CYANOESTERS AND DINITRILES

I. SYNTHESIS OF MALONONITRILES FROM METHYLENE ETHERS

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ABSTRACT

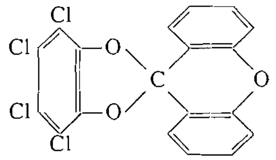
α-(9-Fluorenylidene) malononitrile (V) is obtained by the interaction of malononitrile and 9,9-(tetrachloro-*o*-phenylenedioxy) fluorene (II) in boiling *n*-butanol. Whereas fluorenone phenyl- or benzoyl-hydrazone is similarly obtained by the action of the corresponding hydrazine on II, the latter also undergoes reductive cleavage by hydrazine hydrate to give fluorene and tetrachlorocatechol. The heteropolar structures of methylene ethers are stressed.

Methyl-, ethyl-, isopropyl-, and benzyl-magnesium halides react readily with V to give the 9-dicyanomethyl-9-alkylfluorenes (VII*b*–VII*e*), respectively, which give, upon oxidation with alkaline potassium permanganate, the corresponding 9-alkylfluorene-9-carboxylic acids.

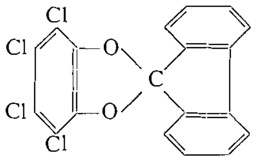
α-(9-Xanthenylidene) malononitrile (VI*a*) reacts similarly with alkylmagnesium halides to give the corresponding 9-xanthenylmalononitriles (VIII*b*–VIII*d*). However, V and VI are reduced by isobutylmagnesium iodide to give 9-fluorenyl- (VII*a*) and 9-xanthenyl-malononitrile (VIII*a*), respectively.

Whereas the infrared spectra of unsaturated malononitriles and cyanoesters show strong absorption in the 4.5 μ region, the spectra of the saturated analogues lack this absorption.

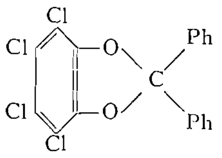
It has been reported throughout (1) that 9,9-(tetrachloro-*o*-phenylenedioxy) xanthene (I), in contrast to the fluorene analogue II, is cleaved readily by active hydrogen compounds in boiling ethanol to give the corresponding xanthenes. Cleavage of II is now brought about readily when the reaction is carried out in the higher boiling *n*-butanol. Thus, when II is refluxed with malononitrile, α-(9-fluorenylidene) malononitrile (V) is produced together with tetrachlorocatechol. With phenyl- or benzoyl-hydrazine, the corresponding fluorenone hydrazone is produced, possibly through the intermediate formation of an unstable open-chain ether by a β-elimination process (1). However, in contrast to other analogous methylene ethers previously investigated, II also undergoes reductive cleavage by hydrazine hydrate, yielding fluorene and tetrachlorocatechol, on prolonged boiling in *n*-butanol. The diphenylmethylene analogue III is not attacked by active hydrogen compounds under similar conditions. It is assumed that the methylene ether is a resonance hybrid of various structures (2) (cf. IV), and the reaction proceeds through the nucleophilic attack of the active hydrogen compound. In the case of I, the heteropolar structure (IV*b* or IV*c*) is greatly stabilized by the strong resonance of the carbonium ion having



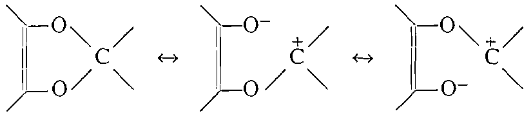
I



II



III



IV*a* IV*b* IV*c*

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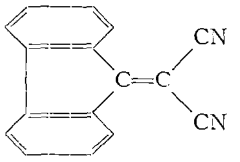
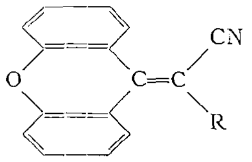
the unshared electron pair on the oxygen of the xanthene residue. In the case of II, the heteropolar structures contribute largely to the actual state of the molecule at higher temperatures.

