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

Antimalarials. 2,5-Diphenyl-3-furyl Amino Ketones and Alcohols[1]

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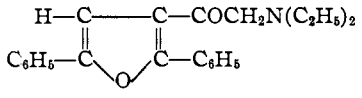
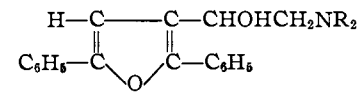
This research was a part of an exploratory program on quinine-type synthetic antimalarials.[3] The objective was the preparation of some novel α-aryl-β-dialkylamino ketones and alcohols of the type I, II, XI (and its alcohol), and XVI, involving the furyl group as the central aromatic nuclear system. Early leads had indicated slight activity



I

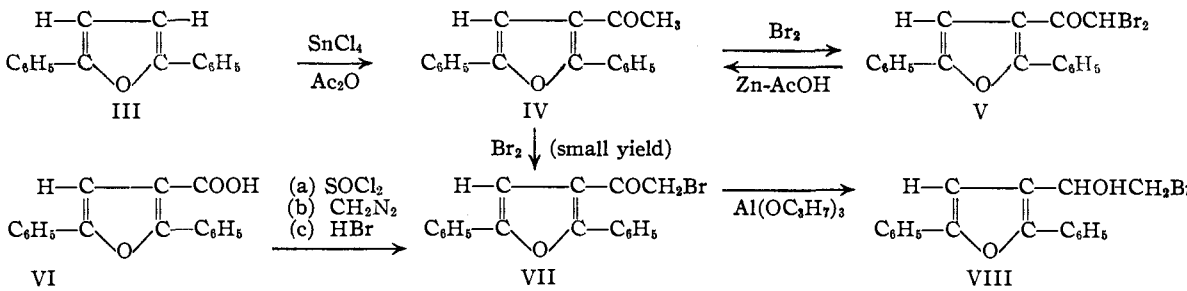


II

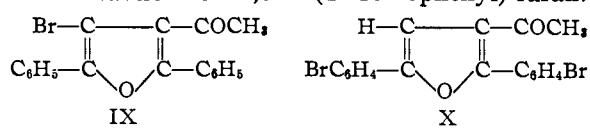
against avian malaria of certain 2,5-diphenylfuran types which contained basic groups,[3c,d] although by present standards of testing[4] few of the compounds so far obtained in this field are to be regarded as active at all, and then only very slightly so. Because of this, although the objectives were only partially achieved, the work was discontinued.

The first attempt to synthesize the key intermediate, 3-bromoacetyl-2,5-diphenylfuran (VII), was through the Friedel–Crafts acylation of 2,5-diphenylfuran followed by bromination. The Friedel–Crafts reaction, although it was unsuccessful using aluminum chloride,[5] proceeds in excellent yields using the combination stannic chloride and acetic anhydride. Bromination of the resulting 3-acetylfuran (IV), however, proved to be difficult to control. Under the various conditions employed only a small amount of the desired bromo ketone (VII) was isolated; the chief product evidently was a mixture which included unchanged material and the dibromo compound (V). This was shown by the reaction of a second molecule of bromine which produced the dibromoacetyl derivative (V) in good yield. It was somewhat surprising to us that the substitution of the second bromine proceeded so rapidly and involved the acetyl group rather than the vulnerable 4-furyl or *para*-phenyl positions, but there is analogy for this in the bromination of 2-acetylfuran.[6]

The nature of the dibromoacetyl compound (V) was demonstrated by the facile reductive dehalogenation back to the acetylfuran (IV), a reaction which showed that the two bromines were aliphatic. The non-reactivity of the 4-nuclear and *para*-phenyl bromines was demonstrated by the stability under the reducing conditions of two compounds, one, the 3-acetyl-4-bromo-2,5-diphenylfuran (IX) which was made from 3-bromo-2,5-diphenylfuran by the Friedel–Crafts reaction, and the other, the isomeric 3-acetyl-2,5-di-(4-bromophenyl)-furan (X), which was made by the Friedel–Crafts reaction with 2,5-di-(4-bromophenyl)-furan.



