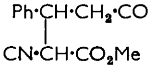
529. *Chalcones and Related Compounds. Part VI.*[*] *Addition of Cyanoacetic Esters to Chalcones.*

By W. DAVEY and D. J. TIVEY.

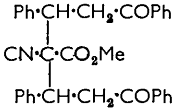
Diethylamine is the preferred catalyst for the addition of cyanoacetic esters to chalcones. Hydrogenation of the benzyl cyanoacetate adducts yields 3 : 5-diaryl-2-cyano-5-oxopentanoic acids. Hydrogenation of ethyl 2-cyano-3 : 5-di-(*p*-methoxyphenyl)-5-oxopentanoate over Raney nickel W7 gives two isomeric tetrahydropyridines, which have been separated, and structures have been assigned to them.

KOHLER, GRAUSTEIN, and MERRILL [1] have shown that, in presence of a small amount of sodium methoxide, methyl cyanoacetate added to chalcone, to give 2-cyano-5-oxo-3 : 5-diphenylpentanoate (I), together with the product of reaction of the primary adduct (I) and a second molecule of chalcone. By the use of the minimum quantity of sodium methoxide and effecting reaction in absolutely dry methanol, these workers limited the formation of the diadduct (II). We found addition of methyl or ethyl cyanoacetate to chalcones by this method to be difficult and to give variable results, so that other basic catalysts were investigated. Ammonia gave incomplete reaction but diethylamine gave reproducible results and the adducts obtained were free from biscondensation products. Although these adducts tended to separate as oils, crystallisation was achieved by extraction with benzene and drying.[2] Our attempts to hydrolyse the adducts by alkali failed, as did acid hydrolysis, *e.g.*, by Bowman's [3] or Bowman and Fordham's method.[4]



$$\begin{array}{l}\mathrm{Ph{\cdot}CH{\cdot}CH_2{\cdot}COPh}\\ \quad|\\ \mathrm{CN{\cdot}CH{\cdot}CO_2Me}\end{array}$$

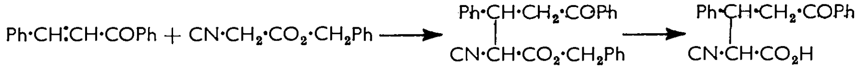
(I)



$$\begin{array}{l}\mathrm{Ph{\cdot}CH{\cdot}CH_2{\cdot}COPh}\\ \quad|\\ \mathrm{CN{\cdot}C{\cdot}CO_2Me}\\ \quad|\\ \mathrm{Ph{\cdot}CH{\cdot}CH_2{\cdot}COPh}\end{array}$$

(II)

Attempts to effect ester interchange between benzyl alcohol and the methyl cyanoacetate adducts failed, and addition of benzyl cyanoacetate in ethanol to chalcone, in presence of diethylamine, followed by attempted hydrogenation, gave ethyl 2-cyano-5-oxo-3 : 5-diphenylpentanoate, ester interchange occurring during the addition. Addition of benzyl cyanoacetate in benzyl alcohol gave an oil, which on hydrogenation in ethyl methyl ketone in presence of palladium–charcoal, gave the required acid. This series of reactions was also carried out with 4 : 4′-dimethoxychalcone and appears to be a general route for the preparation of these hitherto inaccessible cyano-keto-acids.



$$\mathrm{Ph{\cdot}CH{:}CH{\cdot}COPh} + \mathrm{CN{\cdot}CH_2{\cdot}CO_2{\cdot}CH_2Ph} \longrightarrow \begin{array}{l}\mathrm{Ph{\cdot}CH{\cdot}CH_2{\cdot}COPh}\\ \quad|\\ \mathrm{CN{\cdot}CH{\cdot}CO_2{\cdot}CH_2Ph}\end{array} \longrightarrow \begin{array}{l}\mathrm{Ph{\cdot}CH{\cdot}CH_2{\cdot}COPh}\\ \quad|\\ \mathrm{CN{\cdot}CH{\cdot}CO_2H}\end{array}$$

Three tetrahydropyridines are possible and, whilst derivatives of all three are known, only the Δ^3-isomer has been made with certainty. These isomers, obtained on reduction of pyridine with sodium and ethanol, cannot be separated by distillation.[5] Gabriel [6] has described the preparation of 1 : 2 : 3 : 4-tetrahydro-6-propylpyridine and advanced evidence for its structure, and Lipp [7] has described the methyl analogue. Reduction and cyclisation of 3 : 5-diaryl-2-cyano-5-oxopentanoic acids or their esters should give tetrahydropyridines. Compound (III) would be formed by elimination of water from the

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[*] Part V, *J.*, 1958, 2276.

