Acknowledgment.—The authors wish to express their thanks to Mrs. Margaret Petroski for technical assistance.

Summary

2-Aminopyridine and 2-aminopyrimidine and several of their methyl derivatives were alkylated with alkyl halides using sodamide or lithium amide as the condensing agent. Further alkylation of the secondary amines with alkyl or aralkyl halides led to the corresponding tertiary amines, which could be obtained also by condensing halogenated heterocyclic compounds with the corresponding asymmetrically tri-substituted ethylenediamines. Several of these compounds possess strong antihistaminic activity.

SUMMIT, NEW JERSEY RECEIVED FEBRUARY 13, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Use of the Bromo- and Chloromethylation Reactions in the Synthesis of Some Dialkylaminomethyl-2,5-diphenylfurans[1]

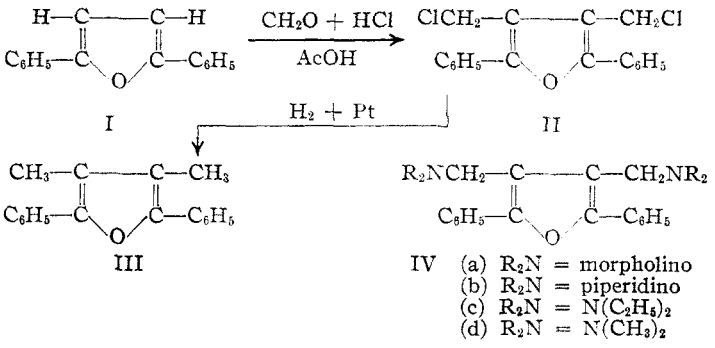
BY ROBERT E. LUTZ AND PHILIP S. BAILEY[2]

The bromomethylation and chloromethylation reactions[3] have been carried out successfully with 2,5-diphenylfuran (I), 2,5-diphenyl-3-(morpholinomethyl)-furan (VI) and 3-chloro-2,5-diphenylfuran (X), and the resulting halogenomethyl compounds have been condensed with a number of secondary amines to give 3-dialkylaminomethyl and 3,4-di-(dialkylaminomethyl)-2,5-diphenylfurans. Many of the products were made as a part of an exploratory program in the search for new types of antimalarial drugs. The work was carried to the extent herein reported because of indication of activity in some of the first members prepared.[4]

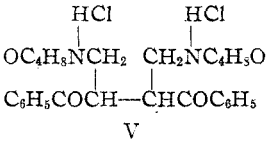
Chloromethylation of 2,5-diphenylfuran (I) yielded only the disubstitution product, 3,4-di-(chloromethyl)-2,5-diphenylfuran (II). Attempts to obtain the mono-(chloromethyl) product failed. The structure of the di-(chloromethyl) compound was proved by catalytic hydrogenolysis which yielded the known 3,4-dimethyl-2,5-diphenylfuran (III).[5]

The reactions between 3,4-di-(chloromethyl)-2,5-diphenylfuran (II) and secondary amines proceeded smoothly to yield the corresponding 3,4-di-(dialkylaminomethyl)-2,5-diphenylfurans (IV). The amines used were morpholine, piperidine, diethylamine, and dimethylamine.

It is interesting to note that analyses of the dihydrochloride of the di-(morpholinomethyl)-furan (IVa) indicated it to be either a monohydrate of extraordinary stability or the open chain saturated diketone (V), whereas the free base analyzed unmistakably for the furan. The molecule of water was not removed by heating at 140° under 1 mm. pressure. This compound is to be contrasted with the salts of the other three of the type, IVb-d,



which analyzed correctly for the furans. It is a possibility that hydrolysis of the one of these furans (IVa) to the saturated diketone (V) occurs during the formation of the salt under the conditions employed, namely, precipitation from acetone by means of ethereal hydrogen chloride, and



that spontaneous furanization occurs upon liberation of the free base by treatment with aqueous sodium carbonate; however, this would be surprising because the conditions involved would not be expected to bring about facile furan ring cleavage and closure and do not do so in the other analogous cases in hand.

