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The Addition of Dibromomalononitrile to Double Bonds. A Route to γ-Lactones

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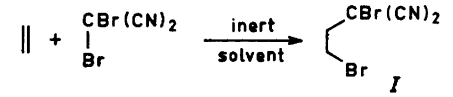
Dibromomalononitrile adds to the double bond. It is suggested that the reaction starts with attack of a bromonium ion followed by addition of the negatively charged bromodicyanomethyl group to the other olefinic carbon atom. The adducts can be selectively debrominated. Alkaline hydrolysis of the product affords α-carboxy-γ-lactones.

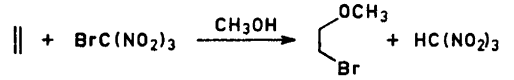
In view of the strong electronegativity of the cyano group one would expect the bromine atoms of dibromomalononitrile to be easily removable as positive ions, *i.e.*, the compound should act as a brominating agent. In fact, reaction with dimethylaniline in aqueous solution afforded *p*-bromodimethylaniline in 54 % yield, and malononitrile has been converted into monobromomalononitrile by the same reagent [1]. In these reactions a proton is abstracted by the brominating agent with formation of monobromomalononitrile.

We anticipated that reaction of dibromomalononitrile with a double bond would give an adduct, as in (1), although



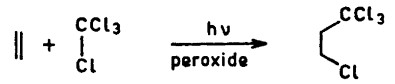
I (1)

allylic bromination was also conceivable. Schmidt *et al.*[2] have published work on the similar reactions between bromonitromethanes or brominated malonic esters and cyclohexene. In methanolic solution 2-bromocyclohexyl methyl ether was formed. The reaction can be depicted in the following manner (2):



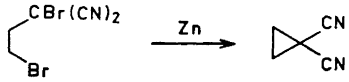
(2)

If an inert solvent had been used the reaction could have taken the course outlined in (1). The Kharash reaction [3] is also of relevance in this connection. Highly halogenated hydrocarbons add to double bonds under the influence of ultraviolet light or peroxides (3). This is a typical radical reaction.



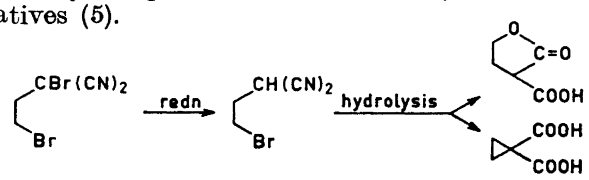
(3)

When styrene and dibromomalononitrile are mixed, heat is evolved and addition of solvent is necessary to moderate the reaction. Cyclohexene on the other hand reacts sluggishly and refluxing in chloroform for several hours is necessary to increase the yield of adduct. Irradiation with ultraviolet light or addition of benzoylperoxide had no marked effect on the yield. Considering the strongly polarized carbon-bromine bond in dibromomalononitrile, we suggest that the mechanism is ionic and is initiated by attack of Br^+. From the reaction mixtures crystalline compounds were isolated analysing correctly for the adducts I. In the case of cyclohexene no 3-bromocyclohexene could be detected. We considered the adducts to be of potential synthetic interest since ring closure of the 1,3 dibromides would give cyclopropane derivatives (4).



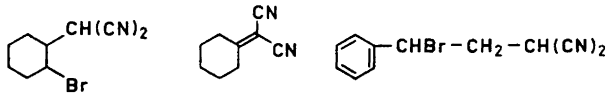
(4)

and selective hydrogenation of one of the bromine atoms, followed by hydrolysis of the cyano groups would lead to γ-lactones or again cyclopropane derivatives (5).

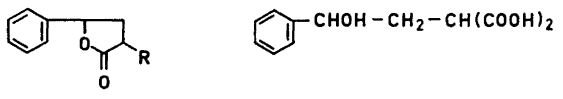


(5)

Zinc reduction of the cyclohexene adduct in acetic acid afforded II in good yield. The same compound was also obtained catalytically using Pt/C. Reduction with zinc in alcoholic solution at 0° gave a product, which showed strong double bond absorption in the IR at 1 650 cm^{-1} and probably consisted mainly of the unsaturated dinitrile III. No cyclopropane formation was detected.



II III IV

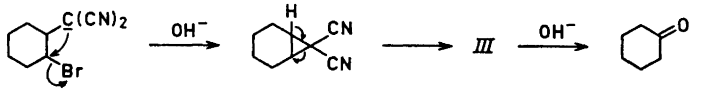


V R=CN
VI R=COOH
VII R=H

VIII

From the catalytic reduction of the crude crystalline styrene adduct the siomer IV was isolated together with a second compound, which besides possessing nitrile absorption in the IR also showed a strong carbonyl band at 1 785 cm^{-1}. This suggested that the compound was V. Alkaline hydrolysis of V gave the carboxylactone VI in a good yield, indentified with an authentic sample prepared by another route. On heating it decarboxylated to VII. Alkaline hydrolysis of the dicyano compound IV gave two products, one of which was identical with VI. The other proved to be VIII and was converted to VI by heating at 90—100° in vacuum for 2 h.

