The Synthesis of Furo[2,3-c]pyridine Derivatives[1a]

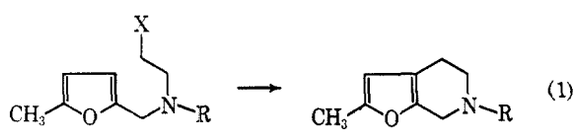
MATHIAS P. MERTES, RONALD F. BORNE,[1b] AND LARRY E. HARE[1c]

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

Received July 31, 1967

The synthesis of derivatives of the previously unreported furo[2,3-c]pyridine ring system is described. A mechanism for the formation of N-benzenesulfonyl-N-benzylamine (**13**) during the Friedel–Crafts cyclization of N-benzenesulfonyl-N-(5-methylfurfuryl)glycine (**6b**) is postulated. Reduction products from the desulfurization of the ethylene dithioketal of **7b** (**20** and **21**) are discussed. Reduction of 4,5,6,7-tetrahydro-2-methyl-4-oxo-6-benzenesulfonylfuro[2,3-c]pyridine (**7b**) under conditions of the Wolff–Kishner reduction afforded 2-methyl-4-hydroxyfuro[2,3-c]pyridine (**22**). Other synthetic approaches to the ring system also are discussed.

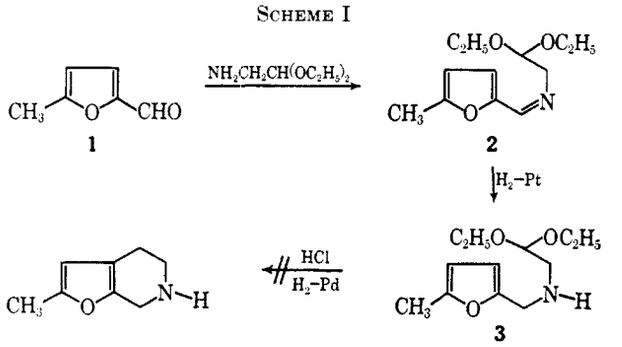
In the course of a program designed to clarify the conformational requirements of the quaternary ammonium group of the cholinomimetics muscarine and muscarone, it was necessary to devise a synthesis of the previously undescribed furo[2,3-c]pyridine ring system. Two general approaches directed toward the synthesis of this system were investigated. This paper deals with approaches aimed primarily at effecting the general ring closure shown in eq 1.



(1)

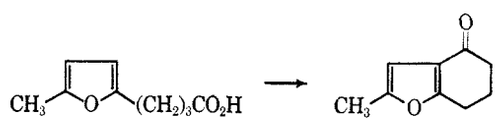
Based upon the synthesis of tetrahydroisoquinolines by a modification of the Pomeranz–Fritsch reaction reported by Bobbitt and coworkers,[2] the approach outlined in Scheme I was attempted. The reductive

SCHEME I

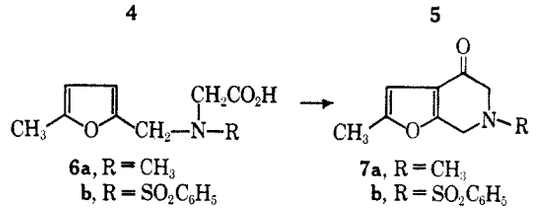


amination product, **3**, from **1** and amino acetal was treated with hydrochloric acid and subsequently hydrogenated. The work-up of this reaction mixture gave largley polymeric material from which no identifiable product could be isolated. Saturated hydrogen chloride solutions of **3** in both absolute ethanol and benzene also gave tars. The N-benzenesulfonyl derivative of **3** was prepared; however, treatment of the sulfonamide in absolute ethanol with a calculated amount of hydrogen chloride gave a tar. The facile synthesis of furo[2,3-b]pyridine derivatives from the condensation of ethyl 5-amino-2-furoate with ethal trifluoroacetoacetate[3] suggested a similar possible ring closure of **2**. However, only starting material was obtained.

Taylor[4] reported the successful synthesis of **5** from **4** in high yield using phosphorus pentachloride and stannic chloride (eq 2). It was anticipated that cyclization



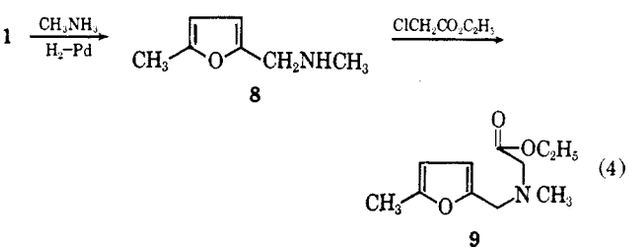
(2)



(3)

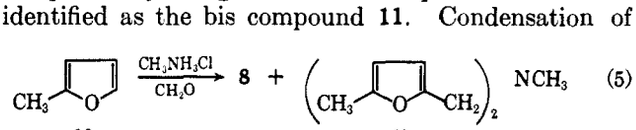
of **6** under similar conditions would give rise to the desired ring system derivative **7** (eq 3).

