yield was first recrystallized from acetic acid (charcoal) and then extracted from a thimble with alcohol, in which it is moderately soluble; bright yellow rectangular prisms, m. p. 315–320°[14] (dark melt).

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.97; H, 5.37 Found: C, 79.98; H, 5.37.

Dehydroketoyobyrine.—A mixture of 100 mg. of ketoyobyrine and 200 mg. of palladium black was heated to 280° (metal-bath). After about fifteen minutes exactly the equivalent of one mole of hydrogen had been liberated; prolonged heating or higher temperature did not increase the amount of hydrogen (8.5 cc.). From the reaction mixture the dehydroproduct was obtained either by sublimation (280°, 0.001 mm.), or by recrystallization from a thimble with ethyl alcohol (twenty-four hours). The compound is very sparingly soluble in ethanol and forms fans of short needles of a yellowish-green color. The yield is almost quantitative. The crystals when powdered or sublimed have the same yellow color as ketoyobyrine and in solution they exhibit a similar powerful fluorescence; melting point 345–350° (transformation into prisms at 310°, mixed melting point with ketoyobyrine, 305–310°).

Anal. Calcd. for $C_{20}H_{14}ON_2$: C, 80.53; H, 4.69. Found: C, 80.32; H, 4.92.

Carboxyyobyrine.—Dehydroketoyobyrine (0.2 g.) was heated under reflux in 4 cc. of amyl alcohol containing 2 g. of caustic potash. A clear yellow solution was obtained after fifteen minutes, whereas ketoyobyrine requires many hours to go into solution under the same conditions. After ten hours water was added and the mixture was extracted with ether. The ethereal layer contained traces of ketoyobyrine, if that was a contaminant of the starting material, and traces of a fluorescent base yielding a picrate (4 mg.), m. p. 255°, showing no depression on admixture with norharmane picrate. The aqueous alkaline layer contained an acid which on acidification with glacial acetic acid separated as a colorless flocculent precipitate. When the alkaline cleavage was carried out in a glass vessel, silicic acid was precipitated first by adding mineral acid to the alkaline solution to *p*H 8.5. The flocculent amino acid (180 mg.) was obtained crystalline when its solution in dilute ammonia was allowed to stand overnight in a slightly evacuated desiccator. In another run, carboxyyobyrine was obtained in beautiful fine needles when it was reprecipitated from dilute alkaline solution with just the necessary amount of acetic acid and was allowed to stand for two days. The colorless aqueous acidic solution of the acid shows the characteristic pure blue harmane fluorescence. On heating the compound becomes yellow at about 100° and shows then the same melting point as dehydroketoyobyrine. For the analysis the substance has to be dried at room temperature.

Anal. Calcd. for $C_{20}H_{16}O_2N_2 \cdot H_2O$: C, 71.85; H, 5.40. Found: C, 71.46; H, 5.49.

Reconversion to Dehydroketoyobyrine.—When recrystallization of carboxyyobyrine was attempted by extracting it from a thimble with methanol in which the amino acid is sparingly soluble, all the yellow material which had crystallized overnight from the alcoholic solution consisted of dehydroketoyobyrine, m. p. 345°. When 20 mg. of carboxyyobyrine mixed with 40 mg. of soda lime was heated *in vacuo* to 350°, no yobyrine could be isolated from the negligible sublimate. The residue gave some dehydroketoyobyrine.

Acknowledgment.—We are indebted to Miss Adelaide Sutton who, through the courtesy of Dr. Elkan R. Blout (Polaroid Corporation, Cambridge), measured the ultraviolet spectra.

Summary

The structure of ketoyobyrine has been shown to be that of a lactam derived from carboxyyobyrine.

