Addition Reactions of Heterocyclic Compounds. Part XLIX.[1] Reactions of Benzimidazoles Possessing an Activated 2-Methylene Group with Acetylenic Esters

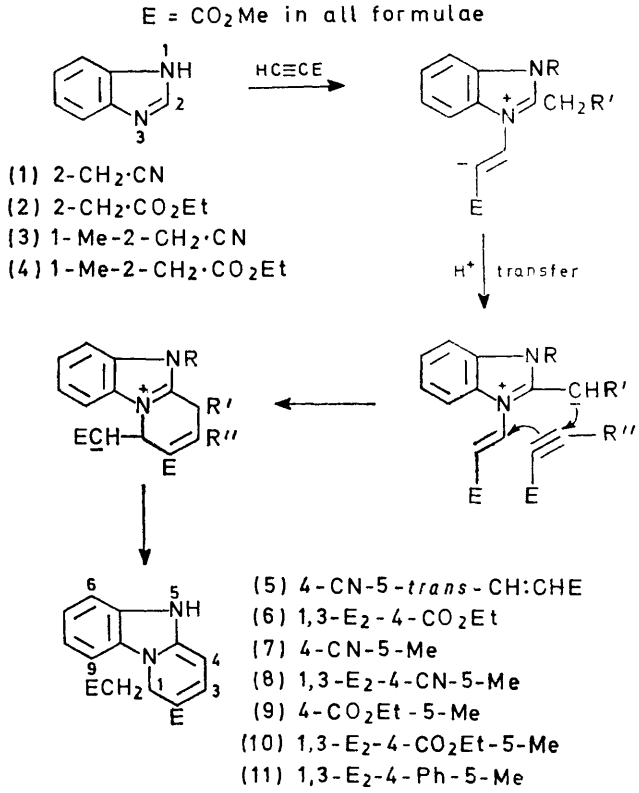
By R. M. Acheson * and M. S. Verlander, Department of Biochemistry, South Parks Road, Oxford OX1 3QU

Benzimidazole-2-acetonitrile, ethyl benzimidazole-2-acetate, and their 1-methyl derivatives were heated with methyl propiolate and with dimethyl acetylenedicarboxylate in acetonitrile. The resulting mixtures, on chromatography gave pyrrolo-, pyrido-, and azepino-[1,2-*a*]benzimidazoles, the structures of which were deduced from their spectral properties.

As an extension of previous studies of the reactions of benzimidazoles with dimethyl acetylenedicarboxylate,[2,3] the reactions of this ester and of methyl propiolate with some substituted benzimidazoles carrying an activated 2-methylene group have been investigated. A particular point of interest was to see if the site of the initial nucleophilic activity of the benzimidazole could be moved from the 3-nitrogen atom to the 2-methylene group, as has been demonstrated for ethyl benzothiazole-2-pyruvate and for methyl benzoxazole-2-pyruvate.[2] As the availability of protons,[4] such as the 1-proton of a benzimidazole, can affect the courses of reactions involving acetylenic esters,[3] it was also necessary to examine the behaviour of both the 2-substituted benzimidazoles and their 1-methyl derivatives.

The reactions investigated usually gave mixtures, which were separated chromatographically; the common types of products are described first. Since the completion of our work Finch and Gemenden have reported [5] only the formation of the appropriate pyridobenzimidazoles [*cf.* structure (20)] from dimethyl acetylenedicarboxylate and the benzimidazoles (1), (2), and (3) in dimethylformamide. They do not appear to have examined their reaction mixtures chromatographically. Our rather different results, illustrated by the observation of compounds (16), (24), and (36), instead of (20) as products from benzimidazole-2-acetonitrile, with acetonitrile as solvent, emphasise the importance of conditions in this type of reaction.

Treatment of the benzimidazoles (1), (3), and (4) with methyl propiolate and of (2), (3), and (4) with dimethyl acetylenedicarboxylate in refluxing acetonitrile gave the 1,5-dihydropyrido[1,2-*a*]benzimidazoles (5)—(10),† but corresponding compounds could not be isolated from reactions of the benzimidazoles (1) and (2) with the dicarboxylic ester and with methyl propiolate, respectively. The mass spectra of the pyridobenzimidazoles (6)—(8) and (10) all show weak molecular ion peaks, with the base peaks corresponding to the loss of one of the substituents from the 1-position. An ester group is preferentially eliminated from compounds (6),



(8), and (10) to give a stable aromatic cation as in the similar fragmentation of the pyridobenzimidazole (11).[2] The u.v. spectra of compounds (5)—(10) (Table 2) are similar and show a partial or virtually complete change to the benzimidazolium chromophore on acidification of

† It should be noted that the correct numbering for compounds of types (5), (31), and (38) is as shown in this paper. Compounds (12), (13), (15), and (19)—(22) of Part XXVI [R. M. Acheson, M. W. Foxton, P. J. Abbot, and K. R. Mills, *J. Chem. Soc.* (*C*), 1967, 882] and compounds (8) and (15) of Part XXXVI (R. M. Acheson and W. R. Tully, *ibid.*, 1968, 1623) should be numbered as compound (5) in this paper. Compound (14) in Part XXVI should be numbered as compound (31) in this paper. Compound (6) in Part XXXV (R. M. Acheson, M. W. Foxton, and J. K. Stubbs, *ibid.*, p. 926) should be numbered as compound (38) here.

[1] Part XLVIII, R. M. Acheson, J. N. Bridson, T. R. Cecil, and A. R. Hands, preceding paper.

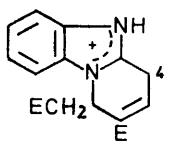
[2] R. M. Acheson and W. R. Tully, *J. Chem. Soc.* (*C*), 1968, 1623.

[3] R. M. Acheson, M. W. Foxton, P. J. Abbott, and K. R. Mills, *J. Chem. Soc.* (*C*), 1967, 882.

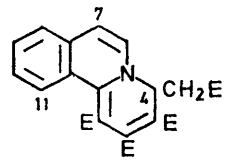
[4] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.

