172. o-*Amino-ketones of the Acetophenone and Benzophenone Types.*

By J. C. E. Simpson and (in part) C. M. Atkinson, K. Schofield, and O. Stephenson.

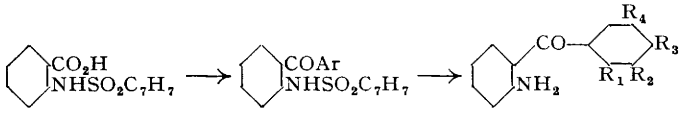
The existing literature of *o*-amino-acetophenones and -benzophenones is summarised, and methods of preparation critically reviewed. In the benzophenone series, a detailed study has been made of the preparative value of the respective Friedel–Crafts reactions between benzene and anisole and the acid chloride of *N*-*p*-toluenesulphonylanthranilic acid. In the work on acetophenones, improvements in the preparation of existing intermediates have been made in a number of instances, and the following new *o*-amino-acetophenones have been prepared : 3- and 5-*Chloro*-, 3-*bromo*-, 3-*methoxy*-, and 5-*cyano*-2-*aminoacetophenone*, also 2 : 3-*diaminoacetophenone*. The constitutions of these acetophenones have been established by arguments independent of reference compounds, in the development of which various other new derivatives of acetophenone have been prepared.

o-Aminobenzophenone and its substituted analogues have been used for the synthesis of fluorenones (Ullmann and Mallet, *Ber.*, 1898, **31**, 1694; Ullmann and Broido, *ibid.*, 1906, **39**, 356; *Chem. Rev.*, 1938, **23**, 287; Lothrop, *J. Amer. Chem. Soc.*, 1939, **61**, 2115), of acridines and acridones (Schöpff, *Ber.*, 1894, **27**, 2316; Staedel, *ibid.*, 1894, **27**, 3362), of cinnolines (Stoermer and Fincke, *Ber.*, 1909, **42**, 3115; Stoermer and Gaus, *ibid.*, 1912, **45**, 3104; Simpson and Stephenson, J., 1942, 353; Simpson, *ibid.*, 1943, 447), and of 2-quinazolones and related substances (Gabriel and Stelzner, *Ber.*, 1896, **29**, 1300; Drawert, *ibid.*, 1899, **32**, 1259; Hanschke, *ibid.*, 1899, **32**, 2021). Of the manifold uses of *o*-aminoacetophenone and its derivatives may be mentioned their applications in the quinazoline field (Bischler *et al.*, *Ber.*, 1893, **26**, 1349, 1384; Bogert and Nabenhauer, *J. Amer. Chem. Soc.*, 1924, **46**, 1702, 1932) and the indigo problem (*e.g.*, Kunckell, *Ber.*, 1900, **33**, 2644; Bamberger and Elger, *ibid.*, 1903, **36**, 1611; Kunckell and Schneider, *J. pr. Chem.*, 1912, **86**, 429; Kunckell and Lillig, *ibid.*, 1912, **86**, 517; Ruggli and Reichwein, *Helv. Chim. Acta*, 1937, **20**, 913; Borsche and Herbert, *Annalen*, 1941, **546**, 293), and also the production of 6-nitro-4-hydroxycinnoline from 5-nitro-2-aminoacetophenone (Borsche and Herbert, *loc. cit.*). Amino-ketones of both types have been employed for the synthesis of indazoles (Fischer and Tafel, *Annalen*, 1885, **227**, 303; Auwers and Meyenburg, *Ber.*, 1891, **24**, 2370; Auwers, *ibid.*, 1896, **29**, 1255), and a study of the conversion of their oximes into indoxazens (αβ-benz*iso*oxazoles) and anthranils (anthroxans, βγ-benz*iso*oxazoles) contributed significantly to the correct interpretation of the Beckmann change (Auwers *et al.*, *Ber.*, 1924, **57**, 461, 800; Meisenheimer *et al.*, *ibid.*, 1924, **57**, 289; 1927, **60**, 1736; *Annalen*, 1926, **446**, 205). Notwithstanding this versatility of reactivity, little recognition has been given to *o*-aminoaryl ketones as a group; at any rate, neither the range of available compounds, nor the principal preparative routes to them, appear to have come under review.

Work now in progress has necessitated a careful search of the literature in respect of both these points, and, as the information may be of general interest, it is summarised in this paper, together with various relevant observations which have been made in our laboratory.

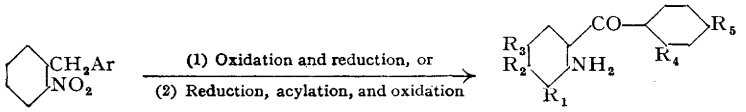
Excluding *o*-aminopropiophenones and higher ketones, and also products made from simpler *o*-amino-ketones, some sixty members of the *o*-amino-acetophenone and -benzophenone classes, of unambiguous constitution, have been described in the literature and prepared by a variety of methods. These are summarised in the following list, for which no claim to exhaustiveness is made, although it is unlikely that there are many omissions. Figures in parentheses indicate references, and the percentages (in Methods I and IX) refer to yields obtained by the authors cited in the first reference; unspecified substituents indicate hydrogen.

Method I.



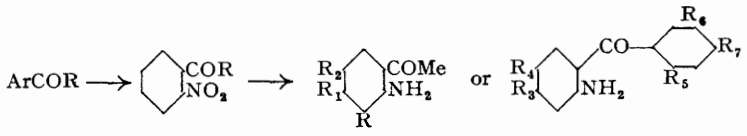
$R_1 = R_2 = R_3 = R_4 =$ H (59%) (1, 3, 4); $R_3 =$ Me (1, 4), OMe (76% crude) (1, 5), Br (28%) (7); $R_1 = R_3 =$ OMe (2); $R_3 = R_4 =$ OMe (62% crude) (2); $R_1 = R_2 = R_3 =$ OMe [not isolated; hydrolysate of tosylamidoketone converted to 3 : 4-dimethoxyxanthone (2)]; $R_1 = R_4 =$ Me, $R_3 =$ OMe (76%) (60); $R_1 = R_2 =$ Me, $R_3 =$ OMe (32%) (60); $R_1 = R_4 =$ OMe (55% crude) (2), Me [obtained only as tosylamidoketone (6)]; 2-aminophenyl 1′-naphthyl ketone (59% crude) (1); 2-aminophenyl 4′-methoxy-1′-naphthyl ketone (58%) (2); 2-aminophenyl 2′-methoxy-1′-naphthyl ketone [obtained only as tosylamidoketone (2)]; $R_2 = R_3 =$ Me (60%) (61).

Method II.



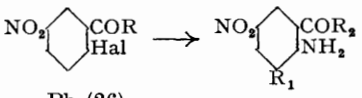
$R_4 = NH_2$ (8, 9, 10); $R_2 = R_5 = NMe_2$ (11); $R_5 = NH_2$ (18), Me (12); $R_2 =$ Me, $R_5 = NH_2$ (13); $R_2 = R_4 = R_5 = NH_2$ (14); $R_1 = R_3 =$ Br (15); $R_1 = R_2 = R_3 = R_4 = R_5 =$ H (16, 17).

Method III.



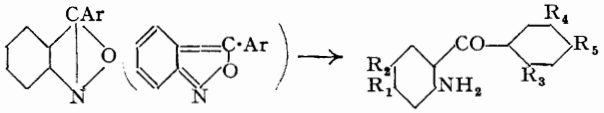
$R = R_1 = R_2 = H$ (19—22); $R_2 = NMe_2$ (23); $R_1 = R_2 = OMe$ (24, 65); $R_3 = Me$ (13, 25); $R_3 = Me$, $R_7 = NH_2$ (13); $R_3 = Me$, $R_6 = R_7 = NH_2$ (13); $R_3 = R_4 = R_6 = R_7 = OMe$, $R_5 = NH_2$ (24); $R = R_1 = Cl$ (62).

Method IV.



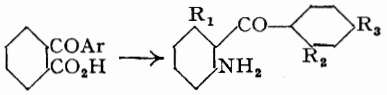
$R_2 = Ph$ (27), Me (28); $R_1 = NO_2$, $R_2 = Ph$ (26).

Method V.



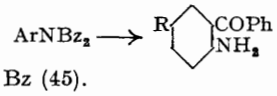
$R_2 = Cl$, $R_5 = NH_2$ (30), OH (34, 35), OMe (35), NMe_2 (33); $R_2 = Cl$, $R_4 = Me$, $R_3 = OH$ (34, 35); OMe (35); $R_5 = Me$ (12), Cl (31), NH_2 (32); $R_1 = NH_2$ (29).

Method VI.



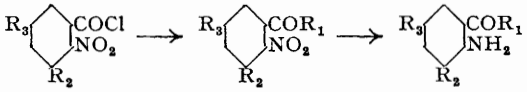
$R_1 = R_2 = R_3 = H$ (1, 3, 36); $R_1 = Br$ (41); $R_2 = R_3 = Me$ (39); $R_3 = Me$ (37), Br (7); 2-aminophenyl 1′-naphthyl ketone (38); 1-aminofluorenone (40, 41).

Method VII.



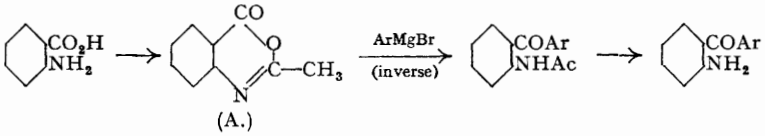
$R = H$ (42), Me (43), Cl (44), Br (44, 35), Bz (45).

Method VIII.



$R_1 = Me$ (46—50), CH_2Cl (49), CH_2Br (49), $CH_2N(CO)_2C_6H_4$ (48), 2 : 5-dimethylphenyl (51); $R_1 = R_2 = Me$ (63); $R_1 = R_3 = Me$ (63).

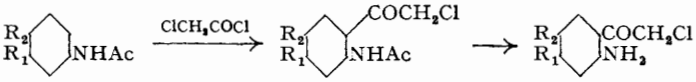
Method IX.



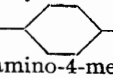
(A.)

Ar = Ph [27% based on (A)], 2-methylphenyl (33%), 3-methylphenyl (10%), 1-naphthyl (36%), 2-naphthyl (8%), 2-methyl-1-naphthyl (23%). 3-Amino-2-naphthyl phenyl ketone (16%); 3-amino-2-naphthyl 2′-naphthyl ketone (4%) (52 for all compounds).

Method X.



$R_2 = Me$ (53); $R_1 = R_2 = Me$ (54); $R_1 = Cl$, $R_2 = Me$ (55).

