CL.—*The Basic Character of the Acetoxylidides and its Influence on the Course of their Substitution.*

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IN continuance of earlier work on substituted diphenic acids, it was desired to examine diphenyl-2 : 6 : 2′ : 6′-tetracarboxylic acid (Mayer, *Ber.*, 1911, **44**, 2301) and its derivatives. During the preparation of the *m*-2-xylidine required for this purpose, an interesting property of its acetyl derivative was observed. In one experiment, for example, in which aceto-*m*-2-xylidide had been boiled with 6 litres of concentrated hydrochloric acid, 440 g. crystallised when the solution was diluted with an equal bulk of water and cooled, but a further 200 g. were precipitated when the liquor was neutralised. Although such treatment with hydrochloric acid is a very usual method of purifying the compound, its very noteworthy basicity seems completely to have escaped notice by previous workers and is not mentioned in the recent paper of Morgan and Hickinbottom (*J. Soc. Chem. Ind.*, 1926, **45**, 2228). It is in fact sufficiently pronounced to permit of the preparation of salts by mixing the acetyl derivative with moderately concentrated mineral acids. The *hydrobromide* and *nitrate*, thus obtained, are stable substances, but the hydrochloride gradually loses hydrogen chloride on exposure to the air. Characteristically crystalline, stable hydrobromides of aceto-*m*-4-, -*p*-, -*o*-3-, and -*o*-4-xylidides and of acetomesidide have been similarly prepared and analysed, so that it would appear that the basic properties of these acetyl derivatives are due at least in part to the general effect of the introduction of methyl groups into the molecule, irrespective of their orientation. Although salts of acetanilide have been prepared, they are unstable in presence of water (Noelting and Weingärtner, *Ber.*, 1885, **18**, 1340; Wheeler, Barnes, and Pratt, *Amer. Chem. J.*, 1897, **19**, 676; Knorr, *Annalen*, 1888, **245**, 375).

Whilst it will be of interest to pursue this matter further in a general manner, it has been first followed up more particularly in connexion with the original purpose of these experiments, namely, the formation of substitution derivatives of *m*-2-xylidine. Previous workers had shown that bromination of the base in glacial acetic acid solution occurs, as might be expected, in the 5-position, but that 4-nitro-derivatives are obtained from both the base and its acetyl derivative (Noelting and Stoecklin, *Ber.*, 1891, **24**, 568; Noelting, Braun, and Thesmar, *Ber.*, 1901, **44**, 2259). Our observations on salt formation suggested that this might be the factor determining the course of nitration, and the idea gained credence when it was found that bromination of the acetyl derivative in chloroform solution occurs in the 5-position, in glacial acetic acid solution chiefly in the 5- but also, as Noelting and Pick had observed, in the 4-position, and in hydrobromic or sulphuric acid suspension very largely, if not solely, in the 4-position. We therefore expected to be able to obtain 5-nitro-*m*-2-xylidine by the use of m-*nitrobenzo*-m-2-*xylidide*. Although, however, this compound is not noticeably basic in character, it also yielded a 4-*nitro*-derivative, whether sulphuric acid were present or not. This result perhaps does not entirely exclude salt formation as a contributory factor in the behaviour of the acetyl derivative, but it is clearly not a necessary one. This became still more apparent when it was found that bromination of the free base in presence of hydrobromic acid, as of acetic acid, occurs in the 5-position.

The complexity of the problem was not diminished when, for purposes of comparison, the behaviour of *m*-4-xylidine was considered. Although the directive influences in this compound and its derivatives would be expected to accord very closely with those in their 2-isomerides, the two series are not in all respects analogous in behaviour. Whilst, for example, bromination of the base in glacial acetic acid solution occurs in the 5-position (Noelting, Braun, and Thesmar, *loc. cit.*), its acetyl derivative is attacked in the 6-position (Genz, *Ber.*, 1870, **3**, 225; Noelting, Braun, and Thesmar, *loc. cit.*). Not only have we confirmed the latter observation, but we have also found that the result is the same in chloroform solution, as well as in presence of hydrobromic acid. Again, not only the base, but also its acetyl derivative, in presence of sulphuric acid suffers nitration in the 6-position, whereas nitric acid alone converts the acetyl derivative into 5-nitroaceto-*m*-4-xylidide. By similar variations of experimental conditions, 5- or 6-*nitro*-derivatives are obtained from m-*nitrobenzo*-m-4-*xylidide*, but, as already mentioned, this is not applicable to the 2-isomeride.

