340. *Hydroxy-carbonyl Compounds. Part XIII. Extensions of the Wolff Rearrangement.*

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Interaction of a series of acid chlorides with diazo-ethane, -*n*-propane and -*n*-butane yields the corresponding diazoketones, (type II, R = alkyl), which have been converted respectively into the amides of the next higher homologues of the parent acids, type (III, R_1 = alkyl). Compared with those in the diazomethane series, the yields obtained in the present work are relatively poor.

Following upon the clarification of the course of the reaction between diazomethane and acid chlorides (Nierenstein *et al.*, *J.*, 1915, **107**, 1491; *J. Amer. Chem. Soc.*, 1925, **47**, 1728) by Arndt and his co-workers (*Ber.*, 1927, **60**, 1364; 1928, **61**, 1122) and by Robinson and Bradley (*J.*, 1928, 1310), a convenient method became available for the preparation of diazoketones of the type (II), and consequently it became possible to utilise, as a general synthetical procedure, the rearrangement discovered by Wolff (*Annalen*, 1912, **394**, 25) whereby these diazens (II) can be readily converted into the acids (III) or their amides; conditions for the conversion of (II) into the ester corresponding to (III) were first described by Arndt and Eistert (*Ber.*, 1935, **68**, 200). In recent years this procedure has found wide application in synthetical work but the examples quoted so far have been confined mainly to the use of diazomethane, although one case with diazoethane has been reported (Eistert, *Angew. Chem.*, 1941, **54**, 124) without experimental details and the rearrangement of several ketones (type II, $R_1 = CO_2Et$) derived from esters of diazoacetic acid have been studied (Eistert, *loc. cit.*; Schroeter, *Ber.*, 1916, **49**, 2704).

In the course of a synthetical investigation where it became necessary to prepare α-methyl-substituted aliphatic acids, the application of the Wolff rearrangement to diazoketones from diazoethane appeared to be a convenient route, and in view of the possible value of this kind of extension of the reaction it was decided to examine the behaviour of ketones formed by the action of acid chlorides on diazo-ethane, -*n*-propane, and -*n*-butane. One of the drawbacks to the employment of the Wolff reaction in this way is the relative inaccessibility of the higher diazohydrocarbons, although to a considerable extent the procedure of Adamson and Kenner (*J.*, **1937**, 1551) overcomes this.

$$\underset{\text{(I.)}}{R\cdot CO\cdot Cl} \longrightarrow \underset{\text{(II.)}}{R\cdot CO\cdot CR_1\colon N_2} \longrightarrow \underset{\text{(III.)}}{R\cdot CHR_1\cdot CO_2H}$$

The method employed in the present work for the preparation of diazoketones was essentially the same as for the derivatives of diazomethane, but in the examples studied, with the exception of *p*-nitrobenzoyldiazoethane, the products were obtained as oils, probably owing, in part at least, to the presence of unavoidable by-products of the reaction; *e.g.*, it is impossible to eliminate entirely the formation of chloro-ketone. In the course of attempts to purify the diazoketones it was found, for example, that chromatography of the product from *p*-methoxybenzoyl chloride and diazoethane in benzene on a column of alumina gave a uniform yellow zone, but on elution the diazoketone did not solidify at room temperature whereas the corresponding diazoketone from α-naphthoyl chloride began to decompose on the column. Characterisation of the diazoketones was effected in several cases by the direct interaction of the compound with *p*-nitrobenzoic acid to give the *p*-nitrobenzoate of the ketol (compare Bradley and Schwarzenbach, *J.*, 1928, 2904). Conversion of the diazoketones into the ketols was carried out in a number of cases by hydrolysis with dilute formic or sulphuric acid but the products were impure, giving several yellow zones when chromatographed on alumina.

The diazoketones of type (II, R_1 = alkyl) have been subjected to the Wolff rearrangement, and because of the difficulty of purifying small amounts of liquid or low-melting acids and their esters, the amide reaction was chosen. In the main the yields of acids or acid derivatives from diazoketones obtained from diazomethane seem to vary between from 40% to 80%, for the cases which have been described, but in the present series, with the exception of phenylbenzoyldiazomethane, the diazoketones of type (II, R_1 = alkyl) gave yields which varied from 10% to 30%, and allowance being made for the presence of impurities in the crude diazoketones it seems certain that in general the yields are decidedly inferior and more resinous by-product is formed, probably owing, in part at least, to the polymerisation of the hypothetical radical $R\cdot CO\cdot C(R_1)\colon$. As far as can be judged at present the yield from (II) decreases as R_1 is changed in the order Ph > $CO\cdot CH_3$ (or CO_2Et) > H > alkyl.