Miscellaneous. (a) *o*-Nitrophenylpropiolic acid ⟶ *o*-aminoacetophenone (37, 56); (b) methylanthranil ⟶ 2-nitroaminoacetophenone ⟶ 3- and 5-nitro-2-aminoacetophenone (5 7); (c) $C_6H_4(CO)_2N$—  —Me + PhCOCl ⟶ 2-amino-5-methylbenzophenone (58); (d) 4 : 6-diacetyl-*m*-cresol ⟶ 2-amino-4-methyl-5-acetylacetophenone (tautomeric with imino-dihydrobenzenoid form) (59); 6-bromo-2 : 3-diphenyl-1-acetylindole ⟶ 4-bromo-2-aminobenzophenone (64).

References.

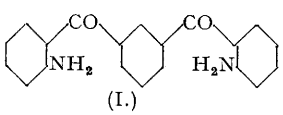
[1] Ullmann and Bleier, *Ber.*, 1902, **35**, 4273.
[2] Ullmann and Denzler, *Ber.*, 1906, **39**, 4332.
[3] Meisenheimer, Senn, and Zimmermann, *Ber.*, 1927, **60**, 1736.

[4] Stoermer and Fincke, *loc. cit.*
[5] Stoermer and Gaus, *loc. cit.*
[6] Schaarschmidt and Herzenberg, *Ber.*, 1920, **53**, 1388.
[7] Miller and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 2443.
[8] Heyl, *Ber.*, 1898, **31**, 3033.
[9] Heyl, *J. pr. Chem.*, 1899, **59**, 436.
[10] Staedel, *Ber.*, 1894, **27**, 2110, 3362.
[11] Kliegl, *Ber.*, 1906, **39**, 1266.
[12] Kliegl, *Ber.*, 1908, **41**, 1845.
[13] Limpricht and Samietz, *Annalen*, 1895, **286**, 321; Plascuda and Zincke, *Ber.*, 1874, **7**, 982.
[14] Gulland and Robinson, J., 1925, **127**, 1493.
[15] Ruggli and Hegedüs, *Helv. Chim. Acta*, 1941, **24**, 703.
[16] Geigy and Königs, *Ber.*, 1885, **18**, 2400.
[17] Tatschaloff, *J. pr. Chem.*, 1902, **65**, 308.
[18] Staedel, *Annalen*, 1894, **283**, 164; Benohr, *J. pr. Chem.*, 1902, **65**, 310.
[19] Bamberger and Elger, *loc. cit.*
[20] Skita and Meyer, *Ber.*, 1912, **45**, 3579.
[21] Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, **42**, 461T.
[22] Elson, Gibson, and Johnson, J., 1930, 1128.
[23] Rupe, Braun, and Zembruski, *Ber.*, 1901, **34**, 3522.
[24] Lawson, Perkin, and Robinson, J., 1924, **125**, 626.
[25] Zincke and Milne, *Ber.*, 1872, **5**, 683.
[26] Ullmann and Broido, *loc. cit.*
[27] Ullmann and Mallet, *loc. cit.*
[28] Borsche and Herbert, *loc. cit.*
[29] Tanasescu and Ramontianu, *Bull. Soc. Chim.*, 1933, (iv), **53**, 918.
[30] Tanasescu and Suciu, *Bull. Soc. Chim.*, 1936, (v), **3**, 1753.
[31] Tanasescu and Silberg, *Bull. Soc. Chim.*, 1936, (v), **3**, 2383.
[32] Tanasescu and Silberg, *Bull. Soc. Chim.*, 1932, (iv), **51**, 1357.
[33] Zincke and Prenntzell, *Ber.*, 1905, **38**, 4116.
[34] Zincke and Siebert, *Ber.*, 1906, **39**, 1930.
[35] Simpson and Stephenson, *loc. cit.*
[36] Graebe and Ullmann, *Annalen*, 1896, **291**, 8.
[37] Kippenberg, *Ber.*, 1897, **30**, 1130.
[38] Graebe, *Ber.*, 1896, **29**, 827; *Annalen*, 1905, **340**, 249.
[39] Drawert, *loc. cit.*
[40] Goldschmiedt, *Monatsh.*, 1902, **23**, 886.
[41] Huntress, Pfister, and Pfister, *J. Amer. Chem. Soc.*, 1942, **64**, 2845.
[42] Chattaway, J., 1904, **85**, 386.
[43] Chattaway and Lewis, J., 1904, **85**, 589.
[44] Angel, J., 1912, **101**, 515.
[45] Chattaway and Lewis, J., 1904, **85**, 1663.
[46] Gevekoht, *Annalen*, 1883, **221**, 323.
[47] Needham and Perkin, J., 1904, **85**, 148.
[48] Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067.
[49] Ruggli and Reichwein, *loc. cit.*
[50] Kermack and Smith, J., 1929, 814.
[51] Boetius and Römisch, *Ber.*, 1935, **68**, 1924.
[52] Lothrop and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363.
[53] Kunckell, *loc. cit.*
[54] Kunckell and Schneider, *loc. cit.*
[55] Kunckell and Lillig, *loc. cit.*
[56] Baeyer and Landsberg, *Ber.*, 1882, **15**, 57; Baeyer and Bloehm, *Ber.*, 1884, **17**, 963.
[57] Bamberger, *Ber.*, 1915, **48**, 537.
[58] Hanschke, *loc. cit.*
[59] Claisen, *Annalen*, 1897, **297**, 74.
[60] Lothrop, *loc. cit.*
[61] Lothrop and Coffman, *J. Amer. Chem. Soc.*, 1941, **63**, 2564.
[62] Roberts and Turner, J., 1927, 1832.
[63] Giacolone, *Gazzetta*, 1935, **65**, 1127.
[64] Koelsch, *J. Amer. Chem. Soc.*, 1944, **66**, 1983.
[65] Mannich and Berger, *Arch. Pharm.*, 1939, **277**, 117.

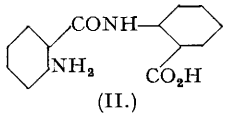
The following general points call for comment. (i) In reactions involving Friedel–Crafts condensations of *o*-nitrobenzyl chloride and *o*-substituted acid chlorides, no attempt has been made to depart from the use of the conventional condensing agent, apart from the work of Boetius and Römisch (51), who have prepared a number of *o*-nitrobenzophenones from *o*-nitrobenzoyl chloride using anhydrous ferric chloride as condensing agent; this led to results unobtainable by means of aluminium chloride, but the yields were still poor and the method is ill-adapted for large-scale work. The recent exploitation, particularly in the United States, of boron fluoride and hydrogen fluoride for *C*-alkylation and -acylation suggests that the use of these reagents with *o*-nitro-compounds would merit trial. The use of beryllium chloride in the Friedel–Crafts reaction has been explored to some extent, but the only recorded examples of *C*-acylation appear to be those of Bredereck, Lehmann, Schönfeld, and Fritzsche (*Ber.*, 1939, **72**, 1414); in the few instances of simple aryl ketones examined by these authors, the method offered no advantages over the use of aluminium chloride. (ii) The oxidation of reactive methylene groups (Method II) has almost invariably been carried out with chromic or nitric acid. Although Gulland and Robinson (14) have obtained good results in the preparation of 2 : 4 : 2′ : 4′-tetra-aminobenzophenone, the method may not be altogether satisfactory, judging from accounts

in the literature (compare Parkes and Morley, J., 1936, 1478). The use of selenium dioxide as an alternative therefore seemed to be worth trial; we find, however, that *o*-nitrodiphenylmethane is practically unchanged after 30 hours' refluxing in acetic acid with the freshly prepared dioxide. Two notable exceptions to the use of chromic or nitric acid are Kliegl's employment of chloranil (11) and Ruggli's oxidation-reduction of *o*-nitrodiphenylmethane to 3 : 5-dibromo-2-aminobenzophenone by means of bromine in boiling tetrachloroethane (15). (iii) Reduction of nitro-groups and of anthroxans has, with few exceptions, been carried out with tin or stannous chloride and hydrochloric acid, although small-scale reductions of a number of anthroxans (no yields given) have been effected by zinc and calcium chloride or ammonium chloride in aqueous alcohol (29—32). In our experience (35 and this paper) the acid reagents mentioned are sometimes unsatisfactory, and excellent results may often be obtained by using iron and acetic acid.

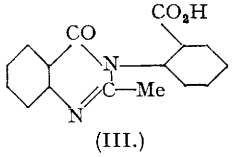
Method I. This route to *o*-aminobenzophenones has been more widely exploited than any of the alternative methods. The results listed suggested that the various amino-ketones should be readily accessible, the only apparent limiting factor being the ease of hydrolysis of the sulphonamidoketone [2-tosylamido-2′-methoxy-1′-dinaphthyl ketone underwent sulphonation on hydrolysis (2), and 2-tosylamido-2′ : 5′-dimethylbenzophenone could not be hydrolysed (6)]. However, the reactions were all carried out on a fairly small scale, and in our experience different cases may vary greatly in their suitability for large-scale preparative work. Thus 2-amino-4′-methoxybenzophenone can be readily prepared in any desired quantity, but the method is not well suited to the large-scale preparation of *o*-aminobenzophenone. Stoermer and Fincke (4) report using 150 g. batches of *p*-toluenesulphonylanthranilic acid, but do not record the yield of amino-ketone, and they also found it necessary to use " ein an der Luft stark korrodiertes Aluminiumchlorid," a procedure which hardly commends itself as a means of securing reproducible results. We find that the yield of *o*-aminobenzophenone is variable, the best being 49·6% (average of a pair of similar experiments), that the reaction always produces considerable amounts of phenyl-*p*-tolylsulphone (mentioned by Ullmann and Bleier as an insignificant by-product), and that slight alterations in the reaction conditions may give rise to significant quantities of (i) a new diamino-diketone, probably 2 : 2′-*diamino*iso*phthalophenone* (I), (ii) an unidentified *sulphonic acid* (produced during hydrolysis of the tosylamido group), and (iii) *N*-*o*-aminobenzoylanthranilic acid (II) [previously obtained by Anschütz, Schmidt, and Greiffenberg (*Ber.*, 1902, **35**, 3477) by alkaline hydrolysis of the quinazolone (III)].



(I.)



(II.)



(III.)

