[CONTRIBUTION NO. 113 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

1,10-DIPHENYL-2,9-DIMETHYL-3,4,7,8-TETRAHYDROFURO[3,2-*g*, 4,5-*g'*]DIISOQUINOLINIUM DIIODIDE

WILSON M. WHALEY AND CLAYTON WHITE

Received October 22, 1952

Japanese interest in the alkaloid cepharanthine as an antitubercular agent led to the synthesis and evaluation of numerous analogs (1). Most of the synthetic work was done by Tomita and the most active compound which he prepared was 2,7-bis(piperidylacetyl)dibenzo-*p*-dioxin (I). A less active compound was 2,8-bis(piperidylacetyl)dibenzofuran (II) (2).

Since cepharanthine has its two nitrogen atoms in tetrahydroisoquinoline rings, it was decided to prepare a dibenzofuran derivative having two tetrahydroisoquinoline rings. A compound similar to the type desired was achieved by the reaction sequence shown (formulas III to VII). However, there was not sufficient product to perform the final reduction to a tetrahydroisoquinoline. 2,8-Bis(piperidylacetyl)dibenzofuran (II) was synthesized as a reference compound for biological activity.

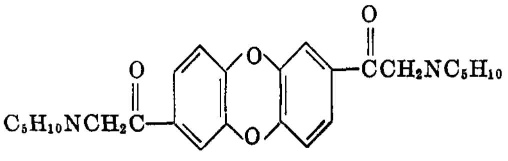
2,8-Dibenzofurandiacetic acid was prepared by the method of Gilman (3, 4), though it was found that the Kindler modification of the Willgerodt reaction gave the same yield and was more convenient than the sealed-tube reaction. Reduction of the dimethyl ester of the diacid III with lithium aluminum hydride proceeded much more efficiently than reduction of the acid itself. The dialcohol IV was easily converted to the dibromide V with hydrogen bromide at 110°, and treatment of the dibromide with ethanolic methylamine at 50° (sealed tube) yielded a diamine which was isolated as the dibenzoyl derivative (VI).

Conversion of the dibenzoyl derivative to 1,10-diphenyl-2,9-dimethyl-3,4,7,8-tetrahydrofuro[3,2-*g*, 4,5-*g'*]diisoquinolinium diiodide (VII) represents the first instance of a double Bischler-Napieralski reaction on a simple condensed-ring system, though a double ring closure has been carried out with a biphenyl derivative (5). A number of previous attempts to perform double cyclizations have failed (6). Cyclization of the dibenzoyl derivative VI was effected with a refluxing mixture of phosphoric anhydride, phosphoric trichloride, and dry xylene. This method is especially suitable for stubborn ring closures (7). The final product of the reaction sequence described was obtained in minute quantity and was consumed by purification and analysis.

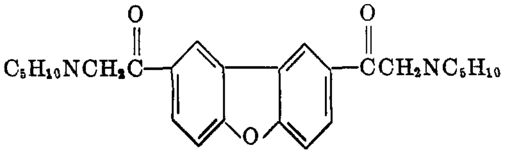
EXPERIMENTAL

2,8-Bis(chloroacetyl)dibenzofuran. The chloroacetylation of dibenzofuran was carried out according to Tomita (2), using chloroacetyl chloride and aluminum chloride in carbon disulfide. There was obtained an 80% yield of tan product melting at 200–210°. Recrystallization from cyclohexanone, then from acetone and water, yielded a solid melting at 213–214°. The melting point has been recorded as 202–209° (2).