III IV V VI VII VIII



IX X

The use of chloro and bromoacetyl chlorides in Friedel–Crafts reactions with 2,5-diarylfurans was unsuccessful except in one case. Bromoacetyl chloride and aluminum chloride reacted with 2,5-di-(4-bromophenyl)-furan to give an intractable mixture which on bromination gave a small yield of the dibromoacetyl compound. The latter compound was obtainable in better yields by the bromination of 3-acetyl-2,5-di-(4-bromophenyl)-furan. These experiments showed that the bromoacylation must have produced some of the desired 3-bromoacetyl derivative, even though it was not isolated as such.

The 3-bromoacetyl-2,5-diphenylfuran (VII) was best obtained from the 3-carboxylic acid (VI) by

(1) A part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Devleopment and the University of Virginia.

(2) Philip Francis du Pont Fellow, 1943–1944. Present address: Chemical Abstracts, Ohio State University.

(3) *Cf.* (a) Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946); (b) *J. Org. Chem.*, **12**, 617 (1947); (c) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945); (d) **68**, 2002 (1946).

(4) F. Y. Wiselogle, "Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

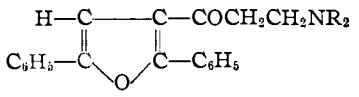
(5) Woodward, Dissertation, Harvard University, 1936.

(6) Brown, *Iowa State Coll. J. Sci.*, **11**, 221 (1937).

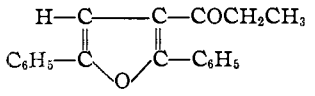
the well known steps, conversion into the acid chloride, diazomethylation, and subsequent treatment with hydrobromic acid.[7]

Condensation of the 3-bromoacetylfuran (VII) with diethylamine gave a typical amino ketone. Condensation of the bromohydrin (VIII) with diethylamine gave a product which resisted crystallization either as the base or the salt. However, a crystalline morpholino alcohol was obtained by this method. Further work in this direction was abandoned because of lack of material.

Six β-dialkylamino ketones of the type XI were made by the Mannich reaction with 3-acetyl-2,5-diphenylfuran, utilizing the following amines: morpholine, piperidine, dimethylamine, diethylamine, dibutylamine and benzylmethylamine. Only two of these compounds were active, and very slightly so, against avian malaria.[4]



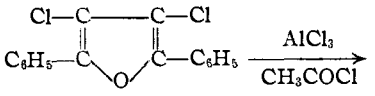
XI



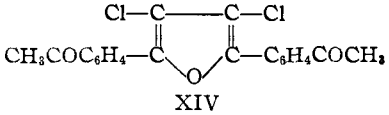
XII

Attempts to reduce these compounds to the amino alcohols by catalytic hydrogen or by aluminum isopropoxide, failed, and only the fission product, the secondary amine, and non-crystalline materials were obtained. From the products of catalytic hydrogenation in one case there was isolated in considerable yields a crystalline deamination product, the ketone XII, which was synthesized independently by the Friedel–Crafts reaction between propionic anhydride and 2,5-diphenylfuran.

In a start toward making an amino alcohol through the *para* position of a phenyl group, a Friedel–Crafts reaction was carried out with 3,4-dichloro-2,5-diphenylfuran (XIII) where the 3,4-furan positions were blocked by chlorine atoms which could be removed later by catalytic hydrogenation. The acylation by means of acetyl chloride and aluminum chloride proceeded twice, however, instead of once as desired, and the di-*para*-acetyl derivative (XIV) was isolated as the chief product. Its structure was demonstrated by oxidation to terephthalic acid.

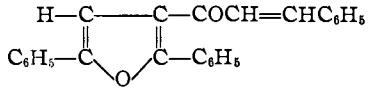


XIII

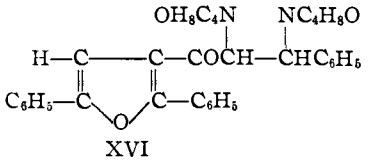


XIV

In connection with the α,β-dimorpholinylbenzylacetophenones,[8] benzaldehyde was condensed with 3-acetyl-2,5-diphenylfuran (IV). The benzal derivative (XV) was brominated and the dibromide reacted with morpholine to give the dimorpholino ketone XVI. This compound showed no activity against avian malaria.