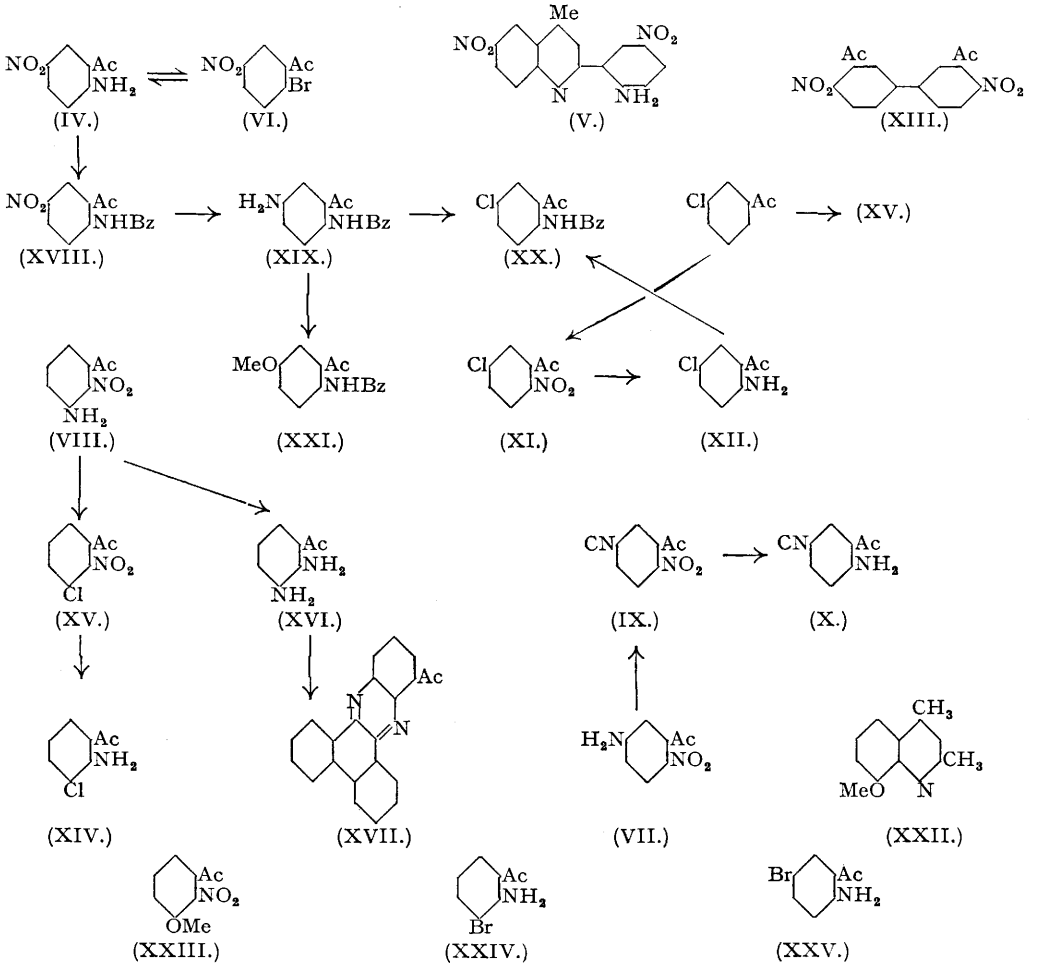
Method II. Applied to *o*-aminobenzophenone, the final stage (reduction of the nitro-ketone) could not be achieved by the literature method (Gabriel and Stelzner, *loc. cit.*), but gave excellent results when iron and acetic acid were used. The preparation of the nitro-ketone by the older methods was not very satisfactory; it proceeded smoothly and in moderate yield (45% based on *o*-nitrobenzyl chloride) using the improved preparation of *o*-nitrodiphenylmethane described by Tanasescu (*Bull. Soc. chim.*, 1926, **39**, 1443) [also referred to by Ruggli and Hegedüs (15)]. Norris and Klemka (*J. Amer. Chem. Soc.*, 1940, **62**, 1432) have found that diphenylmethane can be successfully prepared by the Friedel–Crafts reaction if the double salt $AlCl_3$·NaCl is used in place of aluminium chloride; this modification might be advantageous in the case under consideration.

Method III. The experimental work described in this section deals with the preparation of various *o*-aminoacetophenones, together with proof of structure where necessary.

5-Nitro-2-aminoacetophenone (IV), originally obtained in small amount by Bamberger (57), has recently been made more accessible by Borsche and Herbert (28). Their method of preparation from *o*-bromobenzonitrile *via* *o*-bromoacetophenone (Method IV) is however expensive, as it requires *o*-bromonitrobenzene as starting material. It has now been found that nitration of *o*-acetamidoacetophenone gives, as anticipated, a good yield of the 5-nitro-derivative (IV), converted smoothly into the free amine by acid hydrolysis [alkaline hydrolysis, as shown by Borsche and Herbert, easily brings about condensation to the aryl-lepidine (V)]. *o*-Aminoacetophenone, as has been shown by Morgan and Moss (21), and confirmed by Elson, Gibson, and Johnson (22), is fairly readily prepared from acetophenone, and although the maximum yield of *o*-nitroacetophenone claimed by the former authors is only 43% of the theoretical (the remainder being largely *m*-ketone), the route acetophenone ⟶ *o*-aminoacetophenone ⟶ *o*-acetamidoacetophenone ⟶ 5-nitro-2-acetamidoacetophenone⟶ 5-nitro-2-aminoacetophenone is preferable to that of Borsche and Herbert, both on grounds of cheapness and because the last three stages are rapid and the yields good. 2-Bromo-5-nitroacetophenone (VI) was prepared in good yield from the nitro-amine by the Sandmeyer reaction.

Various substituted *o*-aminoacetophenones have also been prepared in this laboratory from *m*-aminoacetophenone, which is easily obtainable in quantity by the method of Morgan and Moss (*loc. cit.*). Nitration of *m*-acetamidoacetophenone, followed by hydrolysis, gave 47% of 2-*nitro*-5-*aminoacetophenone* (VII) and 5% of the isomeric 2-*nitro*-3-*aminoacetophenone* (VIII). Of these isomers, the former was converted into 2-*nitro*-5-*cyano*- (IX), and thence into 2-*amino*-5-*cyano*-*acetophenone* (X). 5-*Chloro*-2-*nitro*- (XI) and 5-*chloro*-2-*amino*-

acetophenone (XII) were also prepared from (VII), an appreciable by-product of the Sandmeyer reaction being 4 : 4′-*dinitro*-3 : 3′-*diacetyldiphenyl* (XIII). The yield of 5-chloro-2-aminoacetophenone could be considerably increased (to 57% based on *m*-aminoacetophenone) by reversing the order of the two stages involved. *m*-Chloroacetophenone, first obtained by Wahl and Rolland (*Ann. Chim.*, 1928, **10**, 5) from methyl *m*-chlorobenzoylacetate, has now been prepared in 81·5% yield from *m*-aminoacetophenone, and on nitration gave a mixture from which only 5-chloro-2-nitroacetophenone could be obtained in the pure state. Reduction of



the residual material, however, yielded an easily separable mixture of 5-chloro-2-aminoacetophenone and (as minor component) 3-*chloro*-2-*aminoacetophenone* (XIV); the separation was achieved by utilising either the comparative reluctance of the 3-chloro-amine to undergo acetylation or, alternatively, the instability of its hydrochloride. The same substance (XIV) was also prepared from (VIII) by converting it into 3-*chloro*-2-*nitroacetophenone* (XV) followed by reduction. The nitro-amine (VIII) was reduced to 2 : 3-*diaminoacetophenone* (XVI), which was characterised as an *o*-diamine *via* the *phenazine* (XVII). The formation of this phenazine, together with the conversion of each of the amines (XII) and (XIV) into a cinnoline (this vol., p. 520) establishes the orientation of all these derivatives of *m*-aminoacetophenone.

From the nitration of *m*-bromoacetophenone, Elson, Gibson, and Johnson (*loc. cit.*) obtained a single product which they identified as 5-bromo-2-nitroacetophenone by oxidation to the corresponding acid. In repeating and extending this work it has been found that (i) *m*-bromoacetophenone is obtainable from *m*-aminoacetophenone in 87% yield as against the earlier figure of 54%, and (ii) nitration does in fact proceed analogously to that of *m*-chloroacetophenone, giving a mixture of 5-bromo-2-nitroacetophenone and 3-*bromo*-2-*nitroacetophenone*. The latter substance could not be isolated in the pure state from the mixed nitration product, but was readily prepared in a state of purity by the alternative route from 2-nitro-3-aminoacetophenone (VIII), and on reduction gave 3-*bromo*-2-*aminoacetophenone* (XXIV), identical with one of the products obtained by reduction of the mixed bromo-nitro-acetophenones. The other amine, 5-bromo-2-aminoacetophenone (XXV), which resulted from this reduction was first prepared by Gibson and Levin (*J.*, 1931, 2388) by bromination of *o*-acetamidoacetophenone followed by hydrolysis, and its constitution was established by conversion to 2 : 5-dibromobenzoic acid. In confirmation of this result, it has now been

found that 5-bromo-2-acetamidoacetophenone is obtainable both from *o*- and from *m*-aminoacetophenone, an observation which affords a structural proof independent of reference compounds.

The amines (XXIV) and (XXV), like the corresponding chloro-compounds, are easily separated by utilising the resistance of (XXIV) to acetylation under ordinary conditions.

The constitutions of the previously known, and interconvertible, substances (IV) and (VI), although scarcely in doubt on the basis of laws of orientation, have not been formally proved hitherto. A projected proof consisted in the conversion of (VI) and (XII) into one and the same 5-chloro-2-bromoacetophenone, in furtherance of which 2-bromo-5-nitroacetophenone (VI) was reduced to 2-bromo-5-aminoacetophenone; this substance was an oil, which was characterised as the crystalline N-*acetyl* derivative and as the *oxime* of the latter substance. Application of the Sandmeyer reaction to (XII), however, showed that the scheme was unsuitable, the alkali-insoluble fraction of the reaction product consisting of an oil, nitration of which gave only a small yield of solid product. The desired evidence was eventually obtained by way of the changes (IV) ⟶ (XVIII) ⟶ (XIX) ⟶ (XX), the last substance being identical with the product obtained by benzoylating 5-chloro-2-aminoacetophenone (XII), a derivative of *m*-aminoacetophenone.

An attempt to prepare pure 2 : 5-diaminoacetophenone by reduction (iron and acetic acid) of 5-nitro-2-aminoacetophenone was unsuccessful, as the product showed the instability characteristic of *p*-phenylenediamines, and on standing was gradually converted into an almost black mass.

