Addition Reactions of Heterocyclic Compounds. Part LV.[1] Further Reactions of Substituted Benzimidazoles with Dimethyl Acetylenedicarboxylate

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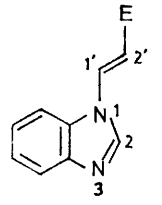
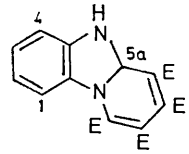
Some 1,2-disubstituted benzimidazoles with dimethyl acetylenedicarboxylate gave pyrido[1,2-*a*]benzimidazoles, azepino[1,2-*a*]benzimidazoles, and pyrrolo[1,2-*a*]benzimidazoles, identified from their u.v., mass, and n.m.r. spectra.

A NUMBER of benzimidazoles were available from earlier studies concerning the addition of methyl propiolate to this ring system;[2] their reactions with dimethyl acetylenedicarboxylate have been examined as a continuation of earlier work.[3]

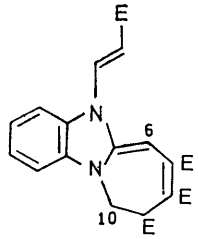
1-Methyl-2-isopropylbenzimidazole and the 1-substituted benzimidazoles (1) and (2), which possess large 2-substituents, with the diester gave the pyridobenzimidazoles (7)—(9) respectively. The u.v. spectra of these products showed a bathochromic shift in comparison with those of corresponding adducts[4] from 1,2-dimethyl- and 2-ethyl-1-methyl-benzimidazoles, and unlike these last adducts, the u.v. spectra in acid solution showed that complete conversion into cations had not taken place. The n.m.r. spectra showed the expected features except that the phenyl derivative (9) possessed an abnormally high field (τ 4·46) aromatic proton signal, appearing as a double doublet. Decoupling this caused the collapse of the double triplet at τ 3·40 to a double doublet, the loss of a 2 Hz coupling with another proton which now appeared as a triplet at τ 3·00, and the sharpening of a double doublet at τ *ca.* 2·84. This established that the high-field proton was associated with three other coupled protons only, as it would not be possible for another triplet of $J \Sigma 16$ Hz to be concealed by the 5-proton singlet assigned to the remaining aromatic protons. The high-field proton must be at position 1 or 4, probably the former, because it is the more likely to be affected by conformational restrictions caused by the phenyl group. In the mass spectrum the molecular ions were particularly weak for both compounds (8) and (9), being formed by loss of t-butyl and methoxycarbonyl groups, respectively.



(1) 2-Bu^t
(2) 2-Ph
(3) 2-Me
(4) 2-PhCH$_2$
(5) 2-Et-1'-E
(6) 2-Ph$_2$CH



(7) 5-Me-5a-Pr^i
(8) 5-*trans*-CH:CHE-5a-Bu^t
(9) 5-*trans*-CH:CHE-5a-Ph



(10) 6-E
(11) 10-E
(12) 6-Ph-10-E

E = CO_2Me in all formulae

In contrast to (1) and (2) the benzimidazoles (3) and (4) gave the azepines (10), (11), and (13), and (12), respectively. Compounds (10) and (13) showed high

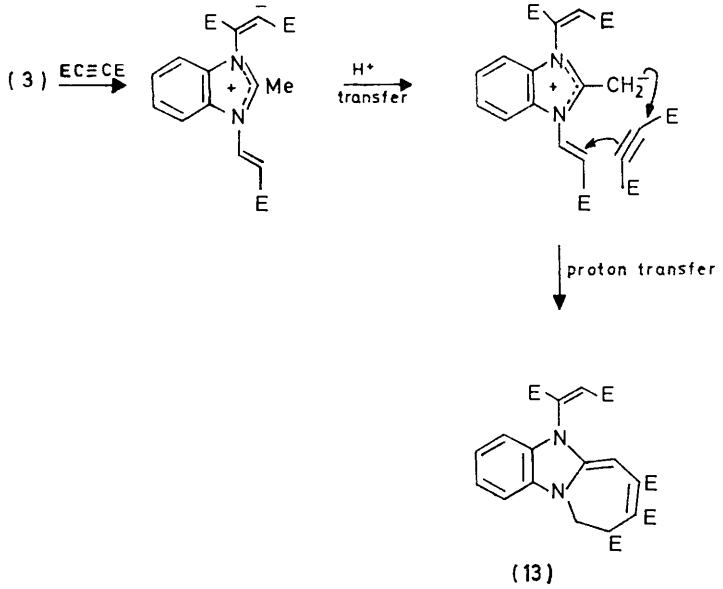
[1] Part LIV, preceding paper.
[2] R. M. Acheson and M. S. Verlander, *J.C.S. Perkin I*, 1973, 2348.
[3] Ref. 2, and papers therein cited.
[4] R. M. Acheson, M. W. Foxton, P. J. Abbott, and K. J. Mills, *J. Chem. Soc.* (*C*), 1967, 882.

