Synthesis of Ethyl 1,2,2-Tricyanocyclopropanecarboxylates from Bromomalononitrile and Ylidenecyanoacetate

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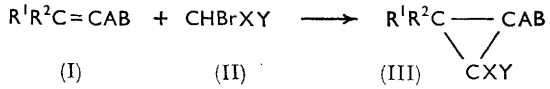
A general synthesis for ethyl 3,3-dialkyl- and 3-aryl-1,2,2-tricyanocyclopropanecarboxylates from bromomalononitrile and ylidenecyanoacetates is described. When stereoisomeric products are possible, the predominant and sometimes exclusive isomer obtained has the larger C-3 substituent and the ethoxycarbonyl group in the *trans*-position.

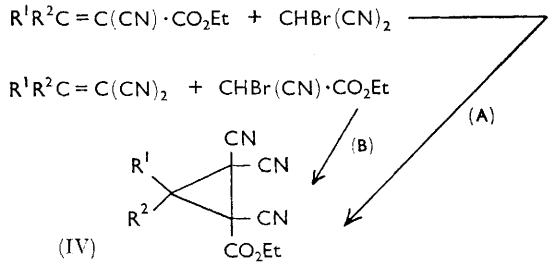
We have extended the scope of a recently reported synthesis of 1,1,2,2-tetracyanocyclopropanes.[1] Ylidenemalonitriles (I; A = B = CN) and bromomalononitrile (II; X = Y = CN) reacted at room temperature to give good yields of tetracyanocyclopropanes (III; A = B = X = Y = CN; R = alkyl, aryl, heterocyclic, H). It is likely that the reaction proceeds in two steps *via* a carbanion intermediate.[2] Groups A and B in the



alkene (I) must be capable of stabilizing the intermediate carbanion. Groups X and Y should be electron-withdrawing to enhance the acidity of the halide (II).†

Here we describe compounds where one group in the pair AB or XY is an ethoxycarbonyl group, while the others are cyano-groups. It was of interest to determine the effect of having the ethoxycarbonyl group in the alkene or the bromide. Since with $R^1 \neq R^2$, two compounds (V) and (VI), all the cyclopropanes are new compounds; their physical properties are given in Table 2.

In general, method (A) is preferred to method (B); three factors may be involved. Bromomalononitrile is



a stronger acid than ethyl bromocyanoacetate by *ca.* one pK_a unit;[4] thus the concentration of attacking anion will be greater in the former case. Secondly, the bromomalononitrile anion is the less bulky of the two, which may be in its favour, particularly when R^1 and R^2 are large. That steric factors are important is indicated by the steady decrease in yield by method (A) for the series of compounds (V)—(VIII), where R^1 remains constant and R^2 steadily increases in size. The stereochemical results discussed below also indicate that steric effects are important. Finally, the ring-closure step may be more favourable when the carbon which bears the bromine to be displaced has two attached cyano-groups, rather than a cyano- and an ethoxycarbonyl group.

Table 1

Synthesis of ethyl 3,3-dialkyl- and 3-aryl-1,2,2-tricyanocyclopropanecarboxylates (IV)

Compd.	R^1	R^2	Yield (%) Method A [a]	Yield (%) Method B [a]	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
(V)	Me	Me	74	29						
(VI)	Me	Et	64	0						
(VII)	Me	Pr^n	37	0	63·65	6·15	17·15	63·65	6·05	17·3
(VIII)	Me	Pr^i	7	0	63·65	6·15	17·15	63·15	6·0	17·3
(IX)	Et	Et	35	0	63·65	6·15	17·15	63·35	6·1	17·05
(X)	$-[CH_2]_4-$		15	0	64·2	5·4	17·3	64·15	5·3	17·35
(XI)	$-[CH_2]_5-$		98	24	65·35	5·9	16·35	65·3	5·8	16·4
(XII)	Ph	H	77	29	67·9	4·2	15·85	67·8	4·1	16·0
(XIII)	*p*-$MeOC_6H_4$	H	36	60	65·1	4·45	14·25	64·75	4·35	14·3

