CCCLXXXII.—*The Acylation of Diazomethane. The Effects of Variations in the Conditions on the Extent of Formation of Chloroacetophenone from Benzoyl Chloride.*

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NIERENSTEIN and his collaborators (for references, see this vol., p. 1311) have described numerous cases of the formation of chloromethyl ketones in high yield as the result of the action of diazomethane on various acid chlorides in ethereal solution.

In the case of *o*-nitrobenzoyl chloride, however, Dale and Nierenstein (*Ber.*, 1927, **60**, 1026) found that the product was "chlornitraldin," $C_8H_6O_3NCl$, which was supposed to be the chloro-derivative of a very interesting substance, $C_8H_7O_3N$, termed nitraldin and obtained by Arndt and Partale (*Ber.*, 1927, **60**, 446) by the action of diazomethane on *o*-nitrobenzaldehyde. Formaldehyde was formed from "chlornitraldin" under the same conditions as from nitraldin itself. Arndt, Eistert, and Partale (*Ber.*, 1927, **60**, 1364) were unable to reproduce the preparation of "chlornitraldin" and obtained instead a substance $C_8H_5O_3N_3$ which they recognised as diazonitroacetophenone. Subsequently the general nature of the reaction for the acylation of diazomethane was established by Arndt and Amende (*Ber.*, 1928, **61**, 1222) and by Bradley and Robinson (this vol., pp. 1310, 1545). The conditions adopted involved the addition of the acid chloride (1 mol.) to an ethereal solution of diazomethane (2 mols.); and these are undoubtedly the best for the preparation of diazo-ketones, since the reactions

(A) and (B) occur to the almost complete exclusion of side reactions such as (C).

$$R{\cdot}COCl + CH_2N_2 = R{\cdot}CO{\cdot}CHN_2 + HCl \quad . \quad . \quad (A)$$
$$CH_2N_2 + HCl = CH_3Cl + N_2 \quad . \quad . \quad . \quad . \quad (B)$$
$$R{\cdot}CO{\cdot}CHN_2 + HCl = R{\cdot}CO{\cdot}CH_2Cl + N_2 \quad . \quad . \quad (C)$$

Maximal yields of the diazo-ketones are obtained in this manner, and if the chloro-ketone is the object of the preparation it is still best to adopt this procedure and to submit the product to the action of hydrogen chloride.

There is no evidence that the interaction of benzoyl chloride and diazomethane yields ω-chloroacetophenone directly, the small quantities that can be detected originating from diazoacetophenone by (C).

Recently, Nierenstein (*Nature*, 1928, **121**, 940) has stated that the correct procedure for the preparation of chloro-ketones in the high yields (ω-chloroacetophenone 72%, ω-chloro-2 : 4-diacetoxyacetophenone 98%) described in the literature consists in adding the diazomethane to the acid chloride rather than *vice versa*. This author is evidently of the opinion that the course of the reaction may be transformed by such a modification of the conditions. We are unable to confirm this suggestion and under all conditions diazoacetophenone is found to be the principal product of the interaction of diazomethane and benzoyl chloride. Our results are such as might be anticipated on the assumption that the reactions taking place are (A), (B), and (C). Of these, (B) is far more rapid than (C), which, however, is a facile reaction; (B) is also more rapid than (A), but not to such an extent that benzoyl chloride in excess is unable to compete effectively with hydrogen chloride for the diazomethane that enters the system.

The results may be interpreted and summarised as follows: When diazomethane is in excess, reactions (A) and (B) greatly predominate; the process is then represented by the equation

$$Ph{\cdot}COCl + 2CH_2N_2 = Ph{\cdot}CO{\cdot}CHN_2 + CH_3Cl + N_2.$$

When benzoyl chloride is in excess, (A) is still the primary reaction, but the relatively diminished concentration of diazomethane permits reaction (C) to occur to a small extent. If the reactants could be mixed instantaneously, or if the introduction of diazomethane were effected very slowly with vigorous stirring of the solution, it is possible that the yield of chloroacetophenone might be somewhat augmented. But under ordinary conditions of rapid addition or gradual addition during a period of 25 minutes we find that the action of diazomethane (1 mol.) on benzoyl chloride (1 mol.) gives only 10—13% (total yield) of ω-chloroacetophenone, whilst the yield of ω-diazoacetophenone actually isolable is approximately 50%.