[5] N. Finch and C. W. Gemenden, *J. Org. Chem.*, 1970, **35**, 3114.

the solution, indicating protonation at position 4 to give a species such as (12). The spectrum of compound (11) [2] is a little different, but this may be due to the greater possibility of resonance interaction involving the 4-substituents and the imidazole ring in compounds (5)—(10) to give a species such as (14). Such resonance is also suggested by the abnormally low C≡N stretching frequencies (2190—2000 cm^{-1}) in the i.r. spectra of compounds (5), (7), and (8) compared with the value of 2232—2218 cm^{-1} normally found for conjugated nitriles.[6] Abnormally low frequency carbonyl absorptions (1660—1670 cm^{-1}) in the i.r. spectra of compounds (6), (9), and (10) suggest a similar resonance involving the 4-ethoxycarbonyl group. The chemical shifts (Table 1) of the 1-proton and the 1-methylene protons for compounds (5), (7), and (9) compare well with those of the similarly situated protons at the 4-position of the isoquinoline derivative (13).[7] The *trans*-configuration of the double bond hydrogen atoms of the 5-acrylate group in compound (5) is established by their large coupling constant. Compounds (5)—(11) could be formed from the benzimidazoles as indicated, nucleophilic attack taking place



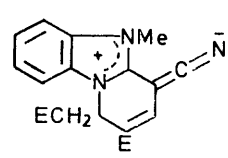
(12)



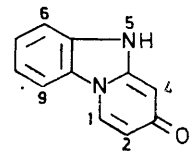
(13)

first from position 3, and then from the methylene group at position 2 of the heterocyclic ring.

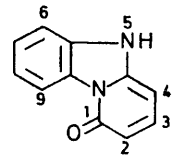
A number of pyrido[1,2-*a*]benzimidazoles (15)—(19) were also isolated from the same reaction mixtures. The n.m.r. spectra for compounds (15)—(18) are consistent with the 3-oxo- rather than the 1-oxo-pyrido-[1,2-*a*]benzimidazole structure [*e.g.* (19), (20),[5] and (21) [5]]. The absence of a deshielded aromatic proton in the spectra of compounds (15), (17), and (18) (Table 1) indicates that a *peri*-deshielding group is not present at position 1, since the 9-proton signal appears at τ 1·19 in compound (19) (Table 1), at 1·50 in (20),[5] and at 1·36 in (22).[2] The absence of a single-proton resonance attributable to the 5-proton in compound (16) may be due to line broadening, to equilibrium between the possible 'keto' (16) and 'enol' (23) forms, or to exchange with the solvent (hexadeuteriodimethyl sulphoxide). However, the very broad i.r. absorption (3250—2500 cm^{-1}) confirms the presence of a strongly hydrogen-bonded O–H or N–H group. The low-field position (τ 1·11—1·20) of the 1-proton signals in the spectra of the pyrido benzimidazoles (15), (17), and (18) may be attributable to a measure of positive charge on the imidazole ring arising from resonance interaction involving this ring and the 3-carbonyl group. In support of this the i.r.



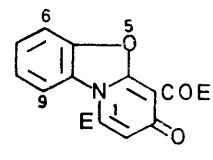
(14)



(15) 4-CN-5-*trans*-CH:CHE
(16) 1-E-4-CN
(17) 2-E-5-*trans*-CH:CHE
(18) 2-E-5-Me



(19) 4-CN-5-*trans*-CH:CHE
(20) 3-E-4-CN
(21) 3-E-4-CN-5-Me



(22)

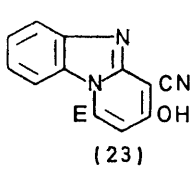
spectra all show abnormally low frequency carbonyl absorptions (1647—1655 cm^{-1}), characteristic of pyridone carbonyl groups.[8] The C≡N stretching frequencies for compounds (15) and (16) are 'normal' for conjugated nitriles, suggesting that the major resonance interaction is between the imidazole ring and the 3-carbonyl group. The u.v. spectra of compounds (15)—(18) (Table 2) are distinct from those of (20) and (21), prepared by treatment of the benzimidazoles (1) and (3) with dimethyl acetylenedicarboxylate in dimethylformamide.[5] A mechanistic scheme which accounts for the formation of the pyridobenzimidazoles (15)—(18) has been suggested for the formation of structurally similar quinolizones from pyridines.[9,10]

The 1-oxopyrido[1,2-*a*]benzimidazole (19) was isolated in low yield from the reaction of benzimidazole-2-acetonitrile (1) with methyl propiolate. The low-field aromatic proton signal (τ 1·19) shows the presence of a *peri*-deshielding group at the 1-position and is at similar field to that of the 9-proton in compound (20);[5] other analogies are available.[2] The chemical shifts of the 3- and 2-protons (Table 1) are close to those of the 4- and 5-protons (τ 2·66 and 3·45, respectively) in 1-methyl-6-oxopyridine-3-carbonitrile.[11] The u.v. spectrum of compound (19) generally resembles that of (21) [5] (Table 2), and the C≡N frequency in the i.r. is 'normal' for a conjugated nitrile, suggesting that the major resonance interaction of the imidazole ring is with the 1-carbonyl group, whose frequency is correspondingly lowered (1686 cm^{-1}). The mass spectrum shows the

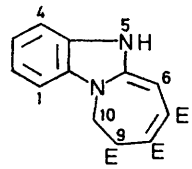
[6] L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1954, p. 264.
[7] R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 362.
[8] L. J. Bellamy and P. E. Rogasch, *Spectrochim. Acta*, 1960, **16**, 30.
[9] R. M. Acheson and D. A. Robinson, *J. Chem. Soc.* (*C*), 1968, 1629.
[10] E. Winterfeldt, *Chem. Ber.*, 1965, **98**, 3537.
[11] R. Mukherjee and A. Chatterjee, *Tetrahedron*, 1966, **22**, 1461.

molecular ion as base peak. The pyridobenzimidazole (19) is probably formed *via* a nucleophilic addition to the ester by the activated 2-methylene group, followed by cyclisation on to the ring nitrogen atom. A similar type of cyclisation has been observed in the pyridine series.[9,10]

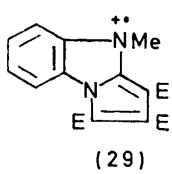
The azepino[1,2-*a*]benzimidazole (24) was isolated from the reaction of benzimidazole-2-acetonitrile (1) with dimethyl acetylenedicarboxylate. Its n.m.r. and u.v. spectra are similar to those of compound (25)[3] (Tables 1 and 2), although the retention of the long wavelength absorption in strong acid solution suggests that in contrast to (25)[3] protonation does not occur at