XV



XVI

Acknowledgment.—The synthesis of XII was carried out by Mr. C. R. Bauer.

Experimental[9]

The Preparation of 2,5-Diphenylfuran (III).—Two hundred and fifty grams of *trans*-dibenzoylethylene was added portionwise to a vigorously stirred and refluxing mixture of 250 g. of stannous chloride and 500 ml. each of concd. hydrochloric and concd. acetic acid. The mixture was refluxed for fifteen minutes, and allowed to cool to 50°, and poured into cold water. The solidified product was crystallized slowly from ethanol; yield 154 g. of m. p. 89.5–90° and 36 g. of m. p. 86–87° (86%).

2,5-Di-(4-bromophenyl)-furan.[10]—Twenty-five grams of di-(4-bromobenzoyl)-ethylene was added to a stirred mixture of 50 ml. of concd. hydrochloric and 200 ml. of concd. acetic acids. The addition was rapid enough to keep the mixture boiling gently under the heat of reaction. After refluxing for forty minutes and cooling, the product was isolated by pouring into water. Crystallization from benzene gave 17 g. (73%); melting point 206.5–208°.

Catalytic reduction of 2,5-di-(4-bromophenyl)-furan using palladium on barium sulfate in 95% ethanol at atmospheric pressure and room temperature for eight hours gave 2,5-diphenylfuran.

3-Bromo-2,5-diphenylfuran[11] was made on a large scale by adding 10 ml. of concd. sulfuric acid to a stirred mixture of 120 g. of dibenzoylbromoethane in 500 g. of acetic anhydride. The temperature rose to 54°. Hydrolysis and crystallization of the product gave 94 g. (83%); m. p. 84–86°.

The Preparation of 3-Acetyl-2,5-diphenylfuran (IV).[5]—The Friedel–Crafts acylation of 2,5-diphenylfuran was carried out by means of acetic anhydride and stannic chloride under a variety of conditions in which the solvents tetrachloroethane, carbon disulfide and benzene were used, and in which the mole ratio of stannic chloride was varied between one and two. Acetic anhydride was always used in about 10% excess. The temperature ranges were from 20–50° and the time one-half to eighteen hours. The yields ranged from 64 to 80%. The best procedure is as follows:

Acetic anhydride [28.6 g. (0.28 mole)] was added slowly to a stirred mixture of 55 g. (0.25 mole) of 2,5-

(7) This reaction scheme has been applied at least twice in the furan series starting from furoic acid [Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1219 (1934); Burger and Harnest, THIS JOURNAL, **65**, 2382 (1943)].

(8) A paper to be published shortly from this Laboratory, dealing with a study of this class of compounds with respect to antimalarial activity.

(9) All melting points are corrected.

(10) Lutz and Eisner, THIS JOURNAL, **56**, 2699 (1934); Perkin and Schloesser, *J. Chem. Soc.*, **57**, 94 (1890).

(11) Lutz and Smith, THIS JOURNAL, **63**, 1148 (1941).

diphenylfuran and 250 ml. of dry thiophene-free benzene. A solution of 65 g. (0.25 mole) of anhydrous stannic chloride in 50 ml. of dry benzene was added slowly over thirty minutes with the mixture temperature starting at 13° and not allowed to exceed 20°. Stirring was continued for thirty minutes (15–20°) and the mixture was poured into ice and concd. hydrochloric acid. The product, recovered from the benzene layer, was crystallized from ethanol (with Darco treatment); yield 52 g. (80%) of m. p. 62–64°.

2,5-Diphenyl-3-propionylfuran (XII) was made exactly as was the 3-acetyl analog, but using propionic anhydride. The yield of the product melting at 92.5–95.5° was 72%. A mixture melting point with the sample prepared by reduction of the 3-(β-dialkylamino) ketones showed no depression; melting point 95.5–96°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.53; H, 5.84. Found: C, 82.04; H, 6.19.

