LXIII.—*The Alkylation of α-Cyano-β-alkylacrylic Esters and of α-Phenyl-β-alkylacrylonitriles.*

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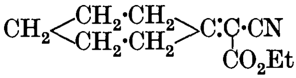
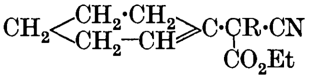
ETHYL *cyclo*hexylidenecyanoacetate (I) (Harding, Haworth, and Perkin, J., 1908, **93**, 1956; Lapworth and McRae, J., 1922, **121**, 2741) readily reacts with phenacyl bromide or methyl iodide in presence of sodium ethoxide, giving derivatives of type (II).

(I.)



$CH_2{<}{}^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}{>}C{:}\underset{CO_2Et}{C}\cdot CN$



$CH_2{<}{}^{CH_2\cdot CH_2}_{CH_2-CH}{>}C\cdot\underset{CO_2Et}{C}R\cdot CN$

(II.)

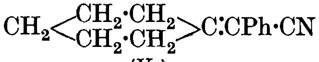
(III.) $C_5H_{11}\cdot CH_2\cdot CH{:}C(CN)\cdot CO_2Et$

This was thought by the former authors to furnish fairly conclusive evidence of the validity of structure (II; R = H) which they assigned to the substance, but the products of decomposition were shown by the latter authors to support the formula (I). Other reactions of this ester were found to be in agreement with this structure and it was pointed out that the formation of alkyl derivatives (II) can be explained on the basis of the structure (I). Strong evidence has been presented by Harding, Haworth, and Perkin for the methyl derivative of ethyl *cyclo*hexylidenecyanoacetate having a structure of type (II), but since a search of the literature disclosed that these seemed to be the only genuine cases of unsaturated α-cyano-esters having the double bond in the βγ-position, it seemed to us desirable to investigate such derivatives of α-cyano-β-alkylacrylic esters by the methods used by Lapworth and McRae in their study of ethyl *cyclo*hexylidenecyanoacetate and ethyl heptylidenecyanoacetate (III) in order to establish conclusively the structure (II) as that of these alkyl derivatives and at the same time to ascertain the behaviour of these substances towards those reagents with which the parent αβ-unsaturated substances give characteristic results.

This has now been done with the *n*-butyl and ethyl derivatives of ethyl *cyclo*hexylidenecyanoacetate and with the *n*-butyl derivative (IV) of ethyl heptylidenecyanoacetate. It was also our intention to prepare and examine in the same way derivatives of

$C_5H_{11}\cdot CH{:}CH\cdot C(C_4H_9)(CN)\cdot CO_2Et$

(IV.)



$CH_2{<}{}^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}{>}C{:}CPh\cdot CN$

(V.)

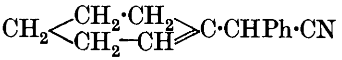
(VI.) $C_5H_{11}\cdot CH_2\cdot CH{:}CPh\cdot CN$

the similarly constituted α-phenyl-β-alkylacrylonitriles, but in repeated attempts we failed to obtain any evidence that either *cyclo*hexylidenephenylacetonitrile (V) or α-phenyl-β-hexylacrylonitrile (VI) forms alkyl derivatives.

Ozone is rapidly absorbed by the above-mentioned three alkyl derivatives and the decomposition of their ozonides leads precisely to those products to be expected from formulæ (II) and (IV); namely, in the case of *ethyl* α-n-*butyl*-Δ^1-cyclo*hexenylcyanoacetate*, ethyl *n*-butylcyanoacetate and adipic acid; from the ozonide of the corresponding *ethyl* derivative, only adipic acid was isolated; and from the ozonide of *ethyl* α-*cyano*-α-n-*butyl*-Δ^β-*nonenoate* (IV), the substances isolated were hexaldehyde, formic acid, and *n*-butylmalonic acid. The behaviour of these alkyl derivatives in absorbing bromine instantly and in giving no reaction with either potassium cyanide or sodium bisulphite is in accord with their $\beta\gamma$-unsaturation and is in such marked contrast with the behaviour of the parent esters towards these reagents that it must be concluded that only the merest trace of the $\beta\gamma$-isomeride can be present in ethyl *cyclo*hexylidenecyanoacetate and that these two forms do not present a case of tautomeric equilibrium in which the position of equilibrium is quickly restored if disturbed.