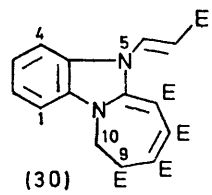
(23)



(24) 6-CN-10-E
(25) 5-Me-10-E
(26) 5-Me-6-E-10-CN
(27) 5-Me-6-Ph-10-E
(28) 5-Me-6-CN-10-E



(29)



(30)

the azepine ring. The absence of a resonance attributable to the 5-proton in the spectrum of (24) (in hexadeuteriodimethyl sulphoxide) may be due to its broadness, to exchange with the solvent, or, possibly, to relatively fast exchange between tautomeric forms in solution. The presence of a broad band (3300—3000 cm^{-1}) in the i.r. spectrum (Nujol mull) suggests that it exists mainly as an N–H tautomer in the solid state. The relatively low frequency C≡N absorption (2200 cm^{-1}) indicates that resonance involving the imidazole ring and the 6-cyano-group is significant, as for some of the compounds already discussed. The strong M — MeOH peak in the mass spectrum of compound (24) is probably formed by loss of methoxyl (metastable-confirmed) and a hydrogen atom. A scheme for the formation of this type of azepine has been put forward.[7]

Treatment of 1-methylbenzimidazole-2-acetonitrile (3) with dimethyl acetylenedicarboxylate also gave the colourless azepino[1,2-*a*]benzimidazole derivative (26). The u.v. spectrum is closely similar to that of compound (27)[2] (Table 2), and in acid solution both compounds show the benzimidazolium chromophore, protonation presumably having taken place at position 6. Structure (26) is distinguished from its isomer (28) by the mass spectrum, which shows loss of 111 mass units to give the base peak. This is consistent with the loss of methyl 3-cyanoacrylate, formed from the 9- and 10-carbon atoms with their associated substituents, to give the stable pyrrolobenzimidazole species (29) in an analogous way to the suggested loss of methyl acrylate, crotonate, and cinnamate from dihydroazepinoquinoline derivatives to give base peaks corresponding to the appropriate pyrroloquinolines.[12,13] The attachment of the 10-cyano-group to a saturated carbon atom in compound (26) is supported by a weak i.r. absorption at 2250 cm^{-1}, the low intensity of the absorption also being consistent with the presence of several oxygenated functions in the molecule.[14] The high frequency ester carbonyl absorption (1769 cm^{-1}) is characteristic of a saturated ester group and is assigned to that at the 9-position. In the n.m.r. spectrum there is a high field AB system (τ 6·30 and 5·44, J 9·8 Hz) assigned to the 9- and 10-protons, corresponding to a similar system (τ 5·50 and 4·36, J 3·5 Hz) in compound (27)[2] where the somewhat different substituents cause the variations between the spectra. The changes in chemical shifts from those of the 9- (τ 6·49) and 10-protons (6·49 and 7·27) of the analogue (30)[15] when the highest field proton is replaced by a cyano-group would be expected[16] to result in τ values of 6·30 and 5·50, respectively, in good agreement with those observed for compound (26). The rather low-field position (τ 5·85) of the 5-methyl signal may be due to resonance interactions developing a positive charge on the 11-nitrogen atom [*cf.* (14)], although Dreiding models suggest that this group may also be deshielded by the 6-ester group. The formation of compound (26) could occur through a spiro intermediate, as suggested for the formation of similar azepine derivatives from 2-ethylquinolines.[13]

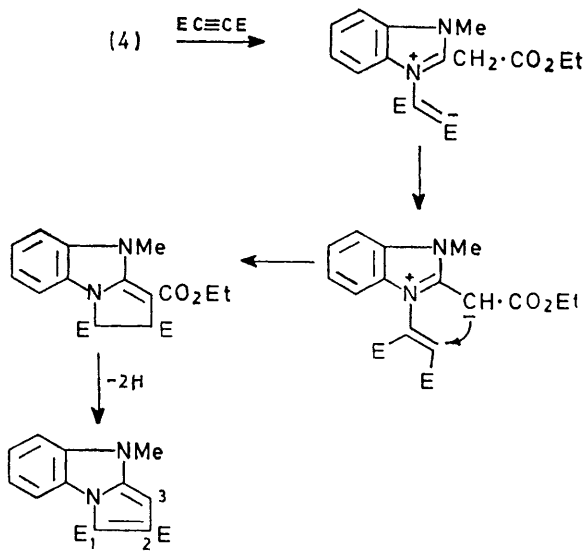
Another compound isolated from the reaction of the benzimidazole (4) with dimethyl acetylenedicarboxylate has been assigned the pyrrolo[1,2-*a*]benzimidazole structure (31)* on the basis of its very close spectral similarity to compound (32).[2,3] A possible route (illustrated) for the formation of (31) requires the loss of hydrogen in an aromatisation step.

A second compound isolated from the reaction of the benzimidazole (2) with methyl propiolate has been formulated as the benzimidazol-2-one derivative (33). Its n.m.r. spectrum is completely symmetrical, the four-proton aromatic region appearing as an A_2B_2 system and the two two-proton doublets (τ 1·93 and 3·28) being assigned to the acrylate protons. The u.v. spectrum of this compound (Table 2) is very similar to

* See footnote on p. 1577.

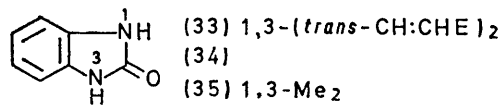
[12] R. M. Acheson, R. T. Aplin, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 383.
[13] R. M. Acheson and D. F. Nisbet, *J. Chem. Soc.* (*C*), 1971, 3291.
[14] Ref. 6, p. 266.
[15] M. S. Verlander, D.Phil. Thesis, Oxford, 1970 (cat. no. d. 5086), p. 92.
[16] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, ' High Resolution N.M.R. Spectroscopy,' Pergamon, London, 1966, p. 846.

those of (34) [17] and (35).[18] Like the benzimidazolone (35), compound (33) also shows an abnormally high frequency carbonyl absorption (1753 cm^{-1}) in the i.r., assigned to the strained ring carbonyl group.