The relationship between the previously prepared 2,5-diphenyl-3-(morpholinomethyl)-furan[4] (VI) and 3,4-di-(morpholinomethyl)-2,5-diphenylfuran (IVa) was established by conversion of the one into the other (VI to IVa) in two steps,

(1) The greater part of this work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(2) Present address: The University of Texas, Austin, Texas.

(3) Fuson and McKeever in Adams, "Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., Vol. I, 1942, p. 63.

(4) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).

(5) Lutz and Taylor, *ibid.*, **55**, 1593 (1933).

namely, bromomethylation to VII followed by condensation with morpholine.

4-(Bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan as the free base was not isolated in crystalline form. Attempts to isolate it led to hydrolysis to a compound corresponding to 2,5-diphenyl - 4 - (hydroxymethyl) - 3 - (morpholinomethyl)-furan (VIII). The high activity of the aliphatic bromine thus indicated was confirmed by the reaction with refluxing isopropanol to give the 4-isopropoxymethyl compound (IX).

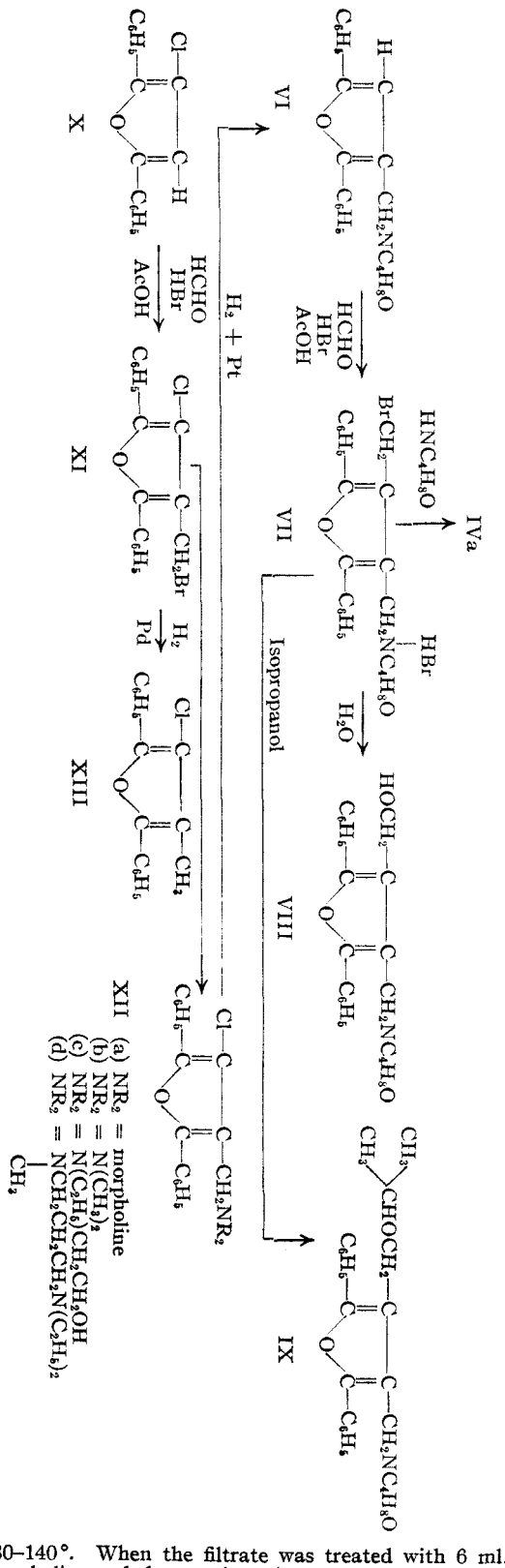
Since chlorine serves to a considerable degree as an activating group in many antimalarial series, the synthesis was undertaken of some analogous dialkylaminomethyl furans starting from 3-chloro - 2,5 - diphenylfuran (X). Bromomethylation gave in good yield 3-bromomethyl-4-chloro-2,5-diphenylfuran (XI) the structure of which was demonstrated by catalytic hydrogenolysis to the known 4-chloro-2,5-diphenyl-3-methylfuran (XIII).[6] The bromomethyl compound (XI) reacted readily with secondary amines to give the corresponding 3-(dialkylaminomethyl)-4-chloro-2,5-diphenylfurans (XII); the amines used were morpholine, dimethylamine, ethanolethylamine and N-(3-diethylaminopropyl)-methylamine.