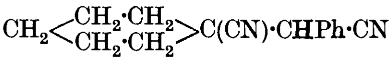
The ozonisation results outlined above dispose of the suggestion of Lapworth and McRae that the sodio-derivatives might have *inter alia* the structure $R'\cdot CNaR''\cdot CR''':C(CN)\cdot CO_2Et$. The preparation of the *n*-butyl derivative of ethyl heptylidenecyanoacetate supplements the results of Lapworth and McRae, who failed to obtain benzyl and phenacyl derivatives of this substance in a state pure enough for characterisation, although reactions with benzyl chloride and phenacyl bromide in the presence of sodium ethoxide occurred readily. Their statement of these results has been misinterpreted by Birch, Kon, and Norris (J., 1923, **123**, 1361) to mean that no alkylation had taken place and a "ready interpretation," now obviated, of this supposed failure to form alkyl derivatives was advanced. The latter authors are of the opinion that to form these alkyl derivatives the $\beta\gamma$-phase of the $\alpha\beta$-unsaturated α-cyano-ester is necessary and it was concluded that this was absent or suppressed in ethyl heptylidenecyanoacetate through a tendency to form a doubly conjugated system. If it be granted that such isomeric change is a necessary preliminary to alkylation, then it can take place apparently with almost equal facility in both ethyl *cyclo*hexylidenecyanoacetate and ethyl heptylidenecyanoacetate.

During the course of our attempts to alkylate *cyclo*hexylidenephenylacetonitrile we obtained further evidence in support of Birch and Kon's contention (J., 1923, **123**, 2440) that this substance should have the constitution (V) rather than the $\beta\gamma$-structure (VII) of Harding and Haworth (J., 1910, **97**, 486), in that it readily combines with hydrogen cyanide, forming 1-*cyano*cyclo*hexylphenylacetonitrile* (VIII).



$CH_2{<}\begin{matrix}CH_2\cdot CH_2\\ CH_2{-}CH\end{matrix}{\geqslant}C\cdot CHPh\cdot CN$

(VII.)



$CH_2{<}\begin{matrix}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{matrix}{>}C(CN)\cdot CHPh\cdot CN$

(VIII.)

(IX.) $C_6H_{13}\cdot CH(CO_2H)\cdot CHPh\cdot CO_2H$

Heptaldehyde has now been condensed with phenylacetonitrile, giving *α-phenyl-β-*n-*hexylacrylonitrile* (VI); this combines with hydrogen cyanide to form a dinitrile, which was not isolated but was hydrolysed to *α-phenyl-α'-*n-*hexylsuccinic acid* (IX).

EXPERIMENTAL.

*Ethyl α-*n-*Butyl-Δ¹-*cyclo*hexenylcyanoacetate* (II; R = C_4H_9).—The sodio-derivative of ethyl *cyclo*hexylidenecyanoacetate prepared from 19·3 g. of the ester and 2·3 g. of sodium in 50 c.c. of absolute alcohol was heated under reflux on a steam-bath for 2 hours with *n*-butyl iodide (23 g.). Water and ether were then added; the ethereal solution was washed with sodium carbonate solution and dried with calcium chloride. After evaporation of the ether the residue was fractionated under reduced pressure; the fraction, b. p. 162—165°/15 mm., on redistillation, yielded 15 g. of the pure *ester*, b. p. 163—164°/15 mm. (Found: C, 72·1; H, 9·4; N, 5·7. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·2; N, 5·6%). The pure ester absorbed bromine readily, but eventually hydrogen bromide was liberated, pointing to a certain amount of substitution. Attempts to effect the addition of hydrogen cyanide gave only the unchanged ester.

