50% methanol–water–chloroform system. Paper chromatography of fraction I using the benzene–cyclohexane–formamide system indicated the presence of yohimbine (R_f 0.03), rauwolscine (R_f 0.08), reserpine (R_f 0.41), ajmalicine (R_f 0.67), heterophyllin (R_f 0.83) and an unidentified substance (R_f 0.52). Paper chromatography of fraction II using the water–acetic acid vapor system indicated the presence of serpentine (R_f 0.13), ajmaline (R_f 0.60) and four other materials (R_f 0.26, 0.40, 0.50, 0.78). Studies are in progress on these as yet uncharacterized substances.

Trial 15-plate Craig countercurrent distributions using the *n*-butyl alcohol–15% acetic acid system led to the separation of ajmaline from serpentine, and the group reserpine–ajmalicine–heterophyllin from the group yohimbine–rauwolscine (see system C, Table I). These groups could then be resolved conveniently into their components by the use of column chromatography, and subsequent crystallization of the alkaloids as the free bases or as salts.

Paper Chromatography.—Systems used for the paper chromatography of the alkaloids were: (1) water (developer) in water–acetic acid atmosphere, (2) benzene–cyclohexane (1:1) on formamide-impregnated paper,[14] (3) benzene–chloroform (1:1) on formamide-impregnated paper. Whatman #1 paper was used. The alkaloids were located on the oven-dried papers (90°, 1 hour) by their ultraviolet absorbance or fluorescence.

It was necessary to use known alkaloids as control references since R_f values varied with the amount of material applied and temperature. R_f values for the alkaloids cited in this paper are summarized in Table II.

Acknowledgments.—We should like to express our thanks to Dr. C. Djerassi for much helpful information and advice, and for the specimens of branches and leaves used in this investigation.

(14) A. Zaffaroni, *et al.*, *Science*, **111**, 6 (1950). Also O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **34**, 108 (1951).

TABLE II

R_f VALUES FOR ALKALOIDS

Alkaloids	Systems[a] 1	2	3
Yohimbine	0.45	0.03	0.40
Rauwolscine	.55	.08	.62
Reserpine	.20	.41	.9
Ajmalicine	.18	.67	.9
Heterophyllin	.27	.83	.9
Serpentine	.13	.0	.0
Ajmaline	.60	.0	.15
Sarpagine	.40	.0	.0
Rescinnamine	0.0–0.18	.38	.9
Papaverine	0.52	.70	.9
Narcotine	.56	.82	.9
Thebaine	.50	.22	.9

[a] The systems are those referred to in the Discussion.

We are grateful too to Drs. A. Chatterjee, C. Djerassi, M. Klohs and E. Schlittler for specimens of authentic alkaloids. Drs. S. Y. P'An and D. Hutcheon kindly provided the pharmacological information. Messrs. G. Hess and T. Toolan and staffs provided all analyses and physical measurements. Messrs. A. Timreck and P. Guercio graciously provided the crude extracts of plant material identified by Dr. L. Nickell. We are grateful to Dr. A. Bavley for his interest and suggestions. We thank Mrs. R. Paradies for her very capable technical assistance.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Furano(3,2-c)pyridines[1]

BY WERNER HERZ AND STANLEY TOCKER

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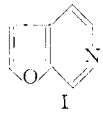
Isoquinoline ring syntheses were investigated in the furan series. A method for applying the Bischler–Napieralski reaction to derivatives of 2-(2-furyl)-ethylamine was devised and the reactions of the products studied. The Pomeranz–Fritsch, Pictet–Spengler and Pictet–Gams reaction could not be carried out successfully.

Replacement of the benzene moiety of isoquinoline by a furan nucleus gives rise to the isosteres shown below. It was of interest to develop syntheses of compounds of this type for the purpose of correlating their physiological properties with those of well-studied benzene analogs.