[a] Details of reaction conditions are given in the Experimental section. All yields are of recrystallized product.

stereoisomeric products are possible we examined the products to determine if there was a stereochemical preference.[3]

Results and Discussion

Two sets of reactants were used, as shown. The solvent was usually aqueous ethanol and reactions were carried out either at room temperature or at reflux point; the results are summarized in Table 1. Except for

† It is possible that, like many Michael condensations, the reaction is subject to both acid and base catalysis.

[1] H. Hart and Y. C. Kim, *J. Org. Chem.*, 1966, **31**, 2784.
[2] Y. C. Kim and H. Hart, *Tetrahedron*, in the press.
[3] G. Westoo, *Acta Chem. Scand.*, 1959, **13**, 683.
[4] R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.

TABLE 2

Properties of some ethyl 1,2,2-tricyanocyclopropanecarboxylates

Compd.	M.p.[a]	Ir. (Nujol) [b] (cm.$^{-1}$)	N.m.r. [$^2H_6$]Me_2CO τ (multiplicity, assignment) [c]
(V)	141—143° [d]	2270, 1747, 1280, 1248, 980	5·62 (q, *J* 7·2, CH_2), 8·62 (t, *J* 7·2 OCH_2CH_3), 8·23 (s, *trans*-CH_3) 8·32 (s, *cis*-CH_3)
(VI)	87—89[e]	2260, 1745, 1275, 978	5·64, 5·65 (q, *J* 7·0, OCH_2CH_3), 8·65 (t, *J* 7·0, OCH_2CH_3), 7·94 (q, *J* 7·5, CH_2CH_3), 8·80, 8·94 (t, *J* 7·5, CH_2CH_3), 8·26, 8·39 (s, *trans*- and *cis*-R^1-CH_3) [f]
(VII)	63—65	2260, 1747, 1269, 979	5·62 (q, *J* 7·2, OCH_2CH_3), 8·64 (t, *J* 7·2, OCH_2CH_3), 8·25, 8·38 (s, *trans*- and *cis*-R^1-CH_3), 8·98 (br t, *J* 7, $-CH_2CH_2CH_3$) above 8·03 (br, m, CH_2) [g]
(VIII)	131—134	2275, 1745, 1256, 1017	5·62 (q, *J* 7·0, CH_2), 8·65 (t, *J* 7·0, OCH_2CH_3), 7·76 (m, *J* 6·8, *CH*), 8·79, 8·99 (d, *J* 6·8, $CH(CH_3)_2$ 8·35 (s, R^1-CH_3)
(IX)	93—95	2255, 1741, 1272, 975	5·62 (q, *J* 7·2, OCH_2CH_3), 8·63 (t, *J* 7·2, OCH_2CH_3), 7·97, 8·00 (overlapping q, *J* 7·5, CH_2CH_3), 8·80, 8·93 (overlapping t, *J* 7·5, CH_2CH_3)
(X)	136—139	2260, 1743, 1282, 970	5·72 (q, *J* 7·2, OCH_2CH_3), 8·66 (t, *J* 7·2, OCH_2CH_3), 7·70—8·40 (br, m, ring CH_2) [h]
(XI)	129—131	2275, 1745, 1274, 981	5·61 (q, *J* 7·2, OCH_2CH_3), 8·64 (t, *J* 7·2, OCH_2CH_3) 7·78—8·08 (br, m, CH_2 attached to the cyclopropane ring), 8·08—8·50 (br, m, remaining CH_2)
(XII)	124·5—126	2260, 1734, 1288, 1233, 1015, 740, 700 [i]	5·61 (q, *J* 7·2, CH_2), 8·64 (t, *J* 7·2, OCH_2CH_3), 5·74 (s, ring H), 2·18—2·72 (br, m, Ar)
(XIII)	95—97	2275, 1743, 1267, 1180, 990, 820 [j]	5·58 (q, *J* 7·2, CH_2), 8·63 (t, *J* 7·2, OCH_2CH_3) 5·79 (s, ring H), 6·19 (s, OCH_3), 2·40, 3·00 (A_2B_2 d, *J* 9, Ar) [k]