The initial synthesis of compounds of type **6** was attempted from **1**. Reductive amination of **1** with aqueous methylamine gave a 23% yield of **8** (eq 4).



(4)

Refluxing **8** with ethyl chloroacetate in acetone and sodium carbonate gave only the hydrochloride of **8**. Alkylation was finally achieved using ethanol and sodium bicarbonate at room temperature. The application of the Mannich reaction to 2-methylfuran (**10**) with various alkylamine hydrochlorides[5] suggested an alternative approach to **8** (eq 5). Thus, **8** was obtained but again in only 23% yield. The reaction was accompanied by a large amount of side product which was identified as the bis compound **11**. Condensation of



(5)

10 and glycine ethyl ester hydrochloride under similar conditions gave **12** (eq 6). The reaction was again accompanied by a considerable amount of side product

(1) (a) This research was supported by a Predoctoral Fellowship to R.F.B. from The National Institutes of Health (F1-NH-12, 708), and by Grant 1K3-CA-10739 from the National Cancer Institute; (b) taken in part from the Ph.D. thesis of R. F. B., The University of Kansas, 1967; (c) National Science Foundation Undergraduate Research Participant 1965–1967.

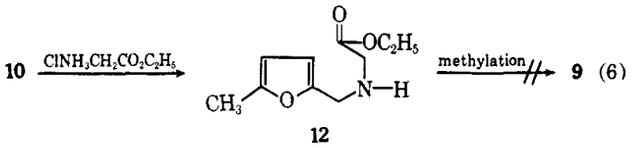
(2) (a) J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. Ind.* (London), 1950 (1964); (b) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965); (c) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *ibid.*, **30**, 2459 (1965).

(3) H. R. Snyder and F. F. Ebetino, *J. Heterocyclic Chem.*, **3**, 202 (1966).

(4) D. A. H. Taylor, *J. Chem. Soc.*, 2767 (1959).

(5) R. Holdren and R. Hixon, *J. Am. Chem. Soc.*, **68**, 1198 (1946).

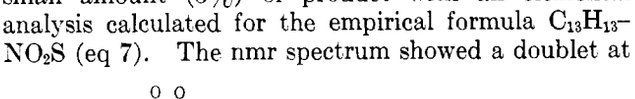
which, based upon the results of the previous condensation and nmr data, was tentatively identified as N,N-



12

di(5-methyl-2-furfuryl)glycine ethyl ester, although attempts to purify the material were unsuccessful. Attempts to N-methylate **12** with formic acid and formaldehyde gave tars. Use of dimethyl sulfate gave a mixture of **9** and **12**, which were not separable by distillation. Condensation of **10** with sarcosine ethyl ester hydrochloride did give good yields of **9**. Attempts to hydrolyze **9** led to difficulties in isolation of the resulting amino acid **6a**. It was decided to delay the N-methylation step until later in the reaction sequence by protecting the secondary amine during ring closure as the sulfonamide. For this purpose, **12** was treated with benzenesulfonyl chloride in excess sodium hydroxide to give the N-benzenesulfonyl derivative with concomitant hydrolysis of the ester **6b**.

Initial attempts to effect cyclization of **6b** under conditions reported for that of **4** gave only polymer. In an effort to effect ring closure, the reaction was repeated using different catalysts ($AlCl_3$, $ZnCl_2$, HF, PPA, and P_2O_5), solvents, reaction times, and temperatures. All variations resulted in intractable tars. The possibility remained that failure to effect closure resulted from evolution of hydrogen chloride during the formation of the acid chloride. The dry sodium salt of **6b** was prepared and treated with excess oxalyl chloride in benzene with a small amount of pyridine added to absorb any hydrogen chloride which may be evolved. Chromatographic work-up of the benzene fraction after decomposition of the reaction mixture gave a 15% yield of **7b**. The structure was established on the basis of elemental analyses and infrared and nmr spectral data.[6] The formation of **7b** was accompanied by the isolation of a small amount (5%) of product with an elemental analysis calculated for the empirical formula $C_{13}H_{13}NO_2S$ (eq 7). The nmr spectrum showed a doublet at

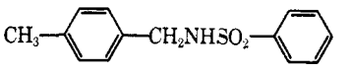


13

4.15, broad absorption at 4.7–5.2, a singlet at 7.23, and a multiplet at 7.4–8.0 ppm whose areas integrated in the ratio of 2:1:1:5:5, respectively. These results suggested structure **13**. An authentic sample of the N-benzenesulfonamide of benzyl amine was prepared and gave an identical nmr spectrum. A mixture melting point with **13** showed no depression.

Interestingly, treatment of the free acid **6b** with oxalyl chloride in benzene and pyridine yielded only **7b**. Attempts to cyclize the N-methyl derivative **9** by hydrolysis of the ester to the sodium salt of the resulting acid and treatment of the salt with oxalyl chloride and stannic chloride gave only tars.