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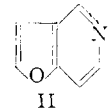


II

The synthesis of furan analogs of isoquinolines from furan derivatives seemed quite formidable in view of the high acid concentration required for the usual isoquinoline ring syntheses[2] which are based on imines, amides or iminoacetals. In fact furan compounds often resinify or undergo ring cleavage[3] under conditions far milder than those employed in cyclizations of this type.[2]

As expected, attempts at cyclization of amides prepared from 2-(2-furyl)-ethylamine by standard methods[2] gave only intractable resins resembling the tars obtained on treating furans with acid. Many experiments indicated that the concentration of acidic material at any given time was critical. A method of cyclization was therefore developed which takes advantage of the fact that the phosphate salt of the cyclized compound is insoluble in toluene and far more stable to carbon–oxygen cleavage than the uncyclized amide. A dilute toluene solution of phosphorus oxychloride was added slowly to a refluxing dilute solution of the amide in toluene. The desired salt was continually precipitated after a critical phosphorus oxychloride concentration (as low as 290 ml. of 0.012 *M* $POCl_3$ for 0.005 mole of amide) had been reached. This modification obviates many trial and error experiments

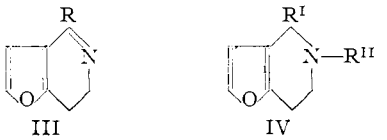
(1) Supported in part by grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare.

(2) Information on this and related subjects is reviewed by W. M. Whaley and T. R. Govindachari and by W. J. Gensler, in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 74–206.

(3) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publ. Corp., New York, N. Y., 1953, pp. 640–658.

to determine the best concentrations for cyclizing a specific amide and may be capable of extension to other sensitive compounds.

Cyclization of N-benzoyl-2-(2-furyl)-ethylamine gave a far greater yield (65%) of the corresponding dihydrofuranopyridine (III, R = phenyl) than experiments with the N-acetyl or N-homoveratroyl derivatives, a fact also observed in the cyclization of N-substituted phenylethylamines.[2] Apparently, resonance stabilization of the positive center of the carboxamide carbon by the adjacent phenyl group facilitates electrophilic attack.



The 3,4-dihydrofurano(3,2-c)pyridines (III = methyl or phenyl) were aromatized or reduced smoothly to the corresponding furanopyridines (II) or tetrahydrofuranopyridines (IV, R_I = methyl or phenyl, R^{II} = H). Use was also made of the recently reported procedure of Whaley and Robinson[4] to prepare N-methyltetrahydrofuranopyridines (R^I = methyl or phenyl, R^{II} = methyl). Due to the instability of 1-(3,4-dimethoxybenzyl)-3,4-dihydrofurano(3,2-c)pyridine, also noted in the isoquinoline series,[5] the substance was aromatized immediately upon formation. The low yields during the cyclization precluded further work with this potentially interesting analog of papaverine.

Attempts to cyclize appropriate furan derivatives in order to prepare the unsubstituted furanopyridines I and II were unsuccessful. Furfural aminoacetal, N-methylene-2-(2-furyl)-ethylamine and N-formyl-2-(2-furyl)-ethylamine failed to cyclize upon reaction with acidic reagents known to effect ring closure with benzene analogs.[2] In these instances, basic resins were formed indicating that the slow electrophilic attack on the furan ring could not compete with ring destruction. Likewise a Pictet–Gams[6] type reaction with N-benzoyl-1-furyl-2-aminoethanol failed to produce the expected 1-phenylfurano(3,2-c)pyridine.

Some of the compounds described in this report are being tested pharmacologically. We wish to thank the Monsanto Chemical Company for the gift of chemicals.

Experimental[7]

2-(2-Furyl)-ethylamine.—The following procedure was more convenient and gave better yields than the two-step method of Yabuta and Kambe.[8] A solution of 50 g. of β-2-nitrovinylfuran[9] in 500 ml. of ether was added dropwise with stirring to a clear solution prepared from 40 g. of lithium aluminum hydride (obtained from a freshly opened can) in 1.5 l. of ether. On working up in the usual way, there was obtained 25 g. (64%) of the amine, b.p. 155° (752 mm.).

N-Benzoyl-2-(2-furyl)-ethylamine.—A mixture of 10 g. of the amine, 100 ml. of water and 12.6 g. of benzoyl chloride was treated, under shaking, with 50 ml. of 20% sodium hydroxide solution in small portions. Recrystallization from anhydrous benzene–ligroin gave 16.1 g. (83%) of colorless product, m.p. 77°.