2,5-Diphenyl-3-furoic acid[5,11] (VI) was made by passing dry carbon dioxide into a cold ether solution of 2,5-diphenyl-3-furylmagnesium bromide which had been made from carefully purified and dried 3-bromo-2,5-diphenylfuran in the usual way in carefully dried apparatus.

2,5-Diphenyl-3-furoyl chloride.—Five hundred milliliters of thionyl chloride was added cautiously to 49 g. of 2,5-diphenyl-3-furoic acid and the mixture was refluxed for thirty minutes. Unused thionyl chloride was distilled under reduced pressure, and the last traces were eliminated by boiling out with added benzene. Crystallization from ligroin with Norit treatment and cooling to −20° for forty-five minutes gave 44 g. of yellow crystals of m. p. 95–97° (83%).

Anal. Calcd. for $C_{17}H_{11}ClO_2$: Cl, 12.54. Found: Cl, 12.54. (This analysis was carried out by solution of the sample in warm alcohol, addition of alcoholic sodium hydroxide and boiling for ten minutes. After acidification with dilute nitric acid the solution was titrated by Mohr's method with standard silver nitrate and 4% potassium dichromate as indicator.[12])

2,5-Diphenyl-3-furyl Diazomethyl Ketone.—A solution of diazomethane in 1300 ml. of methylene chloride[3a] (0.4675 *N* as determined by titration) was cooled to 0°; and 40 g. of 2,5-diphenyl-3-furoyl chloride was added with gentle stirring. Effervescence continued for thirty minutes. After two hours in the ice-bath and standing overnight, the solvent was evaporated under reduced pressure. A small sample was recrystallized from ethyl acetate and melted at 136.5–138°.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: N, 9.71. Found: N, 9.79.

The bulk of the product was used directly in the preparation of the bromoketone.

3-Bromoacetyl-2,5-diphenylfuran (VII).—Attempts to brominate 3-acetyl-2,5-diphenylfuran (IV) with one equivalent of bromine under a variety of conditions gave mixtures of products. When the bromine in carbon disulfide was added slowly to a carbon disulfide solution of IV at room temperature (over one hour), an oil was obtained which, when treated with a small volume of ethanol, gave a low-melting crude solid. Laborious purification from ethanol gave a small amount of moderately pure VII which was identified. The bulk of the residue on further manipulation gave some dibromo compound (V). That the original crude mixture was largely VII was shown by treatment with diethylamine and isolation of the diethylamino ketone (as the hydrochloride) in 54% yield.

The unsuccessful attempts at Friedel–Crafts reactions between bromoacetyl and chloroacetyl chlorides involved the use of aluminum, ferric and stannic chlorides, with carbon disulfide, benzene or tetrachloroethane as solvent, and temperatures ranging from −5 to 60°.

The best preparation of the 3-bromoacetyl compound is as follows: The ether suspension of the diazoketone (prepared as described above from 40 g. of the acid chloride of VI) in 1 liter of dry ether, was cooled to 0° and treated slowly over three hours under stirring with 23 ml. of 48% hydrobromic acid in 23 ml. of dry ether. Stirring was continued for three hours. After washing and evaporating the solvent, the resulting oil slowly crystallized. Crystallizations from ethanol containing a little ethyl acetate, and from 85% ethanol, gave diamond-shaped light yellow plate-like crystals of melting point 62–64°.

Anal. Calcd. for $C_{18}H_{13}BrO_2$: C, 63.37; H, 3.84. Found: C, 63.17; H, 4.17.

3-(2-Bromo-1-hydroxyethyl)-2,5-diphenylfuran (VIII).—A mixture of 375 ml. of 0.6 *N* aluminum isoproxoxide and 25.6 g. of the bromoacetylfuran (VII) was refluxed for one and one-half hours at which time the evolution of acetone had ceased. Hydrolysis in dilute hydrochloric acid and crystallization of the precipitate from 80% ethanol (with Darco treatment), cooling to −20°, gave 17.4 g. (68%). After crystallization it melted at 124–126°.