This yield is maintained whether the solvent is dried by phosphoric oxide or calcium chloride and whether the product is isolated after a few minutes or several hours. Heating the product previous to isolation entails loss of crystallisable diazo-ketone without increasing the proportion of chloro-ketone, and in all circumstances the failure to provide intimate admixture of the reactants leads to a reduction in the proportion of ω-chloroacetophenone.

An account of some further applications of the acylation of diazomethane is included in this communication. *p*-Nitrobenzoyl chloride and diazomethane yielded ω-diazo-*p*-nitroacetophenone, $NO_2\cdot C_6H_4\cdot CO\cdot CHN_2$ (I), and 3 : 4-diacetoxybenzoyl chloride similarly gave the corresponding diazo-ketone, $(AcO)_2C_6H_3\cdot CO\cdot CHN_2$ (II).

EXPERIMENTAL.

p-Nitrobenzoyloxymethyl Benzyl Ketone, $CH_2Ph\cdot CO\cdot CH_2\cdot O\cdot CO\cdot C_6H_4\cdot NO_2$.—A solution of phenylacetyl chloride (2·3 g.; b. p. 107—108°/25 mm.) in ether (10 c.c.) was added during 3—4 minutes to ethereal diazomethane (from 6·3 c.c. of nitrosomethylurethane) cooled to − 10°; the brisk evolution of nitrogen ceased after 10 minutes. The solution was kept over-night, then washed with aqueous potassium bicarbonate, dried, and evaporated in a current of air. The resulting bright yellow oil contained a small proportion of halogen but did not possess lachrymatory properties. A viscous, halogen-free oil was obtained by cooling a solution in light petroleum and this exhibited all the usual properties of diazomethyl ketones, *inter alia*, the reactions with iodine, glacial acetic and mineral acids, and the formation of an α-ketol with cold dilute aqueous-alcoholic sulphuric acid. Sudden decomposition with loss of nitrogen occurred when the substance was heated rapidly to 90—100°. A crystalline derivative was obtained by decomposition with *p*-nitrobenzoic acid, and this reaction is doubtless of general utility for the characterisation of diazo-compounds of low melting point. The crude diazoketone (0·2 g.) was boiled with a solution of *p*-nitrobenzoic acid (0·5 g.) in acetone (10 c.c.) until a portion of the cooled liquid did not evolve nitrogen on the addition of a drop of concentrated hydrochloric acid. The solvent was distilled, and the solid residue dissolved in ether and sodium carbonate solution. The washed and dried ethereal layer gave p-*nitrobenzoyloxymethyl benzyl ketone* in excellent yield (0·35 g.). Recrystallised from aqueous alcohol, this derivative formed colourless, lustrous plates, m. p. 120° (Found : C, 64·2; H, 4·3. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·4%).

ω-*Diazo*-p-*nitroacetophenone* (I).—A solution of *p*-nitrobenzoyl chloride (2·8 g.) in ether (20 c.c.) was added during 4—5 minutes to ethereal diazomethane (from 6·3 c.c. of nitrosomethylurethane); a vigorous and sustained evolution of nitrogen accompanied the separation of large, pale yellow crystals of the diazo-ketone. The reaction appeared to be complete in 10—15 minutes. After 12 hours, the crystalline material was collected and washed with ether (yield, 2·1 g.; m. p. 116—117°). A further quantity (0·9 g.; m. p. 104—108°) was obtained by evaporation of the mother-liquor in a current of air, and this was easily purified by crystallisation from ethyl alcohol (Found: C, 50·4; H, 2·8. $C_8H_5O_3N_3$ requires C, 50·3; H, 2·6%). ω-*Diazo*-p-*nitroacetophenone* melts at 116—117° without immediate decomposition; the cooled melt crystallises at once, and when reheated fuses again at 116—117°. Rapid loss of nitrogen occurs at 120—125°. Exposure to direct sunlight causes rapid deepening of the colour to ochre-yellow, but no further change appears to take place. It is moderately easily soluble in organic solvents with the exception of light petroleum. It exhibits the characteristic behaviour of diazo-compounds towards iodine, acids, and alcoholic sodium hydroxide, but is in each instance less reactive than ω-diazoacetophenone and its 3 : 4-diacetoxy-, 3 : 4 : 5-triacetoxy-, and 3 : 5-dimethoxy-4-benzyloxy-derivatives (Bradley and Robinson, this vol., p. 1541), which are, however, in their turn less reactive than diazoacetone.

