[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Pyridine-1-oxides. II. A New Synthesis of Ricinine[1,2]

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RECEIVED JULY 27, 1955

A new synthesis is described of the alkaloid ricinine from 3-picoline-1-oxide *via* the intermediates 4-nitro-3-picoline-1-oxide, 4-nitronicotinic acid-1-oxide, 4-methoxynicotinic acid-1-oxide, methyl 4-methoxynicotinate-1-oxide, 4-methoxynicotinamide-1-oxide and 2,4-dichloronicotinonitrile. The preparation and reactions of a number of additional pyridine-1-oxide intermediates are discussed.

Ricinine, the toxic alkaloid from the oil of the castor bean (*Ricinus communis* L.), has been conclusively shown to be N-methyl-3-cyano-4-methoxy-2-pyridone (VIII) by extensive degradation studies[5] and by four independent syntheses.[6-9] During the course of an investigation of the chemistry of pyridine-1-oxides, we had occasion to prepare a number of intermediates which afforded a simple synthesis of the alkaloid from 3-picoline. This paper describes the details of this new ricinine synthesis and illustrates by a number of examples the striking utility of the N-oxide grouping as a synthetic intermediate in heterocyclic chemistry.

3-Picoline was converted by previously described methods[1,10] into 4-nitro-3-picoline-1-oxide (I) which was oxidized to 4-nitronicotinic acid-1-oxide (II) in 56% yield by a mixture of concentrated sulfuric acid and sodium dichromate at 20–30°.[11] Considerable difficulty was encountered in establishing suitable oxidation conditions. Alkaline media were avoided, since 4-nitropyridine-1-oxide is somewhat unstable under these conditions,[12,13] and it was anticipated that (I) would behave similarly. An attempt to prepare the 3-aldehyde by chromic acid oxidation of I, according to the method described for the conversion of *p*-nitrotoluene to *p*-nitrobenzaldehyde,[14] was unsuccessful, and only unchanged I could be recovered. More vigorous oxidation with aqueous sulfuric acid and sodium dichromate under conditions suitable for the oxidation of *p*-nitrotoluene to *p*-nitrobenzoic acid[15] resulted in extensive decomposition.

Treatment of II with sodium methoxide in methanol gave 4-methoxynicotinic acid-1-oxide (III). Nucleophilic displacement of a nitro group on the 4-position of a pyridine-1-oxide is a well known reaction[16] but it is particularly facile in the present instance because of the combined activation of the 4-nitro group by both the carboxyl and the N-oxide functions. III was converted into the corresponding methyl ester IV by heating with methanol saturated with dry hydrogen chloride. The ester was quantitatively converted to 4-methoxynicotinamide-1-oxide (V) with liquid ammonia at −33°.

Treatment of the amide V with a mixture of phosphorus oxychloride and phosphorus pentachloride resulted in dehydration of the amide function with concomitant displacement of the 4-methoxy group by chlorine, removal of the N-oxide group and introduction of chlorine in the 2-position to give the known 2,4-dichloro-3-cyanopyridine (VI)[6] in 33% yield. It is remarkable that no 4,6-dichloro-3-cyanopyridine[17] was formed, at least in quantities sufficient to permit isolation. Since VI previously has been converted *via* 2,4-dimethoxy-3-cyanopyridine (VII) to ricinine (VIII)[6] (see also Experimental), the reaction sequence just described from 3-picoline-1-oxide constitutes a new total synthesis of the alkaloid.

It was thought that an alternative route to VIII from 4-nitro-3-picoline-1-oxide (I) might be found *via* 4-chloro-3-picoline-1-oxide (IX), which was prepared in high yield by treatment of I with acetyl chloride. However, all attempts to oxidize IX to 4-chloronicotinic acid-1-oxide (XI) were unsuccessful. Even mild conditions utilizing dilute neutral potassium permanganate resulted in decomposition of 70–75% of the material, with the recovery of 25–30% of unchanged I. Model oxidation experiments under similar conditions with 3-methylpyridine-1-oxide were likewise unsuccessful, and no nicotinic acid-1-oxide[1] could be found as a reaction product, although in every case all the potassium permanganate employed was consumed. These results are particularly surprising in view of the successful conversions of lepidine-1-oxide[18] and quinaldine-1-oxide[19] to the corresponding acids under similar conditions.

