

Chemistry Division, The Norwich Pharmacal Company

## A New Synthesis of Furo[2,3-b]pyridine Derivatives (1)

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A new synthesis of furo[2,3-b]pyridines starting with  $\alpha$ -aminofurans is described.

The reported biological activity of the furo[2,3-b]-quinoline alkaloids (2) prompted an investigation of the simpler furo[2,3-b]pyridine ring. A search of the literature revealed that relatively little work had been reported concerning the synthesis of this ring system. The earliest reference discussed the ring closure of a pyridine derivative to a 2,3-dihydrofuro[2,3-b]pyridine (3). There are several other reports of the synthesis of 2,3-dihydrofuro[2,3-b]pyridines from pyridine compounds (4-6). However, in no case was the dihydro compound dehydrogenated to the aromatic furo[2,3-b]pyridine. The first synthesis of the fully aromatic system was reported by Robertson and Watt (7). This synthesis is based upon a coumarilic acid-type rearrangement of 3,6-dibromo-7-hydroxy-5-methylpyrano[2,3-b]pyridine-2-one. A recent synthesis of the fully aromatic system was reported by Reisch (8). In this case, the synthesis involved the cyclization of an acetylenic pyridine. The new synthesis reported herein involves the formation of the pyridine ring from  $\alpha$ -aminofurans to give the completely aromatic furo[2,3-b]pyridine ring.

The approach followed was based upon the preparation of a pyrazolo[3,4-b]pyridine by the condensation of a 5-aminopyrazole with a 1,3-dicarbonyl compound (9). Ethyl 5-amino-2-furoate (I) was chosen as the starting material since it was easily obtained by the catalytic reduction of ethyl 5-nitro-2-furoate (10,11). Attempts to condense I with 2,4-pentanedione in glacial acetic acid were unsuccessful. However, the condensation of I proceeded very smoothly with ethyl trifluoroacetoacetate (II) to give the furopyridine (III) (see equation 1). The structure of III was assigned on the basis of the work of Dey and Joullié (12) who showed that II condensed with aromatic amines to give 4-quinolinols exclusively. When an aqueous alcoholic solution of I and sodium nitromalonaldehyde monohydrate (IV) (13) was acidified, an orange precipitate formed immediately. The crude material was cyclized in boiling dimethylformamide to give the nitrofuropyridine (V) in 34% yield from I (see equation 2). Hydrolysis of V yielded the free acid (VI) and catalytic reduction produced the aminofuropyridine (VII).