Nitration of *m*-methoxyacetophenone (prepared from *m*-aminoacetophenone in 48% yield) with fuming nitric acid gave exclusively a mixture of *dinitromethoxyacetophenones*, of which one isomer was isolated in the pure state. By the use of weaker acid, however, *m*-methoxyacetophenone was converted in moderate yield into a *mononitro*-derivative. The structure anticipated for this substance was 2-nitro-5-methoxyacetophenone, but an authentic specimen of 2-*benzamido*-5-*methoxyacetophenone* (XXI) [prepared from 5-*amino*-2-*benzamidoacetophenone* (XIX)] was not identical with the *isomer* obtained by reduction and benzoylation of the nitromethoxyacetophenone. However, the *amino-ketone* derived from the latter compound underwent a Friedländer condensation with acetone, yielding 8-*methoxy*-2 : 4-*dimethylquinoline* (XXII), whence it follows that the original nitro-compound is 2-*nitro*-3-*methoxyacetophenone* (XXIII).

Method IV. In the single published example of the preparation of an *o*-aminoacetophenone by this method, the yield is not recorded, and a repetition of the work proved unsatisfactory, the optimum conditions apparently being sharply defined by the tendency of the amino-ketone to condense to the aryl-lepidine (V). With regard to the two *o*-aminobenzophenones, the reaction between ammonia and 2-chloro-5-nitrobenzophenone was found to be extremely sluggish, but to proceed easily with the chlorodinitrobenzophenone. The resultant dinitroaminobenzophenone gave a *benzoyl* derivative with some difficulty, but did not react with acetic anhydride.

Method V. Reference has already been made to the improvement which results from the use of iron and acetic acid in place of tin or stannous chloride and hydrochloric acid.

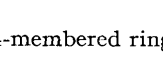
Method VI. This might be expected to be the most generally applicable of all the available routes to *o*-aminobenzophenones, on account of the numerous *o*-benzoylbenzoic acids which have been prepared; in practice, however, it has frequently proved to be unreliable. Thus Meisenheimer, Senn, and Zimmermann (*loc. cit.*) state that Method I gives a distinctly better yield of *o*-aminobenzophenone than the Hofmann degradation, and a short trial of the same experiment in this laboratory also showed it to be unsatisfactory. The final stage is evidently capricious; thus Kippenberg (*loc. cit.*) found that the age of the hypobromite profoundly affected the course of the reaction in the preparation of 4′-methyl-2-aminobenzophenone, and Schaarschmidt and Herzenberg (*loc. cit.*) met with no success in various attempts to make 2′ : 5′-dimethyl-2-aminobenzophenone from the corresponding amide. A further objection to the method is that conversion of the acid chloride to the amide does not always proceed smoothly; in illustration of this point the low yield of amide (18 g. from 35 g. of acid) obtained by Kippenberg (*loc. cit.*) may be cited, and also the notable divergence between the results obtained by Huntress, Pfitzer, and Pfitzer (*loc. cit.*) and by Miller and Bachman (*loc. cit.*) in the case of 3-bromo-2-benzoylbenzoic acid. Both sets of workers prepared the acid by the same method, and obtained the same acid chloride from it. From this compound Miller and Bachman claimed to have prepared an amide, m. p. 135—140°, which gave an amine, m. p. 128—130°. Huntress *et al.*, on the other hand, obtained an amide, m. p. 202°, and an amine, m. p. 85°, which is undoubtedly 6-bromo-2-aminobenzophenone, since it was converted into 1-bromofluorenone of unambiguous orientation. Miller and Bachman's amine, incorrectly formulated as 3-bromo-2-aminobenzophenone, cannot be regarded as an *o*-amino-ketone, because the " bromofluorenone " which they claimed to have obtained from it is not identical with any of the four isomeric bromofluorenones (Huntress *et al.*, *loc. cit.*; Heilbron, Hey, and Wilkinson, *J.*, 1939, 113). It may be pointed out that Miller and Bachman's " aminobenzophenone " and " bromofluorenone " are inadequately characterised, and their molecular formulæ are not rigidly established by the published analytical data.

In connection with the *o*-acylbenzoic acids used as intermediates in this method, the work of de Benneville (*J. Org. Chem.*, 1941, **6**, 462) is worthy of attention; he states that superior yields of these acids, both of the acetophenone and the benzophenone type, may be obtained by the use of acid anhydrides and cadmium dialkyls or diaryls in place of Grignard reagents.

Method VII. This method is of very limited application. The yields are not satisfactory and the method is tedious. It is probably inapplicable to nitro-amines, *e.g.*, 80% and 57%, respectively, of 2-nitro-4-benz-

amidotoluene were recovered after being heated with excess benzoyl chloride for 12 hours at 190° and for 18 hours at 215°. On the other hand, it might well prove satisfactory in the case of substances, *e.g.* *m*-anisidine, which have a highly anionoid position adjacent to the amino group.

Method VIII. As a large-scale route to *o*-aminoacetophenones, this method is inferior to Method III on account of the expensive reagents involved (*o*-nitrobenzoyl chloride and diazomethane or acetoacetic ester). The aminobenzophenone cited, however, does not appear to have been obtained in the pure state by any other method.

Method IX. This is a modern method designed by the authors to obviate the disadvantages of Method I. Its main asset, in addition to rapidity, is that it opens a route to *o*-aminobenzophenones having a wider range of substituents in the non-basic nucleus than are obtainable by other methods. Its preparative value suffers from the defect that acetanthranil (A) is unstable (Bogert, Gortner, and Amend, *J. Amer. Chem. Soc.*, 1911, **33**, 949), much of it being recovered from the reaction as anthranilic acid. Incidentally, the structure (A) used by Lothrop and Goodwin (*loc. cit.*) for acetanthranil is that which at one time gained acceptance, but was later discarded in favour of the 4-membered ring structure,  , for acylanthranils generally by Heller (*Ber.*, 1915, **48**, 1183). Heller's conclusions do not appear to have been subsequently questioned (compare Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2054), and the structure advocated by him explains Lothrop and Goodwin's reaction satisfactorily.

Method X. The three examples of this method, due to Kunckell, of preparing ω-chloro-*o*-aminoacetophenones appear to be the only ones on record. No yields are given, and the scope is evidently limited.

Experimental.

M. p.'s are uncorrected. Nitrations were carried out with mechanical stirring. Cuprous halides for Sandmeyer reactions were prepared as described in *Org. Synth.*, Coll. Vol. I, p. 163.

Method I. A. *o-Aminobenzophenone.*—The aluminium chloride was in all cases roughly ground before use. The results obtained in a number of experiments are summarised below. The general procedure was to decompose the reaction-mixture with ice and hydrochloric acid and to remove solvent in steam. In experiments marked *, the crude non-volatile residue was given a preliminary digestion with warm sodium carbonate solution, after which the sulphonamido-ketone was separated from phenyl-*p*-tolylsulphone by repeated extraction with hot dilute aqueous sodium hydroxide before hydrolysis, which was carried out by heating it for ¾—1 hour on the steam-bath with 15—20 parts by weight of concentrated sulphuric acid; the solution was then diluted with 2 volumes of water, filtered, and basified with ammonia. In unmarked experiments, the treatments with alkali were omitted, and the sulphone was separated from the diluted hydrolysate before basification. The *p*-toluenesulphonylanthranilic acid invariably had m. p. 230—232° (sintering 227°) after crystallisation from aqueous alcohol; Ullmann and Bleier, and Miller and Bachman (*loc. cit.*) record m. p. 217° and 217—218° respectively. The *acid chloride*, made by refluxing the acid (3 parts), phosphorus pentachloride (2·4 parts), and benzene (10 parts by volume) for 1 hour, was easily soluble in benzene; it separated from benzene–ligroin or benzene–ether in colourless prismatic needles, m. p. 125—126° (Found: C, 54·7; H, 4·2. $C_{14}H_{12}O_3NClS$ requires C, 54·3; H, 3·9%). Miller and Bachman (*loc. cit.*) give m. p. 129° for unanalysed material.

Experiment.	Conditions.	Products (g. of recryst. solid). (a).	(b).	(c).	(d).	(e).
*1	40 G. acid, 400 c.c. benzene, 32 g. PCl_5 refluxed 1 hr. Added 60 g. $AlCl_3$ at room temp., left 3 hr., then ½ hr./60°, then overnight/room temp. Total cryst. amino-ketones, 7 g.	—	0·7	Not looked for.		18·6
*2	28·5 G. acid chloride, 200 c.c. benzene, 30 g. $AlCl_3$. Frequent shaking; temp. rose from 20° to 40°. Left at 40°/2 hr./760 mm., then ¼ hr./25—30 mm.	9	—	,,	,,	8
3	153 G. acid chloride, 750 c.c. benzene, 80 g. $AlCl_3$, then 30 g. after ½ hr. Left at 40°/2 hr./760 mm. (frequent shaking), then 1½ hr./50—60 mm.; (a) obtained by prolonged fract. cryst. from alcohol of hydrochlorides of crude amino-ketones (63 g.).	18·2	—	,,	,,	41
4	142 G. acid chloride in 500 c.c. benzene and 100 c.c. nitrobenzene (solvents not dried) added to 80 g. $AlCl_3$ in 200 c.c. nitrobenzene at 10°, then 3 hr./room temp.; 120 g. *p*-toluenesulphonylanthranilic acid recovered.	—	—	,,	,,	—
5	50 G. acid chloride susp. in 200 c.c. benzene added to 30 g. $AlCl_3$ in 70 c.c. nitrobenzene at 5°, then 50 c.c. benzene. Left 3 days at room temp.	—	—	4·8	Probably present (crude acid, m. p. 260—265°).	5
*6	50 G. acid chloride, 500 c.c. benzene, 50 g. $AlCl_3$ in ½ hr. at 40—45°, then 1½ hr./50°, then ¼ hr. nearly boiling; frequent shaking.	14·5	—	2	1·7	8·6
*7	As No. 6, except that soln. was heated to boiling during ¾ hr. after adding $AlCl_3$ and finally refluxed 20 mins.	11	—			14·0

The acid filtrates from the non-steam-volatile material of Nos. 6 and 7 were concentrated to crystallisation point; basification gave an additional 6 g. of (a).

(a) = *o*-Aminobenzophenone; (b) = 2 : 2′-diamino*iso*phthalophenone; (c) = *N*-*o*-aminobenzoylanthranilic acid; (d) = unidentified sulphonic acid; (e) = phenyl-*p*-tolylsulphone.

o-Aminobenzophenone hydrochloride, sparingly soluble in absolute alcohol containing a little concentrated hydrochloric acid, formed needles, often salmon-pink in colour, m. p. 192—193° (decomp.) (Found: C, 66·8; H, 4·95. Calc. for $C_{13}H_{12}ONCl$: C, 66·8; H, 5·2%); a nine-months'-old specimen had m. p. 187—188° after recrystallisation. Graebe and Ullmann (*loc. cit.*) and Hayashi *et al.* (*Bull. Chem. Soc. Japan*, 1936, **11**, 184; A., 1936, 845) both give m.p. 179—180°.

