Synthesis of Malononitriles of Potential Cytostatic and Pesticidal Activity by Reaction of Grignard Reagents with Ylidenemalononitriles

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The preparation of various α-substituted malononitriles, for biological evaluation, by the action of organomagnesium halides on ylidenemalononitriles is described. The nature of the products is dependent on the nature of the Grignard reagent as well as the substrate, in particular their stereochemical requirements. Reaction mechanisms are suggested, and the cytostatic activity of malononitriles is discussed.

RECENTLY, reports have appeared on the biological activity of malononitriles. Wicher and Sheare [1] reported that benzylidenemalononitrile was the most active member of a series of unsaturated malononitriles as a rodent repellent, and the effect of malononitriles on virus infection in mice has been evaluated.[2] The potentialities of αβ-unsaturated malononitriles as possible chemotherapeutic agents in the treatment of cancer have also been considered.[3,4] We have shown [5] that xanthen-9-ylideneacetonitrile (1a) is active as a cytostatic agent in high dilutions, and in this paper report that 9-dicyanomethylxanthen (2a) is more active than (1a) whereas the unsaturated analogue (1b) lacks such activity. However, replacement of the xanthenyl residue in (2a) by fluoren-9-yl [*cf.* (4a)] leads to a drop in activity while substitution of the hydrogen atom

[1] T. H. Wicher, jun., and N. H. Sheare, jun., U.S.P. 2,933,429/1960 (*Chem. Abs.*, 1960, **54**, 15,822f).

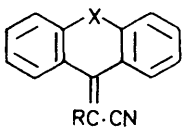
[2] M. Bock and A. Distelmaier, *Med. Chemie, Abhandl. Med. Chem. Forschungsstaetten Farbenfabriken Bayer*, 1963, **7**, 609 (*Chem. Abs.*, 1964, **60**, 16,389f.)

[3] E. M. Gal, F. H. Fung, and D. M. Greenberg, *Cancer Res.*, 1952, **12**, 565; 1956, **16**, 104.

[4] I. Greenberg and E. M. Gal, *Cancer Res.*, 1950, **10**, 221; *J. Amer. Chem. Soc.*, 1951, **15**, 502.

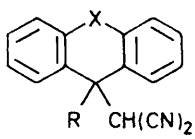
[5] N. Latif, I. F. Zeid, and F. Assad, *Chem. and Ind.*, 1970, 1539.

in the 9-position of the xanthen-9-yl- and fluoren-9-yl-malononitriles by alkyl groups quenches the activity. Apparently, there is more than one factor controlling the cytostatic activity of malononitriles, one of which might be the ease of liberation of HCN from the molecule.



(1)

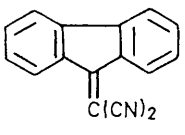
a; R = H, X = O
b; R = CN, X = O
c; R = CN, X = S



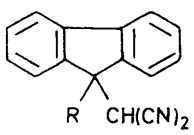
(2)

a; R = H, X = O
b; R = H, X = S
c; R = Me, X = O
d; R = Et, X = O
e; R = Bu^n, X = O
f; R = Me, X = S
g; R = Et, X = S
h; R = Pr^i, X = S
i; R = Bu^n, X = S

We now report the preparation of various malononitriles * for biological evaluation in various directions.



(3)



(4)

a; R = H
b; R = Me
c; R = Et
d; R = Bu^n

9-Methyl- (2f), 9-ethyl- (2g), and 9-isopropyl- (2h) -9-dicyanomethylthioxanthen are readily obtained by the action of the appropriate alkylmagnesium halide on thioxanthen-9-ylidenemalononitrile (1c). The structure of the adducts is inferred from analytical data, lack of ν_{NH} and $\nu_{C=O}$ in their i.r. spectra, and from the similarity of their u.v. spectra to that of 9-(dicyanomethyl)thioxanthen (2b),† lacking the presence of absorption at longer wave-length (due to conjugation with the cyano-group) which appears in the spectrum of the parent ylidenemalononitrile (1c). The slight yellow colour of the adducts is attributed to absorption due to an $n \longrightarrow \pi^*$ transition.‡§

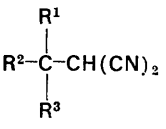
In a similar manner, 1,1-diphenylethyl- (6c), 1,1-diphenylpropyl- (6d), and 2-methyl-1,1-diphenylpropyl- (6e) -malononitrile could be similarly obtained from diphenylmethylenemalononitrile (5a).