In an attempt to rationalize the formation of **13**, the closure was performed in various solvents to determine the origin of the phenyl group in the benzylamine portion of the molecule. The acid chloride was prepared in benzene and, after completion of reaction, the benzene was removed and replaced with chlorobenzene before addition of stannic chloride. This had no effect on either product formation or yields. It was assumed that incomplete removal of benzene accounted for the formation of **13**. The entire reaction sequence was repeated in nitrobenzene, but only polymeric materials were obtained; attempts to isolate **7b** were unsuccessful. Repeating the sequence in toluene gave 20% of **7b** and 5% of **14** which was identified on the basis of its

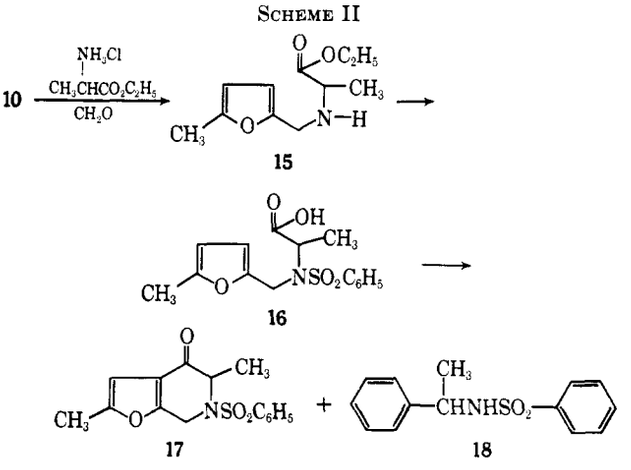


14

identity with an authentic sample. It was thus concluded that this portion of the molecule arises from the interaction of an intermediate of **6b** with solvent.

The origin of the benzylic methylene group of **13** and **14** is not known with certainty. The sequence outlined in Scheme II was performed with the intention of isolating **18** and thus prove that the methylene group arises

SCHEME II



from the glycine portion of **6b**. The Mannich condensation product, **15**, was readily obtained but **16** could be obtained in no greater than 12% yield under the same conditions that an 88% yield of **6b** was obtained. Ring closure of **16** under conditions described for that of **6b** gave 34% of **17** but no **18** could be detected.

Despite the failure to isolate **18**, the formation of **13** is proposed to arise by the mechanism proposed in Scheme III. Decarbonylation may occur in either a stepwise or concerted manner. Although the possibility of initial decarboxylation of **6b** can be considered, many examples of the decarbonylation process during Friedel–Crafts acylations have been reported.[7] Similar decarbonylation processes during cyclization of aralkyl glycyl chlorides have also been described by von Braun and coworkers[8] and, more recently, by Proctor and Thomson.[9] Attempts to effect intramolecular cyclization of N-benzyl-N-methylglycyl chloride[10] and N-ben-

(6) The nmr spectra of the furo[2,3-c]pyridine derivatives described in this paper are discussed separately: R. C. Briden, paper to be published.

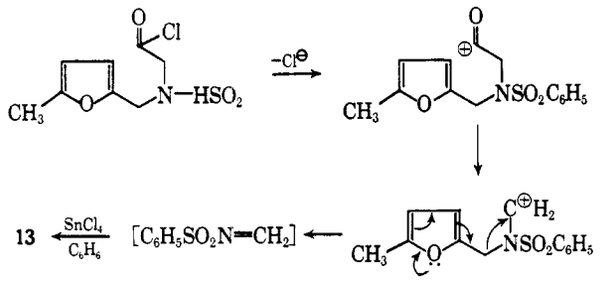
(7) S. Sethna in "Friedel-Crafts and Related Reactions," Vol. III, G. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 35.

(8) (a) J. vonBraun, G. Blessing, and R. Cahn, *Chem. Ber.*, **57**, 908 (1924); J. vonBraun and K. Wirz, *ibid.*, **60**, 102 (1927).

(9) G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957).

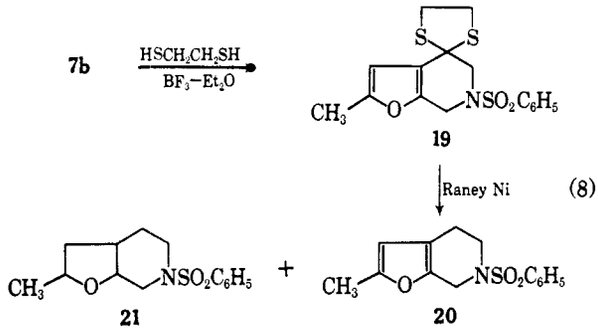
(10) C. Mannich and R. Kuphal, *Chem. Ber.*, **45**, 314 (1912).