EXPERIMENTAL.

1-p-*Nitrobenzoyldiazoethane.*—The addition of *p*-nitrobenzoyl chloride (4·5 g.,) dissolved in ether (50 ml.), to an excess of ethereal diazoethane maintained at 0° in the course of 20 minutes, followed ½ hour later by the evaporation of the excess of diazoethane and the solvent in a vacuum, gave the *diazoketone* (4 g.), which formed pale yellow prisms, m. p. 112°, from benzene–light petroleum (b. p. 60—80°), readily soluble in benzene or ethyl acetate and moderately soluble in alcohol and developing an orange coloration with zinc dust and ammonia (Found: N, 20·9. $C_9H_7O_3N_3$ requires N, 20·5%). Attempts to effect the Wolff rearrangement with this diazen were unsuccessful (compare Walker, *J.*, 1940, 1304).

α-p-*Methoxyphenylpropionamide.*—Interaction of anisoyl chloride with an excess of diazoethane in ether gave a liquid diazoketone which did not solidify on being kept and gave a deep purple coloration with zinc dust and ammonia in alcohol. Chromatographic adsorption of this material on a column of alumina with benzene as the solvent furnished a single yellow zone which on elution yielded an oil. A solution of this material (0·5 g.) and *p*-nitrobenzoic acid (0·5 g.) in acetone (20 ml.) was refluxed until a sample did not evolve nitrogen on the addition of a drop of concentrated hydrochloric acid (3 hours). An ethereal solution of the residue obtained on evaporation of the acetone was washed with aqueous sodium hydrogen carbonate to remove acid, dried, and evaporated, leaving a yellow paste which on repeated crystallisation from acetone gave the p-*nitrobenzoate* of *p*-methoxybenzoylmethylcarbinol in pale yellow needles, m. p. 122° (sintering at 118°) (Found: N, 4·4; *M*, 300. $C_{17}H_{15}O_6N$ requires N, 4·3%; *M*, 329).

Decomposition of the crude diazoketone (1 g.) dissolved in acetone (25 ml.) with 20% formic acid (5 ml.) or 2N-sulphuric acid (5 ml.) during 30 minutes gave rise to the ketol as a yellow oil, readily reducing Fehling's solution. Acylation of this product with *p*-nitrobenzoyl chloride and pyridine gave a small yield of the *p*-nitrobenzoate, m. p. and mixed m. p. 121—122°, identical with the ester prepared directly from the diazoketone.

The foregoing diazoketone (1 g.), dissolved in ether (25 ml.), was added to a solution (with shaking) of 10% silver nitrate (2 ml.) in aqueous ammonia (10 ml., *d* 0·880) and water (50 ml.), and the mixture kept at 70° for 2 hours, cooled, and extracted with ether. Evaporation of the dried extract left a yellow product which partly solidified. Chromatographic adsorption of this material dissolved in benzene on a column of alumina gave several coloured zones with a larger colourless section between the top and the second coloured zone. The colourless section was separated and the *amide* (0·26 g.) eluted with alcohol and crystallised from water, forming colourless needles or plates, m. p. 109·5—110° (Found : C, 67·5; H, 7·4; N, 8·0. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8%).

a-1-Naphthylpropionamide.—Prepared the interaction of α-naphthoyl chloride and diazoethane in ether, the diazoketone was obtained as a yellow oil which gave a purple-violet coloration with zinc dust and ammonia in alcohol. A solution of this compound (1 g.) in ether (25 ml.) was slowly added to a well-stirred mixture of 10% silver nitrate (2 ml.), ammonia (10 ml., *d* 0·880), and water (50 ml.) kept at 70—80° in an atmosphere of nitrogen for 2 hours. On isolation with ether, the *amide* (0·28 g.) was separated from yellow impurities by chromatography (benzene solution) on alumina (elute with alcohol), and crystallised from water, forming colourless prisms, m. p. 129—129·5° ((Found : C, 78·5; H, 6·8. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%).