Anal. Calcd. for $C_{18}H_{15}BrO_2$: Br, 23.29. Found: Br, 23.26. (The analysis was carried out by warming the sample in alcoholic sodium hydroxide for ten minutes, acidifying with dilute nitric acid, and titrating with standard silver nitrate.[12])

Condensation of the small sample of VIII available, with diethylamine, gave an oil which we were not able to crystallize, either as the base or as the hydrochloride.

3-Acetyl-4-bromo-2,5-diphenylfuran (IX).—Two equivalents of stannic chloride was added dropwise to a stirred and ice-cooled mixture of 3-bromo-2,5-diphenylfuran and a 10% excess of the calculated amount of acetic anhydride in carbon disulfide. Hydrolysis in ice and concd. hydrochloric acid, separation, and evaporation of the solvent gave a crude product which was crystallized from concd. acetic acid to which a small amount of water had been added. Crystallization from 60% ethanol gave pale yellow needles of melting point 81°.

Anal. Calcd. for $C_{18}H_{13}BrO_2$: C, 63.37; H, 3.84. Found: C, 63.18; H, 3.80.

The compound was not affected by zinc dust and concd. acetic acid at boiling-water-bath temperature for thirty minutes.

3-Acetyl-2,5-di-(4-bromophenyl)-furan (X).—To a suspension of 18.9 g. (0.05 mole) of 2,5-di-(4-bromophenyl)-furan in 200 ml. of tetrachloroethane and 26.1 g. (0.1 mole) of stannic chloride, was added over five minutes 5.1 g. (0.05 mole) of acetic anhydride in 20 ml. of tetrachloroethane. After stirring for thirty minutes at room temperature and 1.6 hours at 68–69° (yellow crystals had appeared), and working up the product as above, 22.9 g. (98%) of fairly pure product was obtained.

A reaction using two equivalents of aluminum chloride in the same solvent and adding one equivalent of acetyl chloride (stirring for three hours) gave the same product but in only 77% yield.

After recrystallizations from ethanol containing a small amount of ethyl acetate, the compound melted at 129–130°.

Anal. Calcd. for $C_{18}H_{12}Br_2O_2$: C, 51.46; H, 2.88. Found: C, 52.10; H, 3.21.

3-Dibromoacetyl-2,5-di-(4-bromophenyl)-furan was made in nearly quantitative yield by bromination of X in carbon tetrachloride at room temperature over thirty minutes. It was crystallized from an ethyl acetate-ethanol mixture and melted at 168.5°.

Anal. Calcd. for $C_{18}H_{10}Br_4O_2$: C, 37.41; H, 1.74. Found: C, 37.28; H, 2.41.

In an attempt to obtain the 3-bromoacetyl analog by the Friedel–Crafts acylation of 2,5-di-(4-bromophenyl)-furan with aluminum chloride and bromoacetyl chloride in tetrachloroethane (three hours at room temperature), a difficultly separable mixture was obtained which was evidently largely the desired **3-bromoacetyl-2,5-di-(4-bromophenyl)-furan (m. p. 128–132°)**. Bromination of

(12) See Willard and Furman, "Elementary Quantitative Analysis," 2nd ed., D. Van Nostrand Co., New York, N. Y., 1935.

this in carbon tetrachloride gave the 3-dibromoacetyl compound in 83% yield.

The 3-(β-Dialkylaminopropionyl)-2,5-diphenylfurans (XI).—Mixtures in the ratio of approximately 0.1 mole each of the furan (IV) and the secondary amine hydrochloride or hydrobromide, and 0.11 mole of paraformaldehyde in 100 ml. of 99.5% ethanol and 2 ml. of concd. hydrochloric or hydrobromic acid, were refluxed. The products were precipitated as the salts upon cooling (in some cases after first concentrating the solution under reduced pressure). When the hydrobromide of the amine was used in the reaction, usually with concd. hydrobromic acid instead of hydrochloric, the base was liberated by means of alkali, extracted into ether and converted into the hydrochloride. The crystallizations of the salts, and of the one crystalline base which was handled in that form, were from ethanol, except in the last case where the solvent was ethanol containing a small proportion of ethyl acetate.