[a] All were recrystallized from ethanol. [b] Only principal bands are shown. Assignments for bands with the following approximate frequencies are as follows: 2260 (C≡N), 1745 (C=O), 1270 (C–O), 1000 (cyclopropane ring). [c] *J* is given in Hz. The internal reference was Me_4Si. R^1 refers to Table 1. The terms *cis* and *trans* refer to the relation between a particular group and the ester function. [d] Lit. value [3] 135°. [e] Lit. value [3] 89°. [f] The methylene at τ 7·94 had the general shape of a quartet, but was further split and might better be classified as a multiplet from τ 7·70—8·20, due to the presence of both isomers. For a similar reason, the methyl at τ 8·65 was further split slightly. [g] The only integration possible was the OCH_2CH_3 protons *vs.* the remaining protons. The ratio was 2 : 13. [h] The solvent was [$^2H_6$]Me_2SO. [i] The last two bands indicate a monosubstituted aromatic ring. [j] The last band indicates a 1,4-disubstituted aromatic ring. [k] In [$^2H_6$]Me_2SO, the spectrum was similar, but with the following respective chemical shifts: τ 5·68, 8·66, 5·81, 6·26, 2·54, 3·13.

Although only one structure is possible for (V), (IX), (X), and (XI), the remaining compounds in Tables 1 and 2 may be produced as pairs of stereoisomers. The n.m.r. spectrum of (V) shows two equal, sharp singlets at τ 8·23 and 8·32 for the methyl *trans* and *cis* to the ethoxycarbonyl group. In 3,3-dimethyl-1,1,2,2-tetracyanocyclopropane, the methyls appear at τ 8·25. It seems reasonable to assign the low-field peak in (V) to the methyl which is on the same side of the ring as the two cyano-groups, assuming that *cis*-substituents on a cyclopropane ring affect the chemical shifts of neighbouring groups more than do *trans*-substituents.

Both stereoisomers of (VI) and (VII) were formed, in nearly equal amounts. Each showed two peaks for the R^1-methyl group, nearly equal in area, at *ca.* τ 8·25 and 8·38. Despite the relatively sharp melting points, other features of the n.m.r. spectra also indicated that both isomers were present in comparable amounts. The n.m.r. spectra of the starting ethyl alkylidenecyanoacetates (Table 3; Experimental section) show that both stereoisomers were present, again in nearly equal amounts. Thus, it would not be clear from these results whether or not the reaction showed some stereoselectivity.

The n.m.r. spectrum of (VIII), however, showed a strong singlet at τ 8·35 and only a trace of a peak at τ 8·25, which suggested that the product was essentially one of the two possible isomers. Since the observed ring methyl (R^1) was at high field, it is probably *cis* to the ethoxycarbonyl group. The structure of (VIII) is, therefore, thought to be (VIIIa), with the largest groups (isopropyl and ethoxycarbonyl) in the *trans* position. Here the starting olefin (Table 3) was an approximately 2 : 1 mixture of both possible stereoisomers. It is clear, then, that the geometries of the starting materials and

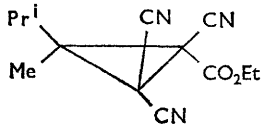
TABLE 3

N.m.r. spectra of ylidene cyanoacetates (R^1R^2C=C(CN)CO_2Et)

