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Keyphrases

Cinchona alkaloids
Ion-exchange resins—alkaloids, exchange equilibria
Sulfate, total—equilibrium mixture
Alkaloid sulfate concentration

Antiradiation Compounds IX. Dithiocarbamates of Strongly Basic Pyridines and Pyrimidines

By WILLIAM O. FOYE and DOUGLAS H. KAY

Dithiocarbamates of exceptionally strong bases in the pyridine and pyrimidine series, *e.g.*, the 1-alkyl-2- and 4-imino derivatives, have been obtained. Significant protection in mice against ionizing radiation was provided by a dithiocarbamate of one of the strong bases, whereas the dithiocarbamates of weaker bases have generally shown a lower level of protection.

BROWN (1) reported that the introduction of an alkyl group on one of the ring nitrogens of aminopyrimidines greatly increases the basicity of the molecule, the amino group being converted to the imino form. For example, 2-aminopyrimidine has a pKa of 3.54 and 1,2-dihydro-2-imino-1-methylpyrimidine has a pKa of 10.75. Likewise, in the aminopyridine series Albert (2) reported that 2-aminopyridine and 4-aminopyridine have pKa values of 6.9 and 9.2, respectively, whereas the alkylated derivatives, 1,2-dihydro-2-imino-1-methylpyridine and 1,4-dihydro-4-imino-1-methylpyridine have pKa values of 12.2 and 12.5, respectively.

Dithiocarbamates of these exceptionally strong bases were desired as potential antiradiation agents. Such compounds could be considered cyclic dithio acid analogs of mercaptoethylguanidine, which is also strongly basic. Of the compounds mentioned above, only 1,2-dihydro-2-imino-1-methylpyridine has previously been treated with carbon disulfide (3), giving a compound described as 1,2-dihydro-1-methyl-2-pyridinylimmonium 1,2-dihydro-1-methyl-2-pyridinyldithiocarbamate (I). The reactions of amino and imino pyrimidines and pyridines with carbon disulfide described here also gave dithiocarbamate salts rather than zwitterions. The latter might be expected since dithiocarbamate formation takes place preferentially on the weaker of two competing bases and cation formation on the stronger (4). Infrared absorption spectra of the dithiocarbamates of the strongly basic imines showed stretching frequencies for both C=S (~1000 cm.$^{-1}$) and C=N (1650–1675 cm.$^{-1}$), which supports the structures proposed (I). Dithiocarbamates of the corresponding weak (nonalkylated) bases were also prepared for comparison of radiation-protective activity.

Antiradiation testing results show that the dithiocarbamate of one of the imines protects mice at a higher level of radiation (1,000 r) than has generally

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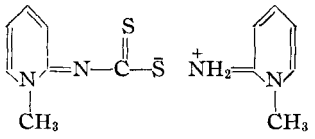
been shown by the dithiocarbamates of weaker bases.



I

DISCUSSION

The method of Brown (1) was used to prepare 1,2-dihydro-2-imino-1-methylpyrimidine hydriodide, and the free base was obtained in benzene by a modified extraction procedure. A minimum amount of water was found necessary in the neutralization step to prevent rearrangement to 2-methylaminopyrimidine which occurs readily in warm alkaline solution (1). The free base in benzene was treated with carbon disulfide, without heating, to yield the desired dithiocarbamate, obtained as the imine salt. The next higher homolog, 1,2-dihydro-2-imino-1-ethylpyrimidine was converted similarly to the dithiocarbamate salt, obtained by very slow precipitation from toluene. It should be noted that these dithiocarbamates were not recrystallized, thus avoiding the possibility of such further condensations as were recently reported by Takeshima *et al.* (5) for the immonium salt of a dithio acid.

The preparation of 1,2-dihydro-2-imino-1-ethylpyrimidine hydriodide (m.p. 191–193°) has not previously been described. However, Kogon (6) has described an isomer, 2-ethylaminopyrimidine (m.p. 50–51°), its hydriodide (m.p. 154–155°), and the picrate (m.p. 160–161°). The latter hydriodide was obtained by refluxing a solution of 2-aminopyrimidine and ethyl iodide in absolute ethanol. By using a less polar solvent, dioxane, the desired 1,2-dihydro-2-imino-1-ethylpyrimidine hydriodide was obtained. However, this hydriodide was found to rearrange readily in 10% aqueous alkali to 2-ethylaminopyrimidine. A minimum amount of water in the neutralization step was found necessary to prevent this rearrangement. Proof that it did not occur is shown by the formation of the picrate (m.p. 178–179°) of the free base in toluene just prior to treatment with carbon disulfide.