Anal. Calcd. for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.44.

N-Acetyl-2-(2-furyl)-ethylamine.—The oil which resulted on treating 10 g. of the amine in 150 ml. of 20% sodium hydroxide solution with 30 ml. of acetic anhydride was extracted with ether, washed, dried and distilled. The colorless oil, b.p. 136° (3 mm.), yield 11.5 g. (83%), solidified on cooling, m.p. 42°.

Anal. Calcd. for $C_8H_{11}NO_2$: N, 9.14. Found: N, 8.94.

N-Formyl-2-(2-furyl)-ethylamine.—Four grams of the amine and 30 g. of ethyl formate were refluxed on a steam-bath for one hour. Excess formate was removed and the residue fractionated at reduced pressure. The product, yield 2.8 g. (56%), boiled at 138–140° (4 mm.), $n^{20}D$ 1.3588.

Anal. Calcd. for $C_7H_9NO_2$: N, 10.07. Found: N, 10.50.

This substance gave no significant amount of basic material when treated by the general cyclization procedure described below, polyphosphoric acid or a mixture consisting of phosphorus oxychloride and phosphorus pentoxide in refluxing toluene or xylene. Allowing to stand at room temperature in a solution of phosphorus oxychloride in chloroform produced the hydrochloride of 2-(2-furyl)-ethylamine.

N-Methylene-2-(2-furyl)-ethylamine.—Ten milliliters of formalin was added dropwise to 5 g. of 2-(2-furyl)-ethylamine with stirring. The mixture was heated on the steam-bath for one hour, extracted with benzene and the extracts were washed with water, dried and fractionated. Due to the rapid decomposition of the product, wt. 2.0 g. (36%), b.p. 138° (4 mm.), $n^{20}D$ 1.3443, the analytical values were not quite satisfactory.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37. Found: C, 67.35; H, 6.83.

Treatment of this substance with various concentrations of hydrochloric acid at different temperatures, polyphosphoric acid or cyclization under "physiological" conditions[2] failed to give a basic fraction.

N-Homoveratroyl-2-(2-furyl)-ethylamine.—The solid obtained by treatment of a mixture of 2.5 g. of the amine, 100 ml. of water and homoveratroyl chloride (prepared from 4 g. of homoveratric acid) with 40 ml. of 20% sodium hydroxide solution was taken up in benzene. The benzene extracts were washed, dried, decolorized with charcoal, concentrated to 25 ml., diluted with ligroin to incipient turbidity at room temperature, scratched and allowed to stand in the refrigerator overnight. The crystals, wt. 3.4 g. (52%), were recrystallized twice from benzene and melted at 84°.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42: H, 6.62. Found: C, 66.66; H, 6.79.

General Cyclization Procedure.—A solution of the amide (0.005 mole) in 300 ml. of toluene was placed in a three-neck flask containing a Dean–Stark trap topped by a condenser protected from the atmosphere and a separatory funnel. After 25 ml. of toluene had been removed azeotropically, a solution containing 3 ml. of phosphorus oxychloride in 75 ml. of anhydrous toluene was added at the rate of about one drop per second. The solution was refluxed for an additional two or three hours and cooled. The toluene phase was decanted and the black solid mass adhering to the glass wall was thoroughly extracted with water. The aqueous extract was filtered, extracted with ether, made basic with sodium hydroxide solution and the furanopyridine isolated by extraction with ether, drying and distillation.

1-Phenyl-3,4-dihydrofurano(3,2-c)pyridine.—Two grams of N-benzoyl-2-(2-furyl)-ethylamine gave 1.2 g. (65.5%) of base, b.p. 119° (1.4 mm.), m.p. 61° upon recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.62; H, 5.43.

The picrate melted at 176–177°.

Anal. Calcd. for $C_{19}H_{14}N_4O_8$: N, 13.2. Found: N, 13.3.

(4) W. M. Whaley and G. N. Robinson, THIS JOURNAL, **75**, 2008 (1953).

(5) A. Lindenmann, *Helv. Chim. Acta*, **32**, 69 (1949).

(6) A. Pictet and A. Gams, *Compt. rend.*, **149**, 210 (1909).