The relationship between the new tertiary amines (XII) and the known 3-dialkyl-aminomethyl-2,5-diphenylfurans[4] of the type VI was established by catalytic hydrogenolysis of two of them, namely, the morpholino and dimethylamino compounds (XIIa and b) to the corresponding dehalogenated compounds (type VI), thus showing conclusively the position of the dialkylaminomethyl group. It is noteworthy that the furylmethylamine linkage did not undergo the reductive fission of the debenzylation type.

The bromomethylation reaction was found to be much more convenient and was preferred over the chloromethylation reaction; it was carried out in a very simple manner and with good yields by treating the desired furan with a solution of paraformaldehyde in 30% hydrobromic–acetic acid. It is of interest that the halogenomethylation when followed by catalytic hydrogenolysis, serves as a convenient method of making mono and, especially, dimethyl derivatives of furans of the type dealt with here.

Experimental[7]

3,4-Di-(chloromethyl)-2,5-diphenylfuran (II).—Anhydrous hydrogen chloride was passed into a mixture of 1.2 g. of paraformaldehyde and 16 ml. of glacial acetic acid until the paraformaldehyde dissolved. Next was added 2.5 ml. of sirupy phosphoric acid, 6.6 g. of diphenylfuran (I) and 11 ml. of glacial acetic acid. The mixture was stirred at 40–50° for twenty hours, poured into 200 ml. of water, neutralized with sodium carbonate and extracted with ether. The ether extract was washed, dried and evaporated. Crystallization of the residue from diisopropyl ether yielded 1.8 g. of material which melted at 130–140°. When the filtrate was treated with 6 ml. of morpholine and the reaction mixture was worked up, 3.4 g. of 2,5-diphenyl-3,4-di-(morpholinomethyl)-furan (IVa) hydrochloride (see preparation of this compound) was ob-



(6) Lutz and Stuart, THIS JOURNAL, **59**, 2316 (1937).

(7) All melting points reported are corrected. Many of the microanalyses were performed by Clara H. Vondra, Joyce Blume and R. H. Hite.

tained, showing that considerable of the di-(chloromethyl)-furan (II) had not crystallized. Several recrystallizations of the di-(chloromethyl)-furan (II) from acetone raised the melting point to 145–147°.

Anal. Calcd. for $C_{18}H_{14}Cl_2O$: C, 68.15; H, 4.45. Found: C, 68.06; H, 4.82.

Variations of the above procedure which are described in Organic Reactions[8] were tried. In these cases, however, mixtures were obtained which were thought to consist of the mono- and di-chloromethyl compounds. The several attempts to isolate the mono-chloromethyl product were not successful.

Catalytic hydrogenolysis of 1 g. of II in 50 ml. of ethanol with 0.02 g. of platinum oxide catalyst was carried out until the rate appreciably decreased at which point 3.5 moles of hydrogen had been absorbed. The reaction mixture was warmed, filtered and cooled. Crystallization occurred; yield 0.3 g. (40%); m. p. 114–117° (identified as 3,4-dimethyl-2,5-diphenylfuran (III) by a mixture melting point with an authentic sample).[4]

Attempted nitric acid oxidation of II in the usual way[8] or in propionic acid at 0°, gave only intractable products.

3,4-Di-(N-morpholinomethyl)-2,5-diphenylfuran (IVa) (SN 6414).[1]—The following procedure is typical for the various condensations with secondary amines. A suspension of 3.2 g. of the di-chloromethyl compound (II) in 64 ml. of dry ether was treated with 3.6 g. of morpholine. After twenty-four hours, the reaction mixture was filtered and the filtrate was washed and evaporated. Crystallization of the residue gave 3.8 g. (90%); m. p. 139–144°. Several recrystallizations from ethanol raised the melting point to 143–145°.

