201. *Acrylonitrile in Organic Syntheses. Part II.* Conditions for Monocyanoethylation.*

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Conditions are described for the preparation of the monocyanoethylation product of certain compounds containing an active methyl or methylene group by direct cyanoethylation and also by a disproportionation reaction from the di- or tri-cyanoethylation products.

Derivatives of tetrahydropyridine were obtained from δ-keto-nitriles under alkaline conditions.

Acrylonitrile normally causes di- or tri-cyanoethylation of compounds having an active methylene or methyl group and, in general, indirect methods such as the basic hydrolysis of cyanoethylated monoalkylacetoacetic esters [1] are used to afford monocyanoethylation products. We now record some attempts to find conditions which will give predominantly monocyanoethylation in the direct reaction.

Although deoxybenzoin is reported to react with 2 mols. of acrylonitrile in dioxan to give γ-benzoyl-γ-phenylpimelonitrile [2] we find, when using *tert.*-butanol as solvent, that the crystalline monocyanoethylation product, δ-oxo-γδ-diphenylvaleronitrile, frequently crystallises during the reaction. When caused to react in equimolar proportions these reactants give an almost quantitative yield of the mononitrile. Similarly phenylacetone with 1 mol. of acrylonitrile gives 5-oxo-4-phenylhexanonitrile, characterised by hydrolysis to the acid, but in this case monocyanoethylation takes place only if the reaction is carried out at 60—70°. Lower temperatures favour the formation of the crystalline dicyanoethylation product previously prepared by Bruson and Riener.[2] Two closely related compounds, 1-naphthyl- and 3 : 4-methylenedioxyphenyl-acetone, also react with 1 mol. of acrylonitrile in *tert.*-butanol but give lower yields.

A previous paper [3] described conditions for the monocyanoethylation of phenylacetonitrile by use of an excess of boiling nitrile as solvent. Further investigation shows that monocyanoethylation also takes place in refluxing nitrobenzene but not in tetrachloroethane. The reversibility of the cyanoethylation reaction at high temperatures is illustrated in the formation of α-phenylglutaronitrile by treatment of boiling phenylacetonitrile with its dicyanoethylation product. Although this "reversed" Michael-type reaction gives a good yield of the monocyanoethylation product the latter compound is stable if refluxed with *tert.*-butanol containing Triton B, conditions which favour dicyanoethylation in the normal reaction.

Rogers's method [3] may also be used for the cyanoethylation of ketones. Acetophenone and related compounds readily react with 3 mols. of acrylonitrile [4] but when an excess of boiling acetophenone is treated with acrylonitrile a mixture of δ-oxo-δ-phenylvaleronitrile (by monocyanoethylation) and γ-benzoylpimelonitrile (by dicyanoethylation) is obtained. The same two nitriles, which were hydrolysed to the respective acids,[5] are formed when γ-benzoyl-γ-2-cyanoethylpimelonitrile [2] is treated with excess of acetophenone under similar conditions. The cyanoethylation of *cyclo*hexanone has been investigated by Bruson and Riener,[2] Levina, Shusherina, and Kaminskaya,[6] and more recently by Burnell and Taylor.[7] The last workers show that the yield of dicyanoethylation product is greater if limited quantities of acrylonitrile are used. When Rogers's method is used the product is mainly the monocyanoethylation product together with a smaller quantity of dicyanoethylation product.

* Part I, *J.*, 1954, 1377.

[1] Albertson, *J. Amer. Chem. Soc.*, 1950, **72**, 2594; Misra and Shukla, *J. Indian Chem. Soc.*, **1953**, **30**, 37.

[2] Bruson and Riener, *J. Amer. Chem. Soc.*, 1942, **64**, 2850.

[3] Campbell, *J.*, 1954, 1377; cf. Rogers, U.S.P. 2,460,536; *Chem. Abs.*, 1949, **43**, 3446.

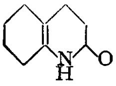
[4] Bruson, "Organic Reactions," 1949, Vol. V, p. 101.

[5] Auger, *Ann. Chim. Phys.*, 1891, **22**, 360.

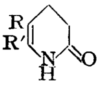
[6] Levina, Shusherina, and Kaminskaya, *Doklady Akad, Nauk. S.S.S.R.*, 1952, **86**, 79.