*Ethyl α-Ethyl-Δ¹-*cyclo*hexenylcyanoacetate* (II; R = Et).—The preparation of this derivative was carried out precisely as described above, except that ethyl iodide (30 g.) was substituted for the *n*-butyl iodide. After three distillations, 10 g. of the pure *ester*, b. p. 168°/22 mm., were obtained (Found: C, 70·1; H, 8·5; N, 6·7. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; N, 6·3%). Its behaviour with bromine and with potassium cyanide is exactly parallel to that of the butyl derivative.

*Ozonisation of Ethyl α-*n-*Butyl-Δ¹-*cyclo*hexenylcyanoacetate.*—A solution of 10 g. of the ester in chloroform was treated with a stream of ozonised oxygen for 15 hours; no further absorption of ozone then seemed to take place. The thick, syrupy residue remaining after removal of the chloroform under reduced pressure was warmed on a steam-bath for 30 minutes with 25 c.c. of 6% sulphuric acid and 3 g. of potassium ferrocyanide. The resulting solution was repeatedly extracted with ether. After being washed several times with sodium bicarbonate solution (A), the combined ethereal extracts were evaporated and the residue was treated again with sulphuric acid and potassium ferrocyanide, ultimately giving another extract (A) and an ethereal solution, which on evaporation yielded an oil (B).

The sodium bicarbonate extract (A) was acidified and extracted with ten successive portions of ether, which were united, washed once with a little water, and evaporated. The oily residue, which readily crystallised, reduced ammoniacal silver nitrate, but did not affect Fehling's solution—properties in accord with those given by Harries (*Ber.*, 1908, **41**, 3557) for the half-aldehyde of adipic acid. It was evaporated to dryness on the water-bath with nitric acid; the residue, after one crystallisation from acetone, yielded 3 g. of adipic acid, identified by melting point (149°) and by comparison with a genuine specimen (Equiv.: found, 73·1; calc., 73·1).

The oily residue (B) was distilled under reduced pressure and two fractions were collected: (i) up to 130°/15 mm. (3·8 g.), (ii) 130—210°/15 mm. (3·8 g.). The first fraction on hydrolysis with alcoholic potash evolved much ammonia. After removal of the alcohol, the solution was acidified and repeatedly extracted with ether. The ethereal extract on evaporation yielded 3·2 g. of an acid which, after recrystallisation from acetone, melted at 102—103°, alone or mixed with a genuine specimen of *n*-butylmalonic acid (Equiv.: found, 80·1; calc., 80·0). The formation of this acid and the production of ammonia establish the fact that ethyl *n*-butylcyanoacetate is one of the original products of the decomposition of the ozonide.

The second fraction, of which the greater portion distilled at 195°/15 mm., deposited a crystalline acid on cooling, which was separated from the oil by repeated extraction with water. The combined extracts on evaporation yielded 1·4 g. of pure adipic acid. The oil on hydrolysis with alcoholic potash yielded a further 1·9 g. of *n*-butylmalonic acid. The recovery of adipic acid (4·4 g.) and of *n*-butylmalonic acid (5·1 g.) was respectively 77 and 79% of that theoretically possible.

Ozonisation of Ethyl α-Ethyl-Δ^1-cyclo*hexenylcyanoacetate.*—Two g. of the ester, subjected to the action of ozone as described in the case of the *n*-butyl derivative, yielded 0·6 g. of pure adipic acid. There was insufficient neutral ester to make a search for ethylmalonic acid feasible.

*Ethyl α-Cyano-α-*n*-butyl-*Δ^β*-nonenoate* (IV).—The ester (III) required for this preparation was prepared by a modification of Lapworth and McRae's method (*loc. cit.*). A mixture of 57 g. of ethyl cyanoacetate and 1 g. of piperidine is cooled in salt and ice, and 57 g. of heptaldehyde are added at such a rate that the temperature remains below 0°. The mixture is kept in ice for 24 hours and then treated in the usual way. The yield of pure ester, boiling at 152—154°/13 mm. rather than at 144—145°/13 mm. as previously recorded, is 80—84 g.