In contrast to other alkylmagnesium halides, isobutylmagnesium iodide does not alkylate the ylidene-malononitriles (1c) or (5a) but simply hydrogenates the olefinic double bond affording 9-dicyanomethylthioxanthen (2b) and diphenylmethylmalononitrile (6a), respectively. This is similar to the previously reported reduction of xanthen-9-ylidene- (1b) and fluoren-9-ylidene- (3) -malononitrile with the same reagent.[6]

$R^1R^3C{=}C(CN)_2$

(5)

a; $R^1 = R^2 = Ph$ b; R^1 = 1-naphthyl, $R^2 = H$



(6)

	R^1	R^2	R^3
a;	Ph	Ph	H
b;	1-$C_{10}H_7$	H	H
c;	Ph	Ph	Me
d;	Ph	Ph	Et
e;	Ph	Ph	Pr^i
f;	1-$C_{10}H_7$	H	Me
g;	1-$C_{10}H_7$	H	Et
h;	1-$C_{10}H_7$	H	Pr^i
i;	1-$C_{10}H_7$	H	Bu^i
j;	1-$C_{10}H_7$	H	$PhCH_2$
k;	1-$C_{10}H_7$	H	Ph
l;	1-$C_{10}H_7$	H	*p*-MeC_6H_4
m;	1-$C_{10}H_7$	H	*p*-MeO·C_6H_4
n;	1-$C_{10}H_7$	H	1-$C_{10}H_7$

n-Butylmagnesium bromide reacts with (1b) and (1c) affording the 1,4 adducts (2e) and (2i) respectively, together with the reduction products 9-dicyanomethylxanthen and -thioxanthen. However, the ratio of the reduction product to the adduct in the case of (1b) is less than in the case of (1c). Fluoren-9-ylidene-malononitrile (3) is alkylated by n-butylmagnesium bromide to give 9-n-butyl-9-dicyanomethylfluorene (4d) and no reduction product could be isolated.

In contrast to the ylidenemalononitriles (1b), (1c), and (3), 1-naphthylmethylenemalononitrile (5b) is not hydrogenated by isobutylmagnesium iodide but alkylated by this reagent as well as by other Grignard reagents to give 1,4 adducts ¶ in excellent yields. Thus, the 1-naphthylalkylmalononitriles (6f—i) are obtained in excellent yield by the action of the appropriate alkylmagnesium halide on (5b). Analytical data, lack of colour, and i.r. spectra of the adducts support the assigned structure. Their u.v. spectra are similar to that of the known 1-naphthylmethylmalonitrile,[8] which can be obtained by the action of sodium borohydride on (5b). In this connection it is found that the spectrum of the parent 1-naphthylmethylenemalononitrile (5b) exhibits strong absorption in the 220 nm region due to band I of naphthalene, similar to the saturated adducts, in spite of the presence of the conjugated cyanovinyl

* The preparation of various 9-alkyl-9-dicyanomethyl-fluorenes and -xanthens has been described previously.[6]

† Compound (2b) is readily obtained by the acid catalysed interaction of thioxanthen-9-ol with malononitrile.

‡ The spectra of (2b) and (2f) exhibit absorption of weak intensity at longer wavelength characteristic of R bands (2b) $\lambda_{max.}$ (ethanol) 410 nm (ε 45); $\lambda_{max.}$ (benzene) 415 nm (ε 25).

§ The u.v. data for compounds (2g), (6d, g, k, l, and n), (7), and (8) are listed in Supplementary Publication No. 20920 (4 pp.) (for details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1972, index issue).

¶ The non-reduction of (5b) by isobutylmagnesium bromide is similar to the previously reported reactivity of furfurylidene-malononitrile towards this reagent.[7]

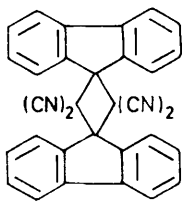
[6] N. Latif and N. Mishriky, *Canad. J. Chem.*, 1966, **44**, 1271.

[7] N. Latif, N. S. Girgis, and F. Michael *Tetrahedron*, 1970, **26**, 5765.