Attempted esterification of 4-nitronicotinic acid-1-oxide (II) with methanolic hydrogen chloride re-

(1) For the initial paper in this series, see E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

(2) Presented in part before the Division of Medicinal Chemistry at the 126th Meeting of the A.C.S., September, 1954, New York, N. Y.

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(4) Parke, Davis and Co. Fellow, 1953–1955.

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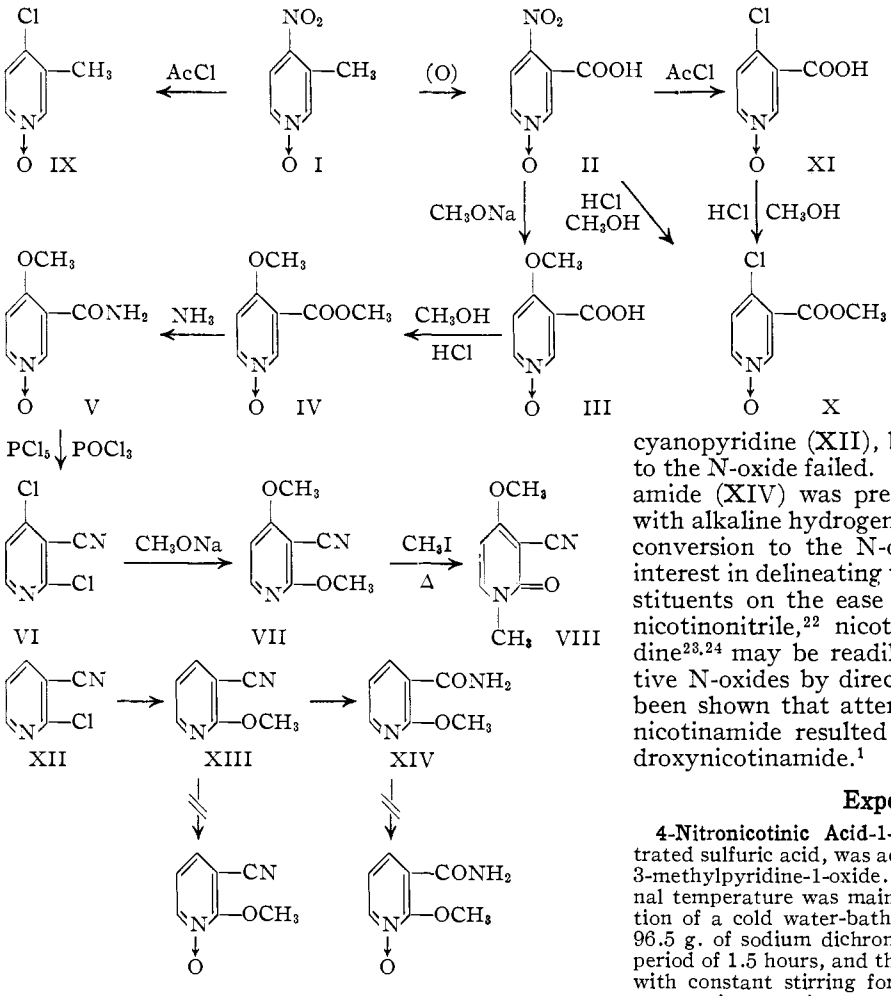

sulted in the evolution of nitrogen oxide fumes and the formation of a chlorine-containing ester which did not possess a nitro group (infrared). The identity of this product as methyl 4-chloronicotinate-1-oxide (X) was confirmed by an independent synthesis of X. 4-Nitronicotinic acid-1-oxide (II) was converted in high yield by the action of acetyl chloride to 4-chloronicotinic acid-1-oxide (XI), which was esterified with methanolic hydrogen chloride to X. It is interesting to note that the latter reaction was accompanied by considerable decomposition and gave X in poor yield, while the former synthesis (from II) gave X in 67% yield with no visible signs of decomposition.

Both II and X were unstable. Aqueous solutions of II evolved nitrous fumes when heated and the solid lost nitrogen oxides when heated at 100°. Methyl 4-chloronicotinate-1-oxide (X) rapidly polymerized to a red tar when exposed to the air at room temperature.

