411. *The Rearrangement of* NN-*Diacylanilines and the Nuclear Benzoylation of Anilines.*

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The rearrangement of diacetyl- and dibenzoyl-aniline to amino-ketones under the influence of freshly fused zinc chloride, first studied by Chattaway, has been re-examined, and the evidence now appears to favour an intermolecular mechanism. The direct preparation of several amino-ketones from monoacylanilines and benzoyl chloride under simple Friedel–Crafts conditions has also been investigated, and a standard procedure is recommended which leads to improved yields of products.

The literature contains a few scattered references to the preparation of aromatic amino-ketones under Friedel–Crafts conditions (summarised by Dippy and Wood, *J.*, 1949, 2179). The earlier work was that of Chattaway and his co-workers (*J.*, 1904, **85**, 386, 589, 1663; 1912, **101**, 515) who introduced acyl groups into aniline and various substituted anilines by heating the amine with two molecular proportions of acyl chloride at approximately 220° in the presence of a small amount of fused zinc chloride as catalyst (5% of the total weight of reactants). Chattaway considered that the *NN*-diacylaniline was formed initially, and then underwent intramolecular rearrangement to an aromatic amino-ketone, in the form of the monoacyl derivative, and, in support, he demonstrated that *NN*-diacetylaniline, when heated with zinc chloride, gave *p*-acetamidoacetophenone. This view was later supported by Derick and Bornmann (*J. Amer. Chem. Soc.*, 1913, **35**, 1269).

We prefer, on the other hand, to regard the reaction as one of direct substitution at nuclear carbon along orthodox Friedel–Crafts lines, for the following reasons. Shah and Chaubal (*J.*, 1932, 650) introduced the benzoyl group into the nucleus of *NN*-dimethylaniline by Friedel and Crafts's procedure at a relatively low temperature, and, moreover, we find that in the reaction of *p*-acetotoluidide with benzoyl chloride in the presence of zinc chloride, the only amino-ketone that can be isolated is 2-amino-5-methylbenzophenone, whereas on Chattaway's theory, since a diacyl derivative would be the initial product, some 2-amino-5-methylacetophenone could also be expected. We have also found that acyl groups of diacetyl- and dibenzoyl-aniline can be removed in the form of acyl chloride on distillation with freshly fused zinc chloride, and we have demonstrated that the acyl groups in these compounds will migrate to a " foreign " nucleus, provided by toluene or by chlorobenzene [compare similar migrations (Kursanov, *J. Gen. Chem. Russia*, 1943, **13**, 286) in connection with *N*-monoacylanilines]. The much greater yield of *p*-aminoacetophenone obtained from diacetylaniline, compared with acetanilide (see Dippy and Wood, *loc. cit.*, who used aluminium chloride), can be attributed to the greater facility with which the diacylanilines generate acyl chloride for nuclear acylation, in the presence of the catalyst.

There is now reason, therefore, to consider that a *NN*-diacylaniline rearranges by an intermolecular mechanism along lines similar to those proposed by Dippy and Wood (*loc. cit.*) for the rearrangement of acetanilide under the influence of anhydrous aluminium chloride.

We have demonstrated experimentally that an addition compound between the catalyst and the diacylaniline is produced, and such compounds, involving (*a*) zinc chloride and (*b*) stannic chloride, have been isolated and shown to possess a 1 : 1 molecular composition. From such a compound, acyl chloride has been generated, and the production of acylium ions by interaction of an acyl chloride and anhydrous aluminium chloride is already well known. The suggestion here is that anhydrous zinc chloride is also capable of giving rise to such ions. Consistently with the fact that zinc chloride is utilized in liberating acyl chloride from the diacyl compound, we have been able to increase the yield of *p*-aminoacetophenone from 3% to 45% by increasing the quantity of catalyst from the 5% by weight (*i.e.*, the approx. 0·125 mole arbitrarily employed by Chattaway) to at least 1 mole. Similarly, from dibenzoylaniline and 1 mole of zinc chloride, a 30% yield of *p*-aminobenzophenone was obtained which approached that obtained from the " direct " nuclear acylation of benzanilide with benzoyl chloride; the latter reaction, as might be expected in the circumstances, progressed satisfactorily with only 5% of zinc chloride. In this connection it is interesting that Burton and Praill (*J.*, 1951, 726) have recently shown that good yields of *p*-methoxyacetophenone are obtained on acylation of anisole even if the zinc chloride catalyst is reduced to very small proportions. Furthermore, these authors claim that their experiments on this system, involving zinc chloride, afford conclusive evidence of the formation of the acetylium ion.

