Benzoyl Migration $O \rightarrow N$ in the Phenothiazine Series (1)

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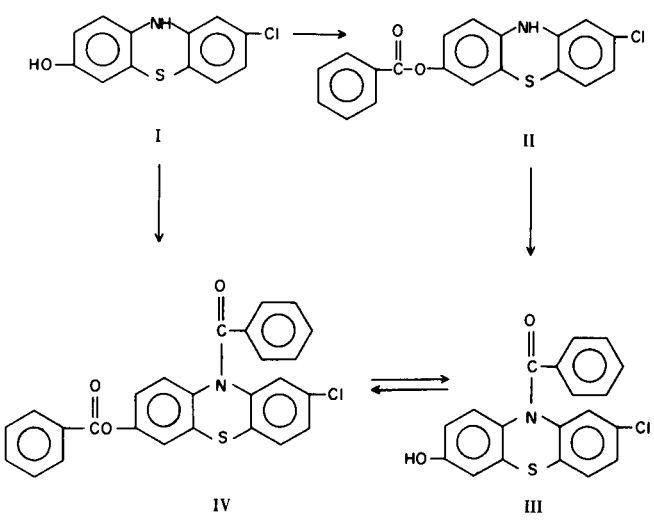
Scheme I outlines an $O \rightarrow N$ benzoyl transfer encountered in our work with the hydroxyphenothiazines. Also included in the scheme are several reactions used to confirm this migration.

SCHEME I



Low temperature benzoylation of 2-chloro-7-hydroxyphenothiazine (I) (2) gave the *O*-benzoyl derivative (II). The infrared spectrum of II (good elemental analyses, C, H, Cl, N) displayed the expected needle-like peak at 3.0 μ (-NH-) and a strong peak at 5.9 μ (ester -C-).

An attempt to *N*-alkylate II in dimethyl sulfoxide-sodium hydride at room temperature gave, instead of the anticipated product, a compound (III) which elemental analysis indicated was isomeric with II. Repetition of this experiment in the absence of alkylating agent, again produced III. In dimethyl sulfoxide alone, II remained unchanged.

The infrared spectrum of the new compound had the broad, weak peak at 3.0 μ often associated with -OH absorption in this series. The peak at 5.9 μ, observed in the spectrum of II, had disappeared. In its stead the new spectrum contained a strong peak at 6.1 μ (-C-N$\leq$).

Simultaneous tlc analysis of II and III, on the same plate, revealed single spots with divergent Rf, thereby eliminating the possibility of dimorphism. The ferric chloride test for phenols was positive for III and negative for II.

Further structural proof for III was initiated with the *O,N*-dibenzoylation of I with excess benzoyl chloride at 80-100°. The infrared spectrum of the resulting compound (IV) showed no absorption in the neighborhood of 3 μ but contained strong ester and amide carbonyl peaks at 5.7 and 6.0 μ respectively.

Hydrolysis of IV with dilute ethanolic base cleaved the ester linkage and provided a compound whose melting point and infrared spectrum were identical with those of III. Conversely, benzoylation of III returned the dibenzoyl derivative (IV).

We have not investigated the mechanism of this migration. However, the rarity of intramolecular para $O \rightarrow N$ acyl shifts makes it likely that intermolecular aminolysis is involved.

EXPERIMENTAL

Melting points were determined in sealed, evacuated capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected.

All reactions were mechanically stirred under dry nitrogen in the absence of strong light.

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 137B Infracord spectrophotometer.

Organic solutions were dried with anhydrous magnesium sulfate and decolorized with Darco G-60. Concentration and complete solvent removal were carried out under reduced pressure.

7-Benzoyloxy-2-chlorophenothiazine (II).

A mixture of 25 g. (0.1 mole) of 2-chloro-7-hydroxyphenothiazine (I) (2), 125 ml. of pyridine and 0.1 g. of sodium dithionite, cooled to 0°, was treated dropwise, during 5 minutes, with 21.4 g. (0.15 mole) of benzoyl chloride. After stirring for 2 hours at room temperature the mixture was poured into 1 l. of 10% hydrochloric acid. The resulting solid was filtered, washed on the filter with cold acetone and in a Waring Blendor with chloroform to yield 31.2 g. (87%) of II, m.p. 224-225°. Crystallization from

acetone-DMF (2:1) provided an analytical sample, m.p. 228-229°.