2,4-Dichloronicotinamide, which conceivably could arise by chlorination of II or XI, followed by ammonolysis, appeared to be an attractive intermediate for further possible conversion to ricinine. However, attempts to chlorinate these N-oxides with mixtures of phosphorus oxychloride and phosphorus pentachloride gave only red-brown resins, and no characterizable products were obtained. This failure might be ascribed to the high reactivity of the 4-chloropyridine intermediates possibly formed in the chlorination reaction, since 4-halopyridines are known to polymerize readily.[20,21]

Early in this investigation it appeared that useful intermediates might be prepared from 2-methoxy-3-cyanopyridine-1-oxide (or the corresponding amide). 2-Methoxy-3-cyanopyridine (XIII) was prepared readily by the action of sodium methoxide on 2-chloro-3-cyanopyridine (XII), but all attempts to oxidize it to the N-oxide failed. Likewise, 2-methoxynicotinamide (XIV) was prepared by treatment of XIII with alkaline hydrogen peroxide, but it also resisted conversion to the N-oxide. These results are of interest in delineating the cumulative effects of substituents on the ease of N-oxide formation, since nicotinonitrile,[22] nicotinamide[1] and 2-ethoxypyridine[23,24] may be readily converted to their respective N-oxides by direct oxidation. It already has been shown that attempted oxidation of 2-chloronicotinamide resulted only in hydrolysis to 2-hydroxynicotinamide.[1]

Experimental[25]

4-Nitronicotinic Acid-1-oxide.—To 335 ml. of concentrated sulfuric acid, was added with stirring 50 g. of 4-nitro-3-methylpyridine-1-oxide. During the addition the internal temperature was maintained at 20–25° by the application of a cold water-bath. With the temperature at 30°, 96.5 g. of sodium dichromate dihydrate was added over a period of 1.5 hours, and the reaction was allowed to proceed with constant stirring for 2.5 hours. The resulting dark green, viscous mixture was poured onto about 700 g. of crushed ice with stirring, the reaction flask was washed out with ice-water and the washings added to the ice mixture. The total ice-water volume was brought to 900–1000 ml. and the mixture allowed to stand at 5° for 6–8 hours.

The product was filtered and washed with ice-cold water until the solid appeared light yellow. It was pressed as dry as possible and then allowed to dry overnight *in vacuo* over calcium chloride. The yield of 4-nitronicotinic acid-1-oxide (with a slight green coloration) was 33.5 g. (56%), m.p. 170–172° (rapid dec.). This product was suitable for further reactions, but could be recrystallized from acetone. The acid was unstable at 100° either in the dry state or in boiling water, generating nitrogen dioxide fumes.

Anal. Calcd. for $C_6H_4N_2O_5$: C, 39.1; H, 2.2; N, 15.2. Found: C, 39.7; H, 2.1; N, 15.2.

4-Methoxynicotinic Acid-1-oxide.—To 25 g. of 4-nitronicotinic acid-1-oxide and 288 ml. of absolute methanol, was added a cooled solution of sodium methoxide prepared by the addition of 6.88 g. of clean sodium to 210 ml. of absolute methanol. The resulting mixture was heated under reflux on a steam-bath with continuous stirring for 1.75 hours, during which time the sodium salt of 4-methoxynico-

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(25) All melting points are corrected. The authors are indebted to Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth of the University of Illinois, and to Dr. Joseph F. Alicino of Metuchen, N. J. for the microanalyses.

tinic acid-1-oxide separated. The reaction mixture was distilled to dryness with continuous stirring and the residue dissolved in 100 ml. of cold (0°) water. Concentrated hydrochloric acid was added to constant *p*H 3 to decompose sodium nitrite formed during the reaction and to neutralize the sodium salt of the product. The resulting mixture was chilled at 5° for 6–8 hours and the product filtered by suction, washed with ice-water, and dried at 100° to give 17.6–18.7 g. (76.6–81.5%) of a light green-white solid, m.p. 200° dec. The crude product was recrystallized twice from ten parts of boiling water to give 13.7–14.3 g. (59.6–62.2%) of white platelets of 4-methoxynicotinic acid-1-oxide, m.p. 202° dec.

Anal. Calcd. for $C_7H_7NO_4$: C, 49.7; H, 4.2; N, 8.3. Found: C, 49.7; H, 3.9; N, 8.7.