It is noteworthy that Chapman (*J.*, 1925, **127**, 2818) first claimed that the rearrangement considered here is of an intermolecular character, although he proposed a different course for it. He considered that, for satisfactory conversion, heating in the presence of both zinc chloride and hydrogen chloride was necessary, the latter being responsible, in his view, for the production of acyl chloride; actually, he showed that during the heating of diacetylaniline to fusion point in presence of hydrogen chloride, there was some generation of acetyl chloride. In our experience, however, added hydrogen chloride is unnecessary for successful rearrangement; freshly fused zinc chloride alone will liberate acyl chlorides from diacylanilines, and also effects satisfactory conversions into amino-ketones, provided that the experimental conditions are favourable.

We have attempted to improve the yields of amino-ketones obtained by the direct treatment of the monobenzoyl derivatives of amines with benzoyl chloride, in the presence of zinc chloride, by suitable modifications of Chattaway's reaction conditions. The following table sets out the results obtained under our modified standard conditions for direct nuclear acylation (p. 2209).

Amine (as monobenzoyl derivative)	Product	Yield, % (based on amine)
Aniline	4-Aminobenzophenone	45
o-Toluidine	4-Amino-3-methylbenzophenone	50
p-Toluidine	2-Amino-5-methylbenzophenone	5
p-Fluoroaniline	2-Amino-5-fluorobenzophenone	5
o-Chloroaniline	4-Amino-3-chlorobenzophenone	30
p-Chloroaniline	2-Amino-5-chlorobenzophenone	15
o-Bromoaniline	4-Amino-3-bromobenzophenone	33
p-Bromoaniline	2-Amino-5-bromobenzophenone	10
p-Iodoaniline	4-Aminobenzophenone	45
N-Methylaniline	4-Aminobenzophenone	trace
β-Naphthylamine	2-Amino-1-benzoylnaphthalene	40

It is seen that the percentage conversion into ketone is low (5—15%) for *p*-substituted anilines, but for *o*-substituted anilines the yield varies from 30 to 50%, and in this connection it is noteworthy that with aniline and *o*-toluidine substitution of the benzoyl group occurs preferentially at the *p*-position. The generation of weakly basic tars throughout is unavoidable, and the reason doubtless lies in the fact that the *o*- and the *p*-amino-ketones are reactive compounds which are known to undergo further change in the presence of acid catalysts, giving, according to constitution, lepidines, acridones, and quinazolines.

Certain substituted anilines behaved anomalously when nuclear acylation was attempted. The iodine from *p*-iodoaniline was liberated, and a substantial quantity of *p*-aminobenzophenone produced. The only product from *p*-anisidine was a phenolic substance possessing no primary amino-group, and from *N*-methylaniline a little *p*-aminobenzophenone alone was recovered. The alkyl group attached to oxygen and nitrogen has evidently been withdrawn in the last two reactions, under the vigorous experimental conditions.

In conclusion, it may be claimed that the preparation of amino-ketones by nuclear acylation under Friedel–Crafts conditions has more to recommend it than has been hitherto supposed, especially when it is borne in mind that there are only two experimental stages involved and that the starting materials are, as a rule, relatively accessible.

EXPERIMENTAL

Preparation of Diacetylaniline.—This compound was best prepared by Sudborough's method (*J.*, 1901, **79**, 533), and by this means a specimen of m. p. 36° (in sealed tube) was obtained in 50% yield (Sudborough records m. p. 37°). The compound was stored in a vacuum-desiccator until required.

Rearrangement of Diacetylaniline.—Diacetylaniline (20 g.) was heated with dry, freshly fused zinc chloride (2 g.) at 150° for 8 hours, and the dark-brown mass so obtained was hydrolysed for 16 hours with 100 ml. of ethanol–hydrochloric acid (3 : 1 by vol.). The solution was rendered alkaline with sodium hydroxide solution, and the mixture steam-distilled; the distillate, which contained ethanol, aniline, and ethyl acetate, showed no yellow colour, indicating that no *o*-aminoacetophenone had been formed. The contents of the distillation flask were extracted with ether, and the ethereal solution washed with 2N-hydrochloric acid. This acidic extract, after neutralisation with concentrated aqueous sodium hydroxide, deposited crude *p*-aminoacetophenone, m. p. 104° (0·4 g., 3%); recrystallisation from aqueous ethanol gave buff-coloured needles, m. p. 106° (Klingel, *Ber.*, 1885, **18**, 2687, gives m. p. 105—106°).

The experiment was repeated with the same quantity of diacetylaniline, but with one molecular proportion (17 g.) of anhydrous zinc chloride. By the same method of working-up, 7·0 g. (45%) of pure *p*-aminoacetophenone were obtained.