Anal. Calcd. for $C_{26}H_{30}N_2O_2$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.65; H, 7.00; N, 6.82.

The dihydrochloride was usually made directly from diphenylfuran (I) without isolating any of the intermediates. It was also prepared by acidifying an acetone solution of the pure base with ethereal hydrogen chloride. The melting point after recrystallization from methanol was 241–245°.

Anal. Calcd. for $C_{26}H_{30}N_2O_2.2HCl.H_2O$: C, 61.29; H, 6.73. Found: C, 61.50; H, 6.50. Found, after heating for twenty-four hours at 100° and 1 mm. pressure, C, 61.24; H, 6.44; after heating for five hours at 140° under 1 mm. pressure; C, 61.80; H, 6.58.

The dihydrochloride was converted back into 3,4-di-(morpholinomethyl)-2,5-diphenylfuran (IVa) by treating an aqueous suspension with sodium carbonate, extracting with ether, evaporating the ether extract, and crystallizing the residue. Identification was by a mixture melting point with an authentic sample.

Attempted oxidation of the dihydrochloride with nitric acid in acetic acid solution at room temperature yielded only starting material. When the reaction was tried at 60° for forty-five minutes, only non-crystalline material was obtained.

2,5-Diphenyl-3,4-di-(N-piperidinomethyl)-furan (IVb) Dihydrochloride (SN 5049).—This compound was prepared in 61% yield from 2,5-diphenylfuran (I) through the di-(chloromethyl) compound (II) without actually isolating the latter compound; crystallized from isopropanol, m. p. 246–247°.

Anal. Calcd. for $C_{28}H_{34}N_2O.2HCl$: C, 68.98; H, 7.44. Found: C, 68.79; H, 7.74.

3,4-Di-(diethylaminomethyl)-2,5-diphenylfuran (IVc) dihydrochloride (SN 6417).—Crystallized from absolute ethanol by the addition of dry ether gave m. p. 239–240°.

Anal. Calcd. for $C_{26}H_{34}N_2O.2HCl$: C, 67.37; H, 7.83. Found: C, 67.11; H, 7.69.

3,4-Di-(dimethylaminomethyl)-2,5-diphenylfuran (IVd) dihydrochloride (SN 6419) was prepared by saturating a cold (0°) ether solution of crude 3,4-di-(chloromethyl)-2,5-diphenylfuran (II) [made from 9.2 g. of diphenylfuran(I)] with dry dimethylamine gas and allowing the mixture to stand for twenty-four hours; yield of the dihydrochloride was 8.5 g. (50%); crystallized from aqueous ethanol, m. p. 297–298°.

Anal. Calcd. for $C_{22}H_{26}N_2O.2HCl$: C, 64.86; H, 6.93. Found: C, 64.85; H, 6.64.

4-(Bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan Hydrobromide (VII). The Bromomethylation of 2,5-Diphenyl-3-(morpholinomethyl)-furan (VI).—An aqueous solution of 2.5 g. of the hydrochloride of VI was neutralized with sodium carbonate and extracted with ether. The ether extract was washed, dried and evaporated under reduced pressure. The oily amine was dissolved in 10 ml. of glacial acetic acid and treated with a solution of 0.3 g. of paraformaldehyde in 10 g. of 30% hydrobromic acid. Solution occurred and soon a precipitate began to form; after twenty-four hours, 2.5 g. was isolated, m. p. 215–217°. Dilution of the filtrate with water gave an additional 0.3 g. Neutralization of the filtrate with sodium carbonate and extraction with ether gave 0.2 g. of material melting at 171–175° (identified as 2,5-diphenyl-4-(hydroxymethyl)-3-(morpholinomethyl)-furan (VIII) by a mixture melting point). The higher melting compound after several recrystallizations from dioxane melted with decomposition at 210–214°.

Anal. Calcd. for $C_{22}H_{22}NO_2.HBr$: C, 53.57; H, 4.70; N, 2.84. Found: C, 53.74; H, 5.31[9]; N, 2.88.