Methyl 4-Methoxynicotinate-1-oxide.—A suspension of 14.3 g. of 4-methoxynicotinic acid-1-oxide in 510 ml. of absolute methanol was cooled to 0°–(−10°) (internal temperature) in an ice–salt mixture. Dry hydrogen chloride gas was passed through the methanolic solution for one hour while maintaining the internal temperature at 0–10°. The reaction mixture was then heated under reflux on a steam-bath for 2.5 hours and the excess methanol distilled. The residual oil (about 10–20 ml.) was dissolved in cold water and the resulting solution was made alkaline (*p*H 9–10) by the addition of anhydrous sodium carbonate and then extracted with chloroform. The extracts were dried over anhydrous sodium carbonate and distilled to dryness to give 8.51 g. (55%) of almost white methyl 4-methoxynicotinate-1-oxide, m.p. 141–143° dec. The product turned pink on exposure to sunlight over a short period, and decomposed during all attempts to recrystallize it. The material was therefore characterized as its picrate, m.p. 146–147°, which was prepared from equimolar portions of the ester and picric acid in methanol, and which was best recrystallized from absolute methanol.

Anal. Calcd. for $C_8H_9NO_4 \cdot C_6H_3N_3O_7$: C, 40.8; H, 2.9; N, 13.6. Found: C, 41.1; H, 3.0; N, 13.7.

4-Methoxynicotinamide-1-oxide.—Liquid ammonia (about 125 ml.) was collected in a glass liner containing 7.47 g. of methyl 4-methoxynicotinate-1-oxide and the liner placed in a vacuum flask. Glass wool was packed around the liner to serve as insulation, and the mixture was allowed to stand with occasional stirring for 4 hours. The insulation was then removed and the ammonia allowed to boil off slowly (about 6–8 hours). The residue was dried at 80–100° to give 6.59–6.80 g. (96–99%) of 4-methoxynicotinamide-1-oxide, m.p. 208–209° (with slight decomposition). Recrystallization from methanol raised the decomposition point to 210–211°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.0; H, 4.8; N, 16.7. Found: C, 50.2; H, 4.8; N, 16.7.

2,4-Dichloronicotinonitrile.—A mixture of 3.07 g. of 4-methoxynicotinamide-1-oxide, 5.32 g. of phosphorus pentachloride and 10 ml. of phosphorus oxychloride was heated at 115–120° for a period of 1.5 hours. The excess phosphorus oxychloride was distilled under reduced pressure and the residual oil poured onto ice with vigorous stirring. The resulting brown solid was filtered with suction, washed with water, suspended in 10 ml. of 3% sodium hydroxide and stirred for 10 minutes, and the solid again filtered and washed until the filtrates were no longer alkaline. This process was repeated. The solid was then dried *in vacuo* and transferred to a Soxhlet thimble containing a layer of anhydrous sodium carbonate and extracted with anhydrous ether. Distillation of the extracts to dryness gave 1.05 g. (33.2%) of colorless solid, m.p. 107° (with preliminary sintering at 101°). Sublimation at 70–80° (0.05 mm.) gave 0.95 g. of 2,4-dichloronicotinonitrile, m.p. 113–115° (with preliminary sintering at 111°). The analytical sample was prepared by recrystallization from aqueous dimethylformamide followed by sublimation at 80° (0.05 mm.), m.p. 114–115° (lit.[6] 112–113°).

Anal. Calcd. for $C_6H_2N_2Cl_2$: C, 41.6; H, 1.2; N, 16.3. Found: C, 41.9; H, 1.5; N, 16.1.

2,4-Dimethoxy-3-cyanopyridine.—This compound was prepared in almost quantitative yield by heating a mixture of 2,4-dichloro-3-cyanopyridine and sodium methoxide in methanol for 5 hours, according to the procedure of Späth and Koller.[6] The product was readily purified by recrystallization from ethanol followed by sublimation at 100–110°; m.p. 146.5–147.5° (lit.[6] 145–146°).

Ricinine.—The alkaloid was prepared from 2,4-dimethoxy-3-cyanopyridine by heating with methyl iodide in a sealed tube at 155° for 10 hours, essentially according to the directions of Späth and Koller.[6] After venting off the methyl iodide, the residue was fractionally sublimed under vacuum. Unchanged starting material was sublimed at 80–100° (0.05 mm.), and the ricinine fraction sublimed in the range 170–180° (0.05 mm.), m.p. 200–202°. The previously reported melting point for ricinine is 197°[6,7] and 201.5°.[26]