TABLE 1

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

Compound	Proton resonances	Ester methyls
(7)	ArH(1), 2·9m; ArH(2), 3·2—3·4m; ArH(1), 3·46d,[a] J 7·5; 5-Me, 6·86; 5a-Me_2CH, 7·5m; 5a-Me_2CH, 9·10[b]	5·91, 6·17, 6·20, 6·23
(8)	ArH(4), 2·55—3·25m; 1′-H, 2·05d; 2′-H, 4·19d, J 14; 5-Me_3C, 8·95	5·90, 6·15, 6·18, 6·21, 6·21
(9)	ArH(5), 2·40;[c] 1′-H, 2·03d; 2′-H, 4·52d, J 14·2; 1-H, 2·84q;[d] 2-H, 3·00m;[d] 3-H, 3·40m;[d] 4-H, 4·46q;[d] $J_{1,2}$ 8·1; $J_{2,3} = J_{3,4}$ 7·8; $J_{1,3} = J_{2,4}$ 1·5	6·07, 6·12, 6·25, 6·25, 6·60
(10)	ArH(1), 2·5m; ArH(3), 2·80;[e] 1′-H, 0·28d; 2′-H, 3·86d, J 14·3; 9H, 10-H, 6·3—6·7m; 10-H, 7·1—7·5m	6·15, 6·15, 6·24, 6·30, 6·30
11)	ArH(4), 2·4—2·9m; 1′-H, 2·12d; 2′-H, 3·69d, J 14·2; 6-H, 5·23; 9-H, 4·51d; 10-H, 4·10d, J 5·3	6·11, 6·13, 6·20, 6·28, 6·40
(12)	ArH(1), 2·4m; ArH(7), 2·5—2·8m; ArH(1), 3·1m; 1′-H, 2·39d; 2′-H, 3·62d, J 14; 9-H, 5·48d; 10-H, 4·35d, J 3·5	6·16, 6·32, 6·40, 6·47, 6·78
(13)	ArH(3), 2·7—3·2m; ArH(1), 4·86d,[a,f] J 8; 2′-H, 3·14;[e] 6-H, 2·95;[e] 9-H, 10-H, 6·4—6·9m;[g] 10-H, 6·95—7·3m	6·04, 6·20, 6·20, 6·42, 6·66
(16)	ArH(1), 2·2m; ArH(2), 2·4—2·7m; 5-H, 1·10m; 1′-H, 0·38d; 2′-H, 3·63d, J 14·5	6·00, 6·04, 6·06, 6·10
(17)	ArH(3), 2·55;[e] 5-H, 1·13m; 2′-H, 3·25	6·18, 6·21, 6·24, 6·40, 6·47
(19)	1-H, 5·02d, J 9·9; 2-H, 4·81m; 3-H, 5·52d, J 7·5; 4-H, 2·22; 8-H, 1·40m; 9-H, 10-H, 2·4—2·75m; 11-H, 2·20m	6·06, 6·06, 6·28, 6·36, 6·50, 6·74
(20)	1-H, 5·03d, J 9·9; 2-H, 4·74m; 3-H, 5·33d, J 7·5; ArH(7), 2·3—2·8m; 8-H, 1·42m; 11-H, 2·14m	6·06, 6·31, 6·38, 6·42, 6·52, 6·86

[a] Small additional coupling. [b] Apparent triplet, J 7. [c] Apparent singlet. [d] This four-spin system could be assigned the other way round. [e] These assignments could be interchanged. [f] Decoupling experiments show that this proton is coupled with the other aromatic protons. [g] Partially obscured by OCH_3 resonances.