p-*Nitro*-ω-*acetoxyacetophenone*, $NO_2{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}OAc$.—The diazo-ketone (0·88 g.) was warmed with glacial acetic acid (5 c.c.) during 25 minutes, until the nitrogen evolution appeared to be complete, and then boiled for 2 minutes. Dilution of the cooled solution with ether (20 c.c.) caused the crystallisation of the ω-acetoxy-ketone (0·51 g., m. p. 120—121°), and a further quantity (0·24 g., m. p. 120—121°) separated when the acid was neutralised with sodium carbonate. Evaporation of the ethereal layer yielded 0·06 g. (m. p. 117—119°), the remainder being recovered as an oily solid. Recrystallised twice from ethyl alcohol, p-*nitro*-ω-*acetoxyacetophenone* was obtained in thick, pointed prisms, m. p. 121—122°, somewhat more deeply yellow than the corresponding diazo-ketone (Found: C, 53·5; H, 4·0. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·1%). It is easily oxidised by warm Fehling's solution.

A substance crystallising from alcohol in small, dark-coloured needles, m. p. 132°, is described as *p*-nitro-ω-acetoxyacetophenone by Dale and Nierenstein (*Ber.*, 1927, **60**, 1026).

ω-*Diazo*-3 : 4-*diacetoxyacetophenone* (II).—Finely powdered *o*-diacetylprotocatechuic acid (10 g.) in carbon tetrachloride (15 c.c.) was converted into the chloride by warming with phosphorus pentachloride (9·5 g.) (compare Fischer, Bergmann, and Lipschitz, *Ber.*, 1918, **51**, 55). Recrystallised from carbon tetrachloride–light petroleum, the product had m. p. 48—50° (Malkin and Nierenstein, *Ber.*, 1928, **61**, 797, give m. p. 55°).

A solution of the chloride (5 g.) in ether (75 c.c.) was cooled to 0° and added during 5 minutes to ethereal diazomethane (from 9·2 c.c. of nitrosomethylurethane) cooled to — 5°. Nitrogen was evolved and the product quickly crystallised in pale yellow, pointed prisms (yield, 3·25 g.; m. p. 75—77°). The mother-liquor was kept over-night and then concentrated in a current of air and the yellow, crystalline residue was dissolved in benzene and recovered by the addition of light petroleum to the warm solution (yield, 1·35 g.; m. p. 71—76°, and 75—77° after recrystallisation). As in previous instances, this product was already almost pure. Recrystallised twice from the same solvent, lemon-yellow, slender, rhomboidal prisms, m. p. 76—77°, were obtained. Decomposition with loss of nitrogen occurred at 103—105° (Found: C, 54·9; H, 3·8; N, 10·3. $C_{12}H_{10}O_5N_2$ requires C, 55·0; H, 3·8; N, 10·7%). ω-*Diazo*-3 : 4-*diacetoxyacetophenone* exhibits normal behaviour towards iodine, and acetic and mineral acids; the cold alcoholic solution becomes orange on the addition of a drop of sodium hydroxide and a flocculent precipitate slowly separates. It is easily soluble in most organic solvents with the exception of light petroleum.