SCHEME III



zyl-N-toluene-*p*-sulfonylglycine[11] failed. More recently, cyclization of β-arylethylglycines was achieved in appreciable yields only at very low temperatures (−70°).[12]

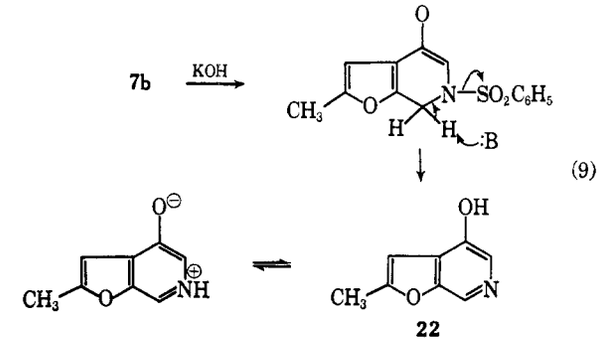
In order to prepare the desoxy analog of **7b** the ethylene dithioketal derivative **19** was synthesized. Attempted concurrent reduction of the dithioketal[13] and the sulfonamide[14] groups by the use of sodium in liquid ammonia afforded a tar. Refluxing **7b** with W-4 Raney nickel in dioxane afforded a residue which, on the basis of thin layer chromatography results, was a mixture of two components. Chromatography of this residue on silica gel yielded products which were identified as **20** and **21** (eq 8). The formation of **21** was not totally



(8)

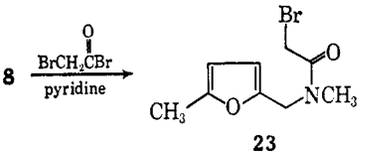
unexpected in view of the observed reduction of the furan ring during desulfurization of furfurylidene rhodanines.[15] Based on the mode of formation and nmr spectral data[6] the stereochemistry of **21** was established as the *cis*-ring juncture.

Under conditions of the Huang-Minlon modification of the Wolff–Kishner reduction, **7b** did not give the expected methylene derivative but rather **22** (eq 9). In the mechanism proposed for the formation of **22**, the elimination of benzenesulfinic acid (although not isolated from the reaction) is similar to that observed by Proctor[16] on treating sulfonamides of activated α-amino ketones with sodium methoxide. Enolization of the carbonyl group to the corresponding dihydropyridine derivative is an important driving force in the elimination of benzenesulfinic acid since treatment of **20** under similar conditions gave a nearly quantitative recovery of starting material.



(9)

Another approach attempted for the synthesis of the ring system was through the anticipated Friedel–Crafts cyclization of **23**. However, attempts to cyclize



23 with stannic chloride in benzene gave only starting material.

Experimental Section[17]

N-(5-Methyl-2-furfuryl)aminoacetaldehyde Diethyl Acetal (3).—5-Methyl-2-furaldehyde[4] (16.5 g, 0.15 mole) and amino acetal (19.9 g, 0.15 mole) were combined in 75 ml of absolute ethanol. Platinum oxide (*ca.* 0.2 g) was added and the mixture hydrogenated on a Paar apparatus. The calculated amount of hydrogen was absorbed, the catalyst removed by filtration, and the filtrate evaporated. The residue was shown by tlc to contain small amounts of starting material. The residue was then distilled at reduced pressure. The distillate (21.6 g, 64%, bp 156–158° (15 mm)) was shown to be **3**; nmr ($CDCl_3$) peaks appeared at 1.60 (1 H, N–H, singlet), 2.33 (3 H, 5-CH_3, singlet), 3.85 (2 H, C=C–CH_2–N, singlet), 2.83 (2 H, N–CH_2–C, doublet), 6.04 and 6.24 (2 H, 3-H, and 4-H, distorted doublets), 1.23 (6 H, O–C–CH_3, triplet), 4.73 (1 H, O –CH–O, triplet), and 3.44–4.02 (4 H, O–CH_2, multiplet).

N-(5-Methyl-2-furfurylidene)aminoacetaldehyde Diethyl Acetal (2).—5-Methyl-2-furaldehyde (3.0 g, 0.027 mole) and amino acetal (3.6 g, 0.027 mole) were combined in 150 ml of benzene and refluxed for 12 hr. A Dean–Stark trap was used to facilitate removal of water. The benzene was removed by distillation under vacuum and the residue distilled to afford the Schiff base (2.0 g, 33%, bp 82° (0.1 mm)); nmr ($CDCl_3$) peaks appeared at 2.34 (3 H, 5-CH_3, singlet), 7.98 (1 H, CH=N, singlet), 6.0 and 6.1 (2 H, 3-H and 4-H, distorted doublets), 1.15 (6 H, CH_3–C, triplet), 4.70 (1 H, O–CH–O, triplet), and 3.2–3.8 (4 H, N–CH_2 and O–CH_2, multiplet).

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.28; H, 8.76; N, 6.29.

N-Benzenesulfonyl-N-(5-methyl-2-furfuryl)aminoacetaldehyde Diethyl Acetal.—The sulfonamide was prepared in the normal manner using 5.0 g (0.022 mole) of **2**, 18 ml of 10% aqueous sodium hydroxide and 3.9 g (0.022 mole) of benzenesulfonyl chloride. Recrystallization from ethanol gave colorless prisms (6.01 g, 75%, mp 76–78°).

Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.86; N, 3.81. Found: C, 58.99; H, 6.81; N, 3.95.