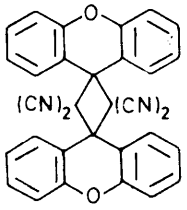
[8] E. Campaigne, D. R. Moulding, and W. C. Roelofs, *J. Org. Chem.*, 1954, **29**, 1548.

side chain. This lack of displacement of the short wave-length band of naphthalene in (5b) is not unexpected. It is known [9] that substituents capable of conjugation at position 1 of naphthalene extend conjugation in a transverse direction and cause bathochromic and hypsochromic effects predominantly in the transverse polarized ^1L_a bands at 286 nm. Consequently the strong absorption in the u.v. spectrum of (5b) at longer wavelength [$\lambda_{max.}$ (ethanol) 350 nm (ε 9575)] is presumably due to the large bathochromic displacement of the ^1L_a band and fusion of the latter with the ^1L_b band.

In contrast to the reactions of the alkylmagnesium halides, the nature of the products obtained from the reaction of arylmagnesium halides with ylidenemalononitriles depends mainly on the nature of the latter. Thus, whereas 1-naphthylmethylenemalononitrile (5b) gives the corresponding 1,4 adducts (6k—n),* fluoren-9-ylidenemalononitrile (3) reacts with phenyl-, *p*-methoxyphenyl-, and 1-naphthyl-magnesium bromides to give in all cases the dimer (7). This compound could be also obtained by the action of magnesium–magnesium iodide on (3) in ether. The cyclobutane structure assigned to the product is inferred from analytical data, molecular weight determination, and lack of colour.



(7)



(8)

The u.v. spectrum of (7) is similar to that of fluorene and lacks the K bands at longer wave-length which indicate conjugation with the cyano-groups [fluorene, $\lambda_{max.}$ 273 nm (ε 12,700); (7), $\lambda_{max.}$ 273 nm (ε 26,800 †)]. Its n.m.r. spectrum contains only signals due to aromatic protons. Upon heating (7) above its m.p., the monomer (3) is regenerated, as is usual with analogous cyclobutanes.[10] Compound (7) is insoluble in concentrated hydrochloric acid, sodium hydroxide, or ammonia solution. This excludes an amino- or imino-structure (possibly formed *via* ketenimines) such as those assigned to the dimeric phenylacetonitrile or isopropylidenemalononitrile.[11]

Xanthen-9-ylidenemalononitrile (1b) reacts similarly with arylmagnesium halides affording the dimer (8) which is similar in properties to the fluorene compound (7). In an attempt to produce the thio-analogue of (8) by the action of arylmagnesium halides on thioxanthen-9-ylidenemalononitrile (1c), the latter was recovered unchanged.‡

Thus the products obtained by the action of Grignard reagents on ylidenemalononitriles depend on the nature of the reagent as well as the substrate and not only on the latter as indicated previously.§ In this connection, ylidenemalononitriles can apparently be classified into two groups: members of the first group have a secondary β-carbon, *e.g.* furfurylidene- and naphthylmethylene-malononitriles, and these mainly afford 1,4 adducts regardless of the nature of the organomagnesium halide; members of the second group, exemplified by (1b), (1c), and (3) have a tertiary β-carbon and these give products whose nature is mainly dependent on the organomagnesium halide. It is thought that conjugate addition of Grignard reagents to ylidenemalononitriles proceeds through the formation of a cyclic transition state similar to that described for β-unsaturated ketones.[14] Consequently the smaller the spatial requirement of the ylidenemalononitrile, as in the case of members of the first group, the easier the formation of such a transition state will be, thus enhancing 1,4 addition with all organomagnesium halides. With malononitriles of the second group where the spatial requirement is large, 1,4 addition takes place only with Grignard reagents with smaller spatial requirements. Thus, with branched alkylmagnesium halides or the aryl derivatives, 1,4 addition becomes difficult and the ylidenemalononitrile is either hydrogenated, dimerized, or recovered unchanged. In some other cases 1,2 addition to the cyano-group to give unsaturated ketones [13] is favoured.