2 : 2′-*Diamino*isophthalophenone crystallised from methyl alcohol in bright yellow prismatic needles, m. p. 110—111° (depressed when mixed with *o*-aminobenzophenone, m. p. 105—107°) (Found: C, 75·7; H, 5·6; N, 9·1. $C_{20}H_{16}O_2N_2$ requires C, 75·9; H, 5·1; N, 8·9%). The *diacetyl* derivative, prepared in pyridine solution at 100°, formed minute straw-coloured prisms, m. p. 106—108° (efferv.), from aqueous alcohol (Found, C, 72·6; H, 5·2; N, 7·4. $C_{24}H_{20}O_4N_2$ requires C, 72·0; H, 5·05; N, 7·0%).

N-*o*-Aminobenzoylanthranilic acid was isolated from Expt. 5 as the ammonium salt, which was thrown out when the filtrate from the sulphone was basified with ammonia, and from Expts. 6 and 7 by extracting the combined crude amino-ketone fractions with water, followed by basification. It separated from rectified spirit in almost colourless, brittle, prismatic needles, m. p. 205—206° (Anschütz, Schmidt, and Greiffenberg, *loc. cit.*, give m. p. 203°) (Found: C, 65·55; H, 5·4; N, 11·3. Calc. for $C_{14}H_{12}O_3N_2$: C, 65·6; H, 4·7; N, 10·9%). Its identity was established by refluxing it (300 mg.) with aqueous sulphuric acid (6 c.c. of 1 : 1 by volume) for ¾ hr. The solution was then made alkaline, benzoylated, filtered, acidified, the precipitate boiled with a little water, and the insoluble residue crystallised from aqueous alcohol; *N*-benzoylanthranilic acid separated in needles, m. p. 180—181° alone and mixed with an authentic specimen.

Sulphonic Acid, $C_7H_9O_3NS$.—This was obtained by evaporation of the filtrates from which the foregoing acid had been isolated in Expts. 6 and 7. The *acid* was practically insoluble in benzene, moderately soluble in hot alcohol and in cold water, and very easily in hot water; it separated from the last named solvents in small prismatic needles, m. p. 341—342° (decomp.) after darkening at 300°, and thin colourless blades, respectively. It did not couple with alkaline β-naphthol after attempted diazotisation; it yielded oils with pyridine–acetic anhydride at 100° and when it was refluxed with methanol–sulphuric acid (Found: C, 44·6, 44·7; H, 5·7, 5·9; N, 7·55; S, 17·6. $C_7H_9O_3NS$ requires C, 44·9; H, 4·9; N, 7·5; S, 17·1%).

B. 2-*Amino*-4′-*methoxybenzophenone*.—For large-scale work, the procedure of Ullmann and Bleier (*loc. cit.*) was modified as follows. *p*-Toluenesulphonylanthranilic acid (150 g.), phosphorus pentachloride (120 g.), and carbon disulphide (500 c.c.) were refluxed for 1 hour. Anisole (100 c.c.) was added to the slightly warm solution, stirred mechanically until the end of the reaction, followed by aluminium chloride (150 g., roughly ground); this was added during ¾—1 hour in 4—5 portions, the heat of reaction being sufficient to keep the mixture gently boiling. It was finally heated on the steam-bath for ¾ hour, the carbon disulphide decanted, and the insoluble complex decomposed with ice–hydrochloric acid (the decomposition is usually delayed for several hours, and finally becomes violent). After standing overnight, the sulphonamido-ketone was filtered off and washed with water and ether, leaving an almost colourless crystalline product (170—175 g.). This was treated with a warm (80°) mixture of concentrated sulphuric acid (700 c.c.) and glacial acetic acid (700 c.c.), heated for 1 hour on the steam-bath, and poured into water (2·8 litres). After filtration (charcoal), the solution was basified with ice and ammonia (*d* 0·880), and the crude amino-ketone filtered off after standing overnight. Four such runs gave 81, 73, 75, and 86 g. of crude product, which after crystallisation from benzene–ligroin formed hard yellow prisms, m. p. 78—80° (279·5 g., 59·7% based on *p*-toluenesulphonylanthranilic acid).

Method II. o-*Aminobenzophenone*.—After the prescription of Geigy and Königs (*loc. cit.*) for the preparation of *o*-nitrobenzophenone had been tried without success, the modification of Tatschaloff (*loc. cit.*) was used. The benzene solution from the Friedel–Crafts reaction using 40 g. of *o*-nitrobenzyl chloride was filtered from resin and evaporated, and a solution of the residue in acetic acid (110 c.c.) was immediately refluxed with chromic anhydride (110 g.) in water (110 c.c.) and acetic acid (220 c.c.) for about 6 hours. The nitroketone had m. p. 103—105° after two crystallisations from alcohol, but the yield (20 and 21·5 g. from two runs) was inferior to that claimed by Tatschaloff. The method of Tanasescu (*loc. cit.*) gave a purer sample of *o*-nitrodiphenylmethane (16·5 g. from 20 g. *o*-nitrobenzyl chloride), from which *o*-nitrobenzophenone (12 g.) was obtained on oxidation.

Reduction of the nitroketone by the method of Gabriel and Stelzner (*loc. cit.*) (stannous chloride and fuming hydrochloric acid), as well as by slight modifications thereof, was unsuccessful, the products being unchanged nitroketone or oily mixtures. Excellent yields resulted from the use of iron and acetic acid; the following is a typical experiment. A solution of the nitroketone (15 g.) in acetic acid (120 c.c.) at 90—95° was treated with iron filings (20 g.) added in 10—12 portions during 1½ hours with frequent shaking. Additions of 30 c.c. portions of water were made at the start of the reaction and after ¾ hour. After 1¾ hours the suspension was diluted with water and extracted with ether. The extract was washed with water, sodium carbonate solution, again with water, dried, and evaporated. A solution of the residue in aqueous alcohol gave *o*-aminobenzophenone (11·65 g., 89%), m. p. 103—105°.

Method III. *Large-scale Preparation of* o- *and* m-*Aminoacetophenone*.—The following conditions, based on those of Morgan and Moss and of Elson, Gibson, and Johnson (*loc. cit.*), were used in large-scale work. A mixture of acetophenone (90 c.c.) and acetic acid (5 c.c.) was added during ¾ hour to nitric acid (420 c.c., *d* 1·50) at a reaction temperature of 0° to − 3°. The solution was maintained for a further ½ hour at the same temperature, and then poured on to crushed ice. Two crystallisations from alcohol of the filtered and washed product gave *m*-nitroacetophenone of sufficient purity (m. p. 75—78°) for reduction. The material in the first alcoholic filtrate gave a further crop; total yield from 1110 g. of acetophenone, 608 g. (40%). Basification of the aqueous acid liquors with solid sodium carbonate and, finally, with aqueous sodium hydroxide, followed by ether-extraction, yielded mixed nitro-ketones amounting to 18—19% of the total neutral nitration products, but on the large scale this recovery was not considered worth the extra labour involved.

Reduction of *m*-nitroacetophenone was carried out in 90 g. batches; each batch was suspended in water (180 c.c.), and added during 1½ hours to a well-stirred suspension of iron filings (105 g.) in water (600 c.c.) and acetic acid (30 c.c.) at 75°. The mixture was then boiled gently for ¾ hour with continued stirring and filtered while hot, the amino-ketone separating rapidly as the filtrate cooled. The iron sludges from several batches were bulked and repeatedly extracted with boiling water; the extracts were combined with the filtrate from the amino-ketone, made just acid to Congo-red, evaporated to a small volume, and basified with ammonia. The total crude amino-ketone, always heavily contaminated with iron compounds, was readily purified by extracting the air-dried material with boiling ether in which it is sparingly soluble in the cold; the pure amine separated in hard, faintly yellow crusts, m. p. 98—99° (Morgan and Moss give m. p. 92—93°, and Elson, Gibson, and Johnson give m. p. 98—99°); yield, *ca.* 80% based on *m*-nitroacetophenone (32% based on acetophenone).

Reduction of crude *o*-nitroacetophenone (contained in the first alcoholic filtrate from the *m*-nitroketone, and freed as far as possible from this by refrigeration) was effected in 50 g. batches with concentrated hydrochloric acid (270 c.c.) and tin (60 g.) during 1 hour. The temperature was allowed to rise freely almost up to the boiling point, as reduction was incomplete if the control of temperature was too rigid (> 80°). Steam-distillation of the amine was essential;

experiments in which this was omitted gave a product contaminated with *m*-aminoacetophenone, which crystallised on standing. Pure *o*-aminoacetophenone had b. p. 130—131°/14 mm.; the oil possessed a remarkably persistent sweet smell in high dilution, and solidified in the ice-box to a crystalline mass (20·5%, based on acetophenone) which melted at room temperature (Elson, Gibson, and Johnson give m. p. 20°, b. p. 130·5°/14 mm.). Experiments using iron and acetic acid as the reducing medium gave unsatisfactory results.

***o*-Aminoacetophenone Derivatives.** 5-*Nitro*-2-*aminoacetophenone*.—*o*-Acetamidoacetophenone (25 g.) was added during ¾ hour to a mixture of nitric acid (125 c.c., *d* 1·48) and concentrated sulphuric acid (25 c.c.) at 0° ± 3°. After a further ¾ hour at the same temperature the solution was poured on to crushed ice; the crude product (25·1 g.), digested with boiling alcohol (500 c.c.) and filtered cold, gave pure 5-nitro-2-acetamidoacetophenone (23·4 g.), m. p. 153—154·5° (Borsche and Herbert, *loc. cit.*, give m. p. 152—153°), as yellow needles with an orange reflex. Although Borsche and Herbert describe the alkaline hydrolysis of this compound to the amine, the conditions are evidently critical, because when a suspension of the acetamido-compound (0·8 g.) in boiling alcohol (10 c.c.) was treated with 15% aqueous potassium hydroxide (2 c.c.), and the whole refluxed for 2 hours, the product (m. p. 308—310°) apparently consisted of the lepidine (V) formed by intermolecular condensation. The free amine was, however, readily obtained by acid hydrolysis; the acetamido-compound (23·4 g.) was heated on the steam-bath with alcohol, concentrated hydrochloric acid and water (115 c.c. of each), a further 115 c.c. of alcohol being added after 20 minutes. The alcohol was then allowed to boil off freely during ½ hour, and 5-nitro-2-aminoacetophenone (18·5 g.) was obtained in the pure state [m. p. 153—154° (depression with starting material); *lit.* m. p.'s, 151—152° (Borsche and Herbert), 150—151° (Bamberger, ref. 57)] by basification with ammonia.