[1] Kohler, Graustein, and Merrill, *J. Amer. Chem. Soc.*, 1922, **44**, 2540.

[2] Davey and Tivey, *J.*, 1958, 2276.

[3] Bowman, *J.*, 1950, 322.

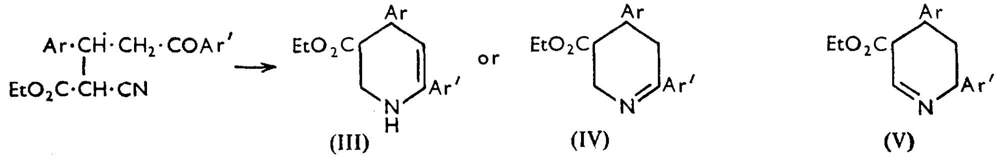
[4] Bowman and Fordham, *J.*, 1952, 3946.

[5] Koenigs and Bernhart, *Ber.*, 1905, **38**, 3042, 3928; 1907, **40**, 3199.

[6] Gabriel, *Ber.*, 1908, **41**, 2010; 1909, **42**, 1242, 4059.

[7] Lipp, *Ber.*, 1885, **18**, 3284.

enolic form of the ketone, whilst (IV) would be formed from the keto-form. Reduction of ethyl 2-cyano-3 : 5-di-(*p*-methoxyphenyl)-5-oxopentanoate catalytically in ethanol with Raney nickel W7 gave an oil, from which two pure picrates were obtained, giving the expected analyses. Regeneration of the bases, one crystalline and the other an oil, also gave satisfactory and identical analyses. Measurements of the p*K* values of the two bases gave very similar results (2·5—3·0) suggesting that both of these weak bases were Δ^1-compounds. Structures with the double bond in other positions should give higher p*K* values as secondary, and not tertiary, bases; *e.g.*, Adams and Mahan [8] found that 1-ethyl-1 : 2 : 3 : 4-tetrahydro-6-methyl- and 1 : 2 : 3 : 4-tetrahydro-6-methyl-pyridine gave p*K* values of 11·6 and 9·6 respectively. One of our bases had infrared bands at 1731 (ester C=O) and 1640 (CN), and aromatic bands at 1605 and 1512 cm.$^{-1}$, suggesting formula (V). The spectrum of the other base showed an ester-carbonyl band at 1715 cm.$^{-1}$, aromatic bands at 1591 and 1517 cm.$^{-1}$, and a band at 1609 cm.$^{-1}$ for the CN group conjugated with the aromatic system, indicating formula (IV; Ar = Ar′ = *p*-C_6H_4·OMe).



(III) (IV) (V)

The conversion of 3 : 5-diaryl-2-cyano-5-oxopentanoic acids into lactones met with only a limited success.

EXPERIMENTAL

Addition of Ethyl Cyanoacetate to Chalcone.—Dropwise addition of sodium ethoxide solution to chalcone (20·8 g., 0·1 mole) and ethyl cyanoacetate (12·3 g., 0·11 mole) in dry ethanol (50 ml.) until the mixture was just alkaline to litmus raised the temperature almost to the b. p. and, after 1 hour's refluxing on a steam-bath and cooling in ice, crystals were obtained. Recrystallisation gave *ethyl* 4-*cyano*-1 : 7-*dioxo*-1 : 3 : 5 : 7-*tetraphenylheptane*-4-*carboxylate* as plates, m. p. 220—225° (decomp.) (19·0 g., 75%) (Found: C, 79·0; H, 5·6; N, 2·3. $C_{35}H_{31}O_4N$ requires C, 79·4; H, 5·9; N, 2·6%). Attempts to isolate the monoadduct were not successful.

Addition of Methyl Cyanoacetate to Chalcone.—Addition of methyl cyanoacetate (6·5 g., 0·063 mole) to chalcone (10·4 g., 0·05 mole) in methanol (25 ml.) in presence of sodium methoxide as above gave methyl 4-cyano-1 : 7-dioxo-1 : 3 : 5 : 7-tetraphenylheptane-4-carboxylate as plates, m. p. 223—225° (decomp.) (Kohler *et al.*[1] give m. p. 226°) (8·2 g.). Dilution of the methanol filtrate with water (11 ml.) gave an oil which was taken up in benzene (50 ml.); the benzene was removed *in vacuo*. The residual oil crystallised during 6 months and methyl 2-cyano-5-oxo-3 : 5-diphenylpentanoate (1·8 g.) was obtained as plates (from ether), m. p. 74—75° (Kohler *et al.*[1] give m. p. 76°).