Attempts to isolate the free base by neutralizing the hydrobromide in the cold yielded only the hydroxymethyl compound (VIII) (see below) and an oil. Attempts to crystallize the oil merely caused more of the hydroxymethyl compound to be formed. Treatment of the oil with morpholine yielded the di-(morpholinomethyl)-furan (IVa).

2,5-Diphenyl-4-(hydroxymethyl)-3-(morpholinomethyl)-furan (VIII).—To a suspension of a small amount of 4-(bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan hydrobromide (VII) in boiling water was added enough sodium carbonate to make the mixture alkaline. The mixture was extracted with ether and the ether extract was evaporated. Crystallization of the residue from isopropanol gave a white crystalline compound which melted at 175–176°. Two recrystallizations from isopropanol did not change the melting point. The compound gave a negative Beilstein test for halogen.

Anal. Calcd. for $C_{22}H_{22}NO_3$: C, 75.62; H, 6.64. Found: C, 75.67; H, 6.86.

This compound was recovered unchanged after it was dissolved in refluxing morpholine and allowed to remain in solution overnight at room temperature.

2,5-Diphenyl-4-(isopropoxymethyl)-3-(morpholinomethyl)-furan hydrobromide (IX) was obtained by recrystallization of 4-(bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan hydrobromide (VII) from isopropanol; the melting point after several recrystallizations from isopropanol was 146–148°.

Anal. Calcd. for $C_{25}H_{29}NO_3.HBr$: C, 63.56; H, 6.40. Found: C, 63.60; H, 6.42.

Conversion of 4-(Bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan Hydrobromide (VIII) to 3,4-Di-(morpholinomethyl)-2,5-diphenylfuran (IVa).—Two grams of VII was treated with an aqueous solution of sodium carbonate at room temperature and the free base was extracted with ether; the ether extract was washed, dried and treated with 5 g. of morpholine. After twenty-four hours, the ether was filtered to remove the morpholine hydrobromide, washed and evaporated. Crystallization of the residue gave 1.5 g. (88%), m. p. 140–142° (identified by mixture melting point).

3-(Bromomethyl)-4-chloro-2,5-diphenylfuran (XI).—To a solution of 14 g. of paraformaldehyde in 150 g. of 30% hydrobromic–acetic acid was added 250 ml. of glacial acetic acid and 89 g. of 3-chloro-2,5-diphenylfuran (X). The resulting mixture was shaken mechanically for twenty-

(8) Lutz and Wilder, THIS JOURNAL, 56, 978 (1934).

(9) Microanalyses for hydrogen were running consistently high at this time.

five hours during which time a heavy white precipitate formed. The solid was filtered and washed thoroughly with water; yield 96 g. (79%), m. p. 79–86°.

Anal. Calcd. for $C_{17}H_{12}BrClO$: C, 58.73; H, 3.48. Found: C, 58.57; H, 3.62.

Catalytic hydrogenolysis of 1 g., suspended in 50 ml. of ethanol with 0.5 g. of palladium–barium sulfate catalyst, was interrupted after the rate of reduction sharply decreased and after one equivalent of hydrogen had been absorbed. The solution was filtered and evaporated. Crystallization of the residue from ethanol yielded 0.5 g. which was identified as 4-chloro-3-methyl-2,5-diphenylfuran (XIII)[6] upon recrystallization from ethanol (m. p. 79–81°) by a mixture melting point with an authentic sample. Neither this compound nor 3-chloro-2,5-diphenylfuran (X) reacted with morpholine at room temperature.

When a mixture identical to the one above was allowed to absorb two equivalents of hydrogen and was worked up the same way, there was obtained 0.2 g. of 4-chloro-2,5-diphenyl-3-methylfuran (XIII) and 0.2 g. of a compound melting at 173–193°. The latter compound will be studied at a later date.

4-Chloro-3-(morpholinomethyl)-2,5-diphenylfuran (XIIa).—Crystallized from isopropanol; m. p. 117–118°.

Anal. Calcd. for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70. Found: C, 71.23; H, 5.92.