Formation of Acetyl Chloride from Diacetylaniline on Treatment with Freshly Fused Zinc Chloride.—During the heating of equimolecular proportions of zinc chloride and diacetylaniline the gaseous products of reaction were withdrawn as they were produced, so as to minimise the tendency for nuclear acylation.

Diacetylaniline (10 g.) was heated at 150° with freshly fused zinc chloride (8 g.) in a vessel through which a slow current of dry air was circulated. The gaseous products were passed through a glass-wool filter and into a 10% aqueous "AnalaR" potassium hydroxide solution. After 4 hours, heating was discontinued, whereupon the alkaline solution gave positive reactions for both chloride and acetate ions, but no such reactions were obtained in control experiments with zinc chloride and diacetylaniline separately under identical conditions.

Migration of an Acetyl Group from Diacetylaniline into a " Foreign " Aromatic Nucleus.—(i) *Into toluene.* Diacetylaniline (18 g.), dissolved in dry toluene (200 ml.), was treated with fused zinc chloride (14 g., 1 mol.). Warming yielded a dark-brown, viscous oil and, as a forcing condition in this experiment, further zinc chloride (32 g.) was added. The mixture was refluxed for 6 hours, and the toluene layer, recovered after steam-distillation, was dried (Na_2SO_4) and fractionally distilled. The small residue (of high b. p.), when refluxed with a saturated solution of 2 : 4-dinitrophenylhydrazine in acidified ethanol (30 ml.), deposited a dark-red solid (*ca.* 0·05 g.) which on recrystallisation from benzene (in which it was sparingly soluble) gave red leaflets, m. p. 255°, which did not depress the m. p. of an authentic specimen of the 2 : 4-dinitrophenylhydrazone of *p*-methylacetophenone, m. p. 255° (lit.,* 258°), prepared from toluene and acetyl chloride by the Friedel–Crafts reaction.

(ii) *Into chlorobenzene.* The experiment was repeated with the same quantities of diacetylaniline and zinc chloride as in (i), but chlorobenzene (200 ml.) was substituted for the toluene. By the same procedure a 2 : 4-dinitrophenylhydrazone (*ca.* 0·05 g.) was obtained, m. p. 232° unchanged when admixed with an authentic specimen of the 2 : 4-dinitrophenylhydrazone of *p*-chloroacetophenone, m. p. 236° (lit., 239°), prepared from chlorobenzene and acetyl chloride.

Addition Compounds formed between Diacetylaniline and the Catalyst.—(i) *Zinc chloride.* To diacetylaniline (20 g.), dissolved in warm benzene (200 ml.), fused zinc chloride (10 g., 0·67 mol.) was added, and the mixture heated to boiling. A reddish-brown oil began to separate almost immediately, and its formation was complete in ¼ hour. The zinc chloride employed was apparently insufficient to react completely with all the diacetylaniline because some of the latter was recovered unchanged from the benzene solution. The benzene layer was decanted, and the residual oil, after being washed several times with 20-ml. portions of boiling benzene to remove excess of diacetylaniline, was kept overnight in a vaccum-desiccator, and a dark red, brittle, hygroscopic solid was obtained; a suitable weight of this was dissolved in 10% aqueous " AnalaR " potassium hydroxide (filtered from a trace of insoluble material), and the zinc and chlorine contents were determined volumetrically (Found: Zn, 17·0; Cl, 18·6%; Zn/Cl = 0·914. $C_{10}H_{11}O_2,ZnCl_2$ requires Zn, 20·9; Cl, 22·65%; Zn/Cl = 0·923). The zinc chloride and diacetylaniline therefore formed a 1 : 1 *complex*. (The low experimental values must be attributed to the fact that the compound is hygroscopic and could not be purified.) Our conclusions were supported by the formation of the following complex, which could be prepared in a much purer condition.

(ii) *Stannic chloride.* Diacetylaniline, dissolved in dry, pure carbon disulphide, was treated with a solution of freshly distilled anhydrous stannic chloride in the same solvent. The white solid which was precipitated was filtered off, washed well with carbon disulphide, dried *in vacuo*, and analysed for chlorine as above. Further preparations showd that the 1 : 1 composition of the *complex* was independent of the proportions of diacetylaniline and stannic chloride employed [Found (mean of several analyses): Cl, 32·0. $C_{10}H_{11}O_2N,SnCl_4$ requires Cl, 32·5%].