Methyl 2-*Cyano*-5-*oxo*-3 : 5-*diphenylpentanoate* (I).—Addition of diethylamine (2 ml.) to chalcone (20·8 g., 0·1 mole) and methyl cyanoacetate (10·5 g., 0·11 mole) in dry methanol (80 ml.) at 50° caused a rapid rise in the temperature to the b. p. and after 15 minutes' refluxing the whole was diluted with water (80 ml.) and cooled in ice. Extraction of the oil with benzene (2 × 100 ml.) and removal of the benzene as above gave the cyano-ketone (20 g., 67%), m. p. 69—70° (Kohler *et al.*[1] give m. p. 76°).

Treatment of this ester with methanolic potassium hydroxide (Kohler *et al.*[1]) gave the diadduct (II) and only a trace of acid; heating the ester with sulphuric–acetic acid failed to achieve hydrolysis.

Benzyl Cyanoacetate.—(*a*) Slow distillation of ethyl cyanoacetate (56 g.), benzyl alcohol (54 g.), benzene (500 ml.), and sodium (0·5 g.) and fractionation under reduced pressure gave benzyl cyanoacetate (80 g., 92%), b. p. 130—135°/0·1 mm. (*b*) Benzyl alcohol (54 g.) with cyanoacetic acid (42·5 g.) in benzene (500 ml.) and sulphuric acid (0·5 ml.; *d* 1·84) gave benzyl cyanoacetate (72 g., 82%), b. p. 138—140°/1 mm. Newman and Magerlein [9] give b. p. 134—136°/0·5 mm.

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[8] Adams and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588.

[9] Newman and Magerlein, *ibid.*, 1946, **68**, 2112.

Addition of Benzyl Cyanoacetate to Chalcone.—Addition of diethylamine (2 ml.) to benzyl cyanoacetate (22 g., 0·13 mole) and chalcone (25 g., 0·12 mole) in ethanol (250 ml.) gave an oil, which was hydrogenated in ethanol (120 ml.) over 10% palladium–charcoal (2 g.). The oily product was *ethyl* 2-*cyano*-5-*oxo*-3 : 5-*diphenylpentanoate* (Found: C, 74·5; H, 5·7; N, 4·0. $C_{20}H_{19}O_3N$ requires C, 74·8; H, 5·9; N, 4·4%). Hydrogenation of the oil in ethyl methyl ketone gave the same product.

2-*Cyano*-5-*oxo*-3 : 5-*diphenylpentanoic Acid.*—Addition of benzyl cyanoacetate (22 g.) to chalcone (25 g., 0·12 mol.) in benzyl alcohol (100 ml.) at 90° with diethylamine (2 ml.) as catalyst, gave oily *benzyl* 2-*cyano*-5-*oxo*-3 : 5-*diphenylpentanoate* (Found: C, 77·5; H, 5·0; N, 4·2. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5; N, 3·7%) (44·6 g.). Hydrogenation in ethyl methyl ketone in presence of 10% palladium–charcoal (2 g.) then yielded an oil (30 g., 84%) which solidified during a week to white needles, m. p. 155° (decomp.) [Kohler *et al.*[1] give m. p. *ca.* 160° (decomp.)]. Heating the acid (2 g.) at 200° until evolution of gas ceased, and cooling, gave 4-cyano-1 : 3-diphenylbutan-1-one (0·7 g.), needles (from methanol), m. p. 74—75° (Kohler *et al.*[1] give m. p. 76°).

5-*Hydroxy*-3 : 5-*diphenylpent*-4-*enoic Lactone.*—2-Cyano-5-oxo-3 : 5-diphenylpentanoic acid (8 g.) was refluxed in acetic anhydride (20 ml.) for 30 min., then cooled, and the black solution was poured into water. The dark precipitate was filtered off, dissolved in benzene and light petroleum (b. p. 60—80°), and chromatographed on alumina. Elution gave an oil which slowly crystallised. 5-Hydroxy-3 : 5-diphenylpent-4-enoic lactone was obtained as needles, m. p. 140—160° (1·3 g.), after three crystallisation from ethanol (Found: C, 81·3; H, 5·5. Calc. for $C_{17}H_{14}O_2$: C, 81·6; H, 5·6%). Vorländer and Knotzsch [10] record no m. p. for this compound. Reduction of 2-cyano-5-oxo-3 : 5-diphenylpentanoic acid (5 g.) with potassium borohydride (1·5 g.) in 1 : 9 aqueous ethanol (40 ml.) at room temperature yielded an oil from which no solid lactone could be isolated.