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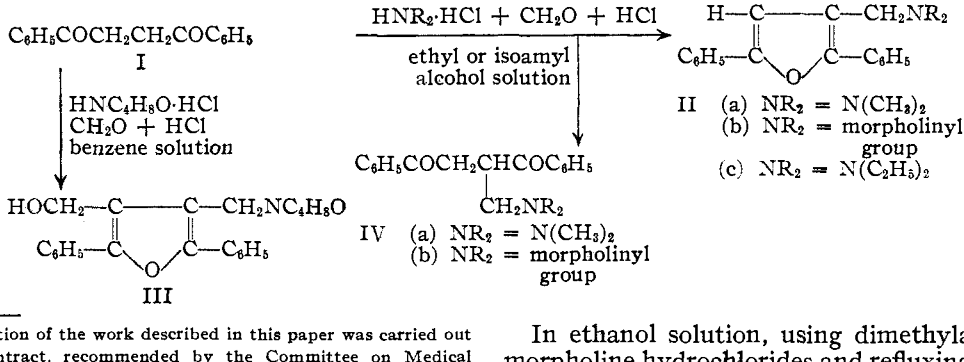
[14] All melting points are corrected.

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

The Mannich Reaction with 1,2-Dibenzoylethane[1,2]

BY PHILIP S. BAILEY[3] AND ROBERT E. LUTZ

The Mannich reaction has been carried out with 1,2-dibenzoylethane, using secondary amine hydrochlorides and paraformaldehyde in ethyl or isoamyl alcohol solution and in benzene solution.[4]



II (a) $NR_2 = N(CH_3)_2$
(b) NR_2 = morpholinyl group
(c) $NR_2 = N(C_2H_5)_2$

IV (a) $NR_2 = N(CH_3)_2$
(b) NR_2 = morpholinyl group

In ethanol solution, using dimethylamine and morpholine hydrochlorides and refluxing for forty-eight hours, the products were the respective substituted furans (IIa and IIb), both of which have previously been made by other methods.[5] When

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[1] A portion of the work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

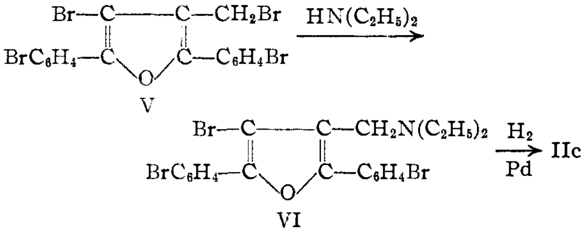
[2] Presented in combination with a paper from The University of Texas at the Chicago meeting of the American Chemical Society, April, 1948.

[3] Holder of Philip Francis du Pont Fellowships, 1942–1944. Present location, The University of Texas, Austin, Texas.

[4] For a discussion of the use of benzene as a solvent in the Mannich reaction see Fry, *J. Org. Chem.*, **10**, 259 (1945).

[5] Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).

the reaction was carried out under less acidic conditions, low yields of the respective mono-(aminomethyl)-dibenzoylethanes (IV) were obtained. Never were any di-(aminomethyl)-dibenzoylethanes isolated. When diethylamine hydrochloride was used in ethanol solution, very little reaction occurred. When isoamyl alcohol was used as the solvent, however, a 32% yield of IIc was obtained. The structure of this compound was proved by the same method used in the proof of structure of the other (aminomethyl)-furans,[5] namely, conversions V to IIc.



When the reaction was carried out in benzene solution,[4] using morpholine hydrochloride, the product was a mixture from which was isolated some of the (morpholinylmethyl)-furan (IIb) and the known 3-(hydroxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran (III).[6,7] The respective yields of these products seem to vary with the acidity of the reaction medium. When 1% by volume of concentrated hydrochloric acid was used in the reaction mixture, compound III was the principal product, but when the amount of hydrochloric acid was cut in half, compound IIb was the principal product.

The basis for the structure assigned to compound III was its synthesis from compound IIb by a bromomethylation reaction followed by a hydrolysis of the resulting bromomethyl compound.[6] Further substantiating this structure was the reaction of the hydroxymethyl compound (III) with acetic anhydride and sulfuric acid or benzoic anhydride and sulfuric acid to yield the acetate or the benzoate, respectively.