N-2-Pyridyldithiocarbamate was obtainable as the triethylammonium salt by the procedure of either Fairfull and Peak (7) or Knott (8). This product was found to be light-sensitive. The preparation of 2-pyridylammonium *N*-2-pyridyldithiocarbamate was previously reported, using the sodium salt of 2-aminopyridine in nonaqueous media with carbon disulfide (9).

4-Pyridylammonium *N*-4-pyridyldithiocarbamate was more conveniently prepared than the triethylammonium salt (8). In regard to the former compound, Camps (10) reported that reaction of 4-aminopyridine, ethanol, and carbon disulfide yielded a product melting at 152°, which he suspected to be the pyridylammonium salt of the dithiocarbamate. No elemental analyses were reported, and it is probable that Camps' product was a thiourea derivative rather than the pyridylammonium salt of the dithiocarbamate, which was found to melt at 134–135°.

The methods of Chichibabin were used to prepare 1,2-dihydro-2-imino-1-methylpyridine hydriodide (11) and 1,4-dihydro-4-imino-1-methylpyridine hydriodide (12). The free base of the 2-imino isomer was obtained by extracting an aqueous alkaline solution of the hydriodide with benzene. The other isomer was obtained by triturating the hydriodide with powdered potassium hydroxide in benzene and extracting with warm benzene. The dithiocarbamate salt of 1,2-dihydro-2-imino-1-methylpyridine (I) was prepared by the procedure of Topchiev (3). The corresponding 4-imino isomer was prepared by treating a benzene solution of the free base with carbon disulfide.

Although the tendency for a shift of the methyl group from the ring nitrogen of an aminopyridine to form a methylamino derivative appears to be much less than in the pyrimidine series, proof that this shift did not occur was obtained by preparing the picrates of the free bases in benzene prior to treatment with carbon disulfide. These picrates differed substantially from those of the rearranged bases. Additional evidence that rearrangement did not occur to give the dithiocarbamates of the *N*-methylaminopyrimidines was shown by the failure of the rearranged 2-methylaminopyrimidine to give a dithiocarbamate under the reaction conditions employed. 2-Aminopyrimidine also failed to undergo dithiocarbamate formation using any of the methods described.

Isomeric with these imines are 3-aminomethylpyridine and 4-aminomethylpyridine. Treatment of these amines in absolute ethanol with carbon disulfide gave the respective dithiocarbamate salts.

Antiradiation Properties—Antiradiation screening for several of the compounds has been carried out at the Walter Reed Army Institute of Research under the direction of Dr. D. P. Jacobus. Tests were done as previously indicated (13) in mice *versus* 1,000 r (γ-rays), and results received so far show that 1,2-dihydro-1-methyl-2-pyridinylimmonium 1,2-dihydro-1-methyl-2-pyridinyldithiocarbamate (I) provided up to 24% protection with doses up to 350 mg./Kg. The dithiocarbamates of the corresponding 4-iminopyridine and of the 2-imino-1-methylpyrimidine showed no protection at this radiation level with doses of less than 50 mg./Kg. A previous report (14) of radiation-protective activities of dithiocarbamates of weaker bases showed activity only at a lower level of radiation dosage (600 r, X-rays).

EXPERIMENTAL

Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England, or by Carol K. Fitz, Needham, Mass. Sulfur analyses done by Parr bomb peroxide fusion. Melting points were taken on a Mel-Temp apparatus and are corrected. Infrared absorption spectra were obtained with a Perkin-Elmer model 137B spectrometer.