MANNICH REACTION PRODUCTS

NR_2	SN. No.[a]	Q[b]	Heating time, hr.	Yield, %	M. p., °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$N(CH_3)_2$·HCl	4909	<0.06	22	41	189	$C_{21}H_{21}NO_2$·HCl	70.88	70.79	6.23	6.57
$N(C_2H_5)_2$.HCl	2624	.06	72	75	147	$C_{23}H_{25}NO_2$·HCl	71.95	72.00	6.83	6.77
$N(n\text{-butyl})_2$·HCl	3541	< .06	120[c,d]	45	144	$C_{27}H_{33}NO_2$·HCl	3.18	2.88	(nitrogen)	
Morpholinyl(base)	3543	.03+	4[d,e]	58	101.5	$C_{23}H_{23}NO_3$	76.42	76.40	6.41	6.65
Piperidyl·HCl	6639[f]	< .15	20[d,e]	24[g]	194–195	$C_{24}H_{25}NO_2$·HCl	3.54	3.80	(nitrogen)	
$N(CH_3)CH_2C_6H_5$·HCl	6638	< .03	24[d,e]	47	193[h]	$C_{27}H_{25}NO_2$·HCl	3.24	2.96	(nitrogen)	

[a] The SN number identifies the drug in the Survey Tables.[4] [b] Quinine equivalent determined against Gallinaceum in the chick (see ref. 4). [c] Every twenty-four hours an additional 0.05 mole of paraformaldehyde was added. [d] In these reactions the secondary amine hydrobromide was used instead of the hydrochloride. [e] Hydrobromic rather than hydrochloric acid was used. [f] This compound was formulated erroneously as the monoamylamino ketone under this number in the Survey Table.[4] [g] Fully purified material (the other yields listed above were for partially purified material). [h] Unsharp melting point; softens at 182°.

Attempted reduction of the diethylamino ketone (XI) by aluminum isopropoxide (refluxing for three hours) gave only unchanged material. Reduction of the dibutylamino analog (XI) under refluxing involved only very slow evolution of acetone as shown by test with 2,4-dinitrophenylhydrazine. After eight hours the product was worked up and the only compound isolated (and that in large quantity) was dibutylamine (as the hydrochloride).

Catalytic hydrogenation at atmospheric pressure and room temperature of 21.1 g. (0.055 mole) of the β-diethylamino ketone (XI) with 0.5 g. of platinum oxide in 300 ml. of 99.5% ethanol, was stopped after ten hours and absorption of one equivalent of hydrogen (although the rate of absorption had not dropped). Concentration of the solution gave 5.5 g. of a product which, after crystallization from 60% ethanol, melted at 93° and was identified as 2,5-diphenyl-3-propionylfuran (XII) by mixture melting point.

The same compound was obtained by a similar reduction of the dibutylamino analog (XI). Here the hydrogenation had been allowed to go further (1.3 equivalents).

3-Diethylaminoacetyl-2,5-diphenylfuran Hydrochloride (I).—An absolute ether solution (75 ml.) of 3.4 g. of the bromoketone (VII) and 2.9 g. of diethylamine quickly gave a precipitate. After standing for five hours the diethylamine hydrobromide was filtered (81%), and the solution was washed, treated with Norite, and dried over sodium sulfate. Acetone was added and the solution acidified with ethereal hydrogen chloride and cooled to −20° for two hours; yield 1.84 g. Recrystallization from anhydrous ethyl acetate and absolute ethanol mixture, gave long needles of melting point 202–204°.

Anal. Calcd. for $C_{22}H_{23}NO_2$·HCl: N, 3.79; Cl, 9.59. Found: N, 3.53; Cl, 9.54 (by titration).

2,5-Diphenyl-3-[2-(N-morpholinyl)-1-hydroxyethyl]-furan Hydrochloride (II).—Condensation of morpholine with the bromohydrin (VIII), with no added solvent, and standing for twenty-eight hours, and diluting with ether, gave 88% of the calculated amount of morpholine hydrobromide. Evaporation under reduced pressure and conversion to the hydrochloride in ether gave 2.1 g. (55%). It was recrystallized from ethyl acetate by addition of absolute ethanol; melting point 202–203°.