Experimental[8]

Preparation of 1,2-Dibenzoylethane (I).—The 1,2-dibenzoylethane used in these reactions was prepared by the reduction of 1,2-dibenzoylethylene by means of stannous chloride and hydrochloric acid. Into a hot suspension of 200 g. of stannous chloride in a solution of 300 ml. of 8 *N* hydrochloric acid and 100 ml. of 95% ethanol, was poured with stirring a hot solution of 200 g. of *trans*-1,2-dibenzoylethylene in 1 liter of 95% ethanol. The mixture was then diluted with 100 ml. of water, cooled and filtered. Recrystallization of the crude dibenzoylethane (190 g., m. p. 125–133°) yielded 156 g. (76% yield) of material which melted at 145–147°.

3-(N-Diethylaminomethyl)-2,5-diphenylfuran Hydrochloride (IIc) (SN-3545)[9] from the Mannich Reaction in Isoamyl Alcohol Solution.—A mixture of 12 g. of 1,2-dibenzoylethane (I), 12 g. of diethylamine hydrochloride, 5 g. of paraformaldehyde, 1 ml. of concentrated hydrochloric acid and 50 ml. of isoamyl alcohol was refluxed for thirty hours, after which the solvent was evaporated under vacuum. An ether suspension of the residue was shaken with dilute hydrochloric acid until everything dissolved in one or the other of the layers, after which the ether layer was evaporated. From the residue was isolated 1.3 g. of 2,5-diphenylfuran which was identified by a mixture melting point with an authentic sample. The hydrochloric acid extract was neutralized with sodium carbonate and extracted with ether. The ether extract was washed with salt solution several times, dried over sodium sulfate and evaporated. An acetone solution of the residual oil was acidified with ethereal hydrogen chloride solution and diluted with dry ether. White crystals were obtained, which weighed 5.4 g. (32% yield) and melted at 168–175°. Several recrystallizations from acetone solution, by the addition of dry ether, raised the melting point to 177–179°.

Anal. Calcd. for $C_{21}H_{23}NO \cdot HCl$: C, 73.77; H, 7.08. Found: C, 73.74; H, 7.16.

The preparation also was attempted using other solvents. In the case of ethanol, reaction was obtained only when excess paraformaldehyde was added daily over a period of fifteen days; yield of IIc, 18%. When the reaction was carried out in benzene solution a mixture of basic products was obtained which was not studied further, due to difficulty in effecting a separation.

4-Bromo-2,5-di-(*p*-bromophenyl)-3-(N-diethylaminomethyl)-furan (VI).—A mixture of 2.8 g. of V[10] and 10 ml. of diethylamine in 25 ml. of isopropyl ether was allowed to react without attention for two days. The diethylamine hydrochloride which precipitated was filtered off and the filtrate was washed several times with salt water and dried over sodium sulfate. Evaporation of the ether solution and crystallization of the residue from 2-propanol gave 2.5 g. (91% yield) of white crystals, m. p. 95–98°; recrystallized from 2-propanol, m. p. 97–98°.

Anal. Calcd. for $C_{21}H_{20}Br_3NO$: C, 46.52; H, 3.72. Found: C, 46.34; H, 3.65.

In a separate experiment it was shown that 4-bromo-3-methyl-2,5-diphenylfuran will not react with amines under the above conditions.

3-(N-Diethylaminomethyl)-2,5-diphenylfuran (IIc) from 4-Bromo-2,5-di-(*p*-bromophenyl)-3-(N-diethylaminomethyl)-furan (VI).—Catalytic hydrogenolysis of 1 g. of VI in 50 ml. of ethanol with 1 g. of palladium-barium sulfate catalyst was carried out until the rate appreciably decreased, at which point 3.5 mole-equivalents of hydrogen had reacted. The reaction mixture was filtered and the filtrate evaporated; the residue was suspended in sodium carbonate solution and the mixture was extracted with ether. The ether extract was washed, dried over sodium sulfate and evaporated. An acetone solution of the residue, acidified with ethereal hydrogen chloride solution and diluted with absolute ether, yielded 0.6 g. of a white crystalline material (m. p. 177–178°), which was shown by a mixture melting point to be the same compound obtained from the Mannich reaction described above.