[7] Burnell and Taylor, *J.*, 1954, 3486.

During preliminary investigations certain δ-oxo-nitriles were found to give isomeric hydro-oxopyridines when refluxed with potassium hydroxide in *tert.*-butanol, the products being similar to those obtained by acid-catalysed rearrangement:[8,9] 2-2′-cyanoethyl*cyclo*hexanone gave 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-2-oxoquinoline (I) which was readily dehydrogenated to 2-quinolone, and δ-oxo-γδ-diphenylvaleronitrile and 5-oxo-4-phenylhexanonitrile afforded 1 : 2 : 3 : 4-tetrahydro-2-oxo-5 : 6-diphenylpyridine (II; R = R′ = Ph) and 1 : 2 : 3 : 4-tetrahydro-6-methyl-2-oxo-5-phenylpyridine (II; R = Ph, R′ = Me) respectively which were dehydrogenated to 5 : 6-diphenyl- (III; R = R′ = Ph) and 6-methyl-5-phenyl-2-pyridone (III; R = Ph, R′ = Me). The infrared spectra of the three hydro-oxopyridines showed absorption bands near 3200 and 3070 cm.⁻¹ characteristic of the NH stretching frequency of cyclic lactams[10] and at about 1670 cm.⁻¹ (broad or double band) due to the carbonyl group. This is in accordance with the structures previously assigned. These isomerisations show that refluxing conditions should be avoided when using potassium hydroxide as the catalyst in the cyanoethylation of ketones in *tert.*-butanol.



(I)



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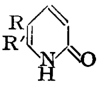

(III)

EXPERIMENTAL

δ-Oxo-γδ-diphenylvaleronitrile.—Acrylonitrile (6 g.) was added dropwise with stirring to deoxybenzoin (22 g.) and " Triton B " (2 g.) in *tert.*-butanol (50 g.) with cooling to 45—50°. After 3 hours' stirring at 50° the mixture was poured into dilute hydrochloric acid, and the precipitate was filtered off and recrystallised from ethanol, to give the *nitrile* (26 g.), needles, m. p. 86·7—87° (Found : N, 5·7. $C_{17}H_{15}ON$ requires N, 5·6%). Hydrolysis by aqueous potassium hydroxide gave δ-oxo-γδ-diphenylvaleric acid (90%) as needles, m. p. 134—135° (from ethanol) (Knoevenagel[11] gives m. p. 136°). It gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 122—123°, as yellow prisms from ethanol (Found : N, 12·2. $C_{23}H_{20}O_6N_4$ requires N, 12·5%).

5-Oxo-4-phenylhexanonitrile.—Phenylacetone (13 g.) was similarly treated with acrylonitrile (5 g.) with cooling to 60—70°. The oil obtained on acidification of the mixture was taken up in ether and distilled, to give the *nitrile* (12 g.), b. p. 185—190°/18 mm. (Found : N, 7·8. $C_{12}H_{13}ON$ requires N, 7·5%). The residue afforded γ-acetyl-γ-phenylpimelonitrile (2·5 g.), m. p. 110° on recrystallisation from ethanol (charcoal). Bruson and Riener[2] give m. p. 109—110°.

5-Oxo-4-phenylhexanoic Acid.—Acidification of the mixture from the hydrolysis of the above nitrile (36 g.) (6 hr. with boiling aqueous potassium hydroxide) gave the *acid* (36 g.) which was distilled (b. p. 215—220°/18 mm.) and afforded prisms, m. p. 42°, on crystallisation from benzene–light petroleum (Found : C, 70·0; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It gave a *semicarbazone*, m. p. 168—168·5° (Found : N, 16·7. $C_{13}H_{17}O_2N_3$ requires N, 16·9%), and an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 116—117° (Found : N, 14·6. $C_{18}H_{18}O_6N_4$ requires N, 14·5%), both as needles from ethanol. Recrystallisation of the acid from water gave the *monohydrate*, m. p. 51—52° (Found : equiv., 220; C, 63·8; H, 6·8. $C_{12}H_{14}O_3,H_2O$ requires equiv., 224; C, 64·3; H, 7·2%). Cyclisation, by hydrogen fluoride, of the acid obtained on Clemmensen reduction of the keto-acid afforded 4-ethyl-1 : 2 : 3 : 4-tetrahydro-1-oxonaphthalene which gave a semicarbazone, m. p. 181·5—182°. Levy[12] gives m. p. 183° (corr.) for the semicarbazone.