Hydrogenation of the ylidenemalononitriles of the second group by isobutylmagnesium iodide presumably proceeds through hydride transfer involving a β-hydrogen of the Grignard reagent [*cf.* activated complex (9)].[15] Therefore, the more stable the carbonium ion in (9), the easier the hydrogenation. This would explain the enhanced formation of the hydrogenated products (2c) and (2i) besides the expected 1,4 adducts, by the action of the sterically favourable n-butylmagnesium iodide on (1b) and (1c), whereas with (3) only alkylation takes place.

* The products are colourless and their u.v. spectra are similar to those of the alkyl analogues.

† The ε value is double that of fluorene, thus supporting the dimeric structure.

‡ The failure of arylmagnesium halides to react with certain conjugated systems is not unusual; it has been reported [12] that phenylmagnesium bromide, in contrast to the benzyl analogue, does not react with 9,9′-ethanediylidenedifluorene.

§ It is reported [13] that αβ-unsaturated nitriles substituted in the α-position give 1,4 adducts, whereas those substituted in the β-position give mainly 1,2 adducts, irrespective of the nature of the Grignard reagent.

[9] H. H. Jaffé and M. Orchin, 'Theory and Application of Ultraviolet Spectroscopy,' John Wiley, New York, 1965, p. 305.

[10] (*a*) N. Latif, N. Mishriky, and M. A. Hammad, *Chem. and Ind.*, 1972, 339; (*b*) A. Schönberg, A. Mustafa, M. Z. Barakat, N. Latif, R. Monbasher, and A. Mustafa, *J. Chem. Soc.*, 1948, 2126.

[11] (*a*) M. S. Karasch and O. Reinmuth, 'Grignard Reactions of Nonmetallic Substances,' Constable, 1954, p. 221; (*b*) F. S. Prout, *J. Org. Chem.*, 1953, **18**, 928.

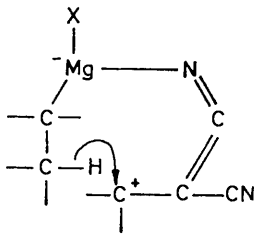
[12] R. C. Fuson, H. A. Dewald, and R. Guerther, *J. Org. Chem.*, 1951, **16**, 21.

[13] V. Migrdichian, 'The Chemistry of Organic Cyanogen Compounds,' Reinhold, New York, 1947, p. 254.

[14] Ref. 11*a*, p. 774.

[15] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Reinhart, and Winston, New York, 1962, p. 403.

Stretching Frequency Bands Due to Nitrile Absorption.—In contrast to previous reports [16] it has been shown in this laboratory [6,7] that nitriles containing only carbon and hydrogen in addition to the nitrile group do not necessarily show absorption in the 4·5 μm region and that introduction of oxygenated or electronegative groups into the nitrile molecule does not necessarily lead



(9)

to quenching of the nitrile band. Thus, whereas xanthene-9-ylidene- (1b), fluoren-9-ylidene- (3), and furfurylidene-malononitriles show strong $\nu_{C\equiv N}$ bands, the saturated analogues lack this nitrile absorption. This has been attributed to free rotation of the carbon atom bonded to the two cyano-groups in these saturated compounds.

In the present investigation, similar behaviour for the malononitriles was observed. Thus, the spectra of the unsaturated thioxanthen-9-ylidene- (1c), diphenylmethylene- (5a), and 1-naphthylmethylene- (5b) -malononitriles exhibit strong $\nu_{C\equiv N}$ bands in the 4·5 μm region. However, the spectra of all the saturated malononitriles (2) and (6) practically lack this absorption. As a consequence, we can now generalize, as a rule that open chain monosubstituted malononitriles almost completely lack the presence of the stretching band characteristic of the cyano-group provided that the carbon atom bonded to the cyano-group is saturated.

EXPERIMENTAL

Microanalyses were performed by the Microanalytical Laboratory, National Research Centre, Cairo, Egypt. I.r. spectra were recorded with a Zeiss-Jena UR10 spectrophotometer for potassium bromide discs, and u.v. spectra with Zeiss PMQII and Unicam SP 500 spectrophotometers.