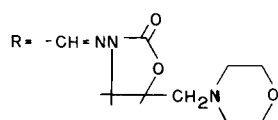
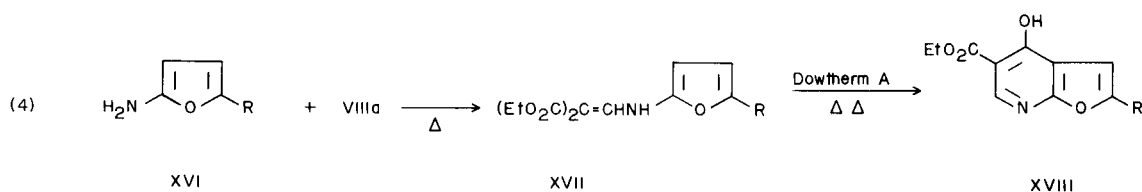
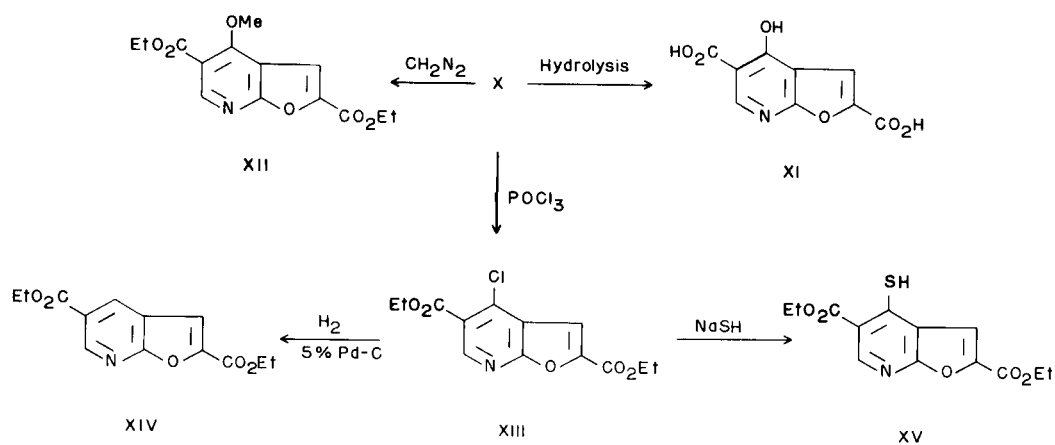
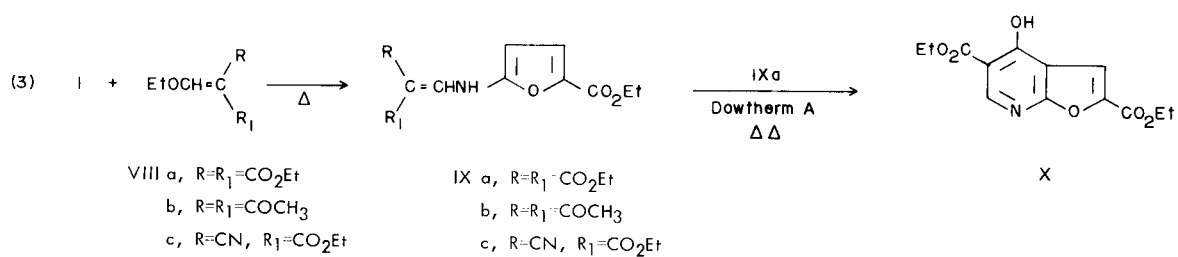
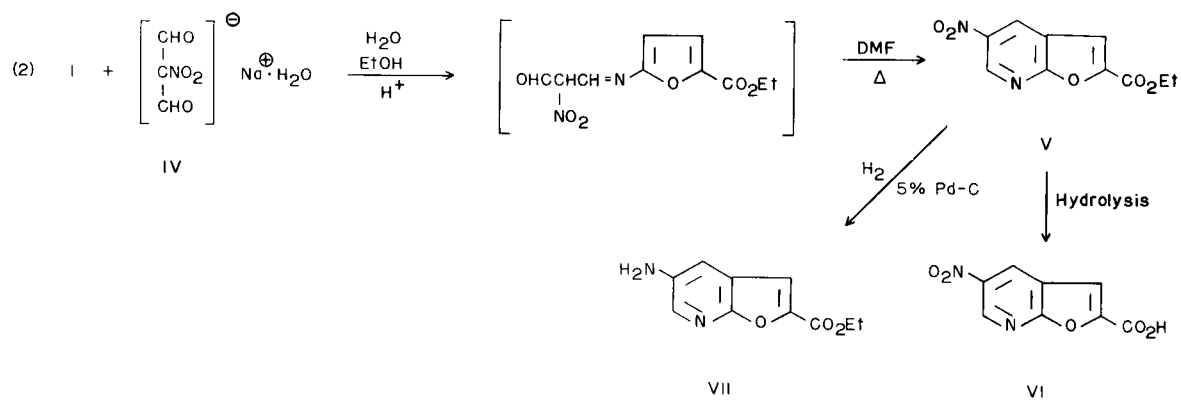
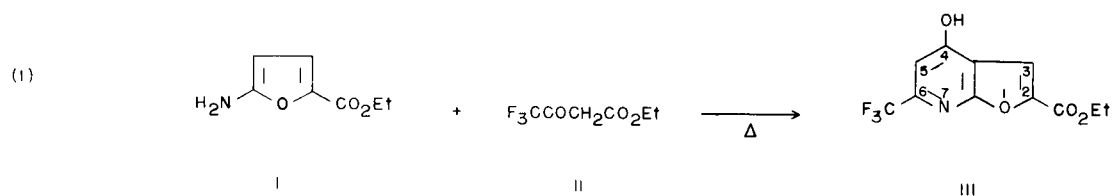
In order to expand the scope of the synthesis, I was condensed with several  $\alpha$ -alkoxymethylene carbonyl compounds (VIII). The condensation of I