Preparation of Dibenzoylaniline.—Freundler's method was used (*Bull. Soc. chim.*, 1904, **31**, 629), and the product obtained in 60% yield with m. p. 164° (Freundler records m. p. 163—164°). The mixed m. p. with benzanilide was 140° (this determination was necessary since dibenzoylaniline and benzanilide have identical m. p.s).

Rearrangement of Dibenzoylaniline.—Dibenzoylaniline (40 g.) was heated for 8 hours at 220° with freshly fused zinc chloride (4 g., 0·13 mol.). The reddish-brown product was hydrolysed with aqueous sulphuric acid (200 ml.; 40% by vol.) until no more benzoic acid was liberated; sodium hydroxide was added to the solution obtained, and unchanged aniline removed by steam-distillation. The cold alkaline residue was extracted with ether, and the ethereal solution washed with 2N-hydrochloric acid. The acidic washings, when basified, deposited 0·2 g. of crude *p*-aminobenzophenone, which, after recrystallisation from aqueous ethanol, gave buff-coloured needles, m. p. 123° (Doebner, *Annalen*, 1881, **210**, 266, records m. p. 124°).

The experiment was repeated with approximately equimolecular proportions of reactants, dibenzoylaniline (20 g.) and zinc chloride (10 g.) giving *p*-aminobenzophenone (4·5 g., 30%).

Formation of Benzoyl Chloride from Dibenzoylaniline by the Action of Fused Zinc Chloride.—Dibenzoylaniline (20 g.) was heated with zinc chloride (10 g.) at 230°, as in the comparable experiment with diacetylaniline, and the volatile liquid which distilled was proved to be benzoyl chloride by b. p. determination and by hydrolysis to benzoic acid and conversion into benzanilide.

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* Throughout this paper the m. p.s of 2 : 4-dinitrophenylhydrazones quoted from the literature are those given in Vogel's " Text-book of Practical Organic Chemistry," Longmans, Green and Co., 1948.

Migration of a Benzoyl Group from Dibenzoylaniline into the Toluene Nucleus.—Dibenzoylaniline (40 g.), toluene (125 g.), and fused zinc chloride (36 g.) were refluxed for 6 hours (a dark red addition compound being deposited), and the product, treated as described above for a similar experiment with diacetylaniline, afforded an orange-coloured 2 : 4-dinitrophenylhydrazone (*ca.* 10 mg.), m. p. 199° undepressed on admixture with a specimen of the 2 : 4-dinitrophenylhydrazone of *p*-methylbenzophenone, m. p. 200° (lit., m. p. 200°), prepared from toluene and benzoyl chloride (both specimens after long storage had m. p. 226°).

Nuclear Acylation of Aromatic Amines—Conditions of reaction. Chattaway's original method for the direct nuclear acylation of anilines was investigated with a view to the improvement of yields, and the following conclusions were reached on the basis of experiments with benzanilide and benzoyl chloride. (*a*) No improvement in yield of amino-ketone was obtained by increasing the quantity of catalyst to an equimolecular proportion. (*b*) Although other typical Friedel–Crafts catalysts could effectively replace anhydrous zinc chloride in the reaction (*e.g.*, anhydrous stannic chloride, ferric chloride, and aluminium chloride), none of them led to any improvement in the yield of *p*-aminobenzophenone. (*c*) The duration of the reaction could be reduced from 18 hours at 220° (Chattaway) to an optimum period of 4 hours at the same temperature, without disadvantage. (*d*) More vigorous hydrolysis of the reaction product, with use of sulphuric acid solution (40% by vol.) in place of hydrochloric acid–ethanol (Chattaway), enabled the tedious hydrolysis stage to be reduced from 18 hours to approx. 4 hours (in all but one case), varying slightly with the anilide employed.

Standardised procedure. The monobenzoyl derivative of the amine (1 mol.),* benzoyl chloride (1 mol.), and anhydrous zinc chloride (5% of the total weight of reactants) were heated to 220° for 4 hours, and the product hydrolysed with aqueous sulphuric acid (40% by vol.) until there was no more liberation of benzoic acid. The mixture was rendered alkaline with concentrated aqueous sodium hydroxide solution, and the whole steam-distilled to remove unchanged amine (the *p*-amino-ketones are involatile in steam, although the *o*-isomerides distil slowly). The residue, when cold, was extracted in the manner previously described (p. 2207).

The only variation in this procedure was in the preparation of 2-amino-5-fluorobenzophenone, which steam-distilled rapidly together with unchanged *p*-fluoroaniline, and was recovered as a solid from the cooled distillate.