N-(5-Methyl-2-furfuryl)methylamine (8). Method A.—A mixture of **1** (11.0 g, 0.10 mole) and 40% aqueous methylamine (24.0 g, 0.30 mole) was heated to boiling in a low-pressure hydrogenation flask. The mixture was cooled, palladium on charcoal (5%, 1.0 g) added, and the resulting mixture hydrogenated at an initial pressure of 29 psi. The catalyst was removed by filtration and washed with water. After the filtrate was acidified with hydrochloric acid and extracted with ether, the aqueous layer was made basic with 20% sodium hydroxide and reextracted with ether. The aqueous layer was saturated

(11) G. R. Clemo and W. H. Perkin, *J. Chem. Soc.*, 2297 (1925).
(12) M. A. Rehman and G. R. Proctor, *ibid., Sect. C*, 58 (1967).
(13) R. E. Treland, T. I. Wrigley, and W. G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958).
(14) J. Kovacs and U. Ghatak, *J. Org. Chem.*, **31**, 119 (1966).
(15) H. Behringer, E. Dillinger, H. Suter, and K. Kohl, *Chem. Ber.*, **91**, 2773 (1958).
(16) T. Bryce, G. Proctor, and M. Rehman, *J. Chem. Soc.*, 7105 (1965).
(17) Melting points are corrected. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Nmr spectra were obtained on a Varian Model A-60 spectrometer. Peak positions are reported in terms of parts per million from tetramethylsilane.

with sodium chloride and extracted with ether. The ether layers were combined, dried, and evaporated; the residue was distilled at reduced pressure to give 2.8 g (23%) of **8**, bp 88° (20 mm), $n^{28}D$ 1.4712; nmr ($CDCl_3$) peaks appeared at 1.32 (1 H, NH, singlet), 2.29 (3 H, 5-CH_3, singlet), 2.45 (3 H, N-CH_3, singlet), 3.71 (2 H, CH_2-N, singlet), and 5.93 and 6.09 (2 H, 3-H and 4-H, distorted doublets).

Anal. Calcd for $C_{13}H_{14}N_4O_8$ (as picrate salt): C, 44.07; H, 3.98; N, 15.81. Found: C, 44.45; H, 3.99; N, 15.73.

Method B.—Methylamine hydrochloride (101 g, 1.5 moles) and formaldehyde (150 g of aqueous 37% solution, 1.9 moles) were combined and cooled with stirring to 5°. 2-Methylfuran (122 g, 1.5 moles) was added dropwise over a 1-hr period. After completion of addition, stirring was continued for an additional hour in the cold and at room temperature for 2.5 hr. The solution was neutralized with aqueous sodium hydroxide and the resulting oil taken up in ether. The aqueous layer was extracted several times with ether, and the ether extracts were combined, washed with water, and dried over sodium sulfate. The filtrate was evaporated and the residue distilled. The lower boiling fraction was shown to be **8** (bp 86–89° (20 mm), 43.3 g, 23%). The higher boiling fraction, bp 140–142° (10 mm), was identified as **11** through its methiodide.

The methiodide of **11** was prepared in the normal manner and recrystallized from ether–methanol, mp 148° dec.

Anal. Calcd for $C_{14}H_{20}NO_2I$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.46; H, 5.71; N, 3.66.

N-(5-Methyl-2-furfuryl)-N-methylglycine Ethyl Ester (9). Method A.—To a mixture of **8** (0.50 g, 0.004 mole) and sodium bicarbonate (0.40 g, 0.004 mole) in 25 ml of absolute ethanol was added ethyl chloroacetate (0.49 g, 0.004 mole) in 20 ml of ethanol. The mixture was stirred at room temperature for 12 hr and the ethanol removed by distillation. Water was added to the residue and the aqueous mixture saturated with sodium hydroxide and extracted with ether. The ether extracts were combined, dried over magnesium sulfate, and evaporated. The residue (0.30 g, 35%) was shown to be **9**; nmr ($CDCl_3$) peaks appeared at 2.20 (3 H, 5-CH_3, singlet), 2.45 (3 H, N-CH_3, singlet), 3.32 (2 H, C-CH_2-C=O, singlet), 3.75 (2 H, C=C-CH_2-N, singlet), 1.28 (3 H, C-CH_3, triplet), 4.24 (2 H, O-CH_2-C, quartet), and 5.97 and 6.18 (2 H, 3-H and 4-H, multiplets).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.81; H, 8.18; N, 6.67.

Method B.—A suspension of sarcosine (40 g, 0.45 mole) in 500 ml of dry absolute ethanol was saturated with hydrogen chloride. The mixture became homogeneous and was refluxed for 18 hr. The solution was evaporated to dryness and ether was added to the residue. The resulting oil was cooled and subsequently solidified. The colorless crystals were collected, washed with ether, and dried to afford 65 g of the ester hydrochloride (94%), mp 115–117° (lit.[18] mp 121°).

Sarcosine ethyl ester hydrochloride (65 g, 0.42 mole) and aqueous 37% formaldehyde (48 g, 0.55 mole) were combined and cooled to 5°. 2-Methylfuran (34.4 g) was added slowly over a 0.5-hr period and the mixture stirred an additional 0.5 hr at 5° and 3 hr at room temperature. Aqueous sodium hydroxide (16.8 g in 35 ml of water) was added to the solution and the resulting oil taken up in ether. The aqueous layer was extracted several times with ether; the ether extracts were combined and dried. The residue which resulted on evaporation was distilled at reduced pressure to give **9** (42 g, 48%, bp 87° (1.0 mm)).