Addition of Ethyl Cyanoacetate to 4 : 4′-*Dimethoxy- and to* 4-*Hydroxy-chalcone.*—Addition of ethyl cyanoacetate (12 g., 0·11 mole) to 4 : 4′-dimethoxychalcone (26 g., 0·1 mole) in ethanol (80 ml.) with diethylamine (2 ml.) at 50°, followed by 15 minutes' refluxing, dilution with water, and benzene-extraction, gave a viscous mass which crystallised from ethanol as plates, m. p. 115—116°, of *ethyl* 2-*cyano*-3 : 5-*di*-(p-*methoxyphenyl*)-5-*oxopentanoate* (28 g., 74%) (Found: C, 69·0; H, 5·9; N, 3·8. $C_{22}H_{23}O_5N$ requires C, 69·2; H, 6·1; N, 3·7%). The *adduct* from 4-hydroxychalcone was obtained as an oil (Found: C, 70·4; H, 6·2; N, 3·7. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6; N, 4·2%).

Addition of Benzyl Cyanoacetate to 4 : 4′-*Dimethoxychalcone.*—Benzyl cyanoacetate (13·4 g.) and 4 : 4′-dimethoxychalcone (10·4 g.) in ethanol (50 ml.) at 50° with diethylamine (2 ml.) as above gave ethyl 2-cyano-3 : 5-di-(*p*-methoxyphenyl)-5-oxopentanoate, m. p. and mixed m. p. 115—116° (15 g., 78%). Addition of benzyl cyanoacetate (27 g.) to 4 : 4′-dimethoxychalcone (13·4 g.) in benzyl alcohol (60 ml.) with diethylamine (3 ml.) at 90° gave an oil (23 g.) (Found: C, 72·7; H, 5·8; N, 3·0. Calc. for $C_{27}H_{25}O_5N$: C, 73·1; H, 5·7; N, 3·2%). Hydrogenation in ethyl methyl ketone with palladium–charcoal as before gave 2-*cyano*-3 : 5-*di*-(p-*methoxyphenyl*)-5-*oxopentanoic acid* as needles (from benzene), m. p. 175—180° (decomp.) (Found: C, 67·5; H, 5·1; N, 4·2. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4; N, 4·0%).

5-*Hydroxy*-3 : 5-*di*-(p-*methoxyphenyl*)*pentenoic Lactone.*—Refluxing 2-cyano-3 : 5-di-(*p*-methoxyphenyl)-5-oxopentanoic acid (10 g.) with acetic anhydride (25 ml.) for 30 min. gave a dark solution which, when cooled and poured into water, afforded a dark semi-solid material. Chromatography on alumina as before gave the *lactone*, m. p. 128—130° (0·6 g.) (Found: C, 74·0; H, 5·6. $C_{19}H_{18}O_4$ requires C, 73·6; H, 5·8%).

Ethyl Tetrahydro-2 : 4-*di*-(p-*methoxyphenyl*)*pyridinecarboxylate Isomers.*—Ethyl 2-cyano-3 : 5-di-(*p*-methoxyphenyl)-5-oxopentanoate (10 g., 0·026 mole) in ethanol (60 ml.) was hydrogenated in presence of Raney nickel W7 (2 g.), hydrogen uptake corresponding to that required to convert the cyano- into an aminomethyl group. After filtration and evaporation of the filtrate *in vacuo*, a syrup (9 g.) was obtained. This was treated in ether (50 ml.) with picric acid (7 g.) in ether (50 ml.) and the yellow precipitate (11 g.; m. p. 160—180°) filtered off and fractionally crystallised from ethanol and then from benzene, giving the *picrate* of base A as yellow needles, m. p. 176—177° (1·7 g.) (Found: C, 56·6; H, 4·4; N, 9·2. $C_{28}H_{28}O_{11}N_4$ requires C, 56·3; H, 4·7; N, 9·4%), and the *picrate* of base B as yellow needles, m. p. 192—193° (2·5 g.) (Found: C, 56·5; H, 4·9; N, 9·3%). The former with 2N-sodium hydroxide (70 ml.) and

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[10] Vorländer and Knotzsch, *Annalen*, 1897, **294**, 333.

benzene (100 ml.) gave an oil, which crystallised from light petroleum (b. p. 40—60°) as isomer A, *ethyl* 1 : 2 : 3 : 4-*tetrahydro*-2 : 4-*di*-(p-*methoxyphenyl*)*pyridine*-5-*carboxylate*, needles, m. p. 117—118° (0·4 g.) (Found: C, 71·9; H, 6·8; N, 3·7. $C_{22}H_{25}O_4N$ requires C, 71·8; H, 6·8; N, 3·8%). The other picrate gave isomer B, *ethyl* 1 : 2 : 3 : 4-*tetrahydro*-4 : 6-*di*-(p-*methoxyphenyl*)-*pyridine*-3-*carboxylate*, an oil (Found: C, 71·3; H, 6·4; N, 3·5%). Attempts to hydrogenate both isomers in presence of Raney nickel W7 or platinic oxide were not successful.

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