Alkylation of Ylidenemalononitriles by Grignard Reagents.—General procedure. A suspension of the ylidenemalonontrile (0·01 mol) in dry ether (30 ml) was added in portions to an ethereal solution of the organomagnesium halide [prepared from the appropriate halide (0·03 mol) and magnesium (0·03 mol)]. A vigorous reaction took place after each addition. The mixture was refluxed for 3 h, left to cool, decomposed with ice and ammonium chloride, and extracted with ether. The ethereal extract was dried (Na_2SO_4), filtered, and evaporated. The residue was triturated with the suitable solvent then recrystallized. Solvents of crystallization, melting points and analytical data are listed in Supplementary Publication No. SUP 20920 (4 pp.).

9-(*Dicyanomethyl*)*thioxanthen* (2b).—A solution of thioxanthen-9-ol (1 g), malononitrile (1 g) in acetic acid–ethanol (1 : 1; 10 ml) was left for 3 days at room temperature (20°). The crystalline solid which separated out was filtered off and recrystallised from methanol to give pale yellow *crystals* of (2b), m.p. 200—202° (Found: C, 72·9; H, 4·2; N, 10·35; S, 12·4. $C_{16}H_{10}N_2S$ requires C, 73·25; H, 3·85; N, 10·7; S, 12·2%).

Reduction of Thioxanthen-9-ylidenemalononitrile (1c) *with Isobutylmagnesium Iodide.*—The malononitrile (2·6 g) was allowed to react with isobutylmagnesium iodide [prepared from magnesium (0·7 g) and isobutyl iodide (5·4 g) in dry ether (40 ml)] and worked up as mentioned above. The dried ethereal extract was filtered and evaporated to dryness. A few ml of methanol was added to the residue and the separated solid was recrystallized from methanol to give 9-(dicyanomethyl)thioxanthen (2b) as pale yellow crystals (1 g), m.p. 200—202° (undepressed when admixed with an authentic sample prepared as described above).

When the reaction was carried out using diphenylmethylenemalononitrile (5a) (2·2 g) and worked up as usual, diphenylmethylmalononitrile (6a) was obtained as crystals (1·5 g) (from cyclohexane), m.p. 90—92 (lit.,[17] 87°) (Found: C, 82·7; H, 5·05; N, 11·3. Calc. for $C_{16}H_{12}N_2$: C, 82·75; H, 5·2; N, 12·05%).

Reaction of n-Butylmagnesium Iodide with Thioxanthen-9-ylidenemalononitrile.—The malononitrile (1c) (2·6 g) was added in portions to an ethereal solution of n-butylmagnesium iodide [prepared from magnesium (0·7 g) and n-butyl iodide (5·4 g) in dry ether (40 ml)]. The mixture was refluxed for 3 h, left to cool, decomposed as usual, and extracted with ether. The dried ethereal extract was evaporated to dryness and a few ml of methanol was added to the residue. The separated solid was recrystallized from methanol to give 9-*n-butylthioxanthen-9-ylmalononitrile* (2i) as pale yellow crystals (0·6 g), m.p. 145—146° (Found: C, 75·15; H, 5·8; N, 9·65; S, 9·8. $C_{20}H_{18}N_2S$ requires C, 75·45; H, 5·7; N, 8·8; S, 10·5%). The methanolic mother liquor was concentrated and left to cool to give 9-(dicyanomethyl)thioxanthen (2b) as pale yellow crystals (0·5 g), m.p. 200—202° (undepressed when admixed with an authentic sample).

Reaction of n-Butylmagnesium Iodide with Xanthen-9-ylidenemalononitrile (1b).—The malononitrile (2·4 g) was allowed to react with n-butylmagnesium iodide in ether as above. The oily product obtained was extracted with n-hexane and the extract concentrated and cooled. The separated solid was filtered off and extracted again with n-hexane and the extract was concentrated and cooled to give 9-*n-butyl-9-dicyanomethylxanthen* (2e) as crystals (2 g), m.p. 86—88° (Found: C, 79·95; H, 6·25; N, 8·4. $C_{20}H_{18}N_2O$ requires: C, 79·45; H, 6·0; N, 9·25%). The solid left after the last hexane extraction was crystallized from methanol to give 9-dicyanomethylxanthen (2a) as needles (0·1 g), m.p. 186—187° (undepressed when admixed with an authentic sample [6]).