R^1	R^2	τ (no. of protons, multiplicity, assignment) [a]
Me	Me	5·70 (2H, q, *J* 7·2, CH_2), 8·65 (3H, t, *J* 7·2, OCH_2CH_3), 7·57, 7·65 (6H, sharp s, allylic CH_3)
Me	Et	5·77 (2H, q, *J* 7·0, OCH_2CH_3), 8·68 (3H, t, *J* 7·0, OCH_2CH_3), 7·62, 7·71 (3H, sharp s, allylic CH_3) 7·20, 7·41 (2H, overlapping q, *J* 7·0—7·5. CH_2CH_3), 8·76, 8·87 (3H, overlapping t, $-CH_2CH_3$) [b]
Me	Pr^n	5·77 (2H, q, *J* 7·0, OCH_2CH_3), 7·64, 7·72 (3H, s, allylic CH_3) and 2 complex multiplets at 7·05—7·68 (2H, allylic CH_2) and 8·13—9·22 (8, remaining CH_2 and CH_3) [c]
Me	Pr^i	5·76 (2H, q, *J* 7·0, OCH_2CH_3), 8·67 (3H, t, *J* 7·0, OCH_2CH_3), 7·76, 7·84 (3H, s, allylic CH_3), 5·99, 6·72 (1H, heptets, *J* 6·8, methine H) 8·84, 8·90 (6H, d, *J* 6·8, $(CH_3)_2CH$) [d]
Et	Et	5·76 (2H, q, *J* 7·0, OCH_2CH_3), 8·67 (3H, t, *J* 7·0, OCH_2CH_3), 7·22, 7·42 (4H, 2 q, *J* 7·5, CH_2CH_3), 8·79, 8·88 (6H, 2 t, *J* 7·5, CH_2CH_3)
$-[CH_2]_4-$		5·78 (2H, q, *J* 7·2, OCH_2CH_3), 8·69 (3H, t, *J* 7·2, CH_3), 6·88—7·40 (4, m, allylic CH_2), 7·88—8·37 (4H, m, remaining CH_2)
$-[CH_2]_5-$		5·78 (2H, q, *J* 7·0, OCH_2CH_3), 8·70 (3H, t, *J* 7·0 CH_3), 6·83—7·50 (4H, m, allylic CH_2), 8·05—8·45 (6H, br s, remaining CH_2)
Ph	H	5·62 (2H, q, *J* 7·3, CH_2), 8·63 (3H, t, *J* 7·3, CH_3), 1·70 (1, s, =CH), 1·83—2·57 (5, m, Ar) [e]
p-$MeOC_6H_4$	H	5·62 (2H, q, *J* 7·3, CH_2), 8·62 (3H, t, *J* 7·3, OCH_2CH_3), 6·06 (3H, s, OCH_3), 1·80 (1H, s, =CH), 1·92, 2·90 (4H, A_2B_2d, *J* 8·5, Ar) [e]

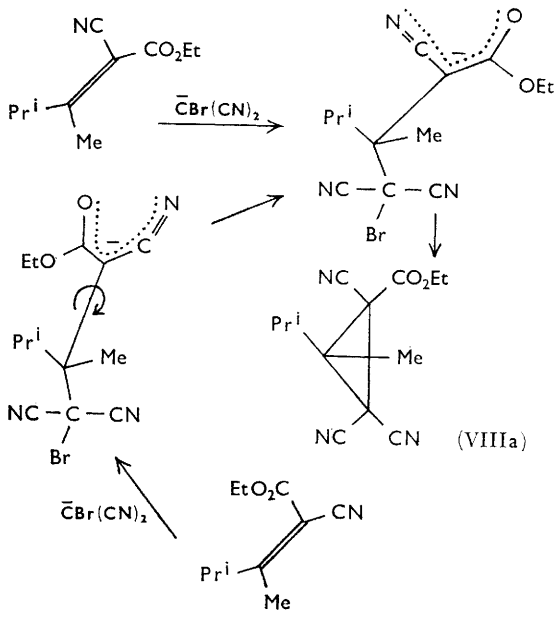
[a] Spectra were run on the neat esters, unless otherwise stated. The internal reference was Me_4Si. *J* is given in Hz. [b] Of the various pairs of peaks which are due to the two stereoisomers, those at τ 7·62, 7·41, and 8·76 were slightly more intense. [c] Of the two allylic CH_3 groups the peak at τ 7·64 was slightly more intense. [d] Peaks due to the two stereoisomers were in the approximate ratio 65 : 35 with the following peaks more intense: τ 7·76, 6·72, 8·84. The spectrum was run in CCl_4. [e] The solvent was [$^2H_6$]acetone.