Anal. Calcd. for $C_{22}H_{23}NO_3$·HCl: C, 68.47; H, 6.27; Cl, 9.18. Found: C, 68.49; H, 6.27; Cl, 9.21 (by titration).

2,5-Di-(4-acetylphenyl)-3,4-dichlorofuran (XIV).—A mixture of 13.4 g. (0.1 mole) of aluminum chloride, 14.5 g. (0.05 mole) of 3,4-dichloro-2,5-diphenylfuran (XIII) and 100 ml. of tetrachloroethane, was treated with 5.9 g. (0.025 mole) of acetyl chloride in 25 ml. of tetrachloroethane (30°, for two hours). Hydrolysis, washing and steam distillation of the solvent gave a residual oil which partly solidified. Crystallization from ethanol gave 11.2 g. of nearly pure product. It was recrystallized from ethanol; yellow needles of melting point 130.5°.

Anal. Calcd. for $C_{20}H_{14}Cl_2O_3$: C, 64.37; H, 3.78. Found: C, 64.42; H, 4.11.

A higher reaction temperature (68°) gave tars, and no reaction occurred at a lower temperature (0–2°).

Oxidation.—A cooled suspension of the furan (XIV) in ten parts of concd. acetic acid and one of concd. nitric acid, was warmed. Reaction began with evolution of oxides of nitrogen at 40–45° and the solid dissolved. The mixture was heated at 80–85° for fifty minutes and poured into water. The product, which we were unable to crystallize, was then oxidized by potassium permanganate in 10% sodium carbonate, and gave almost two equivalents of terephthalic acid (identified by m. p. 301° and mixture melting point with an authentic sample).

3-Benzalaceto-2,5-diphenylfuran[5] (XV).—Eighty milliliters of 10% sodium hydroxide was added dropwise to a well-stirred mixture of 38 g. of the acetylfuran (IV), 500 ml. of ethanol and 21.2 g. of benzaldehyde. An oil separated. Stirring was continued for two hours. The product solidified, and was filtered and crystallized from ethanol; yield 47 g. (93%). Crystallization from ethanol containing a small amount of ethyl acetate gave pale yellow needles; melting point 123°.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.83; H, 5.77.

The dibromide[6] was made by bromination of XV in ether. The yield of material after crystallization from ethanol–ethyl acetate mixture, was 77%; melting point 180°.

Anal. Calcd. for $C_{25}H_{18}Br_2O_2$: C, 58.84; H, 3.56. Found: C, 58.82; H, 3.94.

3-(2,3-Dimorpholinyl-3-phenylpropionyl)-2,5-diphenylfuran (XVI).—A mixture of 30.8 g. of the dibromide of XV, 26.1 g. of morpholine and 200 ml. of absolute ethanol was refluxed for thirty minutes and allowed to stand overnight. The solid product was filtered, washed with water and recrystallized from an ethanol–ethyl acetate mixture; yield 15 g. (48%); melting point 192°.

Anal. Calcd. for $C_{33}H_{34}N_2O_4$: C, 75.83; H, 6.56. Found: C, 75.59; H, 6.89.

Summary

Six β-dialkylamino ketones, one α-dialkylamino ketone and one α-dialkylamino alcohol, were made, based on the 2,5-diphenyl-3-furyl system.

The synthetic work involved a study of (a) the Friedel–Crafts acylation of 2,5-diarylfurans and bromination of the 3-acetyl group, and (b) conversion of the 3-carboxylic acid through the acid chloride and diazomethyl ketone into the bromoketone and bromohydrin.

The α,β-dimorpholino ketone was made from the benzal derivative of the 3-acetylfuran.

Very little or no antimalarial activity was observed in the limited studies in this field.