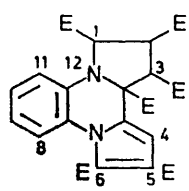


(31) 3-CO_2Et
(32) 3-E

Two similar 1 : 3 molar adducts, isolated from the reactions of the benzimidazoles (1) and (2) with dimethyl acetylenedicarboxylate, have been provisionally assigned structures (36) and (37). Both have low-field aromatic



(33) 1,3-(*trans*-CH:CHE)$_2$
(34)
(35) 1,3-Me_2



(36) 4-CN
(37) 4-CO_2Et

n.m.r. signals (8-H, τ 1·59 and 1·41, respectively; Table 1), consistent with the *peri*-deshielding of proton 8 by the 6-ester group, as shown for the 10-hydrogen atom of compound (38).[19] No such deshielding would be expected for the ester at the 1-position, since it is attached to a saturated carbon atom and will therefore lie out of the plane of the benzene ring. Both compounds (36) and (37) show mid-field AMX systems whose chemical shifts (τ 4·80—5·44) (Table 1) are similar to

TABLE 1

N.m.r. spectra (100 MHz; τ values, J in Hz) for solutions in deuteriochloroform with tetramethylsilane as internal reference

Compd.	Proton resonances	Ester methyls
(5)	ArH_4, 2·2—2·7(m); vinyl 1-H, 1·33(d); vinyl 2-H, 3·55(d) (J 14·2); 3-H, 2·48; 1-H, 3·92(t); 1-CH_2, 7·24(d); $J_{1.1\text{-}CH_2}$ 5·2	6·10, 6·18, 6·45
(6) [a]	ArH, 2·2—2·4(m); ArH_3, 2·5—2·7(m); 4-ester, CH_3·CH_2, 8·79(t), CH_3·CH_2, 5·81(q) (J 7); 1-CH_2, 6·45(d) and 6·82(d), J 14·8	6·24, 6·24, 6·38, 6·58
(7)	ArH_4, 2·4—2·85(m); 5-Me, 6·04; 3-H, 2·47; 1-H, 3·95(t); 1-CH_2, 7·27(d); $J_{1.1\text{-}CH_2}$ 5·1	6·22, 6·47
(8)	ArH_4, 2·6—3·2(m); 5-Me, 5·92; 1-CH_2 6·79	6·14, 6·20, 6·25, 6·40
(9)	ArH, 2·3—2·55(m); ArH_3, 2·67;[c] 5-Me, 6·17; 4-ester, CH_3·CH_2, 8·5—8·8(m), CH_3·CH_2, 5·73(q) (J 7·2); 3-H, 1·83; 1-H, 3·91(t); 1-CH_2, 7·05—7·5(m), J 14·2 and 5·2	6·18, 6·49
(10)	ArH_4, 2·7—3·2(m); 5-Me, 5·96; 4-ester, CH_3·CH_2, 8·70(t), CH_3·CH_2, 5·87(q) (J 7); 1-CH_2, 6·85	6·22, 6·26, 6·60, 6·62
(15) [a]	ArH_2, 1·7—2·15(m); ArH_2, 2·3—2·6(m); vinyl 1-H, 1·40(d); vinyl 2-H, 3·32(d) (J 13·9); 2-H, 3·46(d); 1-H, 1·17(d); $J_{1.2}$ 8·1	6·18
(16) [a]	ArH_3, 2·2—2·7(m); 9-H, 1·37(m); 2-H, 3·47	6·05
(17)	ArH_4, 2·1—2·65(m); vinyl 1-H, 1·94(d); vinyl 2-H, 3·65(d) (J 14); 4-H, 3·37; 1-H, 1·11	6·00, 6·10
(18)	ArH_4, 2·2—2·8(m); 4-H, 3·81; 1-H, 1·20; 5-Me, 6·42	6·02
(19) [a]	ArH, 1·9—2·1(m); ArH_2, 2·2—2·6(m); 9-H, 1·19(m); vinyl 1-H, 1·40(d); vinyl 2-H, 3·24(d) (J 14); 3-H, 2·05(d); 2-H, 3·70(d); $J_{2.3}$ 9	6·15
(24) [a]	ArH, 2·2—2·4(m); ArH_3, 2·4—2·8(m); 9-H, 4·75(d); 10-H, 3·50(d); $J_{9.10}$ 5·8	6·24, 6·33, 6·39, 6·55
(25) [b]	ArH_4, 2·8—2·95(m); 5-Me, 6·59;[d] 6-H, 5·55; 9-H, 4·53(d); 10-H, 4·05(d); $J_{9.10}$ 6	6·15, 6·26, 6·31, 6·47
(26)	ArH_4, 2·85;[c] 5-Me, 5·85; 9-H, 6·30(d); 10-H, 5·44(d); $J_{9.10}$ 9·8	6·16, 6·16, 6·25, 6·33
(31)	ArH_3, 2·4—2·8(m); 3-ester, CH_3·CH_2, 8·64(t), CH_3·CH_2, 5·67(q) (J 7·2); 8-H, 1·20(m); 4-Me, 5·78 [d]	6·01, 6·07
(33)	ArH_4, 2·4—2·7(m); vinyl 2 × 1-H, 1·93(d); vinyl 2 × 2-H, 3·28(d) (J 14·5)	6·14, 6·14
(36) [a]	8-H, 1·59(m); 9-H, 10-H, 2·35—2·6(m); 11-H, 2·11(m); 1-H, 5·12(d); 2-H, 5·01(q); 3-H, 5·44(d); $J_{1.2}$ 10·4; $J_{2.3}$ 6·2	6·07, 6·15, 6·31, 6·41, 6·52, 6·57
(37)	4-ester, CH_3·CH_2, 8·56(t), CH_3·CH_2, 5·45(q) (J 7·0); 8-H, 1·41(m); 9-H, 10-H, 2·4—2·7(m); 11-H, 2·09(m); 1-H, 5·0(d); 2-H, 4·80(q); 3-H, 5·44(d); $J_{1.2}$ 9·7; $J_{2.3}$ 7·25	6·07, 6·12, 6·31, 6·39, 6·40, 6·41
(38) [e]	ArH_3, 2·4—3·0(m); 2-H, 3-H, 5·59—6·03(m); 1-H, 4·75(m);[f] 10-H, 1·19(d);[g] 5-H, 6-H, 6·4—6·75(m); 5-H, 7·52(m) [h]	6·21, 6·21, 6·25, 6·28, 6·31, 6·39

[a] In hexadeuteriodimethyl sulphoxide. [b] Ref. 3. [c] Apparent singlet. [d] Possibly this assignment should be interchanged with an ester methyl. [e] Ref. 19. [f] Centre of apparent quartet. [g] Signs of further splitting. [h] Centre of six-line multiplet.