the products are not related, that there is ample opportunity for bond rotation, and that the product obtained is probably that which is thermodynamically the most



(VIIIa)

stable. This will, in general, be the product with the larger R group and the ethoxycarbonyl group in the *trans* position (Scheme). Several of these steps are probably reversible.



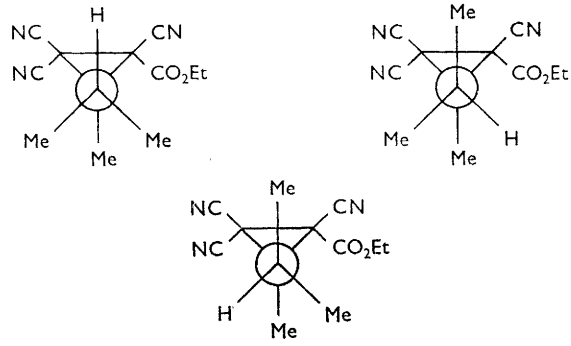
(VIIIa)

SCHEME

Only a single isomer of the two aryl compounds, (XII) and (XIII), seemed to be formed. In the n.m.r. spectrum of each of these compounds, the cyclopropyl hydrogen appeared as one singlet, at τ 5·74 and 5·79 respectively, and this integrated correctly for one proton. The cyclopropyl protons in the corresponding tetracyanocyclopropanes appear at much lower field, τ 5·13 and 5·27 respectively.[2] Because of the higher field position for the cyclopropyl hydrogen in (XII) and (XIII), it seems likely that the proton is *cis* to the ethoxycarbonyl group. Thus, both compounds probably are the thermodynamically more stable products, with the large groups—aryl and ethoxycarbonyl—in the *trans* position. In these cases, the starting ethyl arylidenecyanoacetates were also single isomers (Table 3).[5]

To summarize, the synthesis of ethyl 1,2,2-tricyanocyclopropanecarboxylate usually proceeds better with the combination of reagents designated as method (A). The yield decreases with an increase in the size of the R group and, in general, when $R^1 \neq R^2$, the larger group will appear *trans* to the ethoxycarbonyl group in the product.

Finally, one aspect of the n.m.r. spectrum of (VIIIa) deserves a special word of comment. Although essentially only one stereoisomer is present (see above), the methyls of the isopropyl group appear as two equal doublets at τ 8·79 and 8·99 (J 6·8 Hz). Their magnetic non-equivalence is apparent from the conformational drawings. This phenomenon has been encountered previously.[6]



Conformers of (VIIIa)

EXPERIMENTAL

All m.p.s are uncorrected. Analyses were performed by Spang Microanalytical Laboratories. The n.m.r. spectra were run on a Varian A-60 spectrometer with Me_4Si as an internal reference. The i.r. spectra were determined on a Unicam SP 200 instrument, calibrated with polystyrene.

Preparation of Ethyl Ylidene Cyanoacetates by Method (A).—Ethyl isopropylidenecyanoacetate was prepared according to the procedure of Frout.[7] All other ethyl alkylidenecyanoacetates were prepared after the manner of Cope and Hancock.[8] Published procedures were used for ethyl benzylidenecyanoacetate [9] and ethyl *p*-methoxybenzylidenecyanoacetate.[10] The n.m.r. spectra of these compounds are given in Table 3.

