95. *The Action of Acid Chlorides on Anilides.*

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It has been found that substituted amidines are usually formed when anilides react with acid chlorides; the yield of amidine from formanilide is almost quantitative, whereas the amounts formed from other anilides are relatively small. Hübner and collaborators observed the formation of basic by-products in the reaction, but failed to identify the bases. Paal and Otten reported that the reaction yielded a small quantity of by-product which they regarded as hydrazobenzene; this, too, has been found to be a substituted amidine. A mechanism for the formation of amidines in the reaction is proposed.

The descriptions of this reaction, which was investigated by Hübner and Frerichs (*Ber.*, 1877, **10**, 1720), Hübner, Frerichs, and Meyer (*ibid.*, p. 2165), Paal and Otten (*Ber.*, 1890, **23**, 2587), Pictet (*ibid.*, p. 3011), and Kay (*Ber.*, 1893, **26**, 2853), under conditions varying from the comparatively mild treatment of Hübner to the more vigorous conditions employed by Kay, require amplification and correction in some respects.

Hübner and his collaborators (*locc. cit.*) reported that acetanilide and benzanilide reacted with succinyl chloride or other acid chlorides to form bases which they described, without reporting any analyses, as $C_{29}H_{28}N_4$, m. p. 132—134°, and $C_{42}H_{36}N_4$, m. p. 217°, respectively. These bases have been found to be diphenylacetamidine, $C_{14}H_{14}N_2$, m. p. 132°, and diphenylbenzamidine, $C_{19}H_{16}N_2$, m. p. 144°; the close correspondence between the analytical values required by the two sets of molecular formulæ leaves little room for doubt that these were the substances they described. A product having m. p. 217° could not be obtained from succinyl chloride and benzanilide.

Paal and Otten (*loc. cit.*), in attempting to prepare diacylanilides, treated the sodium derivatives of anilides with acid chlorides, and reported that in the case of sodium form- or acet-anilide, in addition to the anilide produced by an exchange reaction, a small quantity of a compound was formed which they regarded as hydrazobenzene. It has been found that this substance is diphenylformamidine when derived from formanilide, and diphenylacetamidine when derived from acetanilide.

Pictet (*loc. cit.*) also attempted to prepare diacylanilides, using the anilides themselves instead of their sodium derivatives; he reported that between 100° and 150° an exchange reaction occurred almost quantitatively, the reaction being limited in that it only took place if the acid chloride used were of higher molecular weight than that derived from the acid radical of the anilide. This has been confirmed, and, in addition, it has been found that some substituted amidine is always formed. The quantity of this amidine varies from traces in most cases to appreciable quantities when acetanilide is used; with formanilide the yield of diphenylformamidine is almost quantitative, and it is surprising that Pictet, who studied the reaction in detail, failed to make this observation.

Kay's observation that diacylanilides are formed under the more vigorous reaction conditions used by him—200° for 3—4 hours—has been confirmed. It was also found that under these conditions reversal of Pictet's exchange reaction takes place to some extent, and that traces of basic substances, usually insufficient for identification, are also formed.

The following scheme is proposed for the mechanism of amidine formation (compare Stephen and Bleloch, J., 1931, 886; Backeberg, *ibid.*, p. 2814):

$$\mathrm{R{\cdot}CO{\cdot}NHPh + R{\cdot}C(OH){:}NPh \xrightarrow{-H_2O} R{\cdot}CO{\cdot}NPh{\cdot}CR{:}NPh \xrightarrow{H_2O} NHPh{\cdot}CR{:}NPh + R{\cdot}CO_2H}$$

The condensing agent is probably hydrogen chloride, for it is significant that in the case of formanilide, in which hydrogen chloride is liberated in large quantity, the yield of amidine is very much greater than in the other cases (compare Wallach, *Ber.*, 1882, **15**, 208).

Experimental.

The substituted amidine was isolated by acidifying the end-product of the reaction with cold dilute hydrochloric acid and precipitating the base from the filtered solution with ammonia. All substances were identified by mixed m. p. determinations with authentic specimens, and the bases were further identified by means of their picrates. All refluxing apparatus was fitted with a calcium chloride tube to exclude atmospheric moisture.