There would seem to be no very obvious way of embracing these results within one generalisation, so that detailed discussion may be reserved until the behaviour of the other xylidines has been examined. But it would seem that even in the commonest forms of substitution, as well as in mercuration (Coffey, J., 1925, **127**, 1029; Burton, Hammond, and Kenner, J., 1926, 1802), the nature of the entering substituent requires consideration. Also it is clear that the widely accepted doctrine of salt formation as a determining factor on the course of the nitration of amines is at least not unreservedly applicable to every case.

EXPERIMENTAL.

On the addition of hydrobromic acid, b. p. 126°, to aceto-*m*-2-xylidide, the compound passed into solution, but almost immediately small needles of the *hydrobromide* separated (Found: N, 6·0; equiv., 245. $C_{10}H_{13}ON,HBr$ requires N, 5·7%; equiv., 244). By dilution with water a clear solution was obtained, from which the original acetyl derivative was precipitated on the addition of alkali. (This observation applies equally to the other salts to be described.) In each case the salt was prepared for analysis by thoroughly draining it on porous earthenware and finally drying it in a vacuum over solid potassium hydroxide for 12 hours. The *nitrate* was obtained in hexagonal prisms by use of a mixture of nitric acid (*d* 1·42) with three volumes of water (Found: N, 12·4; equiv., 226·3. $C_{10}H_{13}ON,HNO_3$ requires N, 12·4%; equiv., 226). The sulphate also was prepared, but it could not be completely freed from sulphuric acid. *Aceto*-m-4-*xylidide hydrobromide* formed minute prisms (Found: equiv., 247). *Aceto*-m-4-*xylidide hydrochloride* separated from concentrated hydrochloric acid in plates (Found: equiv., 202. $C_{10}H_{13}ON,HCl$ requires equiv., 199·5). *Aceto*-p-*xylidide hydrobromide* forms hexagonal leaflets (Found: equiv., 243), and *aceto*-o-3-*xylidide hydrobromide* rectangular plates (Found: equiv., 247). *Aceto*-o-4-*xylidide hydrobromide*, prismatic crystals, is hydrated (Found: equiv., 261). Acetomesidide was prepared by Feith and Davies (*Ber.*, 1891, **24**, 3546) from the oxime of methyl mesityl ketone, but it can also be easily obtained by boiling a solution of the base (4 g.) in benzene (10 c.c.) with acetic anhydride (4 c.c.). It also furnished a stable *hydrobromide*, which crystallised in small, hexagonal prisms (Found : equiv., 256. $C_{11}H_{15}ON,HBr$ requires equiv., 258).

Substitution in m-2-*Xylidine and its Derivatives.*

Bromination Experiments.—For the purpose of these experiments, authentic 4-bromo-*m*-2-xylidine was prepared by Noelting, Braun, and Thesmar's method (*Ber.*, 1901, **34**, 2261). In this connexion, 4-nitro-*m*-2-xylidine was conveniently converted into 2 : 4-dinitro-*m*-xylene by oxidising a suspension of the base (10 g.) in ice-water (375 g.) with the paste prepared from potassium persulphate (50 g.) and sulphuric acid (100 g.), and oxidising the resulting crude nitroso-derivative with nitric acid (*d* 1·48 ; 75 c.c.) at 40—45°. Reduction of the dinitro-compound by ammonium sulphide as prescribed by the above authors is very slow and is much more effectively achieved by gradual addition of a solution prepared from crystallised (the commercial product gives less satisfactory results) sodium sulphide (7·5 g.), sulphur (2 g.), and water (30 c.c.) to a boiling suspension of the dinitro-compound (5·8 g.) in water (200 c.c.). Furthermore, the use of tin and hydrochloric acid (17 c.c.) was found more satisfactory for reduction of 4-bromo-3-nitro-*m*-xylene (8 g.) than the procedure adopted by Noelting, Braun, and Thesmar.

(*a*) When a solution of aceto-*m*-2-xylidide (2 g.) and bromine (2 g.) in chloroform (10 c.c.) was left in contact with iron wire at the ordinary temperature for 12 hours, the product was 5-bromoaceto-*m*-2-xylidide (Found: N, 5·85%), which was obtained in the pure condition (m. p. 194—195°) after one crystallisation from alcohol.