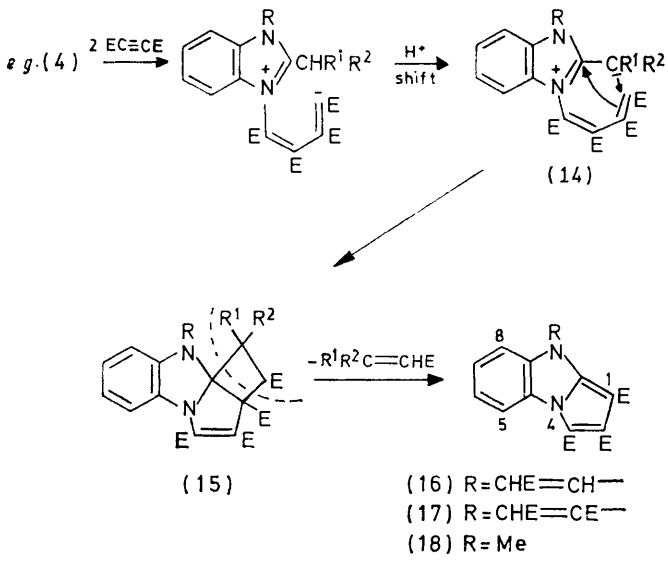
SCHEME 1

field ABX systems in their n.m.r. spectra, lost the elements of methyl acrylate in the mass spectrometer in a similar way to many azepines of this type,[5,6] and could be formed *via* an ester shift [5] or spiro-intermediate [7] as suggested for similar products from 2-methylquinoline. The azepine (13) is particularly interesting in that, as the n.m.r. spectrum shows, the acrylate side chain of the starting material has apparently been replaced by fumarate. This can be explained as shown in Scheme 1. The other azepines (11) and (12) show AX systems in their n.m.r. spectra corresponding to the 9- and 10-protons, the phenyl group of (12) strongly shields the 7-ester methyl group, and both compounds lose ester groups, and not the elements of methyl fumarate, in the mass spectrometer as is characteristic of this type of compound.[6] The stereochemistry of the 5-side-chains of (10)—(12) is established as *trans* from the strong coupling between the vinyl protons. The exceptionally low field position for the 1′-proton of (10) can be attributed to additional deshielding from the 6-ester group, and in a similar way [8] the nitro-group of methyl 4-bromo-α-methoxy-2-nitrocinnamate causes the signal of the nearby vinyl proton to appear at τ −2·60. The resonance for the 2′-hydrogen atom of the azepine (13) is too far downfield for a maleate grouping to be considered. The u.v. spectra of (10), (12), and (13) are

[5] R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 362.
[6] R. M. Acheson, R. T. Aplin, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 383.
[7] R. M. Acheson and D. F. Nisbet, *J. Chem. Soc.* (*C*), 1971, 3291.
[8] R. M. Acheson, C. J. Q. Brookes, D. P. Dearnaley, and B. Quest, *J. Chem. Soc.* (*C*), 1968, 504.

similar and resemble that of tetramethyl 5,6,10,11-tetrahydro-6-methylazepino[1,2-*a*]quinoxaline-7,8,9,10-tetracarboxylate,[9] but on acidification the solutions show the presence of the benzimidazolium chromphore.[4] In contrast, the u.v. spectrum of (11) shows more conjugation and resembles that of tetramethyl 9,10-dihydro-5-methylazepino[1,2-*a*]benzimidazole-7,8,9,10-tetracarboxylate, both as the neutral molecule and as the cation. This difference is best associated with the idea of the 1'-ester group of (13), and the 6-substituents of (10) and (12), keeping the 5-substituent out of the plane of the rings and therefore altering the degree of resonance involving the 5-nitrogen atoms as compared with the situation for compound (11).