4-Chloro-3-picoline-1-oxide.—To 50 ml. of cold (0°) purified acetyl chloride was added slowly 10.0 g. of 4-nitro-3-methylpyridine-1-oxide. The mixture was heated under reflux (in the hood) in the absence of atmospheric moisture for 2 hours. After cooling, the reaction mixture was poured over an excess of crushed ice with vigorous stirring, and the resulting solution made alkaline by the addition of anhydrous sodium carbonate and extracted with chloroform. The extracts were dried over anhydrous potassium carbonate, filtered, distilled to dryness and the residue taken up in water. The aqueous solution was heated on a steam-bath, treated with charcoal and filtered. After washing the charcoal residue with hot water, the combined colorless filtrates and washings were distilled to dryness on a steam-bath under reduced pressure to give 7.0 g. (75%) of product, m.p. 119–122° (with sintering at 110°). Recrystallization from petroleum ether gave 6.53 g. (70%) of colorless 4-chloro-3-picoline-1-oxide, m.p. 121–123°. The analytical sample was conveniently prepared by vacuum sublimation at 105° (0.05 mm.).

Anal. Calcd. for C_6H_6ClNO: C, 50.2; H, 4.2; N, 9.8. Found: C, 50.5; H, 4.4; N, 9.5.

4-Chloronicotinic Acid-1-oxide.—To 30–35 ml. of cold pure acetyl chloride was added 6.0 g. of 4-nitronicotinic acid-1-oxide. A reflux condenser provided with a drying tube was attached and the mixture heated under reflux on a steam-bath for 2.5 hours (hood). The cooled mixture was poured over ice with vigorous stirring, the reaction flask washed with water, the washings added to the ice mixture and the latter allowed to stand until the ice melted. The resulting solution was filtered, and the light green filtrate distilled under reduced pressure to a viscous oil. Ice-water was added and the oil triturated until solidification was complete. Filtration of the solid followed by washing with cold water and subsequent drying gave 3.35 g. (65%) of gray-white 4-chloronicotinic acid-1-oxide, m.p. 145–146° dec. No suitable solvent could be found for crystallization, and the product decomposed in boiling water to give a brown solution.

Methyl 4-Chloronicotinate-1-oxide. Method A.—A mixture of 6.0 g. of 4-nitronicotinic acid-1-oxide and 120 ml. of absolute methanol was cooled to 0° in an ice-bath. Dry hydrogen chloride gas was passed through the mixture at a moderate rate for 10 minutes, a reflux condenser with a drying tube was attached and the mixture heated under reflux for 2 hours (in the hood, since nitrogen oxide fumes were evolved). The excess methanol was distilled under reduced pressure, the residue (about 5–10 ml.) taken up in cold water and the aqueous solution made alkaline by the addition of anhydrous sodium carbonate, and extracted with chloroform. After drying over anhydrous sodium carbonate, the extracts were distilled under reduced pressure on a steam-bath. When the volume of the chloroform solution was 10–15 ml., the heat was removed and the pressure reduced to 20 mm. After the chloroform evaporated there remained 4.1 g. (67%) of tan-white methyl 4-chloronicotinate-1-oxide, m.p. 84° dec.

Method B.—Similar treatment of 4-chloronicotinic acid-1-oxide in methanol resulted in a poor yield of the same ester. During the period of reflux, the reaction mixture underwent progressive decomposition. The product obtained was identical with that prepared in method A above, as shown by a mixed melting point determination and by comparison of infrared spectra (which showed characteristic strong absorption at 1740 and 1225 cm.$^{-1}$ and no absorption in the region characteristic of nitro compounds).

Methyl 4-chloronicotinate-1-oxide was extremely unstable and could not be recrystallized from any solvent investigated without extensive decomposition. The solid polymerized to a red tar on standing at room temperature for two days, but proved to be somewhat more stable when stored under vacuum in the absence of moisture. An at-

(26) L. Maquenne and L. Philippe, *Compt. rend.*, **138**, 506 (1904).

tempt to prepare the picrate in methanol solution resulted in the formation of the picrate of methyl 4-methoxynicotinate-1-oxide, m.p. 146–147°, identical with a sample prepared from methyl 4-methoxynicotinate-1-oxide.