(7) Melting points and boiling points are uncorrected. Analyses by Clark Microanalytical Laboratory, Urbana, Illinois, and Drs. Weiler and Strauss, Oxford.

(8) T. Yabuta and K. Kambe, *Proc. Imp. Acad. (Japan)*, **4**, 126 (1928); *C. A.*, **22**, 4503 (1928).

(9) V. O. Moldenhauer, W. Irion, D. Mastaglio, R. Pfluger and H. Doser, *Ann.*, **583**, 50 (1954).

The methiodide melted at 237°.

Anal. Calcd. for $C_{14}H_{14}NOI$: N, 4.15. Found: N, 4.28.

1-Phenyl-1,2,3,4-tetrahydrofurano(3,2-c)pyridine.—A solution of 1.2 g. of the previous substance in 25 ml. of anhydrous ether was reduced with 1 g. of lithium aluminum hydride. Evaporation of the ether extract yielded a white crystalline substance, wt. 1.2 g., m.p. 83°. The material was recrystallized from benzene–petroleum ether to a constant m.p. of 85–86°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.76; H, 6.00. Found: C, 78.42; H, 6.18.

1-Phenylfurano(3,2-c)pyridine.—A mixture consisting of 25 ml. of dry xylene, 0.5 g. of 5% palladium on charcoal and 1.1 g. of crude 1-phenyl-3,4-dihydro(3,2-c)pyridine was refluxed for four hours, filtered and concentrated to about 10 ml. Upon addition of ligroin to incipient turbidity, a brown tar and a white solid separated consecutively. Fractional precipitation yielded 0.7 g. of the white solid which was further purified by crystallization from acetonitrile to a constant m.p. of 91–92°.

Anal. Calcd. for $C_{13}H_9NO$: N, 7.18. Found: N, 7.16.

N-Methyl-1-phenyl-1,c,3,4-tetrahydrofurano(3,2-c)pyridine.—Six tenths of a gram of 1-phenyl-3,4-dihydrofurano-(3,2-c)pyridine methiodide was dissolved in 15 ml. of ethanol and reduced with 1.0 g. of sodium borohydride. On working up in the usual manner and evaporation of the ether extract there was obtained a basic solid which was sublimed at 90° (bath temperature, 0.5 mm.) and recrystallized from ligroin (b.p. 65–100°), m.p. 84–85°, yield 0.3 g. (79.5%).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.58; H, 6.63; N, 6.60.

1-Methyl-3,4-dihydrofurano(3,2-c)pyridine.—Cyclization of 1.0 g. of N-acetyl-2-(2-furyl)-amine gave an average yield of 0.22 g. (25%) of this substance, b.p. 92° (4 mm.), $n^{27}D$ 1.5412. Because of its instability, it was converted to the picrate, m.p. 173–173.5°, before analysis.

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: N, 15.47. Found: N, 15.3.

1-Methyl-1,2,3,4-tetrahydrofurano(3,2-c)pyridine.—Eight tenths of a gram of the previous compound, reduced in the same manner as the phenyl analog, gave 0.74 g. (91%) of the base, b.p. 107° (1 mm.), $n^{20}D$ 1.5058.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.03; H, 8.08; N, 10.01. Found: C, 69.55; H, 8.13; N, 10.40.

1-Methylfurano(3,2-c)pyridine.—A solution of 0.53 g. of the dihydro compound in 25 ml. of toluene was refluxed with 1 g. of 5% palladium on charcoal. The basic fraction was distilled at a bath temperature of 121° (2 mm.) and gave 0.23 g. of a colorless liquid which readily formed a picrate, m.p. 214–215°.

Anal. Calcd. for C_8H_7NO: C, 46.44; H, 2.78; N, 18.47. Found: C, 46.53; H, 2.75; N, 15.40.