(*b*) On the other hand, if the acetyl derivative and bromine in the same proportion were allowed to interact at the ordinary temperature for ½ hour in glacial acetic acid (20 c.c.), the 5-bromo-derivative was obtained in the pure condition only after two crystallisations from dilute alcohol, and fractions of lower melting point were recovered from the mother-liquors. These were not further investigated in view of the definite statement of Noelting, Braun, and Thesmar (*loc. cit.*, p. 2262) that the 4-bromo-derivative is also produced under such conditions.

(*c*) The finely ground suspension resulting from the mixture of aceto-*m*-2-xylidide (12 g.) with hydrobromic acid (b. p. 126°; 120 c.c.) was first converted at the ordinary temperature by addition of bromine (12 g.) into a pasty mass, which resolidified after some time. The product collected after 12 hours was 4-bromoaceto-*m*-2-xylidide (12 g.), which was obtained in the pure condition after two crystallisations from dilute alcohol. It then melted at 135—136° and did not depress the melting point of an authentic specimen. A similar result was obtained when sulphuric acid (110 c.c.) was employed in place of the hydrobromic acid. Since the melting-point test of identity is sometimes fallible, the nature of the product was further established by hydrolysing it (10 g.) by boiling for 4 hours with 50% sulphuric acid (although Noelting, Braun, and Thesmar, *loc. cit.*, p. 2260, state that they were unable to effect a satisfactory hydrolysis). The base (6·5 g.), b. p. 159—161°/24—25 mm., furnished a m-*nitrobenzoyl* derivative, which separated from alcohol in small rosettes, m. p. 170—171° (Found : N, 8·15. $C_{15}H_{13}O_3N_2Br$ requires N, 8·0%). Its melting point was depressed by addition of the isomeric compound described below.

(*d*) Bromination of *m*-2-xylidine in presence of glacial acetic acid was found by Noelting, Braun, and Thesmar to furnish the 5-bromo-derivative, but no yield was recorded. Repetition of their experiment gave the pure material in a yield of 88%, and no indication of the 4-isomeride was obtained on acetylation.

(*e*) Again, the addition of bromine (8 g.) to a solution of the base (6 g.) in hydrobromic acid (b. p. 126°; 40 c.c.) at 15—20° yielded the 5-bromo-derivative, together with some oily material (2·3 g.). This oil was recovered by extraction of the porous earthenware used to dry the crude product, and on acetylation it was found to consist essentially of the 5-bromo-base. This was further characterised by its m-*nitrobenzoyl* derivative, which separated from dilute acetic acid in long needles, m. p. 186—187° (Found : N, 8·2. $C_{15}H_{13}O_3N_2Br$ requires N, 8·0%).

Chlorination Experiments.—4-*Chloro*-2-*nitro*-m-*xylene*, prepared from 2-nitro-*m*-4-xylidine, separated from alcohol in yellow needles, m. p. 72—73° (Found : N, 7·9. $C_8H_8O_2NCl$ requires N, 7·5%). It was converted by means of tin and hydrochloric acid into 4-*chloro*-m-2-*xylidine*, b. p. 136—138°/17 mm. (Found : N, 9·1. $C_8H_{10}NCl$ requires N, 9·0%). 4-*Chloroaceto*-m-2-*xylidide* crystallises from dilute alcohol in white needles, m. p. 146—147° (Found : N, 7·2. $C_{10}H_{12}ONCl$ requires N, 7·1%).

5-*Chloro*-2-*nitro*-m-*xylene*, prepared from 2-nitro-*m*-5-xylidine, forms plates, m. p. 44—45° (Found : N, 7·75%). 5-*Chloro*-m-2-*xylidine* crystallises in long, silky needles, m. p. 44—45° (Found : N, 9·0%); it was characterised by its *acetyl* derivative, which separates from dilute alcohol in plates, m. p. 195° (Found : N, 7·0%).