1,2 - Dihydro - 1 - methyl - 2 - pyrimidinylimmonium 1,2 - Dihydro - 1 - methyl - 2 - pyrimidinyldithiocarbamate—Fifteen grams (0.063 mole) of 1,2-dihydro-2-imino-1-methylpyrimidine hydriodide (1) was placed in a glass mortar immersed in an ice bath. The solid was covered with 50 ml. of dry benzene, and powdered potassium hydroxide (15 Gm.) was added slowly during 30 min. to the cooled mixture (below 10°) with trituration. The yellow benzene extract was decanted, and the residue was triturated with an additional 150 ml. of anhydrous benzene in three portions during 1 hr. The benzene

extracts were combined and dried, and the residue was stored in a stoppered container with 40 ml. of anhydrous benzene at 0° for 2 days.

The combined benzene extracts were dried and filtered into a flask equipped with a drying tube. The benzene solution of 1,2-dihydro-2-imino-1-methylpyrimidine was ice-cooled, and 2 ml. (0.03 mole) of carbon disulfide in 10 ml. of anhydrous benzene was added slowly with stirring during 15 min. Stirring with ice-cooling was continued for 4 hr., and the mixture was allowed to stand overnight at room temperature.

An additional milliliter of carbon disulfide was added and the mixture was stirred for 3 hr. at room temperature. The orange-colored solid was collected quickly, was washed three times with 40-ml. portions of anhydrous benzene, and dried *in vacuo*, giving 1.7 Gm. of product that melted at 111–113°. Further washing with benzene gave 1.5 Gm. melting at 115–117° with slight decomposition beginning about 110°; $\nu_{min.}^{Nujol}$ 970, 1000, 1140, 1180, 1325, 1540, 1600, 1650, 1670.

Anal.—Calcd. for $C_{11}H_{14}N_6S_2$: C, 44.89; H, 4.76; N, 28.57. Found: C, 45.09; H, 4.69; N, 28.40.

1,2 - Dihydro - 2 - imino - 1 - ethylpyrimidine Hydriodide—Ten grams (0.105 mole) of 2-aminopyrimidine and 130 ml. of dioxane were heated to boiling, filtered, and refluxed with 20 ml. (0.25 mole) of ethyl iodide for 1 hr. The mixture was kept at room temperature for 24 hr., and this procedure was repeated twice. The precipitated solid was removed prior to each reflux period. After recrystallization from 95% ethanol 8.0 Gm. (30.3%) of product was obtained, m.p. 191–193°.

Anal.—Calcd. for $C_6H_{10}IN_3$: C, 28.70; H, 4.01; I, 50.56; N, 16.73. Found: C, 29.15; H, 4.07; I, 49.90; N, 16.28.

The picrate was crystallized from 95% ethanol, m.p. 178–179°.

Anal.—Calcd. for $C_{12}H_{12}N_6O_7$: C, 40.92; H, 3.43. Found: C, 41.35; H, 3.26.

1,2 - Dihydro - 1 - ethyl - 2 - pyrimidinylimmonium 1,2 - Dihydro - 1 - ethyl - 2 - pyrimidinyldithiocarbamate—Ten grams (0.04 mole) of 1,2-dihydro-2-imino-1-ethylpyrimidine hydriodide was placed in a glass mortar containing 10 Gm. of powdered potassium hydroxide. The mixture was triturated with 200 ml. of toluene, in four portions, during 1 hr. The combined toluene extracts were filtered and then dried.

The toluene extract (5 ml.) was treated with 5 ml. of a saturated solution of picric acid in toluene, giving a picrate melting at 178–179°, the value for the picrate of 1,2-dihydro-2-imino-1-ethylpyrimidine.

The toluene solution of 1,2-dihydro-2-imino-1-ethylpyrimidine was treated with 5 ml. (0.07 mole) of carbon disulfide, and mechanically stirred during a 3-week period. A yellow solid slowly precipitated which became orange in color by the end of the first week. The orange solid was collected, washed with two 25-ml. portions of anhydrous ether, and dried. About 1.2 Gm. of orange solid was obtained that melted at 101–105°.

Anal.—Calcd. for $C_{13}H_{18}N_6S_2$: C, 48.42; H, 5.62; N, 26.06. Found: C, 48.73; H, 5.80; N, 25.55.

Triethylammonium N-2-Pyridyldithiocarbamate—The procedure of Fairfull and Peak (7) was used. From 6.27 Gm. (0.07 mole) of 2-aminopyridine, 7.0 Gm. (39%) of product was obtained that melted at 88–89°, which agrees with the reported value (7); $\nu_{min.}^{KBr}$ 980, 1030, 1090, 1150, 1235, 1300, 1500, 1575, 2450, 2600.