Alkylation was effected by adding 23 g. of *n*-butyl iodide to the sodio-derivative prepared by adding 22 g. of the ester (IV) to a cooled solution of 2·3 g. of sodium in 50 c.c. of absolute alcohol, and warming the mixture gently on a water-bath for 90 minutes. The mixture was then poured into a large volume of dilute acid and extracted with ether, and the extract was washed successively with dilute sodium carbonate solution and with water. After the ethereal solution had been dried and evaporated, the residue was fractionated under reduced pressure. By combining the fractions, b. p. 160—180°/17 mm., from several operations and redistilling them, the pure *ester*, b. p. 154—156°/11 mm., was obtained (yield, 10%) (Found: C, 72·4; H, 10·0; N, 5·7. $C_{16}H_{27}O_2N$ requires C, 72·5; H, 10·2; N, 5·3%). The sodium carbonate extract mentioned above gave 6 g. of a strongly acid substance on acidification. A pure substance has not been isolated from it. The ester readily absorbs bromine in carbon tetrachloride solution, and hydrogen bromide is liberated in appreciable quantity only on prolonged treatment. A pure dibromo-derivative was not isolated.

*Ozonisation of Ethyl α-Cyano-α-*n*-butyl-Δ^{β}-nonenoate* (IV).—After a stream of ozonised oxygen had been passed into 6 g. of the pure ester for 35 hours, the material was heated on a water-bath for 1 hour with 50 c.c. of 4% sulphuric acid and then steam-distilled until 50 c.c. of distillate had been collected, leaving an oily mixture in the distilling flask (A). The distillate was shaken with sodium bisulphite, and an oil which remained undissolved was extracted with ether (B). The aqueous bisulphite solution was made alkaline with sodium carbonate and distilled in steam. The distillate was shaken with an excess of semicarbazide hydrochloride and sodium acetate. A solid semicarbazone separated which was filtered off and cautiously washed with ether. The melting point of this product (0·5 g.), alone or mixed with a genuine specimen of hexaldehyde semicarbazone, was 106°. Admixture with an equal weight of the semicarbazone of heptaldehyde (m. p. 106°) caused a depression of over 6°. Recrystallisation from methyl alcohol did not change the melting point.

The ethereal solution containing the oil (B) was evaporated, and the residue heated with alcoholic potash until evolution of ammonia ceased. The acidified solution was repeatedly extracted with ether. The ethereal solution on evaporation left a thick oil, from which 0·1 g. of an acid, m. p. 89°, crystallised in several days. On heating to a higher temperature, a gas, probably carbon dioxide, was evolved. The crude acid yielded an equivalent of 85 (*n*-butylmalonic acid requires equiv. 80·0). When calcium chloride solution was added to a neutral solution of the sodium salt, a crystalline calcium salt was precipitated. Although insufficient acid was obtained to identify it further, the authors regard this as slightly impure *n*-butylmalonic acid.

Examination of the oil (*A*). *Isolation of* n-*butylmalonic acid.* The oil was extracted with ether, and then hydrolysed with alcoholic potash, ammonia being evolved in considerable quantity. From the product of hydrolysis, 0·6 g. of *n*-butylmalonic acid was isolated as described above and identified by its melting point, 102°, and its equivalent (Found, 81).

Examination of the aqueous solution remaining in the distillation flask. Detection of formic acid. The aqueous solution was heated to expel the ether and distilled until only a small volume remained. The distillate (150 c.c.) was strongly acid and gave the following tests for formic acid : (*a*) The odour of ethyl formate on esterification; (*b*) reduction of mercuric chloride to mercurous chloride and of silver nitrate to metallic silver ; (*c*) reduction with magnesium powder yielded an appreciable quantity of formaldehyde.