5-Nitro-2-benzamidoacetophenone, prepared from the amine (10 g.), benzoyl chloride (10 c.c.), and pyridine (30 c.c.), and isolated by precipitation with alcohol (13·6 g., m. p. 193—194°; Borsche and Herbert give m. p. 193°), formed pale yellow fern-like aggregates from acetone–alcohol (Found: C, 62·9; H, 4·5. Calc. for $C_{15}H_{12}O_4N_2$: C, 63·4; H, 4·3%).

2-*Bromo*-5-*nitroacetophenone*.—A suspension of 5-nitro-2-aminoacetophenone (0·67 g.) in hydrobromic acid (6 c.c., *d* 1·45) and water (3 c.c.) was diazotised with 5% aqueous sodium nitrite, and the filtered solution added to one of cuprous bromide (prepared from 1·73 g. of copper sulphate crystals) in hydrobromic acid (4 c.c.). After ½ hour at room temperature, the suspension was warmed for ¼ hour on the steam-bath, and the resultant bromo-compound (0·53 g.) recrystallised from alcohol, from which it formed long, almost colourless blades, m. p. 85—87° alone and when mixed with a sample prepared by nitrating *o*-bromoacetophenone (Meisenheimer, Zimmer, and v. Kummer, *Annalen*, 1926, **446**, 20; Borsche and Herbert, *loc. cit.*).

Reduction of the nitro-ketone (1 g.), carried out in the manner described below for analogous compounds with acetic acid (6 c.c.), water (6 c.c.), and iron filings (1·5 g.), gave an oily amine, from which, by warming with acetic anhydride and then basifying with ammonia, 2-*bromo*-5-*acetamidoacetophenone* was obtained. This substance crystallised from ether in sheaves of long, soft, hydrated needles, which when dried at room temperature (0·1 mm.) first liquefied and then gradually changed to a brittle crystalline mass, m. p. 90·5—92°, possibly still slightly hydrated (Found: Br, 29·75. $C_{10}H_{10}O_2NBr$ requires Br, 31·2%). The corresponding *oxime* formed thin parallelepipeds, m. p. 199·5—201°, from aqueous alcohol, and contained halogen (Found: C, 44·5; H, 4·15. $C_{10}H_{11}O_2N_2Br$ requires C, 44·3; H, 4·1%).

5-*Amino*-2-*benzamidoacetophenone*.—5-Nitro-2-benzamidoacetophenone (13·6 g.) was reduced in the usual way with acetic acid (105 c.c.), water (100 c.c.), and iron filings (20 g.). After a reaction time of 1½ hours, the suspension was largely diluted with water, the mixture of iron sludge and crystalline amino-ketone filtered off, and the filtrate and mixed solids extracted successively with the same batches of chloroform (ether was unsatisfactory as an extractant). Evaporation of the washed and dried chloroform solution to small bulk followed by addition of ether, gave 5-*amino*-2-*benzamidoacetophenone* (11·3 g.) as a greenish-yellow microcrystalline solid, m. p. 141—143°; the amine separated from aqueous alcohol in small, yellow, prismatic needles, m. p. 143—145° (Found: C, 70·15; H, 5·1. $C_{15}H_{14}O_2N_2$ requires C, 70·8; H, 5·55%).

5-*Chloro*-2-*benzamidoacetophenone*.—The foregoing substance (0·3 g.) and 2N-hydrochloric acid (5 c.c.) gave a colourless suspension of the hydrochloride, which was diazotised with 2½% aqueous sodium nitrite;. owing to the insolubility of the hydrochloride, no reaction occurred until partial solution was effected by adding 2—3 c.c. of acetic acid, and complete formation of the diazonium salt was only achieved by eventual dilution with water, as the salt was very sparingly soluble in moderately concentrated acetic acid. Addition of the suspension of diazonium salt to a solution of cuprous chloride (2 g.) in concentrated hydrochloric acid (10 c.c.) produced a voluminous white precipitate, but nitrogen was not disengaged until the mixture was boiled for 5 minutes. The precipitated 5-*chloro*-2-*benzamidoacetophenone* crystallised from alcohol in long, silky, almost colourless needles, m. p. 140—141·5° alone and when mixed with an authentic specimen of the same m. p. (prepared from 5-chloro-2-aminoacetophenone obtained from *m*-aminoacetophenone) (Found: C, 65·7; H, 4·3. $C_{15}H_{12}O_2NCl$ requires C, 65·8; H, 4·4%).

2-*Benzamido*-5-*methoxyacetophenone*.—A suspension of 5-amino-2-benzamidoacetophenone (1·5 g.) in sulphuric acid (15 c.c. of 2N) was diazotised as completely as possible by the above procedure. The resultant suspension was added in portions during a few minutes to a boiling solution of copper sulphate (5 g.) in water (25 c.c.) and sulphuric acid (10 c.c. of 2N); when all had been added the mixture was boiled for a further 5 minutes. Some tar was precipitated and, on cooling, colourless crystalline material. The whole was extracted with chloroform, the phenol dissolved out by 0·6N aqueous sodium hydroxide and this solution, after extraction with ether, was acidified. The precipitated 5-*hydroxy*-2-*benzamidoacetophenone* was almost pure (0·48 g.) after one crystallisation from aqueous alcohol, a further crystallisation giving brittle, slender yellow needles, m. p. 204—205° (Found: C, 70·4; H, 5·4. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1%). The substance gave no perceptible ferric reaction; it formed a beautiful gold-coloured sodium salt, sparingly soluble in cold 4% sodium hydroxide solution. Addition of methyl sulphate to a warm solution of the phenol in excess of aqueous sodium hydroxide precipitated 2-*benzamido*-5-*methoxyacetophenone*. This crystallised from aqueous alcohol or chloroform–ligroin (b. p. 40—60°) in long yellow prisms, m. p. 117—118° (90—98° when mixed with the 3-methoxy-isomer) (Found: C, 71·3; H, 5·4. $C_{16}H_{15}O_3N$ requires C, 71·3; H, 5·6%).

5-*Bromo*-2-*acetamidoacetophenone*.—The following conditions gave a better yield than that obtained by Gibson and Levin (*loc. cit.*). To a shaken solution of *o*-acetamidoacetophenone (5·3 g.) in acetic acid (16 c.c.) bromine (1·6 c.c., diluted to 5 c.c. with acetic acid) was added during ¼ hour. Towards the end of the reaction more acetic acid (5—10 c.c.) was added to facilitate agitation of the mixture which had become almost solid. The temperature was maintained slightly above that of the laboratory by external cooling. When all the bromine had been added the suspension was diluted with water and the separated bromo-compound was twice crystallised from alcohol. It was obtained in colourless needles, m. p. 158—159·5° (6·1 g.), which gave no depression when mixed with a sample prepared from *m*-bromoacetophenone (*q.v.*).

***m*-Aminoacetophenone derivatives.** 2-*Nitro*-3-*amino*- *and* 2-*Nitro*-5-*amino*-*acetophenone*.—Powdered *m*-acetamidoacetophenone (30 g.) was added during ½ hour to a mixture of nitric acid (120 c.c., *d* 1·48) and concentrated sulphuric acid (48 c.c.) at a reaction temperature of − 10° to − 5°. After a further ½ hour at − 5°, the solution was poured

into ice-water (600 g.). The crude products from this and two similar runs were combined and crystallised from aqueous alcohol, giving 83 g. of a product which consisted principally of 2-*nitro*-5-*acetamidoacetophenone*, but could not satisfactorily be purified by crystallisation. A small scale nitration (2 g.), however, readily afforded this substance in the pure state; it was easily soluble in hot aqueous alcohol and separated in pale yellow needles, m. p. 146·5—148°, sparingly soluble in ligroin and benzene (Found: N, 12·9. $C_{10}H_{10}O_4N_2$ requires N, 12·6%).

The above mixture of nitrated acetamido-derivatives (83 g.) was heated for ¾ hour on the steam-bath with concentrated hydrochloric acid (400 c.c.) and water (400 c.c.). The mixture of crude nitro-amines (118 g. from 180 g. of *m*-acetamidoacetophenone), obtained by addition of ammonia, readily yielded 2-*nitro*-5-*aminoacetophenone* as the least soluble component on crystallisation from alcohol (85 g., 47% based on *m*-acetamidoacetophenone); this substance is moderately soluble in hot alcohol, and, from the cold solution, it was obtained in glistening golden, brittle plates, often having a red or purple tinge, m. p. 148—149° (depressed by admixture with 2-nitro-5-acetamidoacetophenone). The amine has a very high crystallising power (Found: C, 53·6; H, 4·2. $C_8H_8O_3N_2$ requires C, 53·3; H, 4·4%). The most soluble fraction in the alcoholic filtrate was a somewhat sticky solid which became granular on digestion with ether (18·3 g., m. p. 75—85°). This was warmed with concentrated hydrochloric acid (50 c.c.), and acetic acid was added until the hydrochloride just dissolved on boiling; on cooling, the salt [12·5 g., m. p. 108—109° (efferv.) after previous softening] separated in long yellow needles. Basification with ammonia and crystallisation from aqueous alcohol furnished 2-*nitro*-3-*aminoacetophenone* (9·2 g.) in bright reddish-orange prisms, m. p. 91—93°. This amine crystallises well from warm methanol and from hot benzene (Found: C, 53·1; H, 4·55. $C_8H_8O_3N_2$ requires C, 53·3; H, 4·4%). It showed little tendency to acetylate under normal conditions, as evidenced by the persistence of the colour, but the point was not investigated in detail.

2-*Nitro*-5-*cyanoacetophenone*.—2-Nitro-5-aminoacetophenone (7·2 g.) was dissolved in a hot mixture of concentrated hydrochloric acid (20 c.c.), water (40 c.c.), and acetic acid (20 c.c.). The suspension obtained on cooling was diazotised with sodium nitrite (2·8 g.) in water (20 c.c.), and the almost clear solution made neutral to Congo-red by addition of solid sodium carbonate. The cold solution was then added in portions during ½ hour to an ice-cold solution of cuprous cyanide (from 12·5 g. of copper sulphate; *Org. Synth.*, Coll. Vol. I, p. 500); reaction was very brisk even in the cold. After 1 hour at room temperature, the suspension was maintained at 60—65° for ¾ hour, and then cooled and extracted with ether. The extract was washed with water, and then with aqueous sodium hydroxide; the amount of phenol present was small, but it gave an intensely purple solution in alkali and could not be completely removed by several extractions. The solution was finally washed with water, dried, and evaporated. The residual red oil readily crystallised in part from alcohol, a further crystallisation giving almost pure *nitrile*, m. p. 109·5—112° (4·2 g.). An analytically pure sample had m. p. 112—113°, and separated from alcohol, in which it was only moderately soluble, in sheaves of brittle deep yellow needles (Found: N, 14·9. $C_9H_6O_3N_2$ requires N, 14·7%).