2-Methoxy-3-cyanopyridine.—To a solution of 2.8 g. of sodium in 250 ml. of absolute methanol was added 10.0 g. of 2-chloronicotinonitrile.[1] The reaction mixture was stirred and heated under reflux on a steam-bath for 1.5 hours and with continued stirring the excess methanol was distilled under slightly reduced pressure. The residual light brown oil crystallized upon addition of 75–100 ml. of water. The white solid was filtered by suction, washed with cold water and dried *in vacuo* to give 7.6 g. (78.5%) of 2-methoxynicotinonitrile, m.p. 75–77°. By making the filtrates alkaline, extracting with chloroform, and evaporating the chloroform, a small amount of oil was obtained which yielded additional product (*ca.* 0.5 g.) on recrystallization from water. Extraction of the latter filtrates with ether yielded 0.34 g. of a second product, m.p. 117–122°, which was purified by vacuum sublimation at 100° to give 2-methoxynicotinamide, m.p. 128–130°, identified by a mixed melting point determination with an authentic sample. The analytical sample of 2-methoxynicotinonitrile was prepared by vacuum sublimation at 55–60°, m.p. 76.5–77.5°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9. Found: C, 63.0; H, 4.7; N, 20.8.

2-Methoxynicotinamide.—To 40 ml. of absolute ethanol was added with stirring 2.0 g. of 2-methoxynicotinonitrile and 0.8 g. of potassium hydroxide. After solution occurred, 40 ml. of 30% hydrogen peroxide was added slowly. The reaction mixture was then heated at 65° (internal temperature) with stirring for 30 minutes, an additional 10 ml. of 30% hydrogen peroxide was added, and heating and stirring were continued for 30 minutes. The reaction mixture was reduced to a volume of 20–25 ml. and chilled. The resulting solid was filtered, washed and dried *in vacuo* to give 1.32 g. of 2-methoxynicotinamide, while concentration of the filtrates to 10 ml. gave an additional 0.27 g. for a total yield of 1.59 g. (70%), m.p. 130–131°. The analytical sample was prepared by vacuum sublimation at 100°.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.3; H, 5.3; N, 18.4. Found: C, 55.5; H, 5.1; N, 18.7.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XIII. Some Amino-substituted Derivatives of Guanine and 6-Thioguanine

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RECEIVED JULY 29, 1955

A variety of 2-substituted amino-6-hydroxypurines has been prepared by the reaction of 6-hydroxy-2-methylmercaptopurine with aliphatic, aromatic and heterocyclic amines. These purines have been converted to the corresponding 6-mercaptopurines by treatment with phosphorus pentasulfide in pyridine.

In pursuance of the investigation of analogs of the nucleic acid bases for possible antimetabolite activity,[1–4] the synthesis of a number of purines structurally related to guanine was undertaken. The finding that the replacement of the hydrogens of the amino groups of adenine and 2,6-diaminopurine weakened their microbiological activities[5,6] made it of interest to determine whether a similar effect would be observed with derivatives of guanine. The fact that 6-thioguanine[7] acts as an inhibitor of the growth of *Lactobacillus casei*,[6,8] embryonic tissue[9] and a number of neoplasms, *e.g.*, sarcoma 180[10] and leukemia L 1210[11,12] further stimulated the investigation of related compounds.

The synthesis of 2-substituted amino-6-hydroxypurines can be approached in a number of ways. Introduction of the substituted amino group into the 2-position of the pyrimidine ring can be accomplished in the first stage of the synthesis by reaction of an amine hydrochloride with dicyandiamide[13] or with cyanoacetic ester. The latter type of condensation leads, however, to a mixture of isomers.[13] It is also possible to replace the 2-methylmercapto group of 4-amino-6-hydroxy-2-methylmercaptopyrimidine by amines[13] and one could then proceed with the total synthesis of each individual purine *via* nitrosation, reduction, formylation and ring closure. However, the most direct method for the synthesis of a series of purines of this type is obviously the introduction of the substituted amino group in the last step, so that a common intermediate, *e.g.*, 6-hydroxy-2-methylmercaptopurine, can be used for all the desired compounds. This method was highly successful in the synthesis of 6-substituted aminopurines from 6-methylmercaptopurine[14] and 8-alkylamino-2-hydroxypurines from 2-hydroxy-8-methylmercaptopurine[15] but presents some difficulties when the methylmercapto group is in the 2-position. Andrews, *et al.*,[16] had found that the 2-methylmercapto group of 2-methylmercaptoadenine could not be replaced successfully by ammonia or amines under a variety of conditions and this experience was duplicated in these laboratories using alkylamines. The primary obstacle to this type of

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