with diethyl ethoxymethylenemalonate (VIIIa) (14) gave the vinyl intermediate (IXa) (see equation 3). When IXa was added to boiling Dowtherm A, ring closure occurred to form the furopyridine dicarboxylic ester (X). Hydrolysis of X yielded the dicarboxylic acid (XI), and treatment of X with diazomethane gave the ether (XII). Refluxing phosphorus oxychloride converted X to the chlorofuropyridine (XIII) (see equation 3). By catalytic reduction, XIII was dehalogenated to the furopyridine (XIV). When XIII was treated with sodium hydrogen sulfide in refluxing ethanol, the chlorine was replaced by a mercapto group to yield XV.

Ethyl 5-amino-2-furoate (I) was condensed with 3-ethoxymethylene-2,4-pentanedione (VIIIb) (15) and ethyl ethoxymethylenecyanoacetate (VIIIc) (14) to yield the vinyl intermediates (IXb) and (IXc), respectively (see equation 3). All attempts to cyclize IXb and IXc to the corresponding furo[2,3-b]pyridines under acidic, basic, and thermal conditions were unsuccessful.

Recently the synthesis of a series of 5-amino-2-furaldehyde derivatives was reported (16). It was of interest to determine if this type of aminofuran could also be converted to a furopyridine derivative. Condensation of 3-(5-aminofurfurylideneamino)-5-morpholinomethyl-2-oxazolidinone (XVI) with VIIIa gave the intermediate (XVII) (see equation 4). Thermal cyclization of XVII in boiling Dowtherm A gave the furopyridine (XVIII). The preparation of XVIII from XVI indicates that this ring synthesis may be generally applicable to 5-aminofurans of this type.

At this point a word should be said regarding the assigned enol structures of III, X, XI, and XVIII. The basis for the assignment resulted from a study of the infrared spectra of the furopyridines prepared. The spectrum of the nitroester (V) showed a carbonyl at 5.8  $\mu$ . Since compounds XII, XIII, XIV also showed a single carbonyl at 5.8  $\mu$ , the carbonyls of the esters at positions 2 and 5 absorb at the same frequency. Next the spectra of III showed the same carbonyl at 5.8  $\mu$ ; there was no second carbonyl which would have been expected if the structure were in the 4-keto form. The spectra of XVIII had a band at 5.65  $\mu$  which was assigned to the oxazolidinone carbonyl and another at 5.94  $\mu$  which was assigned to the carbonyl of the ester.



There was no band at  $5.8 \mu$  which is the normal position for the 5-ester absorption, neither was there a third carbonyl arising from a 4-keto group.

The shift of the ester carbonyl from  $5.8 \mu$  to  $5.94 \mu$  is explained as the result of hydrogen bonding of the 4-hydroxy group with the carbonyl of the ester at position 5. The last compound, X, contained two bands, one at  $5.8 \mu$  assigned to the ester group at position 2, and one at  $5.94 \mu$  assigned to the ester at position 5 which is hydrogen bonded to the 4-hydroxy group. Note that there was no third carbonyl from a keto group at 4. Further evidence for the enol structure was shown by XI which resisted decarboxylation. The 4-keto structure would give rise to a  $\beta$ -keto acid which would be expected to decarboxylate readily. Finally, III, X, XI, and XVIII gave positive ferric chloride tests indicative of enolic and phenolic groups.

#### EXPERIMENTAL

All analyses were carried out by Mr. Marvin Tefft and Mr. Jack Sturr of the Physical and Analytical Chemistry Section. Melting points were taken on a hot stage melting apparatus (Fisher-Johns) and are uncorrected. The infrared spectra were determined with a Perkin-Elmer Infrared spectrophotometer Model 21, the ultraviolet spectra were determined with a Beckman DU spectrophotometer.

Ethyl 4-Hydroxy-6-trifluoromethylfuro[2,3-b]pyridine-2-carboxylate (III).

