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The Rearrangement of N-Monoacylanilines.

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Isomeric rearrangement of acetanilide and propionanilide to amino-ketones has been brought about by prolonged heating with anhydrous aluminium chloride. In the former case there were indications of the production of acetyl chloride which is involved in the mechanism suggested for the rearrangement.

THE migrations of alkyl and acyl groups from oxygen of the side-chain to carbon of the aromatic nucleus are well known and are referred to as the Claisen and the Fries rearrangement, respectively. For compounds containing nitrogen in place of oxygen in the side-chain the migration of alkyl groups is also well established (the Hofmann-Martius rearrangement), but there is very scanty evidence of the movement of acyl groups from nitrogen, *i.e.*, similar to the Fries rearrangement. The work on this subject has been fragmentary although the general inference has been that rearrangement of NN-diacylated aromatic amines can occur. Chattaway (J., 1904, 85, 386) showed that migration of acetyl, propionyl, and benzoyl groups occurred when the NN-diacylanilines were heated for a long time with anhydrous zinc chloride or gaseous hydrogen chloride, the migrating group entering the o- or, preferably, the p-position. From this evidence he concluded that the earlier preparations of amino-ketones by a Friedel-Crafts procedure, *i.e.*, by heating an aromatic amine or monoacylated aniline with acyl chloride in presence of an acidic condensing agent (Kohler, Friedländer's "Fortschritte," vol. III, 21; Klingel, Ber., 1885, 18, 2687; Kunckell, Ber., 1900, 33, 2641; Rousset, Bull. Soc., chim., 1869, 11, 320; Higgin, J., 1882, 41, 132; Clarke and Esselen, J. Amer. Chem. Soc., 1911, 33, 1138), actually involved molecular rearrangements of this kind. This is not necessarily true, and we consider that in such cases the reaction is more probably effected by direct attack by the acyl chloride on the nucleus, and that in the few instances where acylated anilines actually isomerise there is initial formation of an acyl chloride which then attacks the nucleus with the aid of the condensing agent.

The migration in the case of NN-diacylanilines appears to be tardy, and the yields are low; thus the rearrangement of N-monoacylanilines might be expected to be even more difficult to achieve. Apart from the production of traces of o- and p-aminoacetophenone by strongly heating acetanilide alone (Meyer and Hofmann, Monatsh., 1915, 36, 707), the migration of acyl groups in monoacylated anilines has been investigated only recently, by the present authors (*Nature*, 1946, 157, 408) and by Kursanow (*J. Gen. Chem. Russia*, 1943, 13, 286). In both series of experiments anhydrous aluminium chloride was used as a catalyst. Kursanow obtained a small yield of p-aminoacetophenone from acetanilide, and of p-aminobenzophenone from benzanilide; we also obtained p-aminoacetophenone, in somewhat better yield, and detected the formation of some of the o-isomeride. Our conversion of propionanilide led to the p-aminoketone and some ester, probably ethyl propionate. Attempts to improve the yields by modifying experimental conditions, *e.g.*, by the use of solvents, had little success, and also the attempted rearrangement of NN-diphenvlacetamide failed.

Favourable results were obtained only when a high molecular proportion $(2\frac{1}{2} \text{ moles})$ of aluminium chloride was used. This is consistent with the course of reaction suggested below. Stage (ii), probably proceeding through an initial addition (i), follows a course comparable to that which has been demonstrated for the interaction of acetic anhydride and aluminium chloride (Groggins and Nagel, *Ind. Eng. Chem.*, 1934, **26**, 1313; Groggins, Nagel, and Stirton, *ibid.*, p. 1317):

Stages (iii) and (iv) show the formation of the electrophilic acyl ion and its subsequent attack of the benzene ring [the displaced proton in stage (iv) is doubtless eliminated as hydrogen chloride]. The formation of acyl ions as indicated here has already been well demonstrated elsewhere (Fairbrother, Wertyporoch, *et al.*).

The production of acetyl chloride postulated above was proved by critical experiments (see Experimental) with highly purified and scrupulously dried samples of acetanilide and aluminium chloride heated together at 180°. It appears, therefore, that acetanilide serves as a source of acetyl chloride, in much the same way as, for instance, acetic anhydride. This inter-

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molecular mechanism is supported by the fact that Kursanow (*loc. cit.*) has demonstrated the migration of an acyl group from side-chain nitrogen to a "foreign" aromatic nucleus, *viz.*, the movement of acetyl from acetanilide to a nuclear carbon of toluene.

Isomeric rearrangement along the lines discussed in this paper also occurs when 1-acetylindoles and 9-acetylcarbazoles are heated with anhydrous aluminium chloride (Gaudion, Hook, and Plant, J., 1947, 1631; Plant, Rogers, and Williams, J., 1935, 741).

EXPERIMENTAL.

