# Addition Reactions of Heterocyclic Compounds. Part LIII.[1] Reactions of Benzimidazoles with Propiolic Esters

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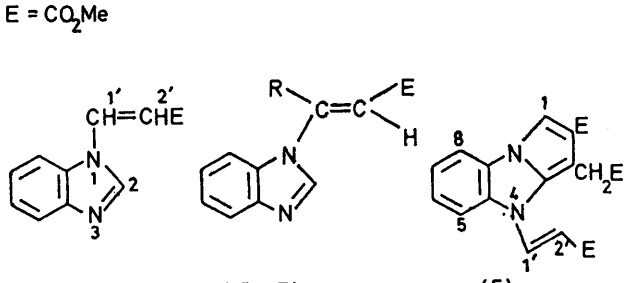
Reactions of methyl propiolate with benzimidazole and its 2-alkyl and aryl derivatives, in acetonitrile, gave the corresponding methyl 3-*trans*-(benzimidazol-1-yl)acrylates, whereas a reaction with benzimidazole in methanol gave the *cis*-isomer exclusively. Similar acrylates were formed from methyl tetrolate and methyl phenylpropiolate. Other products were pyrrolo[1,2-*a*]quinoxalines and a pyrrolo[1,2-*a*]benzimidazole.

BENZIMIDAZOLES combined readily with dimethyl acetylenedicarboxylate to yield a variety of products [2-5] but their behaviour with the much less reactive methyl propiolate is recorded only for derivatives possessing the highly activated 2-cyanomethylene and 2-methoxycarbonylmethylene groups.[2,5] We now describe reactions between a number of alkyl- and aryl-benzimidazoles and some methyl propiolates.

In refluxing acetonitrile, or in some cases without solvent, treatment of these benzimidazoles with a small excess of methyl propiolate gave the corresponding *trans*-acrylates [*e.g.* (1)]. These acrylates are comparable to adducts from the reactions of 2-benzylbenzimidazole




(1) *trans*
(2) *cis*
(3) R = Ph
(4) R = Me
(5)

with dimethyl acetylenedicarboxylate,[3] and of benzimidazole with ethynyl methyl ketone.[6] Their carbonyl stretching frequencies (1708—1741 $cm^{-1}$) are close to that (1734 $cm^{-1}$) for methyl acrylate.[7] It therefore appears that there is little resonance interaction between the ring nitrogen atom and the vinylogous ester group, owing to non-planarity in this group of compounds; the lowest frequency is found for compound (1) itself where steric interference will be minimal. However, some resonance interaction is necessary to account for the long-wavelength band in the u.v. spectra (*ca.* 300 nm) which is characteristic [8] of the 3-aminoacrylate chromophore. This band vanishes when acidification produces the benzimidazolium chromophore. At 34° the n.m.r. spectra of the *trans*-acrylates showed no evidence for restricted rotation of the 1-acrylate group, and the *trans* geometry is deduced from the high coupling constant (13·8—14·6 Hz) for the olefinic protons. A small amount of the *cis*-isomer (2; 2-$PhCH_2$) was obtained in addition to (1; 2-$PhCH_2$) from 2-benzylbenzimidazole, and in the case of benzimidazole the *trans*-product (1) was exclusively formed with acetonitrile as solvent, a mixture of *cis*- and *trans*-isomers was produced in benzene, and only the *cis*-isomer (2) in methanol. The 2-proton of structure (2) is significantly deshielded by the ester carbonyl group, and the ester methyl group of (2; $PhCH_2$) is shielded by the nearby benzyl substituent.

The 3-(benzimidazol-1-yl)acrylates formed cations in acidified methanol, as shown by u.v. spectral changes, and also in trifluoroacetic acid, in which they showed the expected downfield shifts in the n.m.r. spectra. The shift for the 2-proton of the *cis*-isomer (2), surprisingly, is much less than that for the *trans*-compound (1).

On prolonged refluxing in acetonitrile with methyl phenylpropiolate and with methyl tetrolate, benzimidazole gave the acrylates (3) and (4), respectively, identified from their spectra.