A mixture of I (10.11) (38.8 g., 0.25 mole) and II (47.0 g., 0.25 mole) was placed in a flask which was heated in an oil bath ( $125-130^\circ$ ). The mixture which formed a melt at first, solidified after 1 hour. The crude material was recrystallized from methanol (charcoal) to give 29.3 g. (42.5%) of III melting at  $189.5-190^\circ$ .

*Anal.* Calcd. for  $C_{14}H_8F_3NO_4$ : C, 48.01; H, 2.93; N, 5.09. Found: C, 47.90; H, 3.16; N, 5.22.

A significant infrared band occurred at  $5.8 \mu$  (C=O) in a Nujol mull. The ultraviolet spectrum in 5% ethanol had  $\lambda$  max  $327.5 m\mu$  ( $\epsilon$ , 18,100).

Ethyl 5-Nitrofuro[2,3-b]pyridine-2-carboxylate (V).

A solution of IV (13) (51.5 g., 0.326 mole) in water (*ca.* 600 ml.) was added to a solution of I (50.5 g., 0.326 mole) in 95% ethanol (*ca.* 500 ml.). Water or 95% ethanol was added to produce a clear solution. The resulting solution was acidified with concentrated hydrochloric acid, chilled, and filtered. The crude material was suspended in a mixture of dimethylformamide (500 ml.) and water (250 ml.). The mixture was heated until a clear solution was formed. After the solution was allowed to cool to room temperature slowly, it was chilled in an ice bath and filtered. The product was air dried to yield 26.2 g. (34.0%) of V melting at  $164-165^\circ$ . The crude V was recrystallized from 95% ethanol (charcoal) to give 24.1 g. of material melting at  $165-166^\circ$ .

*Anal.* Calcd. for  $C_{10}H_8N_2O_5$ : C, 50.85; H, 3.41; N, 11.86. Found: C, 51.20; H, 3.58; N, 11.93.

The infrared spectrum of a chloroform solution exhibited absorption at  $5.8 \mu$  (C=O) and  $7.4 \mu$  ( $NO_2$ ). Ultraviolet absorption data in 5% ethanol showed  $\lambda$  max  $247.5 m\mu$  ( $\epsilon$ , 30,000).

5-Nitrofuro[2,3-b]pyridine-2-carboxylic Acid (VI).

A solution of V (43.0 g., 0.182 mole) and potassium hydroxide (12.0 g., 0.2 mole) in 95% ethanol (100 ml.) was refluxed for 3 hours. The mixture was cooled and filtered. The collected solid was dissolved in water. The solution was acidified with 10% hydrochloric acid (pH 2), cooled, and filtered. The product was collected and dried to give 30.8 g. (81.0%) of VI melting at  $280-282^\circ$ . An analytical sample was prepared by recrystallization from water (charcoal), m.p.  $282-283^\circ$ .

*Anal.* Calcd. for  $C_8H_7N_2O_5$ : C, 46.16; H, 1.94; N, 13.46. Found: C, 46.13; H, 2.08; N, 13.71.

The infrared spectrum of a Nujol mull possessed absorption peaks

at  $5.85 \mu$  (C=O) and  $7.4 \mu$  ( $NO_2$ ). The ultraviolet absorption data in 5% ethanol showed  $\lambda$  max  $249 m\mu$  ( $\epsilon$ , 28,300).

Ethyl 5-Aminofuro[2,3-b]pyridine-2-carboxylate (VII).

A solution of V (26.6 g., 0.3 mole) in 95% ethanol (*ca.* 600 ml.) containing 5% palladium on charcoal catalyst (15.0 g.) was hydrogenated in a Parr low pressure apparatus at  $50^\circ$ . The hydrogen uptake (initial 50 p.s.i.) was complete in 1 hour. The mixture was heated to boiling and filtered to remove the catalyst. The filtrate was chilled and filtered. The crude material was recrystallized from 95% ethanol (charcoal) to give 42.8 g. (69.4%) of VII melting at  $176-177^\circ$ .

*Anal.* Calcd. for  $C_{10}H_{10}N_2O_3$ : C, 58.25; H, 4.89; N, 13.58. Found: C, 57.99; H, 4.87; N, 13.68.