Reaction of Alkylmagnesium Halides on Unsaturated Dinitriles

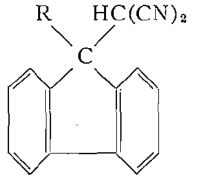
In an attempt to prepare substituted malononitriles for biological purposes and spectral investigation, the action of Grignard reagents on the unsaturated malononitriles (V and VI*a*) has been investigated. It is found that V reacts with methyl-, ethyl-, isopropyl-, and benzyl-magnesium halides to give 9-dicyanomethyl-9-methyl- (VII*b*), 9-dicyanomethyl-9-ethyl- (VII*c*), 9-dicyanomethyl-9-isopropyl- (VII*d*), and 9-dicyanomethyl-9-benzylfluorene (VII*e*), respectively, in good yields. The analogous α-9-xanthenylmalononitriles VIII*b*, VIII*c*, and VIII*d* are similarly obtained by the action of the corresponding alkylmagnesium halides on α-(9-xanthenylidene) malononitrile (VI*a*). However, it is found that the latter is reduced by the action of isobutylmagnesium iodide in ether to give, in good yield, 9-dicyanomethylxanthene (VIII*a*), which is identical with the product obtained by the action of malononitrile on xanthydrol (3). V is similarly reduced by isobutylmagnesium iodide to give 9-dicyanomethylfluorene (VII*a*). Hook and Robinson (4) have reported the isolation of some α-cyano-β-alkylbutyric esters as reduction products from the reaction of alkylidene cyanoesters with Grignard reagents in the presence of cuprous iodide. The α-substituted malononitriles (VII*a*–VII*e* and VIII*a*–VIII*d*) are colorless, whereas V and VI are highly colored. Their infrared spectra do not show the frequency bands characteristic of NH or C=O groups, and thus support the structures given and exclude the possibility of 1,2-addition of the Grignard reagents to the cyano group. The 9-dicyanomethyl-9-alkylfluorenes or 9-dicyanomethyl-9-alkylxanthenes are oxidized by potassium permanganate to the corresponding 9-alkylfluorene- or 9-alkylxanthene-9-carboxylic acids, in good yields, and thus provide a new method for preparing these biologically important acids.[1] 1,4-Addition of Grignard reagents to unsaturated nitriles has previously been recorded (5);



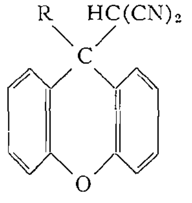
V



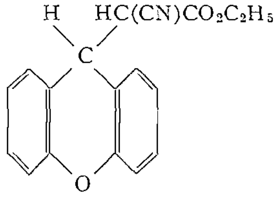
VI*a*, R = CN
VI*b*, R = $COOC_2H_5$



VII*a*, R = H
VII*b*, R = CH_3
VII*c*, R = C_2H_5
VII*d*, R = iso-C_3H_7
VII*e*, R = $CH_2C_6H_5$



VIII*a*, R = H
VIII*b*, R = CH_3
VIII*c*, R = C_2H_5
VIII*d*, R = iso-C_3H_7
VIII*e*, R = $CH_2C_6H_5$



IX

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[1] *Aminoesters of fluorene- and xanthene-9-carboxylic acids proved to have remarkable spasmolytic and related activities (6).*

however, as far as we are aware, nothing has been published on the action of these reagents on arylidene malononitriles.

When the infrared spectra of the substituted malononitriles were investigated, it was found that the spectra of the unsaturated derivatives V and VI*a* showed strong absorption in the 4.5 μ region characteristic of the cyano group (7), whereas the saturated analogues VII and VIII do not show absorption in this region. Similarly, the spectrum of the unsaturated cyanoester VI*b* shows strong absorption whereas that of the saturated analogue IX lacks absorption in this region.[2] Kitson and Griffith (8) have reported that the introduction of an oxygenated group into the molecule results in a quenching of the C≡N absorption intensity to a remarkable extent, or even in the absence of the frequency band characteristic of the cyano group when the oxygenated group is attached to the same carbon atom as the nitrile. It is clear, now, that monosubstituted malononitriles, where the same carbon atom is bonded to two cyano groups, also exhibit this quenching property, provided that, in all cases, this carbon atom is saturated. In the spectra of the unsaturated analogues where the rotation of the carbon atom is not free, strong absorption in the 4.5 μ region is observed.