Oxidation of the furan with nitric acid in acetic acid solution gave an oil which resisted crystallization either as a free amine or as a hydrochloride.

3-(N-Morpholinylmethyl)-2,5-diphenylfuran Hydrochloride (IIb) from the Mannich Reaction in Ethanol Solution.—A mixture of 48 g. of dibenzoylethane (I), 25 g. of paraformaldehyde, 51 g. of morpholine hydrochloride, 200

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(6) Lutz and Bailey, THIS JOURNAL, **68**, 2002 (1946).

(7) Due to an erroneous analysis, the fact was not at first apparent that this compound was identical with that reported in ref. 6. Thanks are due to Mr. Gene Nowlin, graduate student of The University of Texas, for subsequent work which led to the identification of III, and which will be reported soon in a paper from The University of Texas.

(8) All melting points reported here are corrected.

(9) 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 are tabulated in the monograph, F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1947.

(10) Lutz and McGinn, THIS JOURNAL, **64**, 2583 (1942).

ml. of absolute ethanol and enough ethanolic hydrogen chloride to make the reaction mixture slightly acidic, was refluxed for one hundred and thirty-five hours. During this time an additional 2 g. of paraformaldehyde was added every twelve hours. The reaction mixture was worked up in a manner similar to that of the Mannich reaction using diethylamine hydrochloride. Thus was obtained 21 g. of 2,5-diphenylfuran and 30 g. of 3-(N-morpholinylmethyl)-2,5-diphenylfuran hydrochloride (IIb), both of which were identified by mixture melting points with known samples. The use of isoamyl alcohol as a solvent did not improve the yield.

1,2-Dibenzoyl-1-(N-morpholinylmethyl)-ethane (IVb) from the Mannich Reaction.—When a mixture of 4.7 g. of dibenzoylethane (I), 4.2 g. of morpholine hydrochloride, 1.8 g. of paraformaldehyde and 20 ml. of ethanol (no excess hydrogen chloride present) was refluxed for forty hours (1 g. of excess paraformaldehyde was added every twelve hours) and the reaction mixture was worked up as described above, 0.6 g. of dibenzoylethane was recovered in the non-basic extract and 1.6 g. (24% yield) of IVb (m. p. 80–82°) was found in the basic extract. It was isolated as the free amine and was identified by a mixture melting point with an authentic sample.[5]

3-(N-Dimethylaminomethyl)-2,5-diphenylfuran Hydrochloride (IIa) from the Mannich Reaction in Ethanol Solution.—A mixture of 12 g. of dibenzoylethane (I), 8 g. of dimethylamine hydrochloride, 5 g. of paraformaldehyde, 16 drops of concentrated hydrochloric acid and 50 ml. of absolute ethanol was refluxed for forty-three hours. On cooling, a precipitate formed and was filtered; 2.5 g., m. p. 75–135°; identified as dibenzoylethane after recrystallization. When the filtrate was worked up in the same manner as the Mannich reactions described above, 4.5 g. (31% yield) of white crystals (m. p. 217–220°) was obtained and identified as 3-(N-dimethylaminomethyl)-2,5-diphenylfuran hydrochloride (IIa) by a mixture melting point with an authentic sample.[5]

In another run in which one-half the amount of hydrochloric acid was used, 50% of the product was 1,2-dibenzoyl-1-(N-dimethylaminomethyl)-ethane hydrochloride (IVa); separated from the furan by fractional crystallization and identified by a mixture melting point with an authentic sample.[5]