1-*Naphthylmethylmalononitrile* (6b).—A solution of 1-naphthylmethylenemalononitrile (5b) (4·08 g) in propan-2-ol (150 ml) was added in portions with stirring to a suspension of sodium borohydride (2 g) in propan-2-ol (10 ml). After addition was completed, stirring was continued for 8 h. The mixture was decomposed with dilute acetic acid, then evaporated under reduced pressure. The oily residue was extracted with ether and the ethereal extract was

[16] R. E. Kitson and N. E. Griffith, *Analyt. Chem.*, 1952, **24**, 3340; L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' John Wiley, New York, 1964, p. 266.

[17] S. D. Gupte and S. V. Sunthankan, *J. Org. Chem.*, 1959, 1334.

washed with 2N-HCl, then with water, dried, filtered, and evaporated to dryness. The oily residue was triturated with a few ml of methanol and the solid obtained was crystallized from ethanol to give 1-naphthylmethylmalononitrile (6b) as crystals (2 g), m.p. 63° (undepressed when admixed with an authentic sample [8]).

Dimerization of Fluoren-9-ylidenemalononitrile (3) *by Arylmagnesium Halides.*—The malononitrile (4·5 g) was added to an ethereal solution of phenylmagnesium bromide [prepared from magnesium (1·4 g) and bromobenzene (9·5 g) in dry ether (70 ml)]. Dry benzene (30 ml) was added and the mixture refluxed for 3 h, decomposed with ice and dilute hydrochloric acid, and extracted with ether. The dried ethereal extract was concentrated to a very small bulk and left to cool. The separated solid (0·3 g) was unchanged (3) (m.p. and mixed m.p.). The mother liquor was evaporated to dryness and a few ml of methanol was added to the oily residue. The separated solid was filtered and recrystallized from benzene to give *2′,2′,4′,4′-tetracyanodispiro[fluorene-9,1′-cyclobutane-3′,9″-fluorene]* (7) as crystals (2·8 g), m.p. 300—302° (vigorous decomp. and red melt) [Found: C, 83·8; H, 3·9; N, 12·1%; mol. wt., 503 (cryoscopic method). $C_{32}H_{16}N_4$ requires C, 84·2; H, 3·5; N, 12·3%, mol. wt., 456].

Reaction of Compound (3) *with Magnesium–Magnesium Iodide.*—Fluorene-9-ylidenemalononitrile (3) (2·3 g) was added to magnesium–magnesium iodide reagent [prepared from magnesium (0·7 g) and iodine (8 g) in dry ether (30 ml)] and the mixture was refluxed for 3 h and worked up and extracted with ether as in the case of the Grignard reactions. The dried ethereal extract was concentrated to a very small bulk and left to cool to give unchanged (3) (0·1 g). The mother liquor was evaporated to dryness and a few ml of methanol was added. The solid obtained was crystallized from benzene to give (7) as crystals (1 g) (identified by m.p. and mixed m.p.).

Dimerization of Xanthen-9-ylidenemalononitrile by Arylmagnesium Halides.—The malononitrile (2·4 g) was allowed to react with an ethereal solution of phenylmagnesium bromide as above. The dried ethereal extract of the reaction mixture was concentrated to a very small bulk and left to cool to give unchanged (1b) (0·2 g). The ethereal mother liquor was evaporated to dryness and a few drops of methanol was added. The solid formed was filtered off and recrystallized from benzene to give *2′,2′,4′,4′-tetracyanodispiro[xanthen-9,1′-cyclobutane-3′,9″-xanthen]* (8) as crystals (1 g) m.p. 294—296° (decomp. and red melt) [Found: C, 78·3; H, 3·8; N, 11·15%; mol. wt., 544 (cryoscopic method). $C_{32}H_{16}N_4O_2$ requires C, 78·7; H, 3·25; N, 11·4%; mol. wt., 488].

Pyrolysis of Dimer (7).—The dimer (7) (1 g) was heated at 320—325° (bath temperature) under reduced pressure for 1 h. The material melted with vigorous decomposition and the solid which collected on the upper part of the tube was extracted with acetone, concentrated and left to cool. The separated crystalline product (0·6 g) was fluoren-9-ylidenemalononitrile (1b) (m.p. and mixed m.p.).

When (8) (1 g) was similarly heated, xanthen-9-ylidenemalononitrile was produced (0·5 g).

[3/1481 *Received, 7th July,* 1973]