Experiments with cyclo*Hexylidenephenylacetonitrile* (V).—Birch and Kon (J., 1923, **123**, 2446) mention that this nitrile is somewhat difficult to purify. If, however, the substance prepared by Harding and Haworth's method (J., 1910, **97**, 497) is carefully fractionated under reduced pressure, it solidifies, on cooling, to a colourless, crystalline mass, which, after being drained on tile and cautiously washed with ether, melts at 28° and boils at 176—178°/12 mm. Piperidine does not effect the condensation of *cyclo*hexanone with phenylacetonitrile.

The nitrile (19·7 g.) was added to sodium ethoxide made from 2·3 g. of sodium and 40 c.c. of absolute alcohol. The yellow solution was heated under reflux for $3\frac{1}{2}$ hours with 21 g. of *n*-butyl iodide, the neutral mixture poured into water, and the oil extracted with ether. The residue obtained from the dried evaporated extract gave 17·3 g. of an oil, b. p. 178—180°/13 mm., which solidified almost completely when cooled and seeded with *cyclo*hexylidenephenylacetonitrile. A portion pressed on tile and cautiously washed with alcohol melted at 28°, alone or mixed with the original nitrile (Found : C, 85·5; H, 7·8; N, 7·1. Calc. : C, 85·3; H, 7·6; N, 7·1%).

The above procedure was varied by using *n*-butyl bromide, ethyl bromide, and also a large excess of sodium ethoxide, but the unchanged nitrile was recovered almost quantitatively. The alkyl halide was always used up, even in the cold, whereas in the absence of the nitrile reaction is very slow.

A mixture of 19·7 g. of the nitrile (V), 13 g. of potassium cyanide, 20 c.c. of water, and 100 c.c. of alcohol was gently heated on a water-bath for 5 hours. The resulting brown mixture was poured into a litre of boiling, very dilute sodium hydroxide solution, and boiling continued for 20 minutes. The separated oil, which readily crystallised, was filtered off (yield, 18 g.), washed, and recrystallised twice from alcohol. It softened at 258° and began to decompose above 264° (Found : C, 80·4; H, 7·3; N, 12·2. $C_{15}H_{16}N_2$ requires C, 80·5; H, 7·1; N, 12·5%). Partial hydrolysis of the 1-*cyano*cyclo*hexylphenylacetonitrile* (VIII) could be effected by heating on the steam-bath for 10 hours with 90% sulphuric acid. No charring occurred and the mixture of amide and imide on further hydrolysis with potash yielded an acid which was difficult to purify.

*α-Phenyl-*β-n-*hexylacrylonitrile* (VI).—Owing to the ease with which heptaldehyde polymerises, special precautions must be observed in this preparation, especially since piperidine does not effect the condensation. Heptaldehyde (30 g.) was slowly added to a solution, cooled to − 10°, prepared by adding 40 g. of phenylacetonitrile to a solution of 6·1 g. of sodium in 200 c.c. of absolute alcohol. The mixture was left in a freezing mixture for 6 hours, allowed to come to room temperature over-night, and then poured into dilute acid. The oil was extracted with ether, washed with sodium carbonate solution, and dried. The residue obtained after removal of the ether gave 41 g. of a fraction, b. p. 162—173°/13 mm., which after two distillations gave the pure *nitrile*, b. p. 168—170°/13 mm. (Found : C, 84·6; H, 9·0; N, 6·7. $C_{15}H_{19}N$ requires C, 84·5; H, 8·9; N, 6·6%).

Attempts to add on the elements of hydrogen cyanide with subsequent hydrolysis gave in one case a product which seemed to consist largely of *α-phenyl-α′-*n-*hexylsuccinic acid* (IX). In another experiment an acid, m. p. 170°, equiv. 270, was obtained ($C_{16}H_{22}O_4$ requires equiv., 278). The results show that although undoubtedly hydrogen cyanide is added on, the primary process of the reaction is very slow, giving opportunity for the occurrence of secondary reactions (compare Lapworth and McRae, *loc. cit.*, p. 2747). In view of the uncertainty the authors deem it unnecessary to enter into experimental details.

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