CHARLOTTESVILLE, VIRGINIA
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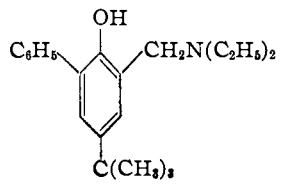
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & COMPANY]

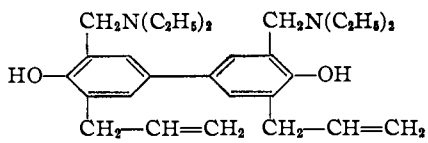
Aminoalkylphenols as Antimalarials. II.[1] (Heterocyclic-amino)-α-amino-o-cresols. The Synthesis of Camoquin[2]

BY J. H. BURCKHALTER,[3] F. H. TENDICK, ELDON M. JONES, PATRICIA A. JONES, W. F. HOLCOMB AND A. L. RAWLINS

In an earlier publication[1] we described a new class of antimalarial compounds represented by 4-*t*-butyl-α-diethylamino-6-phenyl-*o*-cresol (SN 7,744) and 6,6′-diallyl-α,α′-bis-(diethylamino)-4,4′-bi-*o*-cresol (SN 6,771). The high activity of

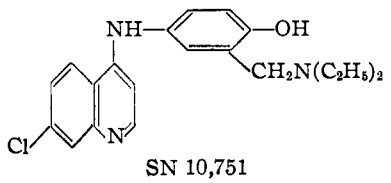


SN 7744



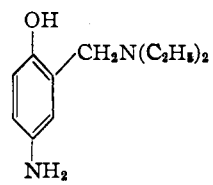
SN 6771

SN 6,771, SN 7,744 and simple analogs led, in 1943, to the synthesis of analogs containing substituent heterocyclic nuclei. This paper describes the work on quinolines, acridines and other heterocyclic compounds which has resulted in the preparation of a new antimalarial, SN 10,751.[2,4]

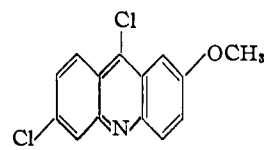


SN 10,751

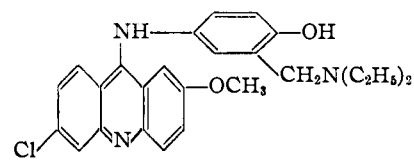
Early attempts to prepare the first member of the new heterocyclic series were unsuccessful. Treatment of 6-chloro-9-(4-hydroxyanilino)-2-methoxyacridine with formaldehyde and diethylamine in the manner of the Mannich reaction failed to yield a product.[5] A method was developed, however, through the preparation of 4-amino-α-diethylamino-*o*-cresol (SN 12,458) and its condensation with 6,9-dichloro-2-methoxyacridine (I) in phenolic solution[6] to give 4-(6-chloro-2-methoxy - 9 - acridylamino) - α - diethylamino-*o*-cresol (SN 8,617).



SN 12,458



I



SN 8,617

The intermediate 4-amino-α-diethylamino-*o*-cresol (SN 12,458) is new and has been prepared both by acid deacetylation of 4-acetamido-α-diethylamino-*o*-cresol (SN 7,767) and by reduction of 4-nitro-α-diethylamino-*o*-cresol (SN 7,292). The last two compounds were obtained from 4-

(1) For paper I see Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

(2) (a) Camoquin is the Parke, Davis name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-*o*-cresol, SN 10,751. (b) The designation SN identifies a compound in the monograph *A Survey of Antimalarial Drugs*, 1941–1945, F. Y. Wiselogle, Editor, J. W. Edwards, Ann Arbor, Mich., 1946.

(3) Present address: University of Kansas, Lawrence, Kansas.

(4) This drug has been receiving extensive clinical trial in many parts of the world with promising results. Chemical data are summarized in Table VI, compound 9.

(5) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 10. Subsequently, incomplete studies have shown that the reaction can be effected with certain substituted aminophenols, *e. g.*, see compound 3, Table XII (VI).

(6) Because of the objection to the handling of phenol, this and similar condensations were later carried out in dilute mineral acid according to a procedure used by Banks, THIS JOURNAL, **66**, 1127 (1944).