N-(5-Methyl-2-furfuryl)glycine Ethyl Ester (12).—Glycine ethyl ester hydrochloride (140 g, 1.0 mole) and 37% aqueous formaldehyde (81 g, 1.0 mole) were combined and cooled to 5°. 2-Methylfuran (81 g, 1.0 mole) was slowly added over a 90-min period and the reaction carried out in the previously described manner. The ether extracts resulting after neutralization were combined, washed with water, and dried. Distillation of the residue from evaporation gave **12** (73.2 g, 37%), bp 88° (0.4 mm), $n^{26}D$ 1.4731; nmr ($CDCl_3$) peaks appeared 1.97 (1 H, NH, singlet), 2.29 (3 H, 5-CH_3, singlet), 3.43 (2 H, N—CH_2—C=O, singlet), 3.78 (2 H, C=C—CH_2-N, singlet), 1.27 (3 H, C-CH_3, triplet), 4.22 (2 H, O-CH_2-C, quartet), and 5.92 and 6.10 (2 H, 3-H and 4-H, distorted doublets).

Anal. Calcd for $C_{16}H_{18}N_4O_{10}$ (as picrate salt): C, 45.08; H, 4.25; N, 13.14. Found: C, 45.01; H, 4.16; N, 13.29.

N-Benzenesulfonyl-N-(5-methyl-2-furfuryl)glycine (6b).—Sodium hydroxide (60 g, 1.5 moles in 300 ml of water) and 100 g of **12** (0.5 mole) were combined and cooled with stirring to 5°. Benzenesulfonyl chloride (88 g, 0.5 mole) was added in portions and the mixture stirred in the cold for 1 hr and at room temperature for 12 hr. The solution was recooled and neutralized with 10% hydrochloric acid. The oil which separated was cooled by refrigeration and subsequently solidified. The solid was collected, washed with water, and recrystallized from aqueous ethanol to give 127 g (83%) of **6b**, mp 114–116°.

Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.35; H, 4.89; N, 4.53; S, 10.37. Found: C, 54.29; H, 4.96; N, 4.60; S, 10.51.

4,5,6,7-Tetrahydro-2-methyl-4-oxo-6-benzenesulfonylfuro-[2,3-*c*]pyridine (7b). A. In Benzene.—A solution of 25 g of **6b** (0.08 mole) in 100 ml of ethanol was made basic by the addition of a 10% sodium hydroxide solution. The solvents were removed under vacuum; the residue was dried at 80° and 20 mm for 12 hr. Dry benzene (300 ml) and pyridine (1 ml) were added to the residue; the mixture was cooled with stirring to 10°; and 61 g of oxalyl chloride (41 ml, 0.48 mole) was added dropwise. The mixture was stirred for 3 hr and excess oxalyl chloride removed under vacuum. Benzene was added to bring the volume of the solution to 300 ml. The mixture was cooled to 10° and 41.7 g of stannic chloride (19 ml, 0.16 mole) added; the mixture was stirred for 3.5 hr then poured onto ice containing 30 ml of hydrochloric acid. The mixture was transferred to a separatory funnel and the benzene layer separated from the polymeric and aqueous layers. The latter two layers were extracted several times with benzene and the benzene extracts were combined, washed with water, dried over sodium sulfate, and evaporated. The resulting residue was chromatographed on a silicic acid column.

From Skelly B–ethyl acetate (85:15) was obtained a solid, mp 85–87° (from aqueous methanol, lit.[19] mp 88°), which was identified as the benzenesulfonamide of benzylamine (**13**).

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.40; H, 5.44; N, 5.65.

From Skelly B–ethyl acetate (3:1) was obtained a colorless solid, mp 122–123° (ethanol), which was identified as the desired ketone **7b**.

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.71; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.95; H, 4.38; N, 4.95; S, 11.25.

B. In Toluene.—The formation of the acid chloride and cyclization were performed as described but in toluene. The toluene layer resulting from work-up was washed with water, dried, and evaporated and the residue chromatographed on a column of silicic acid. From Skelly B–ethyl acetate (85:15) was obtained a solid, mp 85–87° (benzene–Skelly B, lit.[20] mp 79°), which was shown to be identical with an authentic sample of the benzenesulfonamide of *p*-methylbenzylamine.

Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.11; H, 5.88; N, 5.53.

From Skelly B–ethyl acetate (3:1) was obtained **7b**.

N-(5-Methyl-2-furfuryl)alanine Ethyl Ester (15).—The procedure described for the preparation of **12** was essentially followed using 25 g (0.16 mole) of alanine ethyl ester hydrochloride, 16 g of 37% aqueous formaldehyde (0.16 mole), and 13 g of 2-methylfuran (0.16 mole). After neutralization and extraction with ether, the ether extracts were combined, washed with water, and dried over sodium sulfate. The ether was removed and the residue distilled to give 14.4 g (43%) of **15**, bp 76° (0.1 mm); nmr ($CDCl_3$) peaks appeared at 2.00 (1 H, N-H, singlet), 2.25 (3 H, 5-CH_3, singlet), 3.72 (2 H, CH_2-N, singlet), 1.30 (3 H, CH_3-C-N, doublet), 1.27 (3 H, CH_3-C-O, triplet), 3.40 (1 H, N-CH-C, quartet), 4.18 (2 H, O-CH_2-C, quartet), and 5.8 and 6.1 (2 H, 3-H and 4-H, distorted doublets).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.61; H, 8.33; N, 6.63.