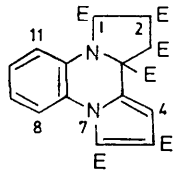
From the benzimidazoles (4) and (6), and 2-ethylbenzimidazole [which presumably reacts first with the acetylenic ester to give (5)], the pyrrolobenzimidazoles (16) and (17) (respectively) were obtained. The methyl analogue (18) has been obtained previously as one of the products from both 2-benzyl-[10] and 2-ethyl-1-methylbenzimidazoles[4] and dimethyl acetylenedicarboxylate. As the adduct (7) was not converted into the corresponding pyrrolobenzimidazole by heat or irradiation, this type of compound is unlikely to be an intermediate in the formation of (16)—(18). Scheme 2 [formation of



SCHEME 2

the zwitterion (14), which cyclises to the cyclobutane (15), followed by scission of an acrylate system] accounts for the loss of the original 2-substituent of the benzimidazoles and the formation of the products.

2-Benzyl- and 2-methyl-benzimidazole with dimethyl acetylenedicarboxylate yield the 1 : 3 adducts (20) and (19) which have in general very similar spectra to analogous compounds (21) formed from benzimidazol-2-ylacetonitrile and ethyl benzimidazol-2-ylacetate.[11] Further evidence for these provisional structures has not yet been obtained, but a scheme accounting for their formation can be put forward.[12]



(19)
(20) 4 - Ph
(21) 4 - CN or 4 -CO_2 Et

EXPERIMENTAL

The instruments and general procedures have been described in earlier papers in the series. All analyses for new compounds were within accepted limits for C, H, and N and are available as Supplementary Publication No. SUP 20896 (5 pp.),* which also gives details of u.v. and mass spectra.

General Procedure.—The benzimidazole (1—3 g) was refluxed with dimethyl acetylenedicarboxylate (2 mol. equiv.) in dry acetonitrile (50 ml). The solvent and unchanged ester were removed at *ca.* 70° *in vacuo*, and the residue was triturated with methanol. Compound (8) solidified, but in the other cases the methanol was evaporated off and the residual oil was chromatographed over deactivated alumina. The products were all recrystallised from methanol; yields and m.p.s are given in Table 2.

TABLE 2

Preparations

Product	Reflux time (days)	Solvent ratio [a]	M.p. (°C)	Appearance	Yield (%)
(7)	1	*b*	115—117 [c]	Red parallelepipeds	65
(8)	5	*d*	200—201	Yellow rods	29
(9)	5	*e*	190—191	Yellow prisms	14
(10)	5	5 : 1	180—181	Rods	19
(11) [f]	5	4 : 1	206—208	Yellow crystals	4·6
(12) [g]	6	3 : 1	233—235	Yellow rods	3·5
(13) [h]	5	1 : 1	180	Yellow parallelepipeds	6·5
(16) [i]	10	4 : 1	203	Rods	36
(16) [j]	6	4 : 1	203	Rods	10
(17)	0·5	*k*	237—239	Rods	0·2
(19)	0·3	*l*	206—207 [m]	Prisms	8·5
(20)	0·5	8 : 1	212—213	Prisms	3·5

[a] Chromatography column eluted with benzene–ether in stated ratio (v/v). [b] Eluted with light petroleum (b.p. 60—80°)–benzene, 4 : 1. [c] Solidified and remelted at 127—128°. [d] Crystallised on triturating reaction mixture with methanol. [e] Eluted with benzene. [f] Eluted after (10). [g] Eluted after (16). [h] Eluted after (11). [i] From (6). [j] From (4). [k] Eluted with light petroleum–ether, 1 : 1. [l] Eluted with ether. [m] Decomp.

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* For details of Supplementary Publications, see Notice to Authors No. 7, in *J. Chem. Soc.* (*A*), 1970, Index Issue.

[9] R. M. Acheson and M. W. Foxton, *J. Chem. Soc.* (*C*), 1968, 378.

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

[11] R. M. Acheson and M. S. Verlander, *J.C.S. Perkin I*, 1972, 1577.

[12] M. S. Verlander, D.Phil. Thesis, Oxford 1970 (Science Catalogue No. M.S. D.Phil. d. 5086).