Preparation of Ylidene Malononitriles for Method (B).—Procedures and n.m.r. spectra have been given in previous papers.[1,2]

Ethyl 3,3-Dimethyl-1,2,2-tricyanocyclopropanecarboxylates (V). *Method (A).*—Ethyl isopropylidenecyanoacetate (0·5 g., 3·26 mmoles) and bromomalonitrile (1·0 g., 6·90 mmoles) were dissolved in 85% aqueous ethanol (12 ml.). After 1 hr. at room temperature or 10 min. on a steam-bath crystals of (V) appeared. After several hours they were recrystallized from ethanol (yield 0·52 g.); see Tables 1 and 2 for further details.

[5] See also J. Zabicky, *J. Chem. Soc.*, 1961, 683; R. F. Silver, K. A. Kerr, P. D. Frandsen, S. J. Kelley, and H. L. Holmes, *Canad. J. Chem.*, 1967, **45**, 1001; M. Schwarz, *Chem. Comm.*, 1969, 212.

[6] T. H. Siddall, tert. and C. A. Prohaska, *J. Amer. Chem. Soc.*, 1962, **84**, 2502; S. Goodwin, J. N. Shoolery, and L. F. Johnson, *ibid.*, 1959, **81**, 3065.

[7] F. S. Frout, *J. Org. Chem.*, 1953, **18**, 928.

[8] A. C. Cope and E. M. Hancock, *Org. Synth.*, Coll. Vol. III, 1955, 399.

[9] E. P. Kohler and M. Reimer, *Amer. Chem. J.*, 1905, **33**, 333.

[10] B. B. Corson and R. W. Stoughton, *J. Amer. Chem. Soc.*, 1928, **50**, 2825.

Method (*B*).—Isopropylidenemalononitrile (2 g., 18·9 mmoles) and ethyl bromocyanoacetate (3·84 g., 20 mmoles) were dissolved in 50% aqueous ethanol (25 ml.). Crystals of (V) formed after 5 hr. at room temperature. After 24 hr. the product was collected and recrystallized from ethanol–acetone, to give (V) (1·17 g.). A mixed m.p. with product prepared by method (A) was undepressed.

Ethyl 3-*Ethyl*-3-*methyl*-1,2,2-*tricyanocyclopropanecarboxylate* (VI).—Ethyl 2-butylidenecyanoacetate (1 g., 5·98 mmoles) and bromomalononitrile (1·01 g., 7·00 mmoles) dissolved in 80% aqueous ethanol (12 ml.) was kept at room temperature for 20 hr. Water (2 ml.) was added to the mixture which was then heated under reflux for several hours; it was then cooled in an ice bath. The precipitate which formed was recrystallized from ethanol to give white crystals (0·88 g.).

Ethyl 3-*Methyl*-3-*n*-*propyl*-1,2,2-*tricyanocyclopropanecarboxylate* (VII).—Ethyl 2-pentylidenecyanoacetate (1 g., 5·52 mmoles) and bromomalononitrile (1·02 g., 7·04 mmoles) in 50% aqueous ethanol (15 ml.) were warmed on a steam-bath for several minutes. The dark brown reaction mixture was stored at room temperature for 1 month. Solvent was removed on a rotary evaporator, 10 ml. of water was added to the residue, and the mixture was cooled in ice for 0·5 hour. The precipitate which formed was recrystallized from ethanol to give compound (VII) (0·50 g.).

Ethyl 3-*Isopropyl*-3-*methyl*-1,2,2-*tricyanocyclopropanecarboxylate* (VIII).—Ethyl 3-methyl-2-butylidenecyanoacetate (2·18 g., 12 mmoles) and bromomalononitrile (2·18 g., 15 mmoles) in 80% aqueous ethanol (20 ml.) were heated under reflux for 5 hr. and then kept at room temperature for 2 weeks. Work-up yielded crystalline (VIII) (0·19 g.).