*β-Phenyl*iso*butyramide.*—Prepared by the action of ethereal diazoethane on phenylacetyl chloride the α-phenylacetyldiazoethane was an oil, having a deep red zinc dust–ammonia reaction. On being heated with *p*-nitrobenzoic acid (0·5 g.) in a little acetone this substance (0·5 g.) gave the p-*nitrobenzoate* of phenylacetylmethylcarbinol (0·5 g.), forming pale straw-coloured prisms, m. p. 82—83°, from alcohol (charcoal) (Found : C, 65·2; H, 4·8; N, 4·7. $C_{17}H_{15}O_5N$ requires C, 65·2; H, 4·8; N, 4·5%).

Treatment of the diazoketone (0·9 g.) with ammoniacal silver nitrate at 80° for 1 hour gave rise to the β-phenyl*iso*butyramide (0·25 g.), which separated from dilute alcohol in elongated plates, m. p. 106—108° (Meyer, *Monatsh.*, 1906, **27**, 1091).

p-Methoxyphenylacetyl chloride and diazoethane gave a liquid diazoketone which, on being heated in acetone with 4-nitro- or 3 : 5-dinitro-benzoic acid gave a resin, and by the ammoniacal silver oxide method gave only a small yield of the *iso*butyramide, m. p. 122—124°, identical with an authentic specimen (Woodruff and Conger, *J. Amer. Chem. Soc.*, 1938, **60**, 466).

*γ-(*p*-Methoxyphenyl)-α-methylbutyramide.*—The oil (1 g., having a transient red zinc dust–ammonia reaction) obtained from the interaction of β-(*p*-methoxyphenyl)propionyl chloride and diazoethane was refluxed with *p*-nitrobenzoic acid (0·75 g.) in acetone (25 ml.) for 3 hours. On isolation the yellow neutral material partly solidified, and after the removal of an oily contaminant with a little alcohol the residual p-*nitrobenzoate* of β-*p*-methoxyphenylpropionylmethylcarbinol formed pale yellow needles (0·45 g.), m. p. 87°, from alcohol, insoluble in ligroin. Decomposition of the diazoketone (1 g.), dissolved in acetone (25 ml.), with aqueous formic acid at 70° for 30 minutes gave the ketol (0·8 g.) which by the pyridine method yielded the same *p*-nitrobenzoate, m. p. and mixed m. p. 87° (Found : C, 63·9; H, 5·5; N, 4·2. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·3; N, 3·9%).

When 3 : 5-dinitrobenzoic acid reacted with the diazoketone in acetone a small yield of the corresponding 3 : 5-*dinitrobenzoate* was extracted from the dark viscous product by means of boiling light petroleum (b. p. 60—80°) which separated from chloroform–alcohol in light yellow prisms, m. p. 127·5—128° (Found : N, 6·8. $C_{19}H_{18}O_8N_2$ requires N, 7·0%).

Prepared from the diazoketone by the standard method, γ-(p-*methoxyphenyl*)-α-*methylbutyramide* formed glistening plates, m. p. 162—163°, from very dilute alcohol (Found : N, 6·5. $C_{12}H_{17}O_2N$ requires N, 6·8.

β-Phenyl-α-ethylpropionamide.—Interaction of phenylacetyl chloride and excess of diazo-*n*-propane (Adamson and Kenner, *loc. cit.*) in ethereal solution yielded a lemon-yellow diazoketone which had a deep red zinc dust–ammonia reaction. This substance (1 g.) was allowed to react with concentrated aqueous ammonia (10 ml.) and 10% silver nitrate solution (2 ml.) at 80° for 2 hours, and on isolation the crude amide (0·85 g.) was purified by chromatographic adsorption from benzene on a column of alumina. Pure material was recovered by means of alcohol from the almost colourless zone between two yellow zones. Crystallised from water, the compound formed colourless needles, m. p. 117° (Found : N, 8·0. Calc. for $C_{11}H_{15}ON$: N, 7·9%). Blicke and Cantolella (*J. Amer. Chem. Soc.*, 1938, **60**, 2926) gave m. p. 117—118°.

Prepared from β-*p*-methoxyphenylpropionyl chloride and diazo-*n*-propane, the liquid diazoketone (1 g.) gave under similar conditions a highly impure amide (0·72 g.) which did not solidify and was purified by chromatographic adsorption on alumina from benzene. On isolation γ-(p-*methoxyphenyl*)-α-*ethylbutyramide* crystallised from water in slender needles, m. p. 105—106° (Found : C, 70·3; H, 8·5; N, 6·7. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; N, 6·3%).