2-*Amino*-5-*cyanoacetophenone*.—A solution of the above nitro-nitrile (2 g.) in acetic acid (15 c.c.) was treated at 90—95° with iron powder (3 g.), added in portions during 1 hour; five additions of water (2 c.c. portions) were made, at the start of the reaction and at successive quarter-hour intervals. After a further ½ hour, the product was isolated by dilution and ether-extraction, yielding crude crystalline *amino-nitrile* (1·45 g.), which formed pale soft yellow needles from benzene, and light brown polyhedra, m. p. 132—133·5°, from benzene–ether containing a little ligroin. The amine dissolved very easily in the alcohols, was moderately soluble in benzene, sparingly in ether, and almost insoluble in ligroin (Found: N, 17·5. $C_9H_8ON_2$ requires N, 17·1%).

5-*Chloro*-2-*amino*- *and* 3-*Chloro*-2-*amino*-*acetophenone*.—(a) 2-Nitro-5-aminoacetophenone (14·4 g.) was diazotised as already described and the solution added in portions during 10—15 minutes to one of cuprous chloride (from 25 g. of copper sulphate) in concentrated hydrochloric acid (40 c.c.). Reaction was brisk at 5—10°, and after two hours at room temperature the mixture was finally heated at 55—60° for ¼ hour. The crude solid was filtered cold and digested with ether; 2 g. of 4 : 4′-*dinitro*-3 : 3′-*diacetyldiphenyl*, insoluble in ether, separated. This substance was almost insoluble in alcohol and acetone, and moderately soluble in chloroform and in hot acetic acid, from which it separated in light brown, thin needles, m. p. 213—213·5°; it was free from halogen (Found: C, 58·2; H, 3·4. $C_{16}H_{12}O_6N_2$ requires C, 58·5; H, 3·7%). The aqueous filtrate from the crude Sandmeyer product was extracted with ether and the extract combined with the ethereal filtrate from the diphenyl derivative. This solution was added to that from another experiment using 7·2 g. of the nitroaminoacetophenone (1 g. of diphenyl compound was obtained from this experiment) and the whole was washed with water, aqueous sodium hydroxide, and again with water. On distillation, 5-*chloro*-2-*nitroacetophenone* (13·3 g.) was obtained as a lemon-yellow oil (b. p. 162—163°/13 mm.) which rapidly crystallised. From aqueous methanol it was obtained in almost colourless, long needles, m. p. 63—65° (Found: Cl, 17·7. $C_8H_6O_3NCl$ requires Cl, 17·8%).

A solution of the nitro-ketone (25 g.) in acetic acid (125 c.c.) was treated at *ca.* 95° with iron powder (35 g.), added in portions during 80 minutes with frequent shaking; additions of water (30 c.c. portions) were made at 0, 20, 40, and 60 minutes from the beginning of the reaction. After 2 hours, the product was isolated by dilution with water and extraction with ether, 5-*chloro*-2-*aminoacetophenone* (56·8 g., 89%, from 75 g. of nitro-ketone) separating from ether–ligroin in soft, pale yellow leaflets, m. p. 65—66°, or bright yellow, brittle needles, m. p. 63—64° (Found: C, 56·4; H, 4·4. C_8H_8ONCl requires C, 56·6; H, 4·7%).

5-*Chloro*-2-*acetamidoacetophenone*, prepared with 2·5 parts of acetic anhydride, was appreciably soluble in warm ether, easily soluble in hot alcohol, and sparingly soluble in each cold solvent. From alcohol it crystallised in colourless silky needles, m. p. 134·5—135·5° (Found: N, 7·15. $C_{10}H_{10}O_2NCl$ requires N, 6·6%). The parent amine was readily regenerated by short heating with a mixture of alcohol, water and concentrated hydrochloric acid (1 : 1 : 1).

(b) A solution of *m*-aminoacetophenone (37·8 g.) in hydrochloric acid (2N, 285 c.c.) was diazotised with 20% aqueous sodium nitrite, and the solution added in portions during 20 minutes to one of cuprous chloride (from 87·5 g. of copper sulphate) in concentrated hydrochloric acid (140 c.c.) at 10°. After 2 hours at room temperature, and ½ hour at 60—70°, the mixture was extracted with ether. Distillation of the dried product (2 batches) yielded *m*-chloroacetophenone as a colourless oil, b. p. 110—111°/12 mm. (70 g., 81·5%). The residue from the distillation solidified on cooling, and was obtained as a sticky solid from alcohol. Repeated crystallisation from ethyl acetate gave a substance, presumably 3 : 3′-*diacetyldiphenyl*, which crystallised in halogen-free, pale brown, stout prisms (0·5 g.), m. p. 123—124° (Found: C, 80·7; H, 5·7. $C_{16}H_{14}O_2$ requires C, 80·65; H, 5·9%).

This chloroketone (17·5 g.) was added during 10—15 minutes to nitric acid (85 c.c., *d* 1·5) at − 10° to − 5°. After a further 20 minutes in the freezing-mixture, the solution was allowed to reach 5° during ½ hour, and then poured into ice-water. The solid nitration product (116 g., 89%) was fractionally crystallised from ether and yielded 5-chloro-2-nitroacetophenone (65 g.), m. p. 62—64°, which formed large heavy polyhedra; it did not depress the m. p. of the sample prepared in (a). The residual mixture of nitro-compounds could not be purified by crystallisation; distillation (short Vigreux column) gave a constant-boiling mixture (184—186°/24 mm.). The mixture was therefore reduced with iron and acetic acid as already described for similar cases, and the resultant mixture, consisting of 5-chloro-2-amino-acetophenone (mainly) and a little 3-*chloro*-2-*aminoacetophenone*, was separated by either of the following methods:

(i) The mixture (1 part) was warmed with a mixture of ordinary (4 parts) and concentrated (0·4 part) hydrochloric acid, and the solution decanted from the insoluble oil (A), which was re-extracted with the same amount of fresh acid. The gummy hydrochloride which separated from the combined and concentrated extracts was digested with ether (extract B) and filtered; it had m. p. 170—173° (decomp.), and on basification gave 5-chloro-2-aminoacetophenone, m. p. 65—66°, after crystallisation from aqueous alcohol. Treatment of the oil (A) with a mixture of acetic acid and concentrated hydrochloric acid gave a hydrochloride (C), and, after dilution of the filtrate with water, an ether-soluble crystalline substance (D). The hydrochloride (C) was digested with ether, and the extract combined with (B) and (D) and the solvent removed. The crystalline product which separated from a small volume of benzene–ligroin (b. p. 60—80°) was dissolved in warm ligroin, and from the solution, decanted from a little resin and concentrated, 3-chloro-2-aminoacetophenone separated in brittle, deep yellow prisms, m. p. 52—54° (Found: Cl, 21·5. C_8H_8ONCl requires Cl, 20·9%). The amine, which crystallised readily from aqueous alcohol in pale yellow needles, was also obtained by basification of the hydrochloride (C), m. p. 118—120°.

(ii) The mixture of amines (1 part) was heated for ½ hour on the steam-bath with acetic anhydride (1·5 parts); the solid which separated on cooling was filtered and washed with ether; it was pure 5-chloro-2-acetamidoacetophenone. The acetic anhydride filtrate was taken to dryness in an evacuated desiccator, and the crystalline residue digested with warm ligroin (b. p. 60—80°) until the final extract showed no tendency to crystallise; a small residue (*ca.* 5% of the mixed amines taken) remained (A). The material in the ligroin extracts was separated by means of ether and ligroin into 3-chloro-2-amino- and 5-chloro-2-acetamido-acetophenone, of which the former is considerably more soluble (particularly in ether) than the latter. The substance (A) was digested twice with warm ether to remove 5-chloro-2-acetamidoacetophenone; its m. p. 161—162·5° was unchanged by crystallisation from alcohol and the substance was obtained in colourless, brittle prisms (0·7 g.) (Found: C, 57·1; H, 5·05. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·8%). It was identified as 3-*chloro*-2-*acetamidoacetophenone* by hydrolysis to the amine as described for the 5-chloro-derivative.

The amount obtained of the 5-chloro-amine (either free or as acetyl derivative) from 101 g. of *m*-chloroacetophenone was 72·7 g., and that of the 3-chloroamine was 8·5 g. (57% and 6·7%, respectively, based on *m*-aminoacetophenone).

3-*Chloro*-2-*nitroacetophenone*.—2-Nitro-3-aminoacetophenone (3·6 g.) was dissolved in a warm mixture of 2N and concentrated hydrochloric acid (36 c.c., 1 : 1), and the suspension obtained by cooling in ice was diazotised with 20% aqueous sodium nitrite (7 c.c.). The Sandmeyer reaction was carried out as already described for *m*-chloroacetophenone, using 6·3 g. of copper sulphate. The crude product was dissolved in ether and filtered from insoluble matter (*ca.* 0·5 g.); 3-*chloro*-2-*nitroacetophenone*, recovered from the filtrate, separated from alcohol in yellow leaflets or short prismatic needles (2·5 g.), m. p. 95—96° (Found: C, 48·5; H, 3·1. $C_8H_6O_3NCl$ requires C, 48·1; H, 3·0%). Reduction of the substance (1·5 g.) with acetic acid (7·5 c.c.), water (8 c.c.), and iron filings (2 g.) in the manner already described gave 3-chloro-2-aminoacetophenone (1 g.), identified by m. p. and mixed m. p.

2 : 3-*Diaminoacetophenone*.—Reduction in the usual manner of 2-nitro-3-aminoacetophenone (1 g.) with acetic acid (10 c.c.), water (10 c.c.), and iron powder (1·5 g.) gave the *diamine*, which formed leaflets or thin prisms from benzene, was easily soluble in alcohol, and separated from aqueous alcohol in long, soft, deep yellow compact needles, m. p. 121—122·5° (Found: C, 64·1; H, 6·55. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%). The substance dissolved easily in cold 2N hydrochloric acid, and was not precipitated therefrom by water; the hydrochloride was sparingly soluble in cold concentrated hydrochloric acid. When the diamine (100 mg.) was added to a solution of phenanthraquinone (140 mg.) in boiling alcohol (15 c.c.), the *phenazine* separated almost immediately. The solid was filtered after a few minutes' refluxing and washed with hot alcohol (200 mg., m. p. 224—226°); it separated from acetic acid, in which it was sparingly soluble, in small, pale yellow needles, m. p. 225—225·5° (Found: C, 81·65; H, 4·2. $C_{22}H_{14}ON_2$ requires C, 82·0; H, 4·35%).