EXPERIMENTAL

Melting points were not corrected. Infrared spectra were measured on a Perkin–Elmer infracord spectrophotometer, model 137 (Nujol).

Reaction of 9,9-(Tetrachloro-o-phenylenedioxy) Fluorene (II) with Hydrazine Hydrate

A mixture of the cyclic ether (1 g) and hydrazine hydrate (98–100%, 1 ml) in *n*-butanol (10 ml) was refluxed for 20 h and filtered while hot. The solid which separated out when the solution cooled (0.5 g) proved to be unchanged II. The mother liquor was evaporated to dryness, and the residue was crystallized from ethanol to give fluorene (0.12 g), m.p. 114 °C (undepressed when admixed with an authentic sample).

Reaction of II with Phenylhydrazine

The reaction was carried out as above with 1 g of II, 1 g of phenylhydrazine, and a reflux period of 3 h. The solution was filtered while hot, concentrated, and left to cool. The solid that separated out (0.3 g), m.p. 150–151 °C, proved to be fluorenone phenylhydrazone (melting point and mixed melting point).

Reaction of II with Benzoylhydrazine

The reaction was carried out as above with 1 g of II and 0.6 g benzoylhydrazine. The product that was obtained was recrystallized from alcohol to give fluorenone benzoylhydrazone (0.6 g), m.p. 171 °C (undepressed when admixed with an authentic sample (9)).

Preparation of 9-Dicyanomethyl-9-methylfluorene (VIIb)

α-(9-Fluorenylidene) malononitrile (V) (2 g) was added slowly to an ethereal solution of methylmagnesium iodide (from magnesium (0.7 g) and methyl iodide); the mixture was refluxed for 3 h, cooled, decomposed with ice and dilute hydrochloric acid, and extracted with ether. The dried ethereal extract was evaporated to dryness, a few milliliters of methanol was added to the oily residue, and the mixture was cooled. The solid that formed was crystallized from methanol to give 9-dicyanomethyl-9-methylfluorene (VII*b*) as colorless crystals, m.p. 107 °C (yield 1.2 g).[3]

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.6; H, 4.9; N, 11.5. Found: C, 83.2; H, 4.5; N, 11.8.

Oxidation of VIIb

A hot saturated solution of potassium permanganate was added dropwise to a suspension of the product (VII*b*) (0.5 g) in a solution of sodium hydroxide (2 *N*, 50 ml) heated on the water bath. The addition was continued until the pink color persisted; then the reaction mixture was heated on the boiling water bath for 30 min, left to cool, and filtered. The filtrate was acidified with dilute hydrochloric acid and the product that separated out was crystallized from methanol to give 9-methylfluorene-9-carboxylic acid, m.p. 170 °C (10).[3]

Preparation of 9-Dicyanomethyl-9-ethylfluorene (VIIc)

The dinitrile V (2 g) was allowed to react with ethylmagnesium iodide (from 0.7 g of magnesium) as above. The dried ethereal extract was left to evaporate slowly at room temperature, and the solid that separated out was crystallized from methanol to give 9-dicyanomethyl-9-ethylfluorene (VII*c*) (1 g) as colorless prisms, m.p. 117 °C.[3]

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.7; H, 5.4; N, 10.8. Found: C, 84.0; H, 5.5; N, 10.5.