N,1-Dimethyl-1,2,3,4-tetrahydrofurano(3,2-c)pyridine.—Crude 1-methyl-3,4-dihydrofurano(3,2-c)pyridine (1.1 g.) in 50 ml. of anhydrous benzene was treated with 1.0 g. of activated charcoal and allowed to stand overnight. It was filtered and the clear filtrate was added with stirring to 10 g. of methyl iodide. The combined crops of methiodide, wt. 1.4 g., were dissolved in 25 ml. of methanol and reduced with 2.0 g. of sodium borohydride with stirring. The yield of basic material was 0.4 g. (33%), b.p. 80° (32 mm.). The carbon content was somewhat low.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.48; H, 8.66; N, 9.26. Found: C, 70.16; H, 8.64; N, 9.00.

1-(3,4-Dimethoxybenzyl)-furano(3,2-c)pyridine.—Cyclization of 2.0 g. of N-homoveratroyl-2-(2-furyl)-ethylamine involved a reflux time of six hours. The basic component was distilled in a sublimator at a bath temperature of 155–160° (1 mm.) and gave an extremely viscous colorless mass on the cold finger. It was washed into 25 ml. of toluene and aromatized with 5% palladium–charcoal as described earlier. The base distilled at a bath temperature of 200° (0.5 mm.) and crystallized on scratching. Recrystallization from ethanol furnished 9 mg. of colorless material, m.p. 142°.

Anal. Calcd. for $C_{16}H_{17}NO_3$: N, 5.2. Found: N, 4.9.

The picrate melted at 138.5°.

Anal. Calcd. for $C_{22}H_{20}N_4O_{10}$: C, 52.80; H, 4.03; N, 11.2. Found: C, 52.83; H, 4.05; N, 11.4.

1-Furyl-2-aminoethanol.—The following procedure represents a considerable improvement over the method described by Kanao.[10] Condensation of furfural with nitromethane[9] gave a 62% yield of 1-furyl-2-nitroethanol. Since some decomposition to β-2-nitrovinylfuran took place on distillation, the substance was purified more conveniently for subsequent catalytic hydrogenation by dissolving 5.0 g. in 100 ml. of methanol and allowing to stand with 2.0 g. of activated charcoal overnight. After filtering, 0.3 g. of platinum oxide was added, the methanolic solution saturated with ammonia and then hydrogenated at 4 atmospheres pressure. When the theoretical amount of hydrogen had been absorbed, the solution was filtered. Removal of solvent yielded 3.4 g. (84%) of amine which could be purified by distillation at 108° (1 mm.) and recrystallization from acetonitrile, m.p. 87° (lit.[10] 89°). The amine was also prepared in poorer yield by lithium aluminum hydride reduction of the nitro compound.

Anal. Calcd. for $C_6H_9NO_2$: N, 11.0. Found: N, 11.0.

N-Benzoyl-1-furyl-2-aminoethanol.—Reaction of 5 g. of the aminoalcohol with 6 g. of benzoyl chloride by the Schotten–Baumann procedure gave 7.2 g. (90%) of amide. Recrystallization from acetonitrile furnished colorless crystals, m.p. 124–124.5°. They were insoluble in dilute acid and therefore represented the N-benzoyl derivative.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.68; N, 6.06. Found: C, 67.05; H, 5.63; N, 6.06.

This compound could not be cyclized by various modifications of the general cyclization procedure nor upon treatment with phosphorus pentoxide and polyphosphoric acid, which caused resinification. When a molar excess of benzoyl chloride was used, a white crystalline product of m.p. 148° was isolated which was probably the dibenzoyl derivative.

Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.64; H, 5.11; N, 4.17. Found: C, 71.22; H, 4.92; N, 3.62.

2-Furfurylidene Aminoacetal.—A mixture of 8 g. of furfural, 10 g. of aminoacetaldehyde diethylacetal and 25 ml. of benzene was refluxed in an apparatus fitted with a Dean–Stark trap until there was no further increase in the amount of water. Solvent was removed at reduced pressure and the residue was distilled at the lowest bath temperature possible, b.p. 114° (2 mm.), n^{20} 1.4890, yield 10.1 g. (92%).

Anal. Calcd. for $C_{11}H_{17}NO_3$: N, 6.63. Found: N, 6.76.

This compound could not be cyclized by the general method described above, nor was there any evidence of cyclization on treatment with polyphosphoric acid[11] or dilute sulfuric acid which caused considerable resinification.

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(11) W. Herz and L. Tsai, THIS JOURNAL, **75**, 5122 (1953).