Reactions of Formanilide.—Formanilide was obtained free from diphenylformamidine by distillation under diminished pressure. 8 C.c. of acetyl chloride were added to 11 g. of formanilide and heated under reflux to 100° during 1 hour; at about 45° a vigorous reaction set in, carbon monoxide and hydrogen chloride being evolved. The product, m. p. 259°, consisted of almost pure diphenylformamidine hydrochloride; extraction with hot water gave 0·5 g. of acetanilide. During the extraction much of the amidine was decomposed by hydrolysis; when the solution was made alkaline, 6 g. of diphenylformamidine were obtained, m. p. 139° after crystallisation from benzene or dilute alcohol. This amidine is considerably less stable than either diphenylacet- or benz-amidine; a specimen kept in a corked tube underwent considerable decomposition after several months. The hydrochloride is very readily soluble in cold water, but only sparingly so in dilute hydrochloric acid (2·84 g. in 100 c.c. of 2N-hydrochloric acid at 18°).

Similar results were obtained under the same conditions by the reaction between formanilide and propionyl or benzoyl chloride, except that the yield of amidine was slightly less, and of the corresponding anilide somewhat greater.

Reactions of Acetanilide.—(i) *With acetyl chloride.* 20 G. of acetanilide were refluxed with 100 c.c. of acetyl chloride for 7 hours; the excess of acetyl chloride was then removed under diminished pressure. From the residue, which was mainly unchanged acetanilide, 2 g. of diphenylacetamidine, m. p. 132°, were extracted. Similar results were obtained when equivalent quantities of the reagents and a temperature of 120° was used according to Pictet (*loc. cit.*) or if the temperature was raised to 180° according to Kay (*loc. cit.*). The yield of amidine was, however, somewhat smaller.

(ii) *With propionyl chloride.* 10 G. of acetanilide and 7 c.c. of propionyl chloride were refluxed for 1 hour. From the oily product, which soon solidified on cooling, 0·2 g. of diphenylacetamidine, m. p. 132°, was obtained. The remainder of the product consisted of propionanilide.

(iii) *With succinyl chloride.* 2·4 G. of acetanilide, dissolved in 15 c.c. of chloroform, were refluxed for 7 hours with 2 c.c. of succinyl chloride. From the product, after removal of chloroform and unchanged succinyl chloride under diminished pressure, 0·05 g. of diphenylacetamidine, m. p. 132°, was obtained. The remainder of the product consisted of unchanged acetanilide.

(iv) *With benzoyl chloride.* 10 G. of acetanilide and 8 c.c. of benzoyl chloride were heated under reflux at 170° for 1 hour; the temperature was then raised to 300° for a few minutes. The product consisted almost entirely of benzanilide, and extraction with dilute hydrochloric acid gave only a small trace of basic material insufficient for identification.

Reactions of Propionanilide.—Treatment with acetyl chloride, propionyl chloride or benzoyl chloride by the methods mentioned gave only minute traces of basic products insufficient for identification.

Reactions of Benzanilide.—(i) *With acetyl chloride.* (a) 20 G. of benzanilide were refluxed with 100 c.c. of acetyl chloride for 20 hours. After removal of the excess of acetyl chloride, the residue, which was mainly unchanged benzanilide, gave 0·2 g. of diphenylbenzamidine, m. p. 144°. (b) 10 G. of benzanilide were heated under reflux with 10 c.c. of acetyl chloride at 180° for 1 hour. The product had a pronounced odour of benzoyl chloride, indicating that the reverse of Pictet's exchange reaction had taken place to some extent. This was confirmed by treatment with cold dilute aqueous caustic soda and acidification of the filtered solution, 0·1 g. of benzoic acid being obtained. The product consisted mainly of unchanged benzanilide; acid extraction gave only a trace of basic substance insufficient for identification, and extraction with hot water gave 0·5 g. of acetylbenzanilide, m. p. 78°.

(ii) *With propionyl chloride.* 10 G. of benzanilide were heated under reflux with 8 c.c. of propionyl chloride at 200° for 1 hour. The product had a pronounced odour of benzoyl chloride. It consisted mainly of unchanged benzanilide and, when treated as above, gave 0·1 g. of benzoic acid, 0·5 g. of propanilide, and a trace of basic substance insufficient for identification.

(iii) *With succinyl chloride.* To obtain a basic product in identifiable quantity, the reaction described by Hübner (*loc. cit.*) was carried out in a sealed tube. 2 C.c. of succinyl chloride, 2·2 g. of benzanilide, and 10 c.c. of chloroform were heated at 100° for 8 hours. After removal of the chloroform and unchanged succinyl chloride under diminished pressure, the residue, in which the odour of benzoyl chloride was detected, consisted mainly of unchanged benzanilide. It yielded 0·05 g. of diphenylbenzamidine, m. p. 144°.

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