Ethyl 3,3-*Diethyl*-1,2,2-*tricyanocyclopropanecarboxylate* (IX).—Ethyl 3-pentylidenecyanoacetate (2·0 g., 11 mmoles) and bromomalononitrile (2·2 g., 15 mmoles) in ethanol (30 ml.) were kept at room temperature for 2 days; the mixture was then heated under reflux for several hours. When cooled in ice the mixture gave crystals of (IX); yield 0·95 g. (from EtOH).

Ethyl 1,2,2-*Tricyanospiro*[2,4]*heptane*-1-*carboxylate* (X).—Ethyl cyclopentylidenecyanoacetate (1·8 g., 10 mmoles) and bromomalononitrile (1·9 g., 13 mmoles) in ethanol (5 ml.) was kept for several hours at room temperature. Water (2 ml.) was added to the mixture to give a brown lower oily layer. After 2 days the oil crystallized; recrystallization from ethanol gave (X) (0·35 g.).

Ethyl 1,2,2-*Tricyanospiro*[2,5]*octane*-1-*carboxylate* (XI).—*Method* (*A*). Ethyl cyclohexylidenecyanoacetate (0·50 g., 2·59 mmoles) and bromomalononitrile (0·75 g., 5·00 mmoles) in 80% aqueous ethanol (10 ml.) was shaken gently until dissolution was complete; after 1 hr. at room temperature, crystals of (XI) appeared. After 4 hr. the product was recrystallized from ethanol to give the product (0·65 g.).

Method (*B*). Cyclohexylidenemalononitrile (1 g., 6·85 mmoles) and ethyl bromocyanoacetate (1·54 g., 8·0 mmoles) in 50% aqueous ethanol (15 ml.) was heated under reflux overnight. After several hours at room temperature crystals of (XI) appeared. They were recrystallized from ethanol to give the product (0·42 g.). A mixed m.p. with product from method (A) was undepressed.

Ethyl 3-*Phenyl*-1,2,2-*tricyanocyclopropanecarboxylate* (XII).—*Method* (*A*). Ethyl benzylidenecyanoacetate (1·0 g., 4·98 mmoles) and bromomalononitrile (0·74 g., 5·1 mmoles) in 50% aqueous ethanol (20 ml.) were heated under reflux for several hours, during which time crystals of the product formed. The mixture was cooled and the product was recrystallized from ethanol to give (XII) (1·0 g.).

Method (*B*). Benzylidenemalononitrile (1·0 g., 6·5 mmoles) and ethyl bromocyanoacetate (1·25 g., 6·8 mmoles) in 60% aqueous ethanol (27 ml.) were heated under reflux for 3 hr. The oily layer which separated crystallized after storage in a refrigerator for several hours; it was recrystallized from ethanol to give (XII) (0·50 g.). A mixed m.p. with product from method (A) was undepressed.

Ethyl 3-p-*Methoxyphenyl*-1,1,2-*tricyanocyclopropanecarboxylate* (XIII).—*Method* (*A*). Ethyl *p*-anisylidenecyanoacetate (1·16 g., 5 mmoles), bromomalononitrile (1·5 g., 10·3 mmoles), and ethanol (10 ml.) were shaken until dissolution was complete. The mixture was set aside overnight at room temperature and the crystals which formed were recrystallized from ethanol (Norit) to give (XIII) (0·53 g.).

Method (*B*). *p*-Anisylidenemalononitrile (0·92 g., 5 mmoles), ethyl bromocyanoacetate (2·00 g., 10 mmoles), and ethanol (30 ml.) were shaken until dissolution was complete. After 2 days at room temperature crystals of (XIII) began to be deposited. After 1 week the product was recrystallized from ethanol to give the product (0·89 g.). A mixed m.p. with product from method (A) was undepressed.

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