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A New Synthesis of Anilinoquinolines. Morphanthridines IV (1).

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Because of our interest in the preparation of basic substituted morphanthridines (1,2), we have investigated the Bischler-Napieralski cyclization of 2-acylaminobenzophenones in an effort to obtain the useful intermediates, 11-morphanthridones. This cyclization method was applied quite successfully for the preparation of 6-substituted morphanthridines from 2-acylaminodiphenylmethanes (3,4), as well as for the synthesis of related oxazepines and thiazepines (4,5).

However, when we treated 2-formylamino-5-chlorobenzophenone (Ia) with hot polyphosphoric acid, only 2-amino-5-chlorobenzophenone was isolated. This is in agreement with the reported recovery of 2-aminodiphenylmethane from the attempted polyphosphoric acid cyclization of its 2-formylamino analog, as reported by Jilek, *et al.* (3). Heating the 2-acetylaminoketone (Ib) with polyphosphoric acid resulted in the formation in high yield of a bright yellow crystalline solid. Neither the analytical nor the spectral data of the product were in agreement with those for the expected 11-morphanthridone (II). The elemental assay indicated an empirical formula $C_{28}H_{18}Cl_2N_2O$, while its infrared spectrum was notably lacking in extinctions in the 3.3 to 3.6 μ region, indicating the absence of methyl- and methylene groups. This was confirmed by its nuclear magnetic resonance spectrum. Furthermore, the compound showed a carbonyl absorption at 6.12 μ, which is in the same position as a carbonyl absorption of its precursor Ib, but which had only approximately half its intensity. Comparison of the ultraviolet spectra of the compound in alcohol and in alcohol containing 0.1 *N* hydrochloric acid, showed a shift to shorter wave-length in the latter case (Table I). All this evidence suggested that the cyclization product was the benzoylanilinoquinoline III. A possible reaction mechanism involves acid catalyzed aldol cyclization concomitant with anil formation with the simultaneously formed benzoylaniline (6).

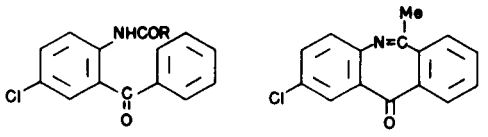
Structure proof of III as well as added support for the proposed mechanism was obtained by an alternate synthesis. Base catalyzed cyclization of the acetylaminobenzophenone Ib according to the method of Hauser (7) afforded 6-chloro-4-phenylcarbostyril (IV) (8), which when treated with phosphorus oxychloride (9) yielded 2,6-dichloro-4-phenylquinoline (V). This was then made to react with 2-amino-5-chlorobenzophenone in order to afford III. Comparison of the infrared spectrum of III with that of the cyclization product, as well as lack of depression of their mixture melting points, proved the compounds to be identical.

As expected, similar cyclization of 2-propionylamino-5-chlorobenzophenone afforded the 3-methyl analog of III.

TABLE I

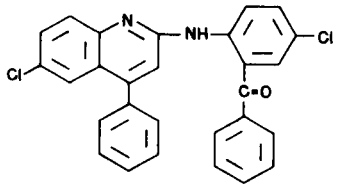
Ultraviolet Spectra, λ max, mμ (ϵ x 10^3)

Ia (EtOH)	III (EtOH)	III (EtOH + 0.1 *N* HCl)
205-6 (24,5)	222-3 (47,3)	251 (30,6)
238 (24,36)	257-8 (34,8)	368 (9,5)
329 (1,97)	285 (30,6)	
	343 (5,12)	
	392-4 (9,0)	

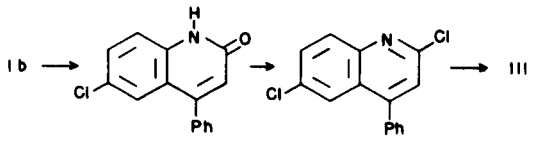


Ia, R = H
b, R = Me

II



III



IV V

EXPERIMENTAL

Melting points were determined in a calibrated Thomas-Hoover capillary melting point apparatus. Infrared spectra were taken using a Beckman IR-8 infrared spectrophotometer, ultraviolet spectra were measured with a Beckman DK-2A spectrophotometer, and the n.m.r. spectrum was taken with a Varian A-60 spectrometer, using deuteriochloroform solvent and tetramethylsilane as the internal standard.

6-Chloro-4-phenylcarbostyril (IV).

To a warm slurry of 6.85 g. (0.025 mole) of 2-acetylamino-5-chlorobenzophenone, 50 ml. of ethanol, and 150 ml. of water was added dropwise with stirring 5 ml. of 33.3% sodium hydroxide solution. The mixture was refluxed for 2.5 hours, the fluffy yellow precipitate was filtered and refluxed 3 hours with 100 ml. of 3 *N* hydrochloric acid. The precipitate was filtered off and recrystallized from ethanol to yield 4 g. (60%) of yellow solid, m.p. 258-261° (lit. m.p. 262°) (8).