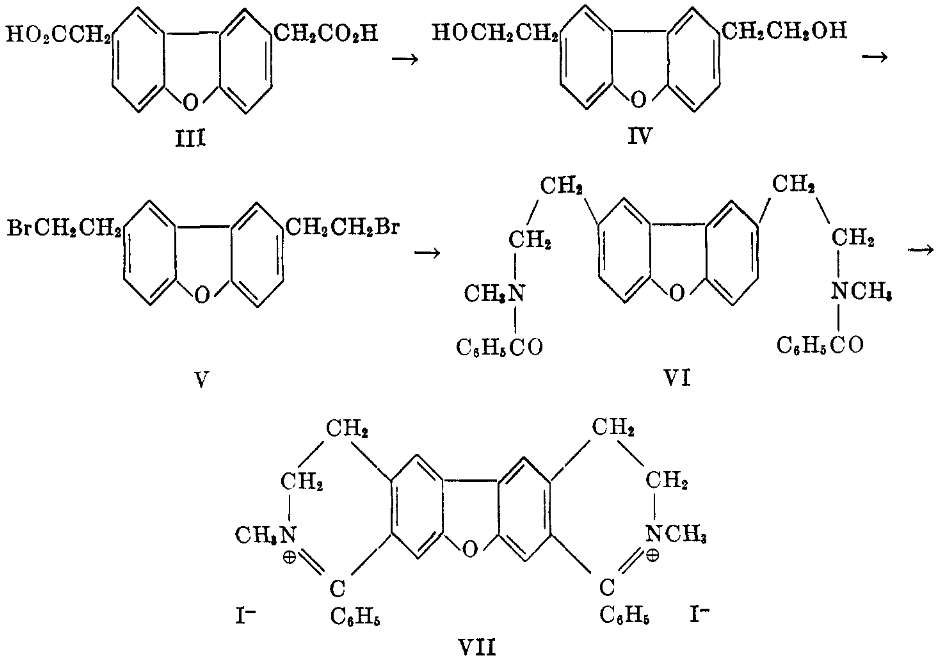
Attempts to replace the chlorine atoms with amino groups by reaction with dry ammonia were unsuccessful, apparently due to the known instability (8) of α-aminoketones. Reduction of the carbonyl groups with lithium aluminum hydride in tetrahydrofuran



I



II



by the method of Lutz (9) for haloketones yielded a substance melting at 226–229°. Analysis of the product indicated that only one carbonyl group had been reduced.

Anal. Calc'd for $C_{16}H_{12}Cl_2O_3$: C, 59.47; H, 3.72.

Found: C, 59.50; H, 3.93.

2,8-Bis(piperidylacetyl)dibenzofuran dihydrochloride (II). This compound was prepared by treating the corresponding dichloro compound with piperidine, then treating the unstable free base with hydrogen chloride. The melting point of the product is above 350°; it has been recorded as being in excess of 300° (2).

2,8-Dibenzofurandiacetic acid (III). 2,8-Diacetyldibenzofuran was prepared in 35% yield by acetylating 2-acetyldibenzofuran according to Gilman (4), the product melting at 165–167°. Subjecting the diketone to the Willgerodt reaction (4) yielded 50% of 2,8-dibenzofurandiacetamide, m.p. 267–269°.

Anal. Calc'd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.93.

Found: C, 67.86; H, 5.00; N, 9.88.

Hydrolysis of the amide with ethanolic potassium hydroxide afforded the 2,8-dibenzofurandiacetic acid (85% yield), m.p. 230–231°. This melting point is identical with that reported by Gilman (3).

The Kindler modification (10) of the Willgerodt reaction yielded a solid thiomorpholide which was at once hydrolyzed by a mixture of acetic acid, sulfuric acid, and water (42% over-all yield).

2,8-Dibenzofurandiacetamide is insoluble in the solvents usually used for lithium aluminum hydride reduction and attempts to use the Soxhlet extractor technique (11) with diethyl ether and dioxane failed to yield the desired diamine. Attempts to convert the diamide to a nitrile or imino chloride with phosphorus pentachloride were unsuccessful. Reduction of the diamide with hydrogen and copper chromite in dioxane at 250° and 3600 p.s.i. would not proceed, starting material being recovered.

Dimethyl 2,8-dibenzofurandiacetate. The dimethyl ester was prepared in 94% yield by refluxing the acid (1.5 g.) with 50 ml. of methanol and 1 ml. of sulfuric acid for 24 hours. The ester melted at 91° after recrystallization from dilute methanol as white needles.

Anal. Calc'd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16.

Found: C, 69.16; H, 5.10.