The cyclohexane derivative reacted differently towards alkali. It was easily dissolved in aqueous sodium hydroxide giving a yellow solution from which cyclohexanone separated slowly.

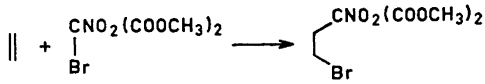


IX X

XI (cis and/or trans) XII XIII XIV

The cyclopropane derivative X is presumably an intermediate, which rearranges *via* III to cyclohexanone. Hydrolysis of II with conc. hydrobromic acid produced a complex mixture of the γ-lactone XI, a carboxy lactone and a compound containing bromine, probably XII. The lactone could be converted to the corresponding amide by the action of ammonia in ethanol and was therefore probably the *trans*-isomer [4]. The acidic materials were difficult to separate and no further work was done with them.

The reaction of some similar compounds such as ethyl bromonitro-malonic ester XIII and carbonyl cyanide XIV was also investigated. XIII is reported to react with double bonds in alcoholic solution according to (2) [2]. From XIII and dimethyl aniline, *p*-bromodimethyl aniline was obtained in 40 % yield using the method previously described [1]. In an inert solvent XIII should add to a double bond according to (6).

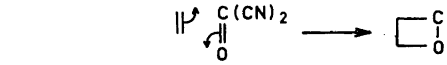


(6)

The intermediate so obtained, on reduction, hydrolysis and decarboxylation would then lead to a γ-hydroxy-amino acid. In fact, the reaction product from styrene or 1-octene no longer showed vinyl double bond absorption in the IR at around 900 cm^{-1}, and on catalytic reduction, hydrolysis and decar-

boxylation a mixture of amino acids was obtained. Paper chromatography showed, besides glycine the presence of one or two unidentified amino acids. However, all attempts to isolate them were unsuccessful.

Recent work by Achmatowich *et al.*[5] on the chemistry of carbonyl cyanide, showed that it adds in a *cis*-fashion to certain types of double bonds (7):



(7)

The action of carbonyl cyanide on β-nitro styrene was therefore investigated, since the adduct formed should be potentially useful for the preparation of serine analogues. However, no reaction between the components could be detected. Radiation with ultraviolet light was without effect.

EXPERIMENTAL

All melting points are corrected.

Dibromomalononitrile. To a cooled mixture of malononitrile (7.0 g) and water (60 ml), bromine (35 g) was added dropwise with stirring. After the addition the solution was stirred for a further hour. The yellow oil which separated was dried over sodium sulphate and distilled in vacuum to give dibromomalononitrile (18 g, 69 %), b.p.$_8$ 48–49°.

(2-Bromocyclohexyl)-bromomalononitrile. A mixture of dibromomalononitrile (5.6 g), cyclohexene (2.0 g), and chloroform (10 ml) was heated under reflux for 48 h. Evaporation of the solvent gave a brown oil, which partially crystallized on addition of methanol at 0° affording the adduct (1.6 g, 22 %). Recrystallisation from methanol gave an analytical sample, m.p. 128–129°. (Found: C 35.29; H 3.38. Calc. for $C_9H_{10}N_2Br_2$ (306.2): C 35.33; H 3.30.)

(2-Bromocyclohexyl)-malononitrile. (a) To a mixture of (2-bromocyclohexyl)-bromomalononitrile (2 g), ethyl acetate (10 ml), acetic acid (40 ml), water (8 ml) and zinc (4 g) was added with stirring at 5°. After 5 min ice-water (200 ml) was added and the aqueous solution extracted three times with ether. The ether was shaken with conc. sodium bicarbonate solution, dried over sodium sulphate and the solvent evaporated. The residue was recrystallized from light petroleum (40–60°) affording (2-bromocyclohexyl)-malononitrile (1.13 g, 77 %) m.p. 65.5–66.5°. (Found: C 47.90; H 5.04; Calc. $C_9H_{11}N_2Br$ (227.0): C 47.62; H 4.85).

(b) (2-Bromocyclohexyl)-bromomalononitrile (0.21 g) in ethyl acetate (20 ml) was reduced catalytically over Pt/C. Hydrogen consumption became slow after the absorption of one mole and on working up 0.14 g of crude product was obtained. After recrystallisation from cyclohexane (2-bromocyclohexyl)-malononitrile, m.p. 65.5–66.5, was obtained, identical with the product from the zinc reduction.

Alkaline hydrolysis of (2-bromocyclohexyl)-malononitrile (II). II (50 mg) in sodium hydroxide (5 N, 0.5 ml) was heated on the water bath for 10 min. An oil separated and the solution turned slightly yellow. Addition of 2,4-dinitrophenylhydrazine solution gave a yellow precipitate (51 mg) which was identified as cyclohexanone 2,4-dinitrophenylhydrazone by m.p. 160–161.5°, and mixed m.p. 159.5–160°.