The hydrochloride salt of VII was prepared by acidifying a hot ethanolic solution of VII with concentrated hydrochloric acid. The salt was collected by chilling and filtering; the decomposition point was  $190^\circ$ .

*Anal.* Calcd. for  $C_{10}H_{10}N_2O_3 \cdot HCl$ : Cl, 14.61. Found: Cl, 14.62. The ultraviolet absorption spectrum in water possessed  $\lambda$  max  $272.5 m\mu$  ( $\epsilon$ , 18,200). The infrared spectrum of a Nujol mull showed a significant band at  $5.77 \mu$  (C=O).

Diethyl [(5-Carboethoxy-2-furylamino)methylene]malonate (IXa).

A mixture of I (310.0 g., 2.0 moles) and VIIIa (14) (432.0 g., 2.0 moles) was placed in a flask and heated in an oil bath ( $130-140^\circ$ ) for 45 minutes. The mixture set to a hard crystalline mass upon cooling. The crude IXa was recrystallized from 95% ethanol (charcoal) to yield 557.0 g. (85.6%) melting at  $86-89^\circ$ . An analytical sample was prepared by several recrystallizations from 2-propanol to give material melting at  $90.5-91.5^\circ$ .

*Anal.* Calcd. for  $C_{15}H_{19}NO_7$ : C, 55.38; H, 5.89; N, 4.31. Found: C, 55.48; H, 5.96; N, 4.28.

The ultraviolet data in 5% ethanol showed a maximum at  $344 m\mu$  ( $\epsilon$ , 30,500). The infrared absorption in chloroform had bands at  $2.9 \mu$  (NH),  $5.85 \mu$  (C=O),  $6.05$  and  $6.15 \mu$ .

Compound IXb was prepared in the same manner as was IXa using I (42.7 g., 0.276 mole) and VIIIb (15) (43.0 g., 0.276 mole). The crude material was recrystallized from 95% ethanol (charcoal) to give 64.0 g. (87.7%) of IXb melting at  $141-142^\circ$ .

*Anal.* Calcd. for  $C_{13}H_{15}NO_5$ : C, 58.86; H, 5.70; N, 5.28. Found: C, 58.63; H, 5.80; N, 5.26.

The infrared spectrum in chloroform showed significant bands at  $2.85 \mu$  (NH),  $5.85 \mu$  (C=O),  $5.9 \mu$  (C=O), and  $6.0 \mu$ . The ultraviolet absorption in 5% ethanol displayed a maximum at  $360 m\mu$  ( $\epsilon$ , 29,600).

Ethyl 5-(2-Carboethoxy-2-cyanovinylamino)-2-furoate (IXc).

Compound IXc was prepared in the same manner as was IXa using I (62.0 g., 0.4 mole) and VIIIc (14) (67.6 g., 0.4 mole). The crude material was recrystallized from 2-propanol (charcoal) to yield 72.5 g. (65.0%) of IXc melting at  $138.5-141^\circ$ . Several recrystallizations from 2-propanol (charcoal) raised the melting point of IXc to  $146-147^\circ$ .

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_5$ : C, 56.11; H, 5.07; N, 10.07. Found: C, 55.98; H, 5.15; N, 10.31.

The infrared spectrum in chloroform displayed significant bands at  $2.9 \mu$  (NH),  $4.45 \mu$  (CN),  $5.85 \mu$  (C=O), and  $6.1 \mu$ . The ultraviolet absorption in 5% ethanol showed a maximum at  $345 m\mu$  ( $\epsilon$ , 30,200).

Diethyl 4-Hydroxyfuro[2,3-b]pyridine-2,5-dicarboxylate (X).

Dowtherm A (1000 g.) was heated to boiling and IXa (163.0 g., 0.5 mole) was added in small portions. After the addition, the mixture was refluxed for 10 minutes, air cooled and finally chilled in an ice bath. The product was collected, washed thoroughly with hexane, and air dried to yield 104.0 g. (74.5%) of X melting at  $162-164^\circ$ . An analytical sample was prepared by recrystallization from 95% ethanol (charcoal), m.p.  $164.5-165.5^\circ$ .