A mixture of the diazo-ketone (0·5 g.) and glacial acetic acid (3 c.c.) was heated at 65—70° and then boiled for 2 minutes, and the product was isolated as in the previous example. The ω : 3 : 4-triacetoxyacetophenone crystallised from aqueous alcohol and finally from benzene–light petroleum in stout, colourless plates, m. p. 92—93°, in fair agreement with that recorded by Voswinckel (94°; *Ber.*, 1909, **42**, 4651) and by Robertson and Robinson (95°; this vol., p. 1528). It reduced Fehling's solution, slowly in the cold, rapidly on heating. When it was boiled with dilute sulphuric acid, a clear solution was obtained and this reduced Fehling's solution immediately in the cold.

ω-*Chloro*-3 : 4-*diacetoxyacetophenone*.—Finely powdered ω-diazo-3 : 4-diacetoxyacetophenone (0·7 g.) was dissolved and suspended in dry ether (50 c.c.), and dry hydrogen chloride admitted into the cold solution until decomposition was complete. Evolution of nitrogen accompanied absorption of the gas, a large excess of the latter being avoided. The solution was filtered from a small amount of flocculent material and evaporated in a current of dry air, leaving a faintly yellow, crystalline residue (0·66 g., m. p. 104—107°). Recrystallisation from benzene–light petroleum gave odourless, almost colourless tables, m. p. 107·5—108° (Found: Cl, 13·1, 13·0.

$C_{12}H_{11}O_5Cl$ requires Cl, 13·1%), in fair agreement with that recorded by Voswinckel (110°; *loc. cit.*); Malkin and Nierenstein (*loc. cit.*), however, find m. p. 94°.

This derivative was insoluble in aqueous sodium carbonate and gave no coloration with ferric chloride in alcoholic solution.

Cinnamoyl Chloride and Diazomethane.—The interaction of cinnamoyl chloride (2·5 g.) with an excess of diazomethane in ethereal solution resulted in the rapid separation of a pale yellow, crystalline substance (1·55 g.), which was unstable and became oily on keeping. It possessed the characteristic properties of a diazo-compound. Somewhat deeply yellow prisms, m. p. 77—78° (Found: N, 22·9%), were obtained by freezing a solution of this product in light petroleum, and these may have consisted mainly of the pyrazoline related to diazomethyl styryl ketone.

Benzoyl Chloride and Diazomethane.—Bradley and Robinson (*loc. cit.*) described the formation of ω-diazoacetophenone in 50% or 90% yield, according as benzoyl chloride (1 mol.) was added to 1 mol. or 2 mols. of ethereal diazomethane. The products formed when the chloride is initially in excess are now described.

Expt. 1. Ethereal diazomethane (70 c.c. containing 2·4 g. of diazomethane by titration) was added in one portion to a molecular proportion of benzoyl chloride (7·9 g.) in ether (25 c.c.) cooled to — 5°. Considerable evolution of nitrogen occurred. The bright yellow solution was kept over-night and then evaporated in a stream of dry air. The residual oil was dissolved in ether (25 c.c.) and shaken with sodium carbonate solution (70 c.c. of 10%) during 7 hours, and benzoic acid (1·06 g., corresponding to benzoyl chloride 1·25 g.) was isolated. After drying and removal of the solvent at 35—40° under reduced pressure, the unhydrolysed material was dissolved in light petroleum. Pale yellow needles of ω-diazoacetophenone (3·85 g., m. p. 45—47°) crystallised on cooling. Evaporation of the mother-liquor yielded oily material; the whole of the solvent was therefore removed and the chlorine content of the residue (2·45 g.), which contained much ω-diazoacetophenone, determined (Found: Cl, 8·6%). On the assumption that the halogen was present wholly as ω-chloroacetophenone, the yield of the latter was about 0·9 g.