Nitration of m-*Methoxyacetophenone*.—*m*-Methoxyacetophenone was prepared as follows. *m*-Aminoacetophenone (27 g.) was dissolved in 2N sulphuric acid (270 c.c.), and the solution, after diazotisation with 20% aqueous sodium nitrite, was added during ½ hour to a solution of copper sulphate crystals (50 g.) in N-sulphuric acid (200 c.c.) at 70—80°. The suspension was then boiled for 10 minutes, cooled, extracted with ether, and the phenol extracted with dilute sodium hydroxide. After acidification of the latter, the phenol was isolated with ether and crystallised (15 g.) from benzene containing a little alcohol in light brown nodules, m. p. 94—96° (Besthorn, Banzhaf, and Jaeglé, *Ber.*, 1894, **27**, 3035, give m. p. 96°). Methylation of this material with methyl sulphate (15 c.c.) in alkaline solution gave *m*-methoxyacetophenone (14·5 g., 48% based on *m*-aminoacetophenone), a colourless sweet-smelling oil, b. p. 125—126°/16 mm. (v. Auwers, *Annalen*, 1915, **408**, 246, gives b. p. 125—126°/12 mm.; Wahl and Silberzweig, *Bull. Soc. Chim.*, 1912, [4], **11**, 68, give b. p. 127—128°/16—17 mm.).

(a) The methoxy-ketone (5·7 g.) was added dropwise during 20 minutes to a mixture of nitric acid (25 c.c., *d* 1·48) and concentrated sulphuric acid (10 c.c.) at a reaction temperature of − 10° to − 5°; nitration was rapid, vigorous, and strongly exothermic. The mixture was poured on to ice after a further 10 minutes, and filtered when granular. No organic acid was present. Several crystallisations from benzene furnished, as least soluble product, a *dinitromethoxyacetophenone*, m. p. 141·5—142·5°, which separated in colourless prismatic needles (Found: C, 45·0; H, 3·4; N, 12·0. $C_9H_8O_6N_2$ requires C, 45·0; H, 3·3; N, 11·7%). The material in the filtrates from this substance was a mixture which could not be separated by means of the common solvents; a representative fraction crystallised from alcohol in dull prisms, m. p. 97—102° (Found: N, 11·9%).

(b) The ketone (5 g.) was dissolved in nitric acid (30 c.c., *d* 1·42) at 5°. No appreciable evolution of heat occurred, and the solution was left at room temperature for 18 hours. Experiments showed that the yield of product was slightly increased by keeping the mixture for a final hour at 40—45°, but that further increase in the time of heating was without significant effect; violent oxidation set in above this temperature. Crystallisation from alcohol of the product obtained by precipitation with water gave almost colourless, thin plates (3 g.), m. p. 128·5—129·5° (depressed when mixed with the foregoing dinitro-compound), of 2-*nitro*-3-*methoxyacetophenone* (Found: C, 55·1; H, 4·6. $C_9H_9O_4N$ requires C, 55·4; H, 4·6%).

2-*Amino*-3-*methoxyacetophenone*.—This *amine*, isolated in almost quantitatve yield (ether-extraction) after the nitro-ketone (2·8 g.) had been reduced in the usual way with acetic acid (15 c.c.), water (15 c.c.), and iron filings (4 g.), crystallised from aqueous alcohol in hard, pale yellow rhombs, m. p. 64·5—66° (Found: N, 8·6. $C_9H_{11}O_2N$ requires N, 8·5%). The N-*benzoyl* derivative, prepared in pyridine solution, formed pale yellow prisms, m. p. 109—110°, from chloroform–ligroin (b. p. 40—60°) (Found: C, 71·7; H, 5·8. $C_{16}H_{15}O_3N$ requires C, 71·3; H, 5·6%).

8-*Methoxy*-2 : 4-*dimethylquinoline*.—A mixture of 2-amino-3-methoxyacetophenone (0·7 g.), acetone (2 c.c.), and a solution of sodium hydroxide (5 g. in 10 c.c.) in water (20 c.c.) and alcohol (80 c.c.) was refluxed for 4 hours, after which the solution was concentrated, water added, and the alcohol finally evaporated as completely as possible. The crude *base*, which crystallised on scratching, was recrystallised from aqueous alcohol and obtained in long needles, which lost solvent before melting and changed to a dull, brittle mass, m. p. 112—113° (Found: C, 76·7; H, 6·2. $C_{12}H_{13}ON$ requires C, 77·0; H, 6·95%).

m-*Bromoacetophenone*.—A solution of *m*-aminoacetophenone (38 g.) in hydrobromic acid (100 c.c., *d* 1·5) and water (200 c.c.) was diazotised with 20% aqueous sodium nitrite. The solution was added in portions during ½ hour at room

temperature to a solution of cuprous bromide (from 87·5 g. of copper sulphate) in hydrobromic acid (140 c.c., *d* 1·5). The reaction was noticeably less vigorous than in the preparation of *m*-chloroacetophenone. From the mixture, after 1½ hours at room temperature and ½ hour at 50—60°, the product was isolated as already described for *m*-chloroacetophenone. From two such batches the colourless oil had b. p. 133°/19 mm. (Elson, Gibson, and Johnson give b. p. 131°/16 mm.).

Nitration of m-*Bromoacetophenone.*—The ketone (30 g., 20·5 c.c.) was added during ½ hour to nitric acid (180 c.c., *d* 1·5) at − 10° to − 6°. After a further 40 mins. at − 10° to − 5° the mixture was poured into ice-water (900 g.). *m*-Bromoacetophenone (143·7 g.) gave pure 5-bromo-2-nitroacetophenone (106·4 g.), m. p. 96—97° after several crystallisations from alcohol (Elson, Gibson, and Johnson give m. p. 98°), and a low-melting mixture (A) (62·8 g.).

3-*Bromo*-2-*nitroacetophenone.*—This substance was prepared from a solution of 2-nitro-3-aminoacetophenone (2 g.) in 10 c.c. each of acetic acid, water, and hydrobromic acid (*d* 1·5) by diazotisation with 10% aqueous sodium nitrite and addition to cuprous bromide solution (from 5·5 g. of copper sulphate); it formed small, yellow leaflets (1·7 g.), m. p. 97—98° (depressed when mixed with the 5-bromo-isomer), from aqueous alcohol (Found: C, 39·5; H, 2·4 $C_8H_6O_3NBr$ requires C, 39·4; H, 2·5%).

3-*Bromo*-2-*aminoacetophenone.*—(a) This *amine* (1·1 g.) was obtained when the foregoing substance (1·5 g.) was reduced in the usual way with iron filings (2·5 g.), acetic acid (8 c.c.) and water (8 c.c.). It showed well-defined dimorphism; a sample, freshly crystallised from ligroin (b. p. 40—60°), formed long yellow needles, m. p. 39—40° (unchanged after 10 hours/0·1 mm.) (Found: C, 44·7; H, 3·6. C_8H_8ONBr requires C, 44·9; H, 3·7%). After 2 months, the m. p. had risen to 62—63°, and a fresh sample, crystallised from ether, seemed to consist entirely of the high-melting variety in well-formed polyhedra.

(b) The mixture (A), referred to above, of bromonitroacetophenones was reduced in the usual way with iron filings (90 g.), acetic acid, and water, giving 53·3 g. of mixed amines. The oil was dissolved in a mixture of equal volumes of concentrated and ordinary hydrochloric acid (230 c.c.), and the crude solid which separated was digested with ether and crystallised from glacial acetic acid containing a little concentrated hydrochloric acid. The same procedure was applied to other crops of hydrochloride obtained by concentrating the original solution, 18·4 g. of 5-bromo-2-aminoacetophenone hydrochloride, m. p. 184—185° (decomp.) (Gibson and Levin, *loc. cit.*, give m. p. 180—181°), being obtained. All filtrates were combined, basified, extracted with ether and the oil so obtained was heated for ¼ hour on the steam-bath with acetic anhydride (50 c.c.). Digestion with ether of the solid obtained by basifying the diluted solution with ammonia gave pure 5-bromo-2-acetamidoacetophenone (4·3 g.), m. p. 158—159° (identified by mixed m. p. with a sample prepared from *o*-acetamidoacetophenone). The ether-soluble material yielded, as sole crystalline product, almost pure 3-bromo-2-aminoacetophenone (23·7 g.), m. p. 54—56° [raised by admixture with the pure amine, m. p. 62—63°, described in (a)].

5-Bromo-2-aminoacetophenone crystallised from aqueous alcohol or ether–ligroin in pale yellow needles which invariably had m. p. 84—85°; Gibson and Levin describe the compound as colourless plates, m. p. 86—88°. 5-*Bromo*-2-*benzamidoacetophenone*, prepared in pyridine solution, formed almost colourless, long, silky needles, m. p. 134·5—135·5°, from alcohol (Found: C, 56·4; H, 3·5. $C_{15}H_{12}O_2NBr$ requires C, 56·6; H, 3·8%).

Method IV.—*Acylation Experiments with* **3**: 5-*Dinitro*-2-*aminobenzophenone.*—Treatment of the amino-ketone with its own weight of benzoyl chloride in excess of pyridine at 100° for 3 hours gave the N-*benzoyl* derivative (25%; with larger excess of benzoyl chloride, *ca.* 40%), which crystallised from methanol in colourless silky needles (plates from benzene–alcohol), m. p. 198° (Found: C, 61·1; H, 3·1. $C_{20}H_{13}O_6N_3$ requires C, 61·4; H, 3·35%). Unchanged amino-ketone was isolated in 50% yield from the mother-liquors.

The amino-ketone was recovered unchanged after being heated with acetic anhydride in pyridine, and also after being refluxed with acetic anhydride, either alone or with the addition of fused sodium acetate or concentrated sulphuric acid (in this case some decomposition occurred).

Grateful acknowledgment is made of a grant from the Research Fund of the Durham Colleges, of grants and help of various kinds from Imperial Chemical Industries, Limited, Dyestuffs Division, and of assistance from Mr. J. Owen in the preparation of *o*- and *m*-aminoacetophenone.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, March 6th*, 1945.]