*Anal.* Calcd. for  $C_{13}H_{13}NO_6$ : C, 55.91; H, 4.70; N, 5.02. Found: C, 55.87; H, 4.81; N, 4.92.

Significant infrared bands occurred at  $5.8 \mu$  (C=O) and  $5.94 \mu$  (C=O) in a chloroform solution. The absorption maximum of the ultraviolet spectrum in 5% ethanol was  $240 m\mu$  ( $\epsilon$ , 24,000).

4-Hydroxyfuro[2,3-b]pyridine-2,5-carboxylic Acid (XI).

Compound X (139.5 g., 0.5 mole) was added to a solution of potassium hydroxide (100.0 g., 1.5 moles, 85%) in water (500 ml.). The mixture was refluxed for 6 hours, cooled and filtered. The filtrate was acidified and filtered to give 70.0 g. (60.0%) of XI decomposing at  $260^\circ$ . A sample was recrystallized from glacial acetic acid (charcoal) to give material decomposing at  $280^\circ$ .

*Anal.* Calcd. for  $C_8H_7NO_5$ : C, 48.44; H, 2.26; N, 6.28. Found: C, 48.30; H, 2.25; N, 6.30.

The ultraviolet absorption data in water showed  $\lambda$  max 234  $\mu$  ( $\epsilon$ , 24,500). The infrared spectrum of a Nujol mull exhibited absorption at 5.85  $\mu$  (C=O).

Diethyl 4-Methoxyfuro[2,3-b]pyridine-2,5-dicarboxylate (XII).

An ethereal solution of diazomethane [prepared from *N*-methyl-*N*-nitrosourea (51.5 g., 0.5 mole)] was added to a solution of X (69.8 g., 0.25 mole) in a mixture of ether and chloroform. Vigorous evolution of nitrogen accompanied the addition (chloroform was added as necessary to keep XII in solution). The mixture was allowed to stand overnight at room temperature. The solvents were removed under reduced pressure (water pump). The crude residue was recrystallized from 95% ethanol (charcoal) to give 53.3 g. (72.6%) of XII melting at 146-148°. A second recrystallization raised the melting point to 149.5-150.5°.

*Anal.* Calcd. for  $C_{14}H_{15}NO_5$ : C, 57.33; H, 5.16; N, 4.78. Found: C, 57.40; H, 5.21; N, 4.80.

The ultraviolet absorption spectrum in 5% ethanol showed  $\lambda$  max 240  $\mu$  ( $\epsilon$ , 28,500). The infrared spectrum in chloroform solution exhibited absorption at 5.8  $\mu$  (C=O).

Diethyl 4-Chlorofuro[2,3-b]pyridine-2,5-dicarboxylate (XIII).

Phosphorus oxychloride (500 ml.) and X (279.0 g., 1.0 mole) were placed in a flask fitted with a reflux condenser and drying tube. The reaction mixture was refluxed for 4 hours at which time the evolution of hydrogen chloride had ceased. The excess phosphorus oxychloride was removed under reduced pressure at steam bath temperature. The residue was poured into water and ice. The crude material was collected and dried to give 216 g. (72.8%) of XIII melting at 90-95°. A sample of XIII was purified for analysis by repeated recrystallizations from 95% ethanol to a constant melting point of 96.5-97°.

*Anal.* Calcd. for  $C_{13}H_{12}ClNO_5$ : C, 52.45; H, 4.06; N, 4.71; Cl, 11.91. Found: C, 52.30; H, 4.12; N, 4.86; Cl, 12.06.

A significant infrared band occurred at 5.8  $\mu$  (C=O) in a chloroform solution. The ultraviolet data in 5% ethanol showed  $\lambda$  max 230  $\mu$  ( $\epsilon$ , 22,800).

Diethyl Furo[2,3-b]pyridine-2,5-dicarboxylate (XIV).

Compound XIII (59.4 g., 0.2 mole) was placed in a pressure bottle together with 95% ethanol (200 ml.) and 5% palladium on charcoal catalyst (6.0 g.). The mixture was shaken under hydrogen (45 p.s.i.) at 50-55°. The required amount of hydrogen was absorbed in 70 minutes. The hot solution was filtered and cooled in an ice bath. The product was collected and recrystallized from hexane (charcoal) to yield 38.2 g. (73%) of XIV melting at 90-91°. Additional recrystallizations of XIV from hexane did not change the melting point.