Acid hydrolysis of II. The malononitrile (0.108 g) was refluxed for one hour with conc. hydrobromic acid (2 ml). Dilution with water and extraction with chloroform gave an oily product (60 mg), which was separated in a neutral fraction (12 mg) and an acidic fraction (46 mg) by extraction with sodium bicarbonate solution. The neutral fraction consisted of the oily lactone XI (IR band at 1 775 cm^{-1}) which was transformed into an amide (amide band in the IR) by treatment with ammonia in ethanol. Distillation of the acid fraction at normal pressure (220°) caused decarboxylation and lactonization (IR band at 1 775 cm^{-1} and a minor peak at 1 725 cm^{-1}, crude product).

The adduct of styrene and dibromomalononitrile. To styrene (6.8 g) in chloroform (50 ml), dibromomalononitrile (14.4 g) was added. The solution became slightly warm and after standing for two days at room temperature the solvent was evaporated affording an oily residue (21 g), which crystallized slowly on standing. This adduct, recrystallized

from light petroleum, had m.p. 75.5–77°. (Found: C 40.22; H 2.79. Calc. for $C_{11}H_8N_2Br_2$ (328.0): C 40.28; H 2.46).

Hydrogenation of the styrene adduct. 1,1-Dicyano-3-bromo-3-phenylpropane. IV. The crude adduct (21 g) in ethyl acetate-ethanol (6:1) was hydrogenated over Pt/C at atmospheric pressure. One mole of hydrogen was absorbed during 2 days. After removal of the solvent in vacuum the product was extracted with cold benzene (20 ml). The yellow insoluble material (1.7 g) was crystallized from ethanol furnishing crystals (0.2 g), m.p. 130–131°, identified as the cyanolactone (V). The light petroleum insoluble part of the benzene extract afforded a further 1.0 g of the cyanolactone V, m.p. 130–131° (lit.[7] 132°), after recrystallization from ethanol. (Found: C 70.32; H 4.89. Calc. for $C_{11}H_9O_2N$ (187.2): C 70.56; H 4.84). The light petroleum soluble part of the benzene extract afforded oily crystals of IV on standing. These were recrystallized from light petroleum and had the m.p. 59–60°, (1.2 g). (Found: C 53.14; H 3.65. Calc. for $C_{11}H_9N_2Br$ (249.1): C 53.19; H 3.64). By evaporation of the mother liquor an additional amount of crude IV (11 g) was obtained. The total yield of IV was 75 %.

α-Carboxy-γ-phenyl-γ-hydroxy butyric acid VIII and α-carboxy-γ-phenyl butyrolactone VI. (a) From crude IV. IV (10 g) was hydrolyzed with 20 % sodium hydroxide (240 ml) on the water bath overnight. A small amount of a yellow insoluble material was filtered off and the filtrate carefully neutralized at 0° with conc. hydrochloric acid. White crystals of VIII (5.0 g, 55 %) separated. After recrystallization from toluene they had m.p. 100–101°. (Found: C 59.06; H 5.20. Calc. for $C_{11}H_{12}O_5$ (224.2): C 58.93; H 5.40). Chloroform extraction of the aqueous phase afforded the lactone VI (0.37 g), identical by mixed melting point and IR spectrum with a sample (m.p. 104–105°) prepared by another route. Decarboxylation of VI at 160° gave γ-phenyl butyrolactone VII in practically 100 % yield.

(b) From the cyanolactone V. The cyanolactone V (80 mg) was hydrolyzed with 20 % sodium hydroxide (2.5 ml). Acidification with conc. hydrochloric acid at room temperature afforded the carboxylactone VI (79 mg crude product). It had m.p. 103–104° after recrystallization from toluene.

α-Carboxy-γ-phenyl butyrolactone. To phenacyl malonic acid[7] (0.23 g) in sodium hydroxide solution (5 ml, 0.8 N) sodium borohydride (70 mg) was added with stirring. After 30 min the solution was acidified with dilute hydrochloric acid. The lactone (125 mg, 59 %) precipitated on standing and had m.p. 104–106° after recrystallization from water (lit.[6] 106°).

Reaction of methyl bromo-nitromalonate with 1-octene and styrene. 1-Octene (1.2 g) and the bromo-nitrodiester XIII[8,9] (2.6 g) were heated on the waterbath for 31 h, after which time the mixture no longer showed vinyl absorbtion in the IR. All attempts to obtain crystalline products from the reaction mixture were unsuccessful. A portion of the product (1.0 g) was refluxed with stannous chloride (4 g) and conc. hydrochloric acid (20 ml) for 0.5 h. Paper chromatography indicated the presence of three amino acids, one of which had the same R_F value as glycine. Attempts to isolate these acids were unsuccessful. Catalytical reduction over Raney-Ni of the crude adduct gave intractable products.

Reaction of styrene and the bromo-nitrodiester XIII also gave an intractable product having no vinyl absorption in the IR.

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