2,8-Bis(2-hydroxyethyl)dibenzofuran (IV). A solution of 1 g. of 2,8-dibenzofurandiacetic acid in 25 ml. of tetrahydrofuran was added slowly to a solution of 1 g. of lithium aluminum hydride in 200 ml. of tetrahydrofuran and then refluxed for two hours. After the complex was decomposed with water the layers were separated and the tetrahydrofuran was evaporated from the organic layer. The gummy residue was recrystallized three times from toluene and once from dilute ethanol. The white needles melted at 98° (22% yield).

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29.

Found: C, 75.19; H, 6.37.

Reduction of 1.55 g. of dimethyl 2,8-dibenzofurandiacetate with 2 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran yielded 0.9 g. (70%) of the dialcohol.

2,8-Bis(2-bromoethyl)dibenzofuran (V). 2,8-Bis(2-hydroxyethyl)dibenzofuran (0.5 g.) was heated to 110° in a 15-ml. centrifuge tube while anhydrous hydrogen bromide was bubbled through it for 1.5 hours. Water was added and the mixture stirred until the product solidified. After recrystallization from ethanol there was obtained a 66% yield of white needles, m.p. 75–76°.

Anal. Calc'd for $C_{16}H_{14}Br_2O$: C, 50.29; H, 3.69.

Found: C, 50.27; H, 3.59.

2,8-Bis[2-(N-methylbenzamido)ethyl]dibenzofuran (VI). Following the technique of Kirkpatrick and Parker (12), 0.5 g. of 2,8-bis(2-bromoethyl)dibenzofuran and 20 ml. of 33% ethanolic methylamine were sealed in a heavy-walled Pyrex tube and heated at 50° for 20 hours. The solvent was distilled *in vacuo* under nitrogen and the residual solid treated with 20 ml. of 10% sodium hydroxide, then extracted with benzene. The benzene was removed *in vacuo* under nitrogen and a light-yellow oil remained. The diamine was not purified, but was at once benzoylated with benzoyl chloride in the presence of diethyl ether and sodium hydroxide. The dibenzoyl derivative obtained by evaporation of the ether crystallized when its solution in dilute alcohol was cooled at a very slow rate. The pale-yellow needles melted at 147–148° (79% over-all yield).

Anal. Calc'd for $C_{32}H_{30}NO_3$: C, 78.34; H, 6.16; N, 5.71.

Found: C, 78.47; H, 6.05; N, 5.64.

1,10-Diphenyl-2,9-dimethyl-3,4,7,8-tetrahydrofuro[3,2-g, 4,5-g']diisoquinolinium diiodide (VII). Attempts to perform the Bischler-Napieralski reaction on 2,8-bis[2-(N-methylbenzamido)ethyl]dibenzofuran with phosphoric trichloride in boiling toluene (13) and with phosphoric trichloride in boiling nitrobenzene (14) were unsuccessful.

A mixture of 0.3 g. of the dibenzoyl derivative, 3 g. of phosphoric anhydride, 5 g. of phosphoric trichloride, and 15 ml. of dry xylene (7) was stirred and refluxed for two hours.

(A similar experiment run for one hour yielded only a trace of product.) The solvent was decanted and the gummy residue dissolved in water. Addition of potassium iodide solution caused immediate precipitation of a yellow solid. The solid was leached with benzene and ether to remove starting material, then dissolved in ethanol and precipitated by addition of water. The product melted at 193–196°. There was insufficient product for further study.

Anal. Calc'd for $C_{32}H_{28}I_2N_2O$: C, 54.10; H, 3.97; N, 3.94.

Found: C, 53.92; H, 5.29; N, 4.08.

SUMMARY

1,10-Diphenyl-2,9-dimethyl-3,4,7,8-tetrahydrofuro[3,2-*g*, 4,5-*g*′]diisoquinolinium diiodide was prepared on a small scale by use of the Bischler-Napieralski reaction on 2,8-bis[2-(N-methylbenzamido)ethyl]dibenzofuran. Intermediates characterized for the first time were dimethyl 2,8-dibenzofurandiacetate, 2,8-bis(2-hydroxyethyl)dibenzofuran, 2,8-bis(2-bromoethyl)dibenzofuran, and 2,8-dibenzofurandiacetamide.

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