Anal. Calcd. for $C_{15}H_{10}ClNO$: Cl, 13.69; N, 5.48. Found: Cl, 13.87; N, 5.48.

2,6-Dichloro-4-phenylquinoline (V).

A mixture of 20.5 g. (0.08 mole) of 6-chloro-4-phenylcarbosytril and 55 ml. of phosphorus oxychloride was heated for 2 hours in an oilbath at 130°. The excess of phosphorus oxychloride was removed *in vacuo* and the viscous residue was quenched on ice. The resulting solid was filtered off and recrystallized from ethanol to yield 17 g. (77%) of product, m.p. 111-113°.

Anal. Calcd. for $C_{15}H_9Cl_2N$: C, 65.50; H, 3.41; N, 5.35. Found: C, 65.69; H, 3.33; N, 5.10.

2-(2-Benzoyl-4-chloroanilino)-4-phenyl-6-chloroquinoline (III).
Method A.

A mixture of 8.22 g. (0.03 mole) of 2,6-dichloro-4-phenylquinoline, 6.96 g. (0.03 mole) of 2-amino-5-chlorobenzophenone, and 200 g. of phenol was stirred and refluxed for four hours. The phenol was distilled off *in vacuo*, and the dark residue was extracted with benzene, washed with water, dried over potassium carbonate, filtered, and concentrated to yield 16 g. of a brown glass. Part of this material (5 g.) was chromatographed over alumina "Merck" and the product was eluted with benzene-chloroform (4:1) to give 700 mg. of a solid, which after crystallization from a mixture of 6 ml. of benzene and 25 ml. of ethanol yielded 550 mg. (12.5%) of III, melting point 188-190°.

Method B.

A stirred mixture of 72 g. (0.262 mole) of 2-acetylamino-5-chlorobenzophenone and 1 kg. of polyphosphoric acid was heated for two hours at 130-140°, cooled, poured into 2.5 l. of ice and water, stirred, filtered, extracted four times with 500 ml. portions of benzene, the extracts dried over potassium carbonate, filtered, and concentrated to afford 81 g. of a yellow solid, which was recrystallized from a mixture of 1.1 l. of benzene and 2 l. of ethanol to yield 55.5 g. (90%) of III, m.p. 190-192°. The mixture melting point of the product, prepared according to methods A and B was 188-191°. The n.m.r. spectrum showed a peak at δ 6.86 (NH) and a peak centered at δ 7.45 (aromatic protons).

Anal. Calcd. for $C_{28}H_{18}Cl_2N_2O$: C, 71.24; H, 3.97; Cl, 15.00; N, 5.88; O, 3.23. Found: C, 71.65; H, 3.87; Cl, 15.11; N, 5.97; O, 3.41.

2-(2-Benzoyl-4-chloroanilino)-3-methyl-4-phenyl-6-chloroquinoline.

A solution of 23.15 g. (0.1 mole) of 2-amino-5-chlorobenzophenone, 45 ml. of benzene, 43 ml. of pyridine, and 43 ml. of propionic anhydride was heated for two hours on á steambath, concentrated, and poured onto 500 ml. of warm water. The product was extracted with benzene, washed with 10% hydrochloric acid, and water. The extract was dried over potassium carbonate, filtered and concentrated to yield 28.5 g. (100%) of 2-propionylamino-5-chlorobenzophenone (Calcd. for $C_{16}H_{14}ClNO_2$: N, 4.87. Found: N, 4.78). Part (14 g.) of this product was heated 2 hours at 130-140° with 200 g. of polyphosphoric acid. The red solution was poured onto 1 kg. of ice and water. The resulting yellow solid was extracted with benzene, washed with water, the benzene solution dried over potassium carbonate, filtered, and concentrated. The residue was recrystallized from a mixture of 100 ml. of benzene and 200 ml. of ethanol to afford 8.1 g. (69%) of product, melting point 229-230°. Ultraviolet spectrum, mμ (ε); λ max (Alcohol), 223-224 (60,000), 256 (35,830), 282-283 (27,340), 334 (5,590), 349 (6,310), 398 (13,020). λ max (Alcohol + 0.1 *N* HCl), 252 (37,170), 344 (8,130), 352 (8,610).

Anal. Calcd. for $C_{29}H_{20}Cl_2N_2O$: C, 72.12; H, 4.34; Cl, 14.67; N, 5.90. Found: C, 72.05; H, 4.17; Cl, 14.67; N, 5.80.

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Received July 5, 1966 Milwaukee, Wisconsin 53201