All the materials were carefully purified. The anilides were twice recrystallised and dried; aluminium chloride (B.D.H. Laboratory Reagent) was resublimed; all solvents were dried and freshly redistilled.

Treatment of Acetanilide with Aluminium Chloride.—Acetanilide (32 g., 1 mol.) and anhydrous aluminium chloride (82 g., $2 \cdot 5$ mols.) were intimately mixed and heated in a round-bottomed flask fitted with a long air-condenser connected by a ground-glass joint and carrying a calcium chloride trap. After 10 hours at $180-200^{\circ}$ the flask contained a reddish-brown resinous mass. Water was added slowly and the whole boiled for $\frac{1}{2}$ hour to complete the extraction. A dark oil separated on the surface and, while still warm (70°), the lower aqueous layer was withdrawn; on cooling, the oil solidified to a crystalline mass. The aqueous layer deposited a large quantity of unchanged acetanilide; the filtrate after removal of the acetanilide was rendered alkaline and steam-distilled. The distillate was pale yellow and gave a positive ketone test (2: 4-dinitrophenylhydrazine); this was presumably due to *o*-aminoacetophenone [the earlier identification mentioned in a letter (*Nature*, *loc. cit.*) has not been confirmed]. The residual liquid also gave a positive ketone test, attributed to p-aminoacetophenone, which is not volatile in steam.

The solidified oil which separated first was purified by removal of acetanilide by means of hot water, and the remaining oil was steam-distilled. No ketone was detected in the steam-distillate. The residual liquid was extracted with ether, and the ethereal liquid dried (Na₂SO₄). Crude p-aminoacetophenone (4.5 g., 15%) was recovered, having m. p. 102—103°. Recrystallisation from alcohol gave cream-coloured crystals, m. p. 106—107°. The identity of the compound was proved by conversion into the acetyl and the benzoyl derivative (m. p.s 166—167° and 204° respectively).

Attempts to prepare the amino-ketone by less drastic methods had failed, although hydrogen chloride was always copiously evolved; the conditions employed are summarised as follows: (i) a suspension of the solids in nitrobenzene was heated for several hours at temperatures from 100° to 200° , molecular proportions of aluminium chloride varying from 1.25 to 2.5 mols.; (ii) a suspension of the solids (including 2.5 mols. of aluminium chloride) was heated in (a) carbon disulphide and (b) ether, under reflux for 4 hours (when carbon disulphide was the solvent, a viscous residue, which gave a positive ketone test, remained after removal of unchanged solid). It is significant that the only indications of ketone production came from experiments in which $2\frac{1}{2}$ molecular proportions of catalyst were employed.

production came from experiments in which 2½ molecular proportions of catalyst were employed. *Treatment of Propionanilide* (1 Mol.) with Aluminium Chloride (2.5 Mols.).—The experimental conditions that gave rise to p-aminoacetophenone were applied to a mixture of propionanilide (7.5 g., 1 mol.) and aluminium chloride (17 g., 2.5 mols.). The principal reaction product was p-aminopropiophenone, m. p. 138—140° (ca. 1 g.); recrystallisation from water yielded pale yellow needles, m. p. 139°. The identity of the product was proved by conversion into the acetyl and the benzoyl derivative (m. p. 172° and 188° respectively). No o-amino-ketone was detected, but approx. 1 ml. of a volatile liquid was recovered which gave a test for an ester and yielded on hydrolysis a product giving the iodoform test. The b. p. (97—99°) indicated that it was impure ethyl propionate.

The monoacetyl derivative of diphenylamine was also treated with 2.5 mols. of aluminium chloride, but all the original anilide was recovered unchanged. The volatile nature of the anilide made it necessary for the heating to be conducted in a sealed tube, and so the experimental conditions were not comparable with those applied to the anilides which underwent rearrangement.

Production of Acetyl Chloride from Acetanilide.—This experiment was conducted in an all-glass apparatus which consisted of a round-bottomed flask bearing a side-arm leading to a closed tube carrying a drying-trap. The neck of the flask was joined to a column packed with glass-wool which the gaseous reaction products traversed. From this column the gases were led through a U-tube filled with anhydrous calcium chloride, to a small flask containing water, and thence to an aspirator. A slow stream of dry air, drawn through the side-arm of the reaction flask and circulated through the apparatus, withdrew volatile reaction products. Acetanilide (5 g.), dried over phosphoric oxide, was placed in the reaction flask and to it purified anhydrous aluminium chloride (5 g.) was added in an ampoule. (The molecular proportion of aluminium chloride was reduced in this experiment in order to minimise the tendency to nuclear acylation.) The mixture was heated in an oil-bath to about 180° for 3 hours, while approximately 101. of dry air were drawn through the apparatus. Subsequently the wash-water was examined, and positive tests for acetate and chloride were recorded. In similar experiments with acetanilide and aluminium chloride singly, neither acetate nor chloride ions were detected; thus the measures to suppress the escape of the reagents during heating had been effective.

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