In the absence of solvent, treatment of benzimidazole with methyl propiolate gave a mixture of compounds (1) and (2) and the pyrrolo[1,2-*a*]benzimidazole (5). The n.m.r. spectrum of compound (5) showed no low-field aromatic proton, excluding the possibility of an ester group at position 1, and the spectrum is similar to

[1] Part III, R. M. Acheson and D. F. Nisbet, *J.C.S. Perkin I*, 1973, 1338.
[2] R. M. Acheson and M. S. Verlander, *J.C.S. Perkin I*, 1972, 1577.
[3] R. M. Acheson and W. R. Tully, *J. Chem. Soc.* (*C*), 1968, 1623.
[4] R. M. Acheson, M. W. Foxton, P. J. Abbott, and K. R. Mills, *J. Chem. Soc.* (*C*), 1967, 882.
[5] N. Finch and C. W. Gemenden, *J. Org. Chem.*, 1970, **35**, 3114.
[6] S. Hoffmann and E. Mühle, *Z. Chem.*, 1968, **8**, 419.
[7] L. J. Bellamy, 'Advances in Infrared Group Frequencies,' Methuen, London, 1968, p. 155.
[8] A. I. Scott, p. 58, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964.

those of various benz[*e*]indolizine esters,[9,10] which appear to be the best spectral models available. The compound could be formed in a similar way to the indolizines obtained from pyridines.[9,10]

From 2-isopropyl-, 2-phenyl-, and 2-benzyl-benzimidazoles and propiolic ester without solvent, the pyrroloquinoxalines (8), (9), and (11) were obtained. As the

TABLE 1

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

| Compound | Protons | $CO_2Me$ |
|---|---|---|
| (1) | $ArH_1$, 2·0—2·2m; $ArH_1$, 2·2—2·4m; $ArH_2$, 2·3—2·7m; 1′-H, 1·81d; 2′-H, 3·67d, *J* 14·6; 2-H ,1·79 | 6·15 |
| (1) [a] | $ArH_4$, 1·8—2·3m; 1′-H, 1·51d; 2′-H, 3·04d, *J* 14·3; 2-H, 0·50 | 5·97 |
| (1; 2-Me) | $ArH_2$, 2·15—2·50m, $ArH_2$, 2·5—2·7m; 1′-H, 1·89d; 2′-H, 3·67d, *J* 14·3; 2-$CH_3$, 7·88 | 6·14 |
| (1; 2-$PhCH_2$) | $ArH_2$, 2·1—2·5m; $ArH_7$, 2·5—2·7m; 1′-H, 1·86d; 2′-H, 3·71d, *J* 14·3; 2-$CH_2$Ph, 5·58 | 6·20 |
| (1; 2-$PhCH_2$) [b] | $ArH_9$, 1·8—2·7m; 1′-H, 1·58d; 2′-H, 3·00d, *J* 14; 2-$CH_2$Ph, 5·18 | 5·88 |
| (2) | ArH, 2·0—2·25m; $ArH_3$, 2·4—2·7m; 1′-H, 2·83d; 2′-H, 4·28d, *J* 10·7; 2-H, 0·78 | 6·20 |
| (2) [a] | $ArH_4$, 1·9—2·5m; 1′-H, 2·49d; 2′-H, 3·46d, *J* 10; 2-H, 0·28 | 6·14 |
| (2; 2-$PhCH_2$) | ArH, 2·1—2·35m; $ArH_8$, 2·5—3·05m; 1′-H, 3·09d; 2′-H, 3·98d, *J* 9; 2-$CH_2$Ph, 5·69 | 6·50 |
| (2; 2-$PhCH_2$) [b] | $ArH_9$, 1·9—2·7m; 1′-H, 2·60d; [c] 2′-H, 3·15d, *J* 9; 2-$CH_2$Ph, 5·34 | 6·22 |
| (3) | ArH, 2·0—2·25m; $ArH_8$, 2·4—3·3m; vinyl H, 3·56; 2-H, 2·0 | 6·41 |
| (4) | ArH, 2·0—2·2m; ArH, 2·2—2·4m; $ArH_2$, 2·45—2·7m; $CH_3$, 7·16; vinyl H, 3·73; 2-H, 1·80 | 6·17 |
| (5) | $ArH_4$, 2·4—2·95m; 1-H, 2·26; 3-$CH_2$ 5·07; 1′-H, 2·02d; 2′-H, 4·64d, *J* 13·6 | 6·10, 6·15, 6·25 |
| (8) | $ArH_2$, 1·9—2·25m; $ArH_2$, 2·35—2·6m; 1-H, 1·60; 4-$CHMe_2$, 6·4—6·8m; 4-$CHMe_2$, 8·60d, *J* 6·5 | 6·17, 6·28 |
| (9) | $ArH_2$, 1·75—2·15m; $ArH_7$, 2·15—2·65m; 1-H, 1·48 | 6·28, 6·60 |
| (11) | $ArH_9$, 2·35—3·20m, 1-H, 2·28; 4-H, 4·19q; 4-$CH_2$, 6·75—7·30m, *J* 4·9, 7·8, and 14; 1′-H, 2·27d; 2′-H, 4·90d, *J* 13·6 | 6·10, 6·10, 6·31 |