4-Pyridylammonium N-4-Pyridyldithiocarbamate—A mixture of absolute ethanol (30 ml.) and 9.4 Gm. (0.1 mole) of 4-aminopyridine was refluxed on a water bath until the 4-aminopyridine dissolved. Then 14 ml. (0.2 mole) of carbon disulfide was added slowly during 10 min. Refluxing was stopped after 15 min. when hydrogen sulfide was evolved.

The reaction solution was stirred with ice-cooling for 2 hr., and then refrigerated overnight. A yellow solid was collected and washed with absolute ethanol. After refluxing the filtrate for 30 min. and cooling, a total of 5.0 Gm. (38%) of product was obtained, m.p. 134–135°. $\nu_{min.}^{KBr}$ 1000, 1060, 1200, 1250, 1300, 1500, 1600, 1650, 2050, 2500.

Anal.—Calcd. for $C_{11}H_{12}N_4S_2$: C, 49.97; H, 4.57; N, 21.19; S, 24.27. Found: C, 50.16; H, 4.55; N, 21.40; S, 24.53.

1,2 - Dihydro - 2 - imino - 1 - methylpyridine—Eighteen grams (0.076 mole) of 1,2-dihydro-2-imino-1-methylpyridine hydriodide (11) dissolved in 50 ml. of 2 *N* sodium hydroxide solution was extracted with 150 ml. of warm benzene for 9 hr. in a liquid-liquid extraction apparatus. The extraction was repeated twice. The combined benzene extracts were evaporated *in vacuo* at 45°/20–25 mm., giving 7.5 Gm. (88%) of a red oil that boiled at 110°/20 mm., which agrees with the reported value (11) for the free base. The picrate of the free base was prepared, and it melted at 205–207° after recrystallization from 95% ethanol. [Lit. m.p. 201° (11).]

1,2 - Dihydro - 1 - methyl - 2 - pyridinylimmonium 1,2 - Dihydro - 1 - methyl - 2 - pyridinyldithiocarbamate—The procedure of Topchiev (3) was used. From 7.5 Gm. (0.07 mole) of 1,2-dihydro-2-imino-1-methylpyridine, 7.2 Gm. (67%) of product was obtained that melted at 153–154° with decomposition beginning about 145°, which agrees with the reported value (3); $\nu_{min.}^{Nujol}$ 950, 1030, 1050, 1070, 1160, 1235, 1560, 1600, 1650, 1670.

1,4-Dihydro-4-imino-1-methylpyridine Hydriodide—The method of Chichibabin (12) was used. From 20 Gm. (0.21 mole) of 4-aminopyridine, 40 Gm. (80%) of product was obtained that melted at 190–192°. [Lit. m.p. 187–188° (12).]

1,4 - Dihydro - 1 - methyl - 4 - pyridinylimmonium 1,4 - Dihydro - 1 - methyl - 4 - pyridinyldithiocarbamate—Thirty grams (0.13 mole) of 1,4-dihydro-4-imino-1-methylpyridine hydriodide was placed in a glass mortar. Anhydrous benzene (50 ml.) was added, and 25 Gm. of powdered potassium hydroxide was added slowly during 30 min. with trituration. The cloudy benzene extract was removed by decantation and filtered under nitrogen. The residue was triturated thoroughly with 350 ml. of warm benzene in seven portions during 1 hr.

About 20 ml. of the combined benzene extract was evaporated with a stream of nitrogen to yield a white hygroscopic solid that melted at 150–151°, which agrees with the reported value (12) for the free base. The picrate of the free base was prepared, m.p. 192–194°, after recrystallization from 95% ethanol. [Lit. m.p. 188–189° (12).]

The cloudy benzene extract was treated with 2 ml. (0.03 mole) of carbon disulfide, which was added

dropwise during 5 min. with constant stirring. The mixture was stirred for 30 min., and the orange solid was collected, washed with two 50-ml. portions of benzene, and dried *in vacuo*. About 5.5 Gm. of product was obtained, m.p. 170–172°. $\nu_{min.}^{Nujol}$ 960, 980, 1040, 1135, 1200, 1540, 1650.