The Mannich Reaction between 1,2-Dibenzoylethane (I), Paraformaldehyde and Morpholine Hydrochloride in Benzene Solution.—A mixture of 48 g. of dibenzoylethane (I), 51 g. of morpholine hydrochloride, 28 g. of paraformaldehyde, 200 ml. of benzene and 2 ml. of concentrated hydrochloric acid was refluxed for forty-eight hours. Two layers were present during the entire time. The solvent was then evaporated under reduced pressure and the residue was suspended in ether. When the resulting mixture was shaken with approximately 6 *N* hydrochloric acid, some material crystallized (15.3 g., m. p. 145–148°) and was identified as dibenzoylethane by a mixture melting point. The acid layer was separated and was neutralized with sodium carbonate. When this mixture was shaken with ether, some material crystallized and was filtered; 18 g., m. p. 152–165°. The filtrate was thoroughly extracted with ether and the ether extract, upon being washed, dried and evaporated, yielded an oil which was converted to a crystalline hydrochloride and identified as IIb by a mixture melting point; yield 1 g. The 18-g. batch of crystals melted at 176–177° after several recrystallizations from ethanol and was shown to be 3-(hydroxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran (III) by a mixture melting point with a known sample.[6] A small amount of the compound (III) was converted into a crystalline hydrochloride by acidifying an acetone solution of the material with ethereal hydrogen chloride solution; recrystallized from methyl ethyl ketone, m. p. 178–180° (it gave a large depression in a mixture melting point with the free amine).

Anal. Calcd. for $C_{22}H_{23}NO_3 \cdot HCl$: C, 68.47; H, 6.27. Found: C, 68.32, 68.29; H, 6.26, 6.11.

In another reaction in which only one-half the quantity of hydrochloric acid was used, the yield of III was one-third less, while the yield of IIb was 37%. In yet another experiment where the amount of paraformaldehyde was cut to one-half, the hydrochloric acid to one-fourth and the reaction mixture was refluxed for only one hour, IVb was the product in 8% yield. The recovery of dibenzoylethane was 91%.

3-(Acetoxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran.—To a suspension of 2 g. of III in 9 ml. of acetic anhydride was added 7 drops of concentrated sulfuric acid. The mixture was allowed to stand for five minutes, after which time it was poured into water. The resulting mixture was neutralized with sodium carbonate and extracted with ether. After the ether extract was washed, dried and evaporated, the residue was converted into a hydrochloride by acidifying an acetone solution of it with ethereal hydrogen chloride solution. Upon cooling and filtering, 1.5 g. of material was obtained (m. p. 183–185°); recrystallized from 2-propanol, m. p. 187–188°.

Anal. Calcd. for $C_{24}H_{25}NO_4 \cdot HCl$: C, 67.36; H, 6.12. Found: C, 67.40, 67.52; H, 6.41, 6.18.

The acetoxy compound was not obtained when acetyl chloride was used in place of acetic anhydride.

The acetoxy compound was converted back to III by treatment with phosphorus pentachloride or methylmagnesium iodide followed by hydrolysis.

3-(Benzoyloxy)-4-(N-morpholinylmethyl)-2,5-diphenylfuran.—A mixture of 1 g. of III and 5 g. of benzoic anhydride was fused at 80°. To the fused mixture was added 4 drops of concentrated sulfuric acid. The reaction mixture was allowed to stand for fifteen minutes at 80°, after which time it was poured into water. The resulting aqueous mixture was extracted with ether and the ether extract was washed four times with dilute sodium hydroxide solution, dried over sodium sulfate, and evaporated. An acetone solution of the residue was acidified with ethereal hydrogen chloride solution, and the resulting crystals were filtered; yield, 1 g.; recrystallized from 2-propanol, m. p. 183–185°.

Anal. Calcd. for $C_{29}H_{27}NO_4 \cdot HCl$: C, 71.08; H, 5.76. Found: C, 71.16; H, 5.73.

The hydroxymethyl compound (III) was not affected by refluxing acetic acid–zinc dust mixture (thirty minutes).

Summary

The Mannich reaction with 1,2-dibenzoylethane has been carried out in benzene and in alcohol solutions. The products isolated were N-substituted 1-(aminomethyl)-1,2-dibenzoylethanes and 3-(aminomethyl)-2,5-diphenylfurans, and in one case 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran. Conditions favoring the formation of each type of product are described.

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