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[2] *Spectra of both malononitrile and cyanoacetic ester show absorption.*

[3] *This experiment is described in the Ph.D. thesis of one of us (N. L.).*

Oxidation of VIIc

The substance was oxidized as above. The colorless product that was obtained was crystallized from petroleum ether (60–80°) to give 9-ethylfluorene-9-carboxylic acid (11), m.p. 145 °C.[3]

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.6; H, 5.9. Found: C, 80.3; H, 5.8.

Preparation of 9-Dicyanomethyl-9-isopropylfluorene (VIId)

This was prepared from V and isopropylmagnesium bromide as above. The dried ethereal extract was concentrated and cooled. The crystals that separated out were filtered off and recrystallized from methanol to give VII*d* as colorless needles (0.9 g), m.p. 159 °C.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.8; H, 5.9; N, 10.3. Found: C, 84.2; H, 6.0; N, 10.1.

When VII*d* was oxidized with potassium permanganate, 9-isopropylfluorene-9-carboxylic acid was obtained as colorless crystals (from benzene), m.p. 204 °C.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 81.1; H, 6.0.

Preparation of 9-Dicyanomethyl-9-benzylfluorene (VIIe)

The reaction between V and benzylmagnesium chloride was carried out as above. The dried ethereal extract was left to evaporate slowly at room temperature. The solid that formed was extracted with warm petroleum ether (40–60°) and the residue was crystallized from petroleum ether (60–80°) to give VII*e* as colorless crystals, m.p. 141 °C.[3]

Anal. Calcd. for $C_{23}H_{16}N_2$: C, 86.2; H, 5.0; N, 8.7. Found: C, 86.3; H, 4.9; N, 8.9.

Preparation of 9-Dicyanomethyl-9-methylxanthene (VIIIb)

The reaction between methylmagnesium iodide (from 0.7 g magnesium) and α-(9-xanthenylidene) malononitrile (VI*a*) (2.4 g) was carried out as usual. The ethereal extract was evaporated to dryness and a few drops of methanol was added to the oily residue. The solid that formed was crystallized from cyclohexane to give VIII*b* as colorless rods (1.1 g), m.p. 128 °C.

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.4; H, 4.7; N, 10.8. Found: C, 78.7; H, 4.7; N, 10.4.

When VIII*b* (1 g) was oxidized as above, 9-methylxanthene-9-carboxylic acid was obtained (0.5 g), m.p. 206 °C (12).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.3; H, 4.9.

Preparation of 9-Dicyanomethyl-9-ethylxanthene (VIIIc)

The reaction was carried out as above with ethylmagnesium iodide and VI*a*. VIII*c* was obtained as colorless prisms (from *n*-hexane), m.p. 97–98 °C.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.8; H, 5.1; N, 10.2. Found: C, 79.2; H, 5.2; N, 10.0.

Preparation of 9-Dicyanomethyl-9-isopropylxanthene (VIIId)

Isopropylmagnesium bromide and VI*a* were allowed to react as above. The ethereal extract was evaporated to dryness. The residue was recrystallized from *n*-hexane several times to give VIII*d* as colorless rods, m.p. 92–94 °C (yield 0.8 g).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.2; H, 5.6; N, 9.7. Found: C, 79.9; H, 5.7; N, 9.7.

Reduction of α-(9-Xanthenylidene) Malononitrile (VIa)

Isobutylmagnesium iodide (from magnesium (0.7 g) and isobutyl iodide (3.4 ml)) and VI*a* (2.4 g) were allowed to react together as usual. The dried ethereal extract was concentrated and cooled, and the solid that separated out was crystallized from methanol to give 9-xanthenylmalononitrile (VIII*a*) (1 g) as colorless rods, m.p. 186–188 °C (undepressed when admixed with an authentic sample (3)). When the reaction was carried out with V instead of VI*a*, 9-fluorenylmalononitrile (VII*a*) was obtained as colorless leaflets (from petroleum ether, 50–75°), m.p. 152 °C.

Anal. Calcd. for $C_{16}H_{10}N_2$: C, 83.5; H, 4.4; N, 12.2. Found: C, 83.3; H, 4.5; N, 12.8.

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