Anal.—Calcd. for $C_{13}H_{16}N_3S_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.08; H, 5.59; N, 19.32; S, 21.10.

4-Pyridylmethylammonium N-4-Pyridylmethyldithiocarbamate—4-Aminomethylpyridine (11 Gm., 0.1 mole) (Reilly Tar and Chemical Corp.) in 30 ml. of absolute ethanol was ice-cooled and stirred while 3.5 ml. (0.05 mole) of carbon disulfide was added dropwise. The mixture was stirred for 15 min. and the solid was collected and washed with two 25-ml. portions of absolute ethanol. About 12 Gm. (80.5%) of a white, light-sensitive solid was obtained, m.p. 131–132°. $\nu_{KBr}^{min.}$ 940, 1000, 1070, 1115, 1225, 1300, 1600.

Anal.—Calcd. for $C_{13}H_{16}N_4S_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.19; H, 5.58; N, 18.70; S, 21.87.

3-Pyridylmethylammonium N-3-Pyridylmethyldithiocarbamate—The same procedure was used as above. From 3-aminomethylpyridine (11 Gm., 0.1 mole) was obtained 13.8 Gm. (92.6%) of a white solid that melted at 130–132°. $\nu_{KBr}^{min.}$ 920, 975, 1050, 1185, 1250, 1300, 1575.

Anal.—Calcd. for $C_{13}H_{16}N_4S_2$: C, 53.39; H, 5.52; N, 19.16; S, 21.93. Found: C, 53.19; H, 5.27; N, 18.55; S, 21.89.

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Keyphrases

Antiradiation compounds
Pyridine dithiocarbamates—synthesis
Pyrimidine dithiocarbamates—synthesis
IR spectrophotometry—structure
Radiation protective properties

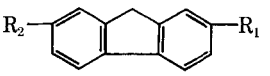
New Compounds: Fluorene Derivatives as Potential Carcinogens

By NELLIE W. PITZER and FRANCIS E. RAY*

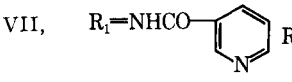
A series of eight new *N*-substituted fluorenamides have been synthesized for evaluation of carcinogenic activity.

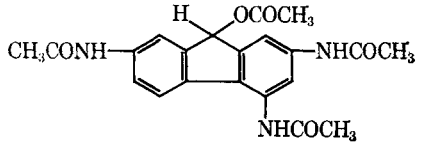
IT HAS BEEN reported that diethylnitrosamine produces hepatic carcinomas in rats (1, 2). Since *N*-2-fluorenylamine is also a carcinogen (3), it was thought that *N*-2-fluorenylethylnitrosamine (I) might have a similar or stronger activity.

Because *N*-2-fluorenylsuccinamic acid is a potent carcinogen (4), additional derivatives (II, III, IV, V and VI) were synthesized. Since nicotinic acid is known to be involved in the biological oxidation systems (5), carcinogenic activity might be found in *N*-2-fluorenylnicotinamide (VII). In the generally less carcinogenic fluorenone series, *N,N',N''*-2,4,7-fluorenylene(9-acetoxy)trisacetamide (VIII) was obtained.[1]



I, R_1 = N·(NO)CH_2CH_3, R_2 = H
II, R_1 = $NHCOCH_2CH_2COOH$, R_2 = $NHCOCH_2CH_2COOH$
III, R_1 = $NHCOCH_2C$:$(CH_2)COOH$, R_2 = H
or R_1 = NHCOC:$(CH_2)CH_2COOH$ (Structural studies on this compound will be presented in a future communication.)
IV, R_1 = $NHCO(CH_2)_6CH_3$, R_2 = H
V, R_1 = $NHCO(CH_2)_6CH_3$, R_2 = $NHCO(CH_2)_6CH_3$
VI, R_1 = $NHCO(CH_2)_{14}CH_3$, R_2 = H

VII, 

VIII, 

EXPERIMENTAL

Ultraviolet spectra were obtained on a Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer in 95% ethanol. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories.

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* Deceased.
[1] Compounds I, II, III, and VIII were proved to be carcinogenic in the preliminary investigation by Dr. Harold P. Morris, National Cancer Institute, Bethesda, Md. All compounds are subject of further studies in this institute.