*α-Benzyl-*n*-valeramide.*—When a solution of phenylacetyl chloride (3 g.) in ether (50 ml.) was slowly added to excess of ethereal diazo-*n*-butane maintained at 0°, and the solvent and butyl chloride were removed in a vacuum one hour later, the diazo-compound remained as an oil having a deep red zinc dust–ammonia reaction. Interaction of this material (0·5 g.) with *p*-nitrobenzoic acid (0·5 g.) in boiling chloroform until a sample did not evolve nitrogen when treated with a drop of concentrated hydrochloric acid gave rise to an oily p-*nitrobenzoate* of the ketol which gradually solidified and then separated from aqueous alcohol in almost colourless needles, m. p. 86° (Found : N, 4·1. $C_{19}H_{19}O_5N$ requires N, 4·1%).

Treatment of the diazoketone dissolved in dioxan with aqueous ammoniacal silver nitrate at 60° during 2 hours gave rise to the *amide*, which crystallised from water in colourless needles, m. p. 121—122° (Found : C, 75·5; H, 9·0; N, 7·3. $C_{12}H_{17}ON$ requires C, 75·4; H, 9·0; N, 7·3%); yield 20%.

An authentic sample of this amide was prepared by the following route : *n*-Propyl bromide was added to a solution of the sodio-derivative of ethyl benzylmalonate (from 3 g. of sodium and 30 g. of ester), and the mixture refluxed until a sample gave a neutral reaction. On isolation, ethyl benzyl-*n*-propylmalonate was purified by distillation in a vacuum and obtained in comparatively large prisms, m. p. 50—52°, b. p. 232°/118 mm. in 87% yield. When this ester (5 g.) was heated with urea (1·5 g.) and alcoholic sodium ethoxide (from 1·2 g. of sodium and 25 ml. of alcohol) in a sealed tube at 130° for 2 hours, the alcohol evaporated, and the residue acidified with concentrated hydrochloric acid, a product was obtained which was partly soluble in 8% aqueous sodium hydroxide. Crystallisation of the alkali-soluble material from alcohol and then benzene gave 5-benzyl-5-*n*-propylbarbituric acid in needles, m. p. 209—210° (Found : C, 64·4; H, 6·1; N, 10·4. Calc. for $C_{14}H_{16}O_3N_2$: C, 64·6; H, 6·1; N, 10·8%) (compare Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 1141, who gave m. p. 210°). The alkali-insoluble material formed elongated, colourless prisms, m. p. 166°, from aqueous alcohol and then benzene (Found : C, 69·2; H, 7·4; N, 9·2%).

When a mixture of ethyl benzyl-*n*-propylmalonate (20 g.), alcohol (134 ml.), and 2N-aqueous sodium hydroxide (134 ml.) was refluxed for 6 hours an excellent yield of the acid ester was obtained which on decarboxylation in glycerol at 110—140° gave ethyl α-benzylvalerate. This ester was purified by distillation and on hydrolysis with N-aqueous sodium hydroxide gave the parent acid, the chloride of which (prepared by means of thionyl chloride), on treatment with ammonium carbonate in ether, gave the amide, m. p. 121—122°, after purification, identical in every way with the specimen obtained from the diazoketone (Found : C, 75·3; H, 8·9%).

Diphenylacetamide.—Phenylbenzoyldiazomethane (Ritter and Wideman, *J. Amer. Chem. Soc.* 1929, **51**, 3583) (2·1 g.), dissolved in ether (50 ml.), was gradually added to a mixture of ammonia (20 ml., *d* 0·880), 10% silver nitrate solution (4 ml.), and water (100 ml.) at 80°, and the mixture then kept at this temperature for 2 hours; after 1 hour 10% aqueous silver nitrate (2 ml.) was added. Separated from the cooled dark red reaction mixture by filtration, the solid, on extraction with warm alcohol, gave the main bulk of the amide; a further small quantity was isolated from the liquor by means of ether. Recrystallisation of the combined products (1·8 g.) from alcohol gave diphenylacetamide in large prisms, m. p. 167—168°. Evaporation of the alcoholic residues left a deep yellow intractable resin.

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