[a] In trifluoroacetic acid at 60 MHz. [b] In trifluoroacetic acid. [c] Partially obscured by aromatic protons.

n.m.r. spectra of these compounds show no really low-field aromatic protons, the presence of *peri*-ester groups is excluded. The chemical shifts of the isolated protons are close to that [10] for methyl 2-methoxycarbonylbenz[*e*]indolizine-3-acetate (τ 1·69), the resonance for (11) being at the highest field. One ester group of (9) resonates at relatively high field, being shielded by the *peri*-phenyl ring. Compound (11) shows an AMX system for the benzylic and ring protons consistent with the attachment of the benzyl group at a chiral centre, and the multiplet was not simplified on raising the temperature. The chemical shift of the ring proton was close to that of the corresponding 6-proton (τ 4·67) of tetramethyl 5,6,10,11-tetrahydro-6-methylazepino-[1,2-*a*]quinoxaline-7,8,9,10-tetracarboxylate.[11] The u.v. spectra of (8) and (9) generally resembled that of the

TABLE 2

U.v. absorption spectra

| Compound | Solvent * | $\lambda_{max.}$/nm ($10^{-4}$ ε) |
|---|---|---|
| (1) | M | 209 (2·05), 262 (3·06), 293infl (1·59), 300 (1·73) |
| | MA | 212 (1·06), 226 (1·33), 257 (1·67), 270infl (1·39), 276infl (1·36) |
| (1; 2-$PhCH_2$) | M | 213 (2·68), 263 (3·06), 297infl (1·97), 301 (2·08) |
| | MA | 212 (2·57), 227infl (1·71), 258 (1·60), 277 (1·53) |
| (1; 2-Ph) | M | 211 (2·43), 228infl (1·48), 267 (2·61), 298 (1·71) |
| | MA | 210 (2·22), 239·5 (1·67), 259infl (1·23), 295 (1·87) |
| [1; 2-(1-naphthyl)] | M | 211infl (5·35), 223 (7·95), 263 (2·96), 296 (2·31) |
| | MA | 212infl (5·65), 222 (7·63), 251infl (1·70), 279 (1·61) |
| (2) | M | 210 (1·44), 263 (2·10), 299 (1·02) |
| | MA | 210 (1·26), 220infl (1·12), 262 (0·97), 269 infl (0·89), 275infl (0·74) |
| (2; 2-$PhCH_2$) | M | 212 (2·52), 262 (2·38), 298 (1·20) |
| | MA | 211 (2·30), 229infl (1·36), 260 (1·22), 276 (1·24) |
| (3) | M | 214 (2·64), 254infl (1·71), 272 (2·25) |
| | MA | 212 (2·20), 226infl (1·36), 272 (2·25), 277 (2·23) |
| (4) | M | 210 (1·80), 262 (1·87), 292 (0·99) |
| | MA | 210 (1·54), 262 (1·02), 270infl (1·00), 276·5infl (0·85) |
| (5) | M | 215 (1·95), 240 (3·14), 262infl (2·22), 315 (2·60) |
| | MA | 211 (1·93), 238 (2·87), 260infl (1·68) |
| (8) | M | 211 (2·75), 254 (3·77), 324 (0·96), 334 (1·05), 347infl (0·71) |
| | MA | 211 (2·26), 245 (3·18) ,254infl (2·96), 267 infl (1·89), 278infl (0·62), 290infl (0·36), 360 (1·14) |
| (9) | M | 211 (3·62), 249infl (3·80), 258 (3·93), 346 (1·04) |
| | MA | 211 (3·31), 246 (3·36), 268infl (1·67), 281 (1·40), 310 (0·94), 358 (1·21) |
| (11) | M | 209 (2·30), 242 (3·33), 263infl (2·44), 316·5 (2·56) |
| | MA | 209 (2·60), 236 (3·46), 263infl (1·83), 319 (1·02) |

* Solvents: M = MeOH, MA = MeOH acidified with 72% $HClO_4$.

benz[*e*]indolizine just mentioned, and showed shifts towards the visible on protonation. This could take place at the pyridine-type nitrogen atom to give a resonance-stabilised cation; acidification caused less change in the u.v. spectrum of (11). The mass spectrum of (8) showed a relatively stable molecular ion, the base peak being formed through apparent loss of methanol. The molecular ion for (11) was weak; the ready elimination of the benzyl group could give a stable pyrrolo-[1,2-*a*]quinoxalinium cation.

Various schemes [12] can be suggested for the formation