Expt. 2. Ethereal diazomethane (85 c.c. containing 2·1 g. of diazomethane by titration) was added during 10 minutes and in portions of about 5 c.c. to a molecular proportion of benzoyl chloride (6·9 g.) in ether (25 c.c.), which was cooled to — 5° and vigorously shaken during the addition. One hour after the evolution of nitrogen had ceased the solution was evaporated in a current of dry air and the yellow residue, which contained much crystalline material, was mixed with light petroleum and cooled to − 10°. Immediate crystallisation of ω-diazoacetophenone ensued, and this was collected and washed with light petroleum. The yield was 3·7 g., m. p. 44—48°. Recrystallisation of this product from the same solvent gave pure ω-diazoacetophenone (2·85 g.). Less pure fractions were obtained by concentrating the mother-liquor, and finally, by strong cooling, colourless, crystalline material (0·05 g., m. p. 29—42°), doubtless impure ω-chloroacetophenone.

The original mother-liquor was evaporated in a current of air, and the residue shaken with sodium carbonate (7 g.) in water (50 c.c.) during 7 hours. The concentrated aqueous solution gave benzoic acid (1·02 g., corresponding to benzoyl chloride 1·18 g.), and no additional quantity was obtained by repetition of the sodium carbonate extraction. The unhydrolysed oil contained both ω-diazo- and ω-chloro-acetophenone; it solidified at − 15°.

The ether employed in expts. 1 and 2 was dried by phosphoric oxide.

Expt. 3. In this case ether dried over calcium chloride was used throughout. Diazomethane (from 10·7 c.c. of nitrosomethylurethane) was distilled during 25 minutes into a solution of benzoyl chloride (6·9 g.) in ether (25 c.c.) cooled to − 10°. The lemon-yellow crystalline residue obtained by evaporating the solvent in a current of air was mixed with light petroleum, collected, washed, and recrystallised from the same solvent (total yield, 4·5 g.; m. p. 46—49°). The oil recovered from the mother-liquor was freed from unchanged benzoyl chloride and then weighed 1·4 g. It contained ω-diazoacetophenone; a very small amount of colourless, crystalline material having the odour of ω-chloroacetophenone was precipitated on the addition of a little cold alcohol.

Expt. 4. Diazomethane (from 10·4 c.c. of nitrosomethylurethane) was distilled during 35 minutes into benzoyl chloride (8·0 g.) in ether (25 c.c.) cooled in ice. The solution was kept over-night and then concentrated to 10 c.c. by evaporation from a water-bath maintained at 50—60°. The residue, diluted with ether (10 c.c.) and shaken with sodium carbonate (7 g.) in water (70 c.c.) during 6 hours, gave benzoic acid (2·1 g., corresponding to 2·45 g. of benzoyl chloride) and a bright yellow oil which, after drying in ethereal solution, weighed 5·1 g. The oil solidified almost completely on cooling to a pale yellow, crystalline mass, which, recrystallised from light petroleum, gave ω-diazoacetophenone (2·6 g.; m. p. 42—48°, and 47—49° after further recrystallisation). The remainder of the material (2·4 g.) separated in an oily condition (Found: Cl, 6·3, 6·5%). It contained much ω-diazoacetophenone. On the assumption that the whole of the halogen was present as ω-chloroacetophenone, the amount of the latter formed in the reaction and subsequent isolation was 0·67 g. (uncorrected for loss due to hydrolysis).

Expt. 5. Ethereal diazomethane (98 c.c. containing 2·54 g. of diazomethane by titration) was added during 5 minutes to a molecular proportion of benzoyl chloride (8·45 g.) in ether (25 c.c., dried by phosphoric oxide) cooled to — 5°, the apparatus having been filled previously with dry carbon dioxide. Brisk evolution of nitrogen occurred and quickly ceased; the gas was collected over concentrated sulphuric acid. After 30 minutes, the apparatus was washed out with carbon dioxide and the gases were kept in contact with the acid until absorption of ether vapour ceased (48 hours). Carbon dioxide was removed by exposure to dilute caustic soda solution; methyl chloride was presumably absent, since no further reduction in volume occurred in contact with alcohol. The final volume was 1000 c.c. at 25° and 758 mm., corresponding to 886 c.c. at N.T.P. The crude reaction product (8·15 g.) (Found : Cl, 11·3%) was isolated by evaporation of the solvent in a current of dry air, and a portion (6·50 g.) was dissolved in ether (25 c.c.) and shaken with 10% sodium carbonate solution (150 c.c.) during 14 hours. The aqueous solution then contained chlorine (0·54 g., corrected for the chlorine content of the original solution); benzoic acid (1·28 g., corresponding to benzoyl chloride 1·49 g.) was isolated by extraction of the acidified solution with ether; the unhydrolysed oil (4·48 g.) was also examined (Found : Cl, 4·1; N, 10·1, 9·9%).