N-Benzenesulfonyl-N-(5-methyl-2-furfuryl)alanine (16).—The amino ester **15** (13.5 g, 0.064 mole) and aqueous sodium hydroxide (7.7 g, 0.192 mole) were combined and cooled to 5°. Benzenesulfonyl chloride (11.3 g, 0.064 mole) was added and the mixture stirred at 10° for 1 hr and at room temperature for 24 hr. The mixture became homogeneous and was cooled and acidified with hydrochloric acid. The resulting mixture was extracted with chloroform; the chloroform extracts were combined, dried over

(18) W. Staudt, *Z. Physiol. Chem.*, **146**, 286 (1925).

(19) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 288.

(20) V. I. Markov and S. I. Burmistrov, *Ukr. Khim. Zh.*, **30**, 1070 (1964); *Chem. Abstr.*, **62**, 3968 (1965).

magnesium sulfate, and evaporated. The resulting oil appeared to be a mixture of desired acid and ester. The oil was dissolved in chloroform and extracted with sodium carbonate solution. The basic layer was acidified and the resulting oil collected in ether. The ether extracts were combined, dried, and evaporated. Recrystallization of the residue from benzene–Skelly B afforded 1.5 g of **16** (8%), mp 93–95°.

Anal. Calcd for $C_{15}H_{17}NO_5S$: C, 55.71; H, 5.30; N, 4.33. Found: C, 55.96; H, 5.46; N, 4.28.

4,5,6,7-Tetrahydro-2,5-dimethyl-4-oxo-6-benzenesulfonylfuro[2,3-*c*]pyridine (17).—The sodium salt of **16** (8.0 g, 0.025 mole) was prepared as described for **6b**. Treatment of the salt with 19.0 g (0.15 mole) of oxalyl chloride and 13.0 g (0.05 mole) of stannic chloride in 100 ml of benzene under conditions described for the preparation of **7b** gave three layers on work-up. The benzene layer was separated, washed with water, and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silicic acid although tlc indicated only one major component. From Skelly B–ethyl acetate (85:15) was obtained a solid which characterized as the ketone **17** (2.6 g, 34%), mp 127–128° (ethanol). No rearrangement products were isolated.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.72; H, 5.05; N, 5.00.

Ethylenedithioketal of 7b (19).—To a slurry of 9.2 g (0.032 mole) of **7b** in 100 ml of methanol was slowly added 5.2 g (4.7 ml, 0.055 mole) of 1,2-ethanedithiol. The mixture was cooled and 2.5 ml of boron trifluoride etherate added. The slurry was stirred for 15 min in the cold then heated until solution was effected. A solid precipitated on cooling and was washed with cold methanol to give 10.3 g (90%) of **19**, mp 149–151°; nmr ($CDCl_3$) peaks appeared at 2.22 (3 H, 2-CH_3, singlet), 3.62 (2 H, CH_2–N, singlet), 4.11 (2 H, C=C–CH_2–N, singlet), 3.44 (4 H, S–CH_2–CH_2–S, singlet), 6.13 (1 H, 3-H, singlet), and 7.5–8.0 (5 H, aromatic, multiplet).

Anal. Calcd for $C_{16}H_{17}NO_3S_3$: C, 52.29; H, 4.66; N, 3.81; S, 26.18. Found: C, 52.37; H, 4.84; N, 3.81; S, 25.75, 25.89.

Desulfurization of 19. Preparation of 20 and 21.—To a suspension of 50 g of W-4 Raney nickel in 250 ml of dioxane was added a solution of 5.0 g (0.135 mole) of **19** in 50 ml of dioxane. The suspension was refluxed with stirring for 12 hr and the catalyst removed by filtration over Filter Cel. The catalyst was washed with hot dioxane and the filtrate evaporated under reduced pressure. The residue was shown by tlc to consist of two major components and was chromatographed on a silicic acid column. Skelly B–ethyl acetate (9:1) gave 0.384 g of a solid which was shown to be 4,5,6,7-tetrahydro-2-methyl-6-benzenesulfonylfuro[2,3-*c*]pyridine (**20**), mp 103–104° (Skelly B).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.36; H, 5.63; N, 5.04.

Skelly B–ethyl acetate (4:1) eluted 0.275 g of a solid which was shown to be 2-methyl-6-benzenesulfonylperhydrofuro[2,3-*c*]pyridine (**21**), mp 97–98° (Skelly B).

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 60.09; H, 6.76; N, 4.99; S, 11.48.