The crude amino-ketones were purified by recrystallisation from water (containing a little hydrochloric acid) (charcoal). Further recrystallisation was effected with ethanol or benzene–light petroleum (b. p. 60—80°) or chloroform–light petroleum (60—80°). In this way the amino-ketones listed on p. 2207 were prepared, further details being as follows.

p-Aminobenzophenone, from aniline, formed buff-coloured needles, m. p. 123° on recrystallisation from ethanol; a trace of the *o*-isomeride was recovered on one occasion.

4-Amino-3-methylbenzophenone, from *o*-toluidine, recrystallised as straw-coloured prisms (from hot water), m. p. 111° (Chattaway and Lewis, *J.*, 1904, **85**, 589, give m. p. 112°). 2-Amino-5-methylbenzophenone, from *p*-toluidine, formed fine, yellow needles, m. p. 62°, from benzene–light petroleum (b. p. 60—80°) (Chattaway and Lewis, *loc. cit.*, give m. p. 66°); the same product was obtained by using *p*-acetotoluidide as starting material. (It is noteworthy that the *o*-amino-ketones are intensely yellow in contrast to the *p*-amino-ketones which have little or no colour.) 2-*Amino*-5-*fluorobenzophenone*, from *p*-fluoroaniline, formed fine, yellow needles, m. p. 118°, from ethanol (Found : C, 72·9; H, 4·6. $C_{13}H_{10}ONF$ requires C, 72·5; H, 4·65%). 4-Amino-3-chlorobenzophenone, from *o*-chloroaniline, formed colourless prisms, m. p. 139°, from chloroform–light petroleum (b. p. 60—80°) (Chattaway, *J.*, 1904, **85**, 340, records m. p. 140° for this compound, prepared by rearrangement of the *N*-chloro-derivative of *p*-acetamidobenzophenone). 2-Amino-5-chlorobenzophenone, from *p*-chloroaniline, formed bright yellow needles (from ethanol), m. p. 97° (Chattaway, *loc. cit.*, gives m. p. 100° for this compound, prepared by rearrangement of the *N*-chloro-derivative of *o*-acetamidobenzophenone). 4-*Amino*-3-*bromobenzophenone*, from *o*-bromoaniline, formed colourless needles after repeated recrystallisation from hot water and then from ethanol and benzene–light petroleum (b. p. 60—80°); it had m. p. 157° (Found; C, 56·0; H, 3·7; N, 4·7; Br, 28·0. $C_{13}H_{10}ONBr$ requires C, 56·5; H, 3·6; N, 5·0; Br, 29·0%).

In assigning the orientations to the last compound and to 2-amino-5-fluorobenzophenone account was taken of the analogy with known amino-ketones, and of the colour and volatility in each case.

2-Amino-5-bromobenzophenone, from *p*-bromoaniline, was obtained as bright yellow

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* The monobenzoyl derivatives were always first prepared, as contact of the free amine with zinc chloride is to be avoided.

needles, m. p. 110°, from benzene–light petroleum (b. p. 60—80°) (Angel, *J.*, 1912, **101**, 515, records m. p. 111°). 2-Amino-1-benzoylnaphthalene, from β-naphthylamine, formed fine yellow needles, m. p. 165° from ethanol (Dziewonski, Kwiencinski, and Stenbach, *Bull. int. Acad. polonaise*, 1934, *A*, 329, give m. p. 167·5—168·5°) (Found: C, 82·3; H, 5·3; N, 5·3. Calc. for $C_{17}H_{13}ON$: C, 82·6; H, 5·2; N, 5·6%).

From α-naphthylamine a light grey solid was recovered which recrystallised with difficulty and had m. p. 114° approx. (Found: C, 82·6; H, 5·0; N, 5·0. Calc. for $C_{17}H_{13}ON$: C, 82·6; H, 5·2; N, 5·6%). Dziewonski *et al.* (*ibid.*, 1933, *A*, 416) record m. p. 106° for 1-amino-4-benzoylnaphthalene.

p-Iodoaniline, under the usual conditions, yielded *p*-aminobenzophenone (45% yield). *N*-Methylaniline, similarly, gave a 5% yield of *p*-aminobenzophenone and a large quantity of tar. *p*-Anisidine yielded a brown solid soluble in water, which has not been identified although it gives the reactions of a secondary amine and of a phenol. It appears likely that in this case the methyl group has migrated from side-chain oxygen to nitrogen. The nitroanilines gave no identifiable product, but large quantities of tar were produced; only small quantities of unchanged nitroanilines were recovered.

One of us (V. M.) gratefully acknowledges the award of a maintenance grant from the Department of Scientific and Industrial Research. The analyses (except for addition compounds) were by Drs. Weiler and Strauss.

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[*Received, January* 15*th*, 1952.]