The figures indicate that 1·22 g. of chlorine were lost as methyl chloride—to this correspond 770 c.c. of nitrogen (at N.T.P.)—and that 0·23 g. of chlorine was present as ω-chloroacetophenone (no account being taken of the small amount lost during hydrolysis)—the volume of nitrogen evolved during the formation of this from ω-diazoacetophenone is 145 c.c. The total calculated volume is 915 c.c., in fair agreement with that actually collected (886 c.c.). The nitrogen present as ω-diazoacetophenone would occupy 448 c.c. at N.T.P.; and the total nitrogen accounted for, 1334 c.c. The volume theoretically obtainable from the diazomethane employed is 1355 c.c. The whole of the nitrogen and chlorine present in the reactants is thus accounted for in the free nitrogen, methyl chloride, ω-diazoacetophenone, and ω-chloroacetophenone in the product.

Expt. 6. Two molecular proportions of benzoyl chloride (16·0 g.) in ether (25 c.c.) were cooled in ice while ethereal diazomethane (95 c.c. containing 2·47 g. of diazomethane by titration) was added during 5 minutes. The solution was well shaken, kept over-night, and heated at the boiling point during 1 hour. It was then divided into two equal portions and one of these was evaporated in a current of air. Hydrolysis with excess of 10% sodium carbonate solution gave benzoic acid (3·45 g., corresponding to benzoyl chloride 4·0 g.) and a pale yellow oil which contained both ω-diazo- and ω-chloroacetophenone. The amount of the latter was considerably greater than the normal yield in experiments involving only one molecular proportion of benzoyl chloride.

Expt. 7. In a second similar experiment, diazomethane (from 5·2 c.c. of nitrosomethylurethane) was distilled during 25 minutes into benzoyl chloride (8·0 g.) in ether (25 c.c.) cooled to — 5°. Thirty minutes after the distillation was complete the product was washed with standard potassium bicarbonate solution; only very little more hydrogen chloride was extracted than from a similar blank experiment with ethereal benzoyl chloride. Isolated and hydrolysed in the usual manner, the product gave benzoic acid (3·7 g., corresponding to benzoyl chloride 4·3 g.). The greater portion of the unhydrolysed material was crystalline and contained much ω-diazoacetophenone; very little ω-chloroacetophenone was present.

The technique involved in the above procedure was critically examined and doubtless gives a substantially correct estimate of the composition of the reaction product. (*a*) Benzoyl chloride (4 g.) in ether (70 c.c.) was hydrolysed, and benzoic acid (3·2 g.) isolated (theory requires 3·5 g.). (*b*) Hydrolysis of ω-chloroacetophenone occurred only to a small extent. Estimation of the amount of hydrogen chloride formed by shaking ω-chloroacetophenone (1·0 g., 3·4 g., and 3·4 g.) in ether (25 c.c.) with 10% sodium carbonate solution (100 c.c., 150 c.c., and 150 c.c.) during (7 hours, 7 hours, and 14 hours) showed that (0·13 g., 0·33 g., and 0·52 g.) of the chloroketone had been hydrolysed. (*c*) The yield of diazomethane from nitrosomethylurethane varied between relatively small limits. In titration experiments, nitrosomethylurethane (12·6 c.c., 25·2 c.c., 12·6 c.c., and 12·6 c.c.) gave diazomethane (2·4 g., 5·1 g., 2·8 g., and 2·8 g.). The yields calculated according to Houben-Weyl ("Die Methoden der Organischen Chemie," 1923, **3**, 124) are 2·4 g., 4·8 g., 2·4 g., and 2·4 g., respectively.

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