*Anal.* Calcd. for  $C_{13}H_{13}NO_5$ : C, 59.31; H, 4.98; N, 5.32. Found: C, 59.33; H, 5.02; N, 5.34.

The infrared spectrum of a chloroform solution exhibited absorption at 5.8  $\mu$  (C=O). The ultraviolet absorption data in 5% ethanol showed  $\lambda$  max 225  $\mu$  ( $\epsilon$ , 22,800).

Diethyl 4-Mercaptofuro[2,3-b]pyridine-2,5-dicarboxylate (XV).

A solution of XIII (124.0 g., 0.417 mole) in hot ethanol (500 ml.) was added slowly to a solution of sodium hydrogen sulfide (112.0 g., 0.834 mole) in hot ethanol. The mixture was refluxed for 3 hours. After cooling in an ice bath, the solution was acidified and filtered. The crude material was recrystallized from ethanol (charcoal) to yield 71.0 g. (57.7%) of XV melting at 150-160°. Purification was effected by recrystallization from ethanol (charcoal) to give material melting at 158.5-159.5°.

*Anal.* Calcd. for  $C_{13}H_{13}NO_5S$ : C, 52.87; H, 4.44; N, 4.74; S, 10.86. Found: C, 52.72; H, 4.49; N, 4.75; S, 10.91.

The infrared spectrum of a Nujol mull displayed a band at 5.85  $\mu$  (C=O). The ultraviolet absorption maximum in 5% alcohol occurred at 275  $\mu$  ( $\epsilon$ , 24,700).

Diethyl 5-(5-Morpholinomethyl-2-oxo-3-oxazolidinyliminomethyl)-2-furylaminomethylenemalonate (XVII).

A suspension of XVI (16) (62.0 g., 0.21 mole) in VIIIa (124 ml.) was heated in an oil bath (130-140°) for 2.5 hours. After cooling overnight, the dark solution was poured into an excess of ether. The precipitate was collected, washed with ether, and dried to yield 83.0 g. (85.0%) of crude XVII melting at 90-120°. The crude material was recrystallized from a benzene-cyclohexane (1:1) mixture (charcoal) to give 41.0 g. of XVII melting at 130-134°. Recrystallization of XVII from 2-propanol (charcoal) gave an analytical sample melting at 131-135°.

*Anal.* Calcd. for  $C_{21}H_{28}N_4O_8$ : C, 54.03; H, 6.08; N, 12.06. Found: C, 54.11; H, 5.99; N, 12.00.

The ultraviolet absorption data in 5% ethanol had a maximum at 370  $\mu$  ( $\epsilon$ , 29,400). The infrared spectrum of a Nujol mull showed significant bands at 5.7  $\mu$  (C=O), 6.05 and 6.2  $\mu$ .

Ethyl 4-Hydroxy-2-(5-morpholinomethyl-2-oxo-3-oxazolidinyliminomethyl)furo[2,3-b]pyridine-5-carboxylate Hemihydrate (XVIII).

Compound XVII (74.0 g., 0.16 mole) was added in small portions to boiling Dowtherm A (740.0 g.) during a period of 10 minutes. The solution was cooled to room temperature, chilled, and filtered. The crude material was washed with hexane and dried to yield 66.0 g. of a compound melting at 100-190°. The crude product was recrystallized from 95% ethanol (charcoal) to give 41.0 g. (60.0%) of XVIII melting at 185-188°. An analytical sample was prepared by recrystallization from 95% ethanol to yield material melting at 188-192°.

*Anal.* Calcd. for  $C_{19}H_{22}N_4O_7 \cdot \frac{1}{2}H_2O$ : C, 53.35; H, 5.42; N, 13.11. Found: C, 53.56; H, 5.45; N, 13.36.

The infrared spectrum of a Nujol mull displayed bands at 5.65  $\mu$  (C=O) and 5.95  $\mu$  (C=O). The ultraviolet absorption data in 5% ethanol showed a maximum at 312.5  $\mu$  ( $\epsilon$ , 31,800).

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