A solution of *m*-2-xylidine (25 g.) in glacial acetic acid (150 c.c.) was treated at 10—15° with dry chlorine, generated from potassium permanganate (15 g.). After 2 hours, the dark blue mixture was diluted, rendered alkaline, and distilled in steam. The first portion of distillate was separated as likely to contain any unchlorinated material, and the oil in it did not solidify. Subsequent portions, however, solidified and furnished 5-chloro-*m*-2-xylidine (15 g.),

m. p. 42°, which was identified by direct comparison with authentic base. A considerable proportion of the material was not volatile in steam, and probably consisted of more highly chlorinated material. Similar results are well known to follow chlorination of the toluidines and their acetyl derivatives, and render chlorinations not very suitable for the present purpose. For the time, therefore, this method was not further pursued.

Nitration Experiments.—(*a*) m-*Nitrobenzo*-m-2-*xylidide*, prepared from *m*-2-xylidine and *m*-nitrobenzoyl chloride in presence of pyridine, separated from alcohol in needles, m. p. 188—189° (Found: N, 10·6. $C_{15}H_{14}O_3N_2$ requires N, 10·4%). A mixture of nitric (*d* 1·42; 1·6 g.) and sulphuric (10 g.) acids was added at 0° to a solution of *m*-nitrobenzo-*m*-2-xylidide (6·5 g.) in sulphuric acid (20 g.). The product was isolated after 12 hours in small, yellow needles, m. p. 165—166° (5·5 g.) after crystallisation from alcohol. Its constitution was established both by its identity with authentic m-*nitrobenzo*-4-*nitro*-m-2-*xylidide*, m. p. 170·5°, prepared from 4-nitro-*m*-2-xylidine (Found: N, 13·5. $C_{15}H_{13}O_5N_3$ requires N, 13·3%), and by hydrolysis with 75% sulphuric acid to 4-nitro-*m*-2-xylidine, m. p. 81°.

(*b*) A similar result was obtained when the m-*nitrobenzoyl* derivative (3 g.) was dusted into nitric acid (*d* 1·42; 15 c.c.) at 25°, and the temperature finally allowed to rise to 50°.

Substitution in m-4-*Xylidine and its Derivatives.*

Bromination Experiments.—(*a*) The statement that aceto-*m*-4-xylidide undergoes bromination in the 6-position in glacial acetic acid solution (Genz, *loc. cit.*; Noelting, Braun, and Thesmar, *loc. cit.*) was confirmed.

(*b*) A mixture of bromine (4 g.) with aceto-*m*-4-xylidide (4 g.) and hydrobromic acid (b. p. 126°; 60 c.c.) was not decolorised even after 8 days. The product, after repeated crystallisation from dilute alcohol, yielded 6-bromoaceto-*m*-4-xylidide (1 g.), m. p. 168—169°, whilst by hydrolysis of the residues with 50% sulphuric acid 1 g. of the corresponding base, m. p. 96—97°, was recovered.

(*c*) The acetyl derivative (5 g.) was very slowly attacked at the ordinary temperature by bromine (5 g.) in chloroform solution (50 c.c.) in presence of iron wire. The product, isolated after 24 hours, yielded 1 g. of 6-bromo-*m*-4-xylidine, m. p. 96—97°. Another experiment showed that bromination was far from complete even after 6 weeks.

Nitration Experiments.—(*a*) m-*Nitrobenzo*-m-4-*xylidide* forms white needles, m. p. 162—163° (Found: N, 10·4. $C_{15}H_{14}O_3N_2$ requires N, 10·4%). The compound (3 g.) was dusted into nitric acid (*d* 1·42; 15 c.c.) at 5—10°, and the temperature was allowed to rise to 30°; the product, after crystallisation from glacial acetic acid, furnished 2·4 g. of material, m. p. 209—210°, identical with authentic m-*nitrobenzo*-5-*nitro*-m-4-*xylidide*, m. p. 210—211° (Found : N, 13·4. $C_{15}H_{13}O_5N_3$ requires N, 13·3%).

(*b*) Addition of a mixture of nitric acid (*d* 1·48; 1·6 g.) with sulphuric acid (10 g.) to a solution of *m*-nitrobenzo-*m*-4-xylidide (5 g.) in sulphuric acid (20 g.) at 0° furnished a product (5 g.), from which needles, m. p. 217—218°, were obtained by crystallisation from glacial acetic acid. The essential nature of the material followed from its identity with authentic m-*nitrobenzo*-6-*nitro*-m-4-*xylidide*, m. p. 224—225° (Found : N, 13·3%), and from its hydrolysis by alcoholic sodium hydroxide to 6-nitro-*m*-4-xylidine, m. p. 117—118°.

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