Anal. Calcd. for $C_{19}H_{12}ClNO_2S$: C, 64.45; H, 3.39; Cl, 10.05; N, 3.96. Found: C, 64.78; H, 3.56; Cl, 9.75; N, 3.92.

Tlc analysis on Eastman chromagram sheet, type 6060 (silica gel), with the solvent system benzene-dioxane-acetic acid (90:25:4), revealed a single spot with R_f 0.75. With the system ethyl acetate-acetone-methanol-diethylamine (68:2:20:15) the R_f was 0.71.

10-Benzoyl-2-chloro-7-hydroxyphenothiazine (III). Method A (from II).

A mixture of 0.57 g. (0.012 mole) of sodium hydride (50% suspension in mineral oil) and 40 ml. of dimethyl sulfoxide was cooled to 0°. To the resulting slush was slowly added 4 g. (0.011 mole) of II. On cessation of gas evolution the reaction was stirred at ambient temperature for 20 hours and the green suspension was poured into 400 ml. of 10% ammonium chloride containing 1 g. of sodium dithionite. The pink solid was washed with water and cold methanol and crystallized from acetone-DMF-water to give 1.8 g. (45%) of III, m.p. 268-269°. Vacuum sublimation (200°, 0.15 mm.) provided white crystals, m.p. 274-275°.

Anal. Calcd. for $C_{19}H_{12}ClNO_2S$: C, 64.45; H, 3.39; Cl, 10.05; N, 3.96. Found: C, 64.45; H, 3.66; Cl, 10.07; N, 4.06.

Tlc analysis, using the same systems described above for II, gave a single spot with each system. The R_f in both cases was 0.55.

From the wash methanol was recovered 1.4 g. (50%) of 2-chloro-7-hydroxyphenothiazine (I).

Method B (from IV).

A mixture of 2.5 g. (0.0055 mole) of IV, 30 ml. of acetone and 5 ml. of 50% aqueous potassium hydroxide was heated under reflux for 3.5 hours poured into 500 ml. of water and acidified with concentrated hydrochloric acid. The resulting solid was crystallized from acetone-DMF-water to give 1.2 g. (62%) of III, m.p. 265°. Infrared and mixture melting point comparison indicated that this material was identical with that obtained using Method A.

Dilution of the crystallization filtrates with water provided 0.6 g. of the completely hydrolyzed compound (I).

10-Benzoyl-7-benzoyloxy-2-chlorophenothiazine (IV). Method A (from I).

To a stirred mixture of 8 g. (0.032 mole) of I in 80 ml. of pyridine was added dropwise, during 30 minutes, 16 g. (0.115 mole) of benzoyl chloride (reaction temperature, 27-35°). The mixture was then heated at 80-100° for 3 hours and poured into 400 ml. of 10% hydrochloric acid. The resulting brown gum was treated successively with 10% sodium bicarbonate and hot ethanol to give 13.4 g. (93%) of IV as tan solid, m.p. 157-160°. Crystallization from aqueous acetone provided the analytical sample as pale yellow crystals, m.p. 168-169°.

Anal. Calcd. for $C_{26}H_{16}ClNO_3S$: C, 68.25; H, 3.51; N, 3.06. Found: C, 68.06; H, 3.61; N, 3.25.

Method B (from III).

A mixture of 1 g. (0.0029 mole) of III, 10 ml. of pyridine and 0.45 g. (0.0031 mole) of benzoyl chloride was stirred at room temperature for 3 hours and poured into 300 ml. of 5% hydrochloric acid. The resulting solid was washed with water and crystallized from aqueous acetone (1:2) to give 1.05 g. (81%) of IV, m.p. 168°.

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REFERENCES

(1) This migration was first described in a progress report (RITU 1967-19) to the Psychopharmacology Research Branch, National Institute of Mental Health, for the period May 16, 1967-July 31, 1967, under Contract SA-43-ph-3758.

(2) E. A. Nodiff and M. Hausman, *J. Org. Chem.*, 31, 625 (1966).