4-1′-Naphthyl-5-oxohexanonitrile.—Acrylonitrile (1·5 g.) and 1-naphthylacetone (5 g.), reacting under conditions similar to those described for phenylacetone, gave the *nitrile* (4·2 g.), b. p. 195—200°/6 mm. (Found : N, 5·6. $C_{16}H_{15}ON$ requires N, 5·9%). Hydrolysis with aqueous sodium hydroxide gave 4-1′-*naphthyl-5-oxohexanoic acid*, b. p. 215—220°/6 mm. (Found : C, 75·0; H, 6·0. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). Plates, m. p. 81—82°, separated from aqueous ethanol on long storage.

4-(3 : 4-*Methylenedioxyphenyl*)-5-*oxohexanonitrile* (10·6 g.), b. p. 220—225°/20 mm., was

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[8] Allen and Ball, *J. Amer. Chem. Soc.*, 1937, **59**, 686.
[9] Kohler, Graustein, and Merrill, *ibid.*, 1922, **44**, 2536.
[10] Bellamy, " Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1954, p. 179.
[11] Knoevenagel, *Ber.*, 1888, **21**, 1351.
[12] Levy, *Compt. rend.*, 1933, **197**, 772.

similarly prepared from 3 : 4-methylenedioxyphenylacetone (36 g.) and acrylonitrile (10·6 g.) (Found: N, 5·8. $C_{13}H_{13}O_3N$ requires N, 6·1%). It was hydrolysed by aqueous sodium hydroxide to the *acid*, b. p. 240—245°/12 mm. (Found : C, 62·1; H, 5·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%), whose *monohydrate* crystallised as needles, m. p. 62—62·5°, from aqueous ethanol (Found : C, 58·1; H, 5·9. $C_{13}H_{14}O_5,H_2O$ requires C, 58·2; H, 6·0%).

α-Phenylglutaronitrile—(*a*) A mixture of acrylonitrile (10·6 g.) and phenylacetonitrile (23·4 g.) was added dropwise during 25 min. to a refluxing solution of nitrobenzene containing sodium cyanide (1 c.c. of a 50% aqueous solution). The solution was refluxed for a further 35 min. and then distilled, to give solvent, followed by α-phenylglutaronitrile (12·8 g.), b. p. 197—199°/14 mm. Campbell[3] gives b. p. 200—205°/15 mm.

(*b*) γ-Cyano-γ-phenylpimelonitrile (5 g.), phenylacetonitrile (50 g.), and sodium cyanide (0·2 g. in 0·3 c.c. of water) were heated at 225° for 3 hr. and the resulting solution was distilled, to give unchanged phenylacetonitrile, followed by α-phenylglutaronitrile (6·25 g.), b. p. 189—193°/8 mm.

δ-Oxo-δ-phenylvaleronitrile and *γ-Benzoylpimelonitrile.*—(*a*) Acrylonitrile (8·1 g.) was added dropwise during 5 min. to a refluxing solution of acetophenone (60 g.) containing sodium cyanide (0·5 g.) and water (0·25 g.). The solution was refluxed a further 30 min. and distilled, to give unchanged acetophenone, followed by two fractions, the first of which afforded δ-oxo-δ-phenylvaleronitrile, b. p. 178—182°/8 mm., on redistillation. Crystallisation from ethanol gave plates of the nitrile (3·2 g.), m. p. 38—39° (Found : C, 76·2; H, 6·1. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·4%); Allen and Ball[8] give m. p. 38°. The second fraction afforded *γ-benzoylpimelonitrile* (3·0 g.), b. p. 203—205°/0·4 mm. (Found : C, 74·3; H, 6·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%), which was hydrolysed by refluxing sulphuric acid, acetic acid, and water (1 : 1 : 1) to *γ-benzoylpimelic acid* which crystallised from water as needles, m. p. 110—111° (Found : C, 63·9; H, 5·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

(*b*) γ-Benzoyl-γ-2-cyanoethylpimelonitrile (10 g.) was refluxed for 3 hr. with acetophenone (50 g.), sodium cyanide (0·25 g.), and water (0·3 g.), and the resulting solution was distilled, to give δ-oxo-δ-phenylvaleronitrile (5·4 g.), b. p. 194—197°/12 mm., m. p. 37—38°, followed by γ-benzoylpimelonitrile (4·5 g.), b. p. 248—256°/12 mm.