The **hydrochloride** was obtained by acidifying an acetone solution with ethereal hydrogen chloride and was crystallized from isopropanol; m. p. 187–190°.

Anal. Calcd. for $C_{21}H_{20}ClNO_2.HCl$: N, 3.59. Found: N, 3.81.

Catalytic hydrogenolysis of 1 g. of XIIa in 50 ml. of ethanol with 0.5 g. of palladium–barium sulfate catalyst, after absorption of 0.9 equivalent of hydrogen, gave 0.4 g. of 2,5-diphenyl-3-(morpholinomethyl)-furan hydrochloride (VI) which was crystallized from methanol (m. p. 216–218°) and identified by mixture melting point with an authentic sample.

4-Chloro-3-(dimethylaminomethyl)-2,5-diphenylfuran (XIIb) (SN 8614).—To a solution of approximately 20 g. of dimethylamine in 80 ml. of di-isopropyl ether at 0° was added 24 g. of 3-(bromomethyl)-4-chloro-2,5-diphenylfuran (XI). The reaction mixture, after standing two days, was filtered from 8.5 g. of dimethylamine hydrobromide. Evaporation of the filtrate and crystallization of the residue from isopropanol yielded 18.7 g.; m. p. 87–91°. Several recrystallizations from isopropanol raised the melting point to 89–90°. The compound was soluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{19}H_{18}ClNO$: N, 4.49. Found: N, 4.41.

Catalytic hydrogenolysis of 1 g. of XIIb in 50 ml. of ethanol (palladium–barium sulfate) gave an oil which was dissolved in acetone and acidified with ethereal hydrogen chloride. Filtration yielded 0.4 g. of 2,5-diphenyl-3-(dimethylaminomethyl)-furan hydrochloride of m. p. 201–211° (identified by a mixture melting point with an authentic sample).[4]

4-Chloro-2,5-diphenyl-3-[N-ethyl-N-(2-hydroxyethyl)-aminomethyl]-furan (XIIc) (SN 8784).—A mixture of 52 g. of 3-bromomethyl-4-chloro-2,5-diphenylfuran (XI) and 27 g. of ethyl-(2-hydroxyethyl)-amine[10] in 300 ml. of ether was allowed to react for eleven days. Filtration yielded 25 g. (99%) of the water soluble secondary amine hydrobromide. The filtrate was washed thoroughly with water to remove the excess ethylethanolamine, dried over anhydrous sodium sulfate and evaporated. Conversion of the residue into a hydrochloride by acidifying an acetone solution with ethereal hydrogen chloride yielded 54 g. (92%); white crystals; m. p. 161–166°. After several recrystallizations from isopropanol, m. p. 165–166°.

Anal. Calcd. for $C_{21}H_{22}ClNO_2 \cdot HCl$: N, 3.57. Found: N, 3.81.

4-Chloro-3-[N-(3-diethylaminopropyl)-N-methylaminomethyl]-2,5-diphenylfuran Dihydrochloride (XIId) (SN 8783).—Condensation of XI with (3-diethylaminopropyl)-methylamine[11] was carried out in di-isopropyl ether (six days). Crystallization was from isopropanol; m. p. 146–149°.

Anal. Calcd. for $C_{25}H_{31}ClN_2O.2HCl$: N, 5.79. Found: N, 5.66.

Summary

The bromomethylation and chloromethylation reactions have been successfully carried out with 2,5-diphenylfuran, 2,5-diphenyl-3-(morpholinomethyl)-furan and 3-chloro-2,5-diphenylfuran. The structures of the resulting halogenomethyl compounds have been demonstrated by reactions leading to known compounds. The halogenomethyl compounds have been condensed with secondary amines, and the structures of the resulting aminomethyl compounds have been proven.

The aliphatic bromine of 4-(bromomethyl)-2,5-diphenyl-3-(morpholinomethyl)-furan has been found to be exceedingly easily displaced in the reactions with water and with isopropanol.

CHARLOTTESVILLE, VIRGINIA RECEIVED MAY 25, 1946

(10) Courtesy of Sharples Chemical Company.

(11) Supplied by Dr. D. W. Cottle of Rutgers University.