitropyridine. The reaction was cooled during the addition. The mixture was stirred all night at room temperature and then heated at 80–90° for one hour. After cooling, it was poured into 500 cc. of cold water and the precipitate filtered, washed well with water and dried. The product weighed 84 g. (90% yield) and melted at 94–96°. Recrystallization from methanol left the melting point unaltered.

*Anal.* Calcd. for $C_{10}H_{12}N_2O_4$: N, 12.5. Found: N, 12.3.

**2-*n*-Hexyloxy-5-nitropyridine (Method B).**—Fourteen grams of sodium was dissolved in 800 cc. of *n*-hexanol, the solution cooled and 95.5 g. of 2-chloro-5-nitropyridine added at room temperature. The resulting mixture was stirred all night and then heated for three hours at 80–85°. After cooling, the sodium chloride was removed by filtra-

tion through "Super Cel" (Johns-Manville). The hexanol was distilled off *in vacuo* and then the nitro compound distilled, b. p. 125–135° (1.5 mm.). The yield was 82.5 g. (67%).

*Anal.* Calcd. for $C_{11}H_{16}N_2O_3$: N, 12.5. Found: N, 12.2.

**2-β-Naphthyloxy-5-nitropyridine (Method C).**—Six grams of sodium was dissolved in 200 cc. of methanol and 34 g. of β-naphthol was added. To this solution was added 40 g. of 2-chloro-5-nitropyridine. The solution spontaneously warmed and deposited a copious precipitate. The suspension was stirred for three hours, cooled, the crystals filtered off, washed and dried. The yield was 40.7 g. (63%). The product formed lemon-yellow crystals from methanol, m. p. 95–96°. More could be obtained by adding water to the alcoholic liquors.

*Anal.* Calcd. for $C_{15}H_{10}N_2O_3$: N, 10.5. Found: N, 10.4.

**2-(β-(2-Pyridyl)-α-ethyloxy)-5-nitropyridine (Method D).**—Seventy-three hundredths of a gram of sodium was dissolved in 12 g. of β-(2-pyridyl)-α-ethanol at 50°. This reaction was very sluggish and required approximately twenty-four hours with final heating to 100°. The resulting solution was cooled to room temperature and 5 g. of 2-chloro-5-nitropyridine added. After a few hours the reaction was heated to 100° for one-half hour. It was then poured into 100 cc. of water and the liquid decanted from the semi-solid precipitate which was produced on cooling. The reaction product was dissolved in dilute hydrochloric acid and unreacted chloronitropyridine removed by ether extraction. After being decolorized with charcoal, the solution was made alkaline and the product extracted with ether. A black tar insoluble in both ether and sodium hydroxide remained. The golden-yellow ether solution gave 3.0 g. of crystals on evaporation (12% yield). The nitro compound was recrystallized from methanol, m. p. 114–116°.

*Anal.* Calcd. for $C_{12}H_{11}N_3O_3$: N, 17.1. Found: N, 17.3.

### Amino-Ethers

**2-Butoxy-5-aminopyridine.**—All the nitro compounds were readily reduced to the corresponding amine in methanol–water solution with iron and acetic acid; therefore, one example will serve to illustrate the method of synthesis. To a solution of 1600 cc. of 50% methanol (by volume) and 32 cc. of glacial acetic acid, there was added 640 g. of iron powder. The stirred suspension was heated to reflux and 320 g. of 2-butoxy-5-nitropyridine was added dropwise at such a rate that the condenser could return the refluxing solvents (approx. three hours for addition). The reaction mixture was refluxed an additional two hours to complete the reduction. The end-point of the reduction was readily observed by the change in color from brown or reddish-brown to deep black. (This color change was characteristic of all the reductions and served as an excellent indicator of the completeness of reduction. In a few cases several days reflux were necessary.) Sixty-five cc. of 20% sodium hydroxide was added to convert the iron into an insoluble form. "Super Cel" was added and the whole filtered through a bed of "Super Cel" and washed well with methanol. The solvent was removed by vacuum distillation, and the residual insoluble oil was extracted with ether. After removal of the ether the amine was vacuum distilled. The yield was 240 g. (88%) of colorless oily liquid of b. p. 148–50° (12 mm.); d. 1.037 (25°). The liquid rapidly colors red in air.

*Anal.* Calcd. for $C_9H_{14}N_2O$: $NH_2$ (nitrite), 9.63. Found: $NH_2$ (nitrite), 9.60, 9.63.

**2-Butoxy-5-aminopyridine Dihydrochloride.**—The freshly distilled amine was dissolved in 10 volumes of absolute ether and excess of dry hydrogen chloride bubbled through with cooling and stirring. The copious white precipitate which resulted was filtered and dried *in vacuo* a short time. The dihydrochloride does not have a definite melting point. On heating it first effervesces at 160–165° (evolution of butyl chloride) while remaining solid and finally melts with decomposition by 220° (the decomposition point is that for 2-hydroxy-5-aminopyridine hydrochloride). For this reason the melting points of the dihydrochlorides are not listed in Table I.

*Anal.* Calcd. for $C_9H_{16}N_2OCl_2$: HCl, 30.5. Found: HCl, 30.5.

In a few cases the dihydrochloride was allowed to equilibrate in an atmosphere of hydrogen chloride after drying *in vacuo*. Some hydrochlorides required crystallization from alcohol or alcohol–ether solution. A few amines could be isolated and crystallized in the form of a stable free base but most colored rapidly in the air.

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## Summary

The preparation of a series of tuberculostatic ethers of 2-hydroxy-5-amino pyridine is described. Maximum activity was found in the *n*-butoxy to *n*-hexyloxy compounds. Substituted alkyl, branched-chain alkyl, aryl and heterocyclic radicals produced compounds of lowered activity.

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