2-2′-*Cyanoethyl*cyclo*hexanone and* 2 : 2-*Di*-2′-*cyanoethyl*cyclo*hexanone.*—A mixture of acrylonitrile (10·6 g.) and *cyclo*hexanone (48 g.) was added dropwise during 30 min. to refluxing *cyclo*hexanone (50 g.) containing sodium cyanide (1 c.c. of a 50% aqueous solution). After refluxing for a further 15 min. the solution was distilled to give *cyclo*hexanone, followed by two fractions. Redistillation of the first fraction gave 2-2′-cyanoethyl*cyclo*hexanone (10·5 g.), b. p. 145—148°/11 mm. (Found : C, 71·3; H, 8·5. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·7%); Bruson and Riener[2] give b. p. 138—142°/10 mm. The second fraction, 2 : 2-di-2′-cyanoethyl*cyclo*hexanone (3·0 g.), was a pale yellow oil, b. p. 243—250°/11 mm. (Found : C, 70·7; H, 7·4; N, 14·0. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·9; N, 13·7%), from which crystals, m. p. 67—68° separated; Bruson and Riener[2] give b. p. 195—198°/1 mm., m. p. 69°, for the dicyanoethylation product.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*Octahydro-2-oxoquinoline.*—2-2′-Cyanoethyl*cyclo*hexanone (11·5 g.) was refluxed for 4 hr. with methyl-alcoholic potassium hydroxide (3 c.c. of a 30% solution) in *tert.*-butanol (20 c.c.). The semisolid which separated after neutralisation with dilute hydrochloric acid and dilution with water was washed with ether and recrystallised from ethanol, to give colourless needles of the quinoline derivative (3·25 g.), m. p. 143—144° (Found : C, 71·3; H, 8·4. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·7%). Lions[13] gives m. p. 144°. The infrared spectrum showed max. (among others) at 3175, 3080, and 1670 cm.$^{-1}$. Dehydrogenation at 360° with 30% palladium–charcoal gave pale yellow needles of 2-hydroxyquinoline, m. p. 193—194°.

1 : 2 : 3 : 4-*Tetrahydro-2-oxo-5* : 6-*diphenylpyridine.*—Similarly prepared from δ-oxo-γδ-diphenylvaleronitrile (10 g.), this *pyridine* derivative recrystallised from ethanol as plates (1·25 g.), m. p. 214—214·5° (Found : C, 81·6; H, 5·7; N, 5·8. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·1; N, 5·6%). The infrared spectrum showed max. (among others) at 3200, 3060, and 1666 cm.$^{-1}$. Starting material (6 g.) was recovered. Dehydrogenation with palladium–charcoal afforded 5 : 6-*diphenyl-2-pyridone* as pale lemon-yellow needles (from ethanol), m. p. 262·5—263° (Found : C, 82·7; H, 5·6. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%).

1 : 2 : 3 : 4-*Tetrahydro-6-methyl-2-oxo-5-phenylpyridine* (3·0 g.), similarly prepared from 5-oxo-4-phenylhexanonitrile (10 g.) (6 hr. at the b. p.), crystallised from ethanol as plates, m. p. 169—170° (Found : C, 76·9; H, 7·4; N, 7·1. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

[13] Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 192.

Included in the infrared spectrum were max. at 3200, 3070, 1650, and 1675 $cm.^{-1}$. An isomeric, unidentified, basic substance, precipitated when the aqueous solution was made alkaline, recrystallised from ethanol as needles (0·5 g.), m. p. 248° (with decomp.) (Found: C, 77·4; H, 6·5; N, 7·7%).

Dehydrogenation of the pyridine derivative afforded 6-*methyl*-5-*phenyl*-2-*pyridone*, plates m. p. 214—215° (from ethanol) (Found: C, 77·9; H, 5·7. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0%.

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