2-Methyl-4-hydroxyfuro[2,3-*c*]pyridine (22).—Potassium hydroxide (1.0 g, 0.02 mole), **7b** (2.0 g, 0.007 mole), and 50 ml of triethylene glycol were combined and shaken until a solution was effected. Hydrazine hydrate (85%, 4.0 g) was added and the mixture refluxed for 2 hr. The temperature of the mixture was elevated to 190° to remove water. Heating was continued at this temperature for 4 hr and the mixture cooled. Water was added and the resulting mixture extracted with ether. The ether extracts were combined, washed with water, and dried over sodium sulfate. Evaporation afforded a white solid which was recrystallized from chloroform–acetone to give a product which was characterized as **22** (0.35 g, 35%), mp 201–202°; nmr (d_6-DMSO) peaks appeared at 2.5 (3 H, 2-CH_3, singlet), 6.8 (1 H, 3-H, singlet), 8.0 and 8.5 (2 H, 5-H and 7-H, singlets), and 4.2–4.9 (N–H, broad absorption).

Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.74; N, 9.39. Found: C, 64.43; H, 4.74; N, 9.24.

N-Methyl-N-(5-methyl-2-furfuryl)-2-bromoacetamide (23).—A mixture of **8** (5.85 g, 0.047 mole), pyridine (3.7 g, 0.047 mole), and 25 ml of dry benzene was cooled to 5°. Bromoacetyl bromide (9.4 g, 0.047 mole) in 25 ml of dry benzene was added dropwise and the resulting mixture allowed to stir at room temperature for 8 hr. The resulting solid was removed by filtration and washed with benzene. The filtrate was evaporated under reduced pressure and the residue chromatographed on a silicic acid column. Elution with Skelly B–ethyl acetate (85:15) gave a clear yellow oil which resisted efforts at crystallization; nmr ($CDCl_3$) peaks appeared at 2.25 (3 H, 5-CH_3, singlet), 4.43 (Br–CH_2–C=O, singlet), 2.95 (3 H, N–CH_3, chemical-shift doublet), 3.90 (2 H, C=C–CH_2–N, chemical-shift doublet), and 5.90 and 6.10 (2 H, 3-H and 4-H, multiplets).

Anal. Calcd for $C_9H_{12}NO_2Br$: C, 43.92; H, 4.92; N, 5.69; Br, 32.47. Found: C, 44.23; H, 4.91; N, 5.78; Br, 32.16.

Registry No.—**2**, 14668-86-1; **3**, 14668-87-2; N-benzenesulfonyl-N-(5-methyl-2-furfuryl)aminoacetaldehyde diethyl acetal, 14668-88-3; **6b**, 14668-89-4; **7b**, 14668-90-7; **8**, 14668-91-8; **9**, 14668-92-9; methiodide of **11**, 14668-93-0; **12**, 14668-94-1; **15**, 14668-95-2; **16**, 14668-96-3; **17**, 14668-97-4; **19**, 14668-98-5; **20**, 14723-32-1; **21**, 14723-33-2; **22**, 14668-99-6; **23**, 14669-00-2.

Acknowledgment.—The authors wish to thank Mr. F. W. Kautz for the preparation of large amounts of certain of the intermediates.

Dimeric Dihydropyridines Derived from 3-Cyanopyridine

D. L. COFFEN

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received March 9, 1967

The enamine function of a 3-cyano-1,2-dihydropyridine derivative has been observed to undergo condensation reactions with the isomeric 1,6-dihydropyridine and corresponding pyridinium salt giving the dimeric 3,4′-dihydropyridine derivatives I and II.

Investigations directed toward elucidating the structures and mode of biological action of the coenzymes NAD and NADP have frequently engendered studies on the chemistry of dihydropyridines.[1] On several occasions the facile formation of dimeric reduced pyridines has been encountered in these studies. The various dimers described in the literature have been prepared by reductive dimerization of the corresponding pyridinium salts[2] and by acid-catalyzed dimerization of 1,4-dihydropyridines.[3,4] Sodium borohydride[5] and electrolytic[6] reductions of NAD yield products which are not enzymically reoxidized and it has been suggested

(1) See, for example, papers by (a) K. Wallenfels and coworkers, *Ann.*, **621**, 86, 106, 137, 149, 166, 178, 188, 198, 215 (1959); and (b) P. Karrer and coworkers, *Helv. Chim. Acta*, **19**, 811 (1936); **20**, 72, 418 (1937); **40**, 740, 751 (1957).

(2) (a) K. Wallenfels and M. Gellrich, *Chem. Ber.*, **92**, 1406 (1959); (b) J. N. Burnett and A. L. Underwood, *J. Org. Chem.*, **30**, 1154 (1965).

(3) R. E. Lyle and D. A. Nelson, *ibid.*, **28**, 169 (1963).

(4) H. L. Ammon and L. H. Jensen, *J. Am. Chem. Soc.*, **88**, 613 (1966).

(5) M. B. Mathews and E. E. Conn, *ibid.*, **75**, 5428 (1953).

(6) B. Ke, *ibid.*, **78**, 3649 (1956); *Arch. Biochem. Biophys.*, **60**, 505 (1956).