[17] D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 1959, 3157.
[18] L. S. Efros and A. V. El'tsov, *Zhur. obshchei. Khim.*, 1957, **27**, 684.
[19] R. M. Acheson, M. W. Foxton, and J. K. Stubbs, *J. Chem. Soc.* (*C*), 1968, 926.

TABLE 2

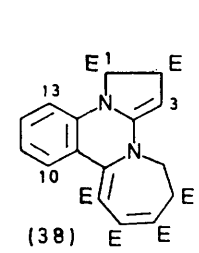
U.v. absorption spectra

Compd.	Solvent*	$\lambda_{max.}$/nm (10^{-4} ε)
(5)	M	213 (3·25), 242 (2·42), 259 (2·33), 280 (2·64), 293infl (1·71), 428 (3·38)
	P	206 (3·12), 268infl (1·87), 282 (1·96), 365 (0·49)
(6)	M	211 (1·82), 217infl (1·72), 225infl (1·56), 248 (1·51), 308 (3·84), 412 (1·95)
	P	215infl (1·77), 247 (0·84), 265 (0·66), 273 (0·70), 281 (0·66), 307 (1·18)
(7)	M	211infl (1·83), 220 (2·37), 248 (1·73), 262infl (1·16), 298·5 (2·06), 409 (2·19)
	P	216infl (1·92), 276 (1·87)
(8)	M	211infl (1·23), 228 (1·98), 283 (3·64), 314infl (1·27), 323 (1·66), 400 (0·32)
	P	233 (1·43), 268 (1·18), 287 (1·29), 305infl (0·83), 321infl (0·70)
(9)	M	213 (2·42), 250 (1·29), 273infl (0·69), 315 (3·77), 398 (2·22)
	MA	211 (2·54), 267infl (0·84), 273 (1·08), 281 (1·05)
(10)	M	208 (1·78), 228 (1·55), 286 (2·68), 330 (1·98), 398 (0·43)
	MA	210 (3·42), 236 (1·48), 269 (1·40), 283infl (0·99)
(11) [a]	M	220infl (3·24), 275 (1·60), 281 (1·55), 315 (1·52), 480 (1·78)
	MA	275 (1·64), 282 (1·54)
(15)	M	211 (2·47), 249 (4·18), 256infl (3·25), 274 (1·95), 283 (1·88), 318 (2·19)
	P	212 (3·08), 249 (2·99), 261 (2·76), 282 (2·11), 323 (1·23)
(16)	M	211 (1·93), 230infl (1·36), 270 (2·94), 283infl (2·58), 308infl (0·99), 416 (0·84)
	P	215infl (2·11), 233 (1·90), 256 (3·21), 271 (3·52), 291infl (1·24), 390 (1·04)
(17)	M	211 (2·45), 219infl (2·24), 259 (4·29), 280infl (1·96), 290infl (1·67), 327 (2·37)
	P	220infl (2·02), 251 (3·41), 262 (3·14), 275 (2·78), 329 (1·57)
(18)	M	212 (2·61), 230 (2·20), 261 (4·70), 306infl (0·94), 315 (1·22), 336 (0·94)
	P	210infl (1·20), 217 (1·30), 258infl (1·93), 267 (2·04), 307 (0·59), 316infl (0·57)
(19)	M	211 (2·57), 224 (2·90), 258 (2·36), 281 (2·10), 358infl (1·85), 371 (2·46), 400 (0·29)
	P	242 (2·73), 259 (2·43), 269infl (2·13), 304 (0·50), 354infl (1·70), 365 (2·10), 402infl (0·23)
(24)	M	208 (1·71), 224 (1·78), 250 (1·26), 288infl (0·85), 298 (1·03), 305infl (0·98), 408 (3·93)
	P	222 (2·20), 248infl (1·12), 295 (0·54), 370 (1·04)
(26)	M	209infl (0·87), 230 (1·64), 264 (0·75), 340 (4·55)
	MA	211 (1·62), 268infl (0·77), 274 (0·91), 282 (0·81)
(31) [b]	M	216 (2·83), 248 (3·27), 292 (2·57), 332·5 (2·05)
(33) [b]	M	210 (2·56), 238·5 (3·35), 284 (4·10)
(34) [c]	E	222·5 (0·72), 280 (0·75)
(35) [d]	M	228 (1·50), 280 (1·63)
(36)	M	209 (2·24), 218infl (1·45), 241infl (0·59), 344 (1·62)
	P	211infl (1·99), 245infl (0·67), 342 (1·57)
(37)	M	210 (2·13), 220infl (1·53), 243infl (0·62), 343 (1·76)
	P	211infl (2·62), 244infl (1·07), 254infl (0·83), 343 (2·56)

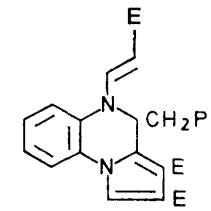
* E = EtOH; M = MeOH; MA = MeOH acidified with 3 drops of 72% perchloric acid; P = MeOH–72% perchloric acid (2 : 1 v/v).

[a] Ref. 2. [b] No change on acidification. [c] Ref. 17. [d] Ref. 18.

those found for the 1-, 2-, and 3-protons of compound (38) (Table 1) where the 3-proton is at relatively high field because it is the β-hydrogen atom of an enamine system with respect to two nitrogen atoms. The u.v. spectra of compounds (36) and (37) (Table 2) resemble



(38)



(39)

that of compound (39).[20] Compounds of type (36) have also been obtained from other benzimidazoles, and their formation will be discussed in a later paper.

EXPERIMENTAL

The instruments and general procedures used have been described previously.[1] Chromatography was performed on deactivated alumina.[1] Details of the i.r. and mass spectra and details of the chromatography are available.[15] † The methyl propiolate prepared as described [21] had b.p. 100—101° at 760 mmHg. *N*-Methyl-2-nitroaniline was obtained by the method of Hempel [22] as large red needles, m.p. 34° (lit.,[23] 35°); reduction of this with zinc dust and aqueous ethanolic sodium hydroxide [24] gave *N*-methyl-1,2-phenylenediamine (90—93%), b.p. 138—145° at 20 mmHg (lit.,[25] 116—120° at 8 mmHg; different synthetic method). Benzimidazole-2-acetonitrile (1) (50%), m.p. 210—212°, and ethyl benzimidazole-2-acetate (2) (70%), m.p. 128—129°, were prepared by the literature method; [26] their 1-methyl derivatives (3), m.p. 131—132° (lit.,[27] 132—134°; different method), and (4), m.p. 64° (lit.,[27] m.p. 60—62°; different method), were obtained by replacing the 1,2-phenylenediamine in the published procedure [26] by *N*-methyl-1,2-phenylenediamine.

Benzimidazole-2-acetonitrile with Methyl Propiolate.—(i) Benzimidazole-2-acetonitrile (1) (6 g) and methyl propiolate (9·5 g) were refluxed in acetonitrile (150 ml) for 12 days. Evaporation gave a tarry solid which, on treatment with methanol, deposited *methyl 4-cyano-3,5-dihydro-3-oxopyrido*[1,2-a]*benzimidazole-5*-trans-*acrylate* (15) (1·34 g), pale yellow crystals (from methanol), m.p. 269—271°, resolidifying above the m.p. and re-melting above 310°

† Copies of the thesis can be obtained, without reference to the author, from the Librarian, Radcliffe Science Library, South Parks Road, Oxford, upon payment of the library's standard fees for this work.

[20] Ref. 15, p. 33.
[21] R. M. Acheson and M. S. Verlander, *J. Chem. Soc.* (*C*), 1969, 2311.
[22] A. Hempel, *J. prakt. Chem.*, 1890, **41**, 161.
[23] J. J. Blanksma, *Rec. Trav. chim.*, 1902, **21**, 269.
[24] E. L. Martin, *Org. Synth.*, 1943, Coll. Vol. II, p. 501.
[25] H. Irving and O. Weber, *J. Chem. Soc.*, 1959, 2296.
[26] R. A. B. Copeland and A. R. Day, *J. Amer. Chem. Soc.*, 1943, **65**, 1072.
[27] W. Ozegowski and D. Krebs, *J. prakt. Chem.*, 1965, **29**, 18.

(decomp.) (Found: C, 65·3; H, 3·8; N, 14·2. $C_{16}H_{11}N_3O_3$ requires C, 65·5; H, 3·8; N, 14·3%), $\nu_{max.}$ 2214, 1716, 1647, 1625, and 1600 cm^{-1}.

Chromatography of the remainder and elution with light petroleum–benzene (1 : 1 v/v) gave a yellow oil which yielded *methyl* 4-*cyano*-1,5-*dihydro*-1-*oxopyrido*[1,2-a]*benzimidazole*-5-trans-*acrylate* (19) (25 mg, 0·16%), yellow crystals (from methanol), m.p. 263—266° (Found: C, 65·4; H, 3·8. $C_{16}H_{11}N_3O_3$ requires C, 65·5; H, 3·8%), $\nu_{max.}$ 2222, 1733, 1686, 1656, and 1619 cm^{-1}, *m/e* 293 (M^+, 100%), 265 (M — CO, 2·0), 262 (M — OMe, 9·5), and 234 (M — CO_2Me, 17), *m** 240, and 187 (293 ⟶ 265 and 293 ⟶ 234).

Further elution (benzene) gave *methyl* 4-*cyano*-1,5-*dihydro*-1-*methoxycarbonylmethyl*-5-(trans-2-*methoxycarbonylvinyl*)*pyrido*[1,2-a]*benzimidazole*-2-*carboxylate* (5) (400 mg, 2·6%), irregular yellow crystals (from methanol), m.p. 159—160° (Found: C, 61·4; H, 4·6; N, 10·1. $C_{21}H_{19}N_3O_6$ requires C, 61·6; H, 4·7; N, 10·3%), $\nu_{max.}$ 2200, 1733, 1723, 1671, 1664, 1625, and 1609 cm^{-1}.

Elution of the next yellow band with benzene–ether (4 : 1 v/v) gave an unidentified compound (600 mg), crystals (from methanol), m.p. 266—267·5° (Found: C, 63·3; H, 4·6; N, 14·7. Calc. for $C_{30}H_{26}N_6O_6$: C, 63·6; H, 4·6; N, 14·8%), $\nu_{max.}$ 1751, 1743, 1728, 1516w, 1445, 1434, and 1420w cm^{-1}, $\lambda_{max.}$ (MeOH) 213 (10^{-4} ε 8·36), 259 (2·76), 270 (2·07), 277 (2·15), and 286 nm (1·78); $\lambda_{max.}$ (MeOH–HCl) 212 (10^{-4} ε 6·90), 260 (2·33), 271 (2·29), 278 (2·58), and 286 nm (2·15); τ [$(CD_3)_2SO$] 2·0—2·3 (m, ArH_2), 2·3—2·8 (m, ArH_6), 4·2—4·4 (2H, m), 4·3—4·6 (1H, m), 4·6—5·0 (1H, m), 5·0—7·2 (5H, m), and 6·21, 6·26, and 6·80 (9H, 3 × Me); *m/e* 566 (M^+, 28%), 535 (12·2), 507 (100), 493 (20), and 326 (34), *m** 507 and 473 (566 ⟶ 535 and 566 ⟶ 507).

Further elution gave the pyridobenzimidazole (15) (800 mg).

1-*Methylbenzimidazole*-2-*acetonitrile with Methyl Propiolate*.—The nitrile (1·2 g), methyl propiolate (1·8 g, 3 mol. equiv.), and acetonitrile (50 ml) were refluxed for 8 days and chromatographed. Elution [light petroleum–benzene (3 : 1 v/v)] gave trimethyl benzene-1,3,5-tricarboxylate (150 mg), m.p. 138—140° (lit.,[28] 144°), identified by mixed m.p.

Elution with benzene–ether (5 : 1 v/v) gave *methyl* 4-*cyano*-1,5-*dihydro*-1-*methoxycarbonylmethyl*-5-*methylpyrido*[1,2-a]*benzimidazole*-2-*carboxylate* (7) (450 mg, 19%), yellow matted rods (from methanol), m.p. 171·5—172·5° (Found: C, 63·9; H, 5·1; N, 12·3. $C_{18}H_{17}N_3O_4$ requires C, 63·7; H, 5·1; N, 12·4%), $\nu_{max.}$ 2190, 1748, 1669, and 1630 cm^{-1}, *m/e* 339 (M^+, 6·2%) and 266 (M — $CH_2{\cdot}CO_2Me$, 100).

Benzimidazole-2-*acetonitrile with Dimethyl Acetylenedicarboxylate*.—The nitrile (16 g) and the ester (32 g) were refluxed in acetonitrile (500 ml) for 24 h and chromatographed. Elution with benzene gave *hexamethyl* 4-*cyano*-1,2,3,3a-*tetrahydrodipyrrolo*[1,2-a : 1′,2′-c]*quinoxaline*-1,2,3,3a,5,6-*hexacarboxylate* (36) (2·1 g, 5%), rectangular plates (from methanol), m.p. 256—259° (decomp.) (Found: C, 55·9; H, 4·5; N, 7·1. $C_{27}H_{25}N_3O_{12}$ requires C, 55·6; H, 4·3; N, 7·2%), $\nu_{max.}$ 2254w, 1775, 1747, 1736, and 1646 cm^{-1}, *m/e* 583 (M^+, 62%), 524 (M — CO_2Me, 49), and 480 (M — CO_2Me — CO_2, 100); *m** 472 and 440 (583 ⟶ 524 and 524 ⟶ 480).

Elution with ether gave oils (2·5 g) and then elution with ether–chloroform (1 : 1 v/v) gave *methyl* 4-*cyano*-3,5-*dihydro*-3-*oxopyrido*[1,2-a]*benzimidazole*-1-*carboxylate* (16) (1·42 g, 4·9%). parallelipipeds (from methanol), m.p. 255—256° (decomp.) (Found: C, 62·5; H, 3·5; N, 15·5. $C_{14}H_9N_3O_3$ requires C, 62·9; H, 3·4; N, 15·7%), $\nu_{max.}$ 3250—2500, 2220, 1736, 1668, and 1614w cm^{-1}; *m/e* 267 (M^+, 100%), 239 (M — CO, 13), 236 (M — OMe, 10), and 208 (M — CO_2Me, 20); *m** 214 and 208 (267 ⟶ 239 and 267 ⟶ 236).

Elution with chloroform–methanol (1 : 1 v/v) gave *tetramethyl* 6-*cyano*-9,10-*dihydro*-5H-*azepino*[1,2-a]*benzimidazole*-7,8,9,10-*tetracarboxylate* (24) (1·93 g, 4%), pale yellow crystals (from methanol), m.p. 253—255° (decomp.) (Found: C, 57·0; H, 4·4; N, 9·5. $C_{21}H_{19}N_3O_8$ requires C, 57·1; H, 4·3; N, 9·5%), $\nu_{max.}$ 3300—3000, 2200, 1755, 1743, 1691infl, and 1685 cm^{-1}, *m/e* 441 (M^+, 60%), 410 (M — OMe, 90), 382 (M — CO_2Me, 100), 350 (M — CO_2Me — MeOH, 60), 324 (22), and 323 (M — $2CO_2Me$, 29); *m** 381, 332, and 301 (441 ⟶ 410, 441 ⟶ 382, and 350 ⟶ 324).

1-*Methylbenzimidazole*-2-*acetonitrile with Dimethyl Acetylenedicarboxylate*.—The nitrile (2·1 g), the ester (3·5 g), and acetonitrile (150 ml) were refluxed for 3 days and chromatographed. Elution with light petroleum–benzene (2 : 1 v/v) gave a red mixture (100 mg), m.p. 110—160°, followed by a mixture of two compounds which was fractionally recrystallised from methanol. The less soluble component was *trimethyl* 4-*cyano*-1,5-*dihydro*-1-*methoxycarbonylmethyl*-5-*methylpyrido*[1,2-a]*benzimidazole*-1,2,3-*tricarboxylate* (8) (600 mg, 10·7%), yellow crystals, m.p. 213·5—215·5° (Found: C, 58·0; H, 4·7; N, 9·2. $C_{22}H_{21}N_3O_8$ requires C, 58·0; H, 4·7; N, 9·2%), $\nu_{max.}$ 2192, 1742, 1717, 1664, and 1626w cm^{-1}; *m/e* 455 (M^+, 5%), 396 (M — CO_2Me, 100), 382 (M — $CH_2{\cdot}CO_2Me$, 18), and 364 (7); *m** 345 and 335 (455 ⟶ 396 and 396 ⟶ 364).

The more soluble component was *tetramethyl* 10-*cyano*-9,10-*dihydro*-5-*methyl*-5H-*azepino*[1,2-a]*benzimidazole*-6,7,8,9-*tetracarboxylate* (26) (260 mg, 4·7%), rods (from methanol), m.p. 184—185° (Found: C, 57·8; H, 4·8; N, 9·0. $C_{22}H_{21}N_3O_8$ requires C, 58·0; H, 4·7; N, 9·2%), $\nu_{max.}$ 2250w, 1770, 1738, 1729, 1683, and 1619 cm^{-1}; *m/e* 455 (M^+, 2·6%), 344 (M — HC·CN:CH·CO_2Me, 100), and 313 (M — HC·CN:CH·CO_2Me — OMe, 20).

Ethyl Benzimidazole-2-*acetates with Methyl Propiolate*.—Ethyl benzimidazole-2-acetate (10 g) and methyl propiolate (8·5 g, 2 mol. equiv.) were refluxed in acetonitrile (150 ml) for 10 days. Evaporation of the solvent and trituration with benzene gave *methyl* 3,5-*dihydro*-5-(trans-2-*methoxycarbonylvinyl*)-3-*oxopyrido*[1,2-a]*benzimidazole*-2-*carboxylate* (17) (1·0 g), rods (from methanol), m.p. 260° (decomp.) (Found: C, 62·4; H, 4·2; N, 8·3. $C_{17}H_{14}N_2O_5$ requires C, 62·6; H, 4·3; N, 8·6%), $\nu_{max.}$ 1740, 1707, and 1649 cm^{-1}.

Chromatography of the remaining material and elution with light petroleum–benzene (3 : 1 v/v) gave trimethyl benzene-1,3,5-tricarboxylate (400 mg).

Elution with light petroleum–benzene (3 : 2 v/v) gave 1,3-*bis*-(trans-2-*methoxycarbonylvinyl*)-1H-*benzimidazol*-2(3H)-*one* (33) (160 mg, 1·3%), needles (from methanol), m.p. 179—180° (Found: C, 59·1; H, 4·6; N, 9·1. $C_{15}H_{14}N_2O_5$ requires C, 59·6; H, 4·7; N, 9·3%); $\nu_{max.}$ 1753, 1724, 1644, and 1610 cm^{-1}; *m/e* 302 (M^+, 100%), 287 (M — Me, 5·3), 271 (M — OMe, 47), 243 (M — CO_2Me, 30), 239 (M — OMe — MeOH, 18), and 215 (M — CO_2Me — CO, 1·5), *m** 272, 243, 195·5, and 190 (302 ⟶ 287, 302 ⟶ 271, 302 ⟶ 243, and 243 ⟶ 215).

Similarly ethyl 1-methylbenzimidazole-2-acetate (3·4 g) and methyl propiolate (4·2 g) gave *methyl* 3,5-*dihydro*-5-*methyl*-3-*oxopyrido*[1,2-a]*benzimidazole*-2-*carboxylate* (18)

[28] H. von Pechmann, *Annalen*, 1891, **264**, 296.

(620 mg, 13%), rods (from methanol), m.p. 292—293° (decomp.) (sublimation above 260°) (Found: C, 65·4; H, 4·9; N, 10·8. $C_{14}H_{12}N_2O_3$ requires C, 65·6; H, 4·7; N, 10·9%), $\nu_{max.}$ 1703, 1655, and 1620 cm^{-1}, and subsequent chromatography yielded trimethyl benzene-1,3,5-tricarboxylate (190 mg) and *methyl 4-ethoxycarbonyl-1,5-dihydro-1-methoxycarbonylmethyl-5-methylpyrido*[1,2-a]*benzimidazole-2-carboxylate* (9) (1·36 g), yellow rods (from methanol), m.p. 172—174° (Found: C, 61·7; H, 5·8; N, 7·3. $C_{20}H_{22}N_2O_6$ requires C, 62·2; H, 5·7; N, 7·3%), $\nu_{max.}$ 1747, 1683infl, 1662, and 1616 cm^{-1}.

Ethyl Benzimidazole-2-acetate with Dimethyl Acetylenedicarboxylate.—Ethyl benzimidazole-2-acetate (1·7 g) and dimethyl acetylenedicarboxylate (2·6 g, 2 mol. equiv.) were refluxed in acetonitrile (100 ml) for 2 days. Chromatography and elution with benzene–ether (2 : 1 v/v), gave *hexamethyl 4-ethoxycarbonyl-1,2,3,3a-tetrahydrodipyrrolo*-[1,2-a : 1′,2′-c]*quinoxaline-1,2,3,3a,5,6-hexacarboxylate* (37) (230 mg, 6·6%), prisms (from methanol), m.p. 248—250° (decomp.) (Found: C, 55·4; H, 5·0; N, 4·6. $C_{29}H_{30}N_2O_{14}$ requires C, 55·2; H, 4·8; N, 4·5%), $\nu_{max.}$ 1764, 1752, 1734, and 1648 cm^{-1}; *m/e* 630 (M^+, 100%), 599 (M − OMe, 3·5), 586 (M − CO_2, 5), 571 (M − CO_2Me, 90), 527 (M − CO_2Me − CO_2, 30), and 499 (35), *m** 570, 545, 517, 486, and 473 (630 ⟶ 599, 630 ⟶ 586, 630 ⟶ 571, 571 ⟶ 527, and 527 ⟶ 499).

Elution with benzene–ether (1 : 2 v/v) gave *trimethyl 4-ethoxycarbonyl-1,5-dihydro-1-methoxycarbonylmethylpyrido*-[1,2-a]*benzimidazole-1,2,3-tricarboxylate* (6) (320 mg, 7·8%), yellow parallelipipeds (from methanol), m.p. 212—213° (decomp.) (Found: C, 57·0; H, 4·8; N, 5·6. $C_{23}H_{24}N_2O_{10}$ requires C, 56·6; H, 4·9; N, 5·7%), $\nu_{max.}$ 3255, 1753, 1742, 1709, 1660, 1624, and 1596 cm^{-1}; *m/e* 485 (M^+, 9%), 454 (M − OMe, 3·3), 426 (M − CO_2Me, 100), and 412 (M − $CH_2{\cdot}CO_2Me$, 12), *m** 425·5, 375, and 342 (485 ⟶ 454, 485 ⟶ 426, and 485 ⟶ 412).

Ethyl 1-Methylbenzimidazole-2-acetate with Dimethyl Acetylenedicarboxylate.—The esters (2·8 and 5·6 g respectively) were refluxed in acetonitrile (70 ml) for 5 days and chromatographed. Elution with benzene gave *3-ethoxycarbonyl-4-methyl-4H-pyrrolo*[1,2-a]*benzimidazole-1,2-dicarboxylate* (31) (140 mg), plates (from methanol), m.p. 140° (Found: C, 60·4; H, 4·9; N, 7·7. $C_{18}H_{18}N_2O_6$ requires C, 60·3; H, 5·1; N, 7·8%), $\nu_{max.}$ 1740, 1726, and 1694 cm^{-1}.

Further elution with benzene gave inseparable mixtures but elution with benzene–ether (5 : 1 v/v) gave *trimethyl 4-ethoxycarbonyl-1,5-dihydro-1-methoxycarbonylmethyl-5-methylpyrido*[1,2-a]*benzimidazole-1,2,3-tricarboxylate* (10) (1·0 g, 15·4%), yellow crystals (from methanol), m.p. 146—147° (Found: C, 57·1; H, 5·2; N, 5·4. $C_{24}H_{26}N_2O_{10}$ requires C, 57·4; H, 5·2; N, 5·6%), $\nu_{max.}$ 1770, 1734, 1720, 1670, and 1643 cm^{-1}, *m/e* 502 (M^+, 4%), 443 (M − CO_2Me, 100), 429 (M − $CH_2{\cdot}CO_2Me$, 30), and 398 (M − $CH_2{\cdot}CO_2Me$ − OMe, 5·6), *m** 391 and 367 (502 ⟶ 443 and 502 ⟶ 429).

We thank Dr. R. G. Bolton for the mass spectra and the S.R.C. for a studentship (to M. S. V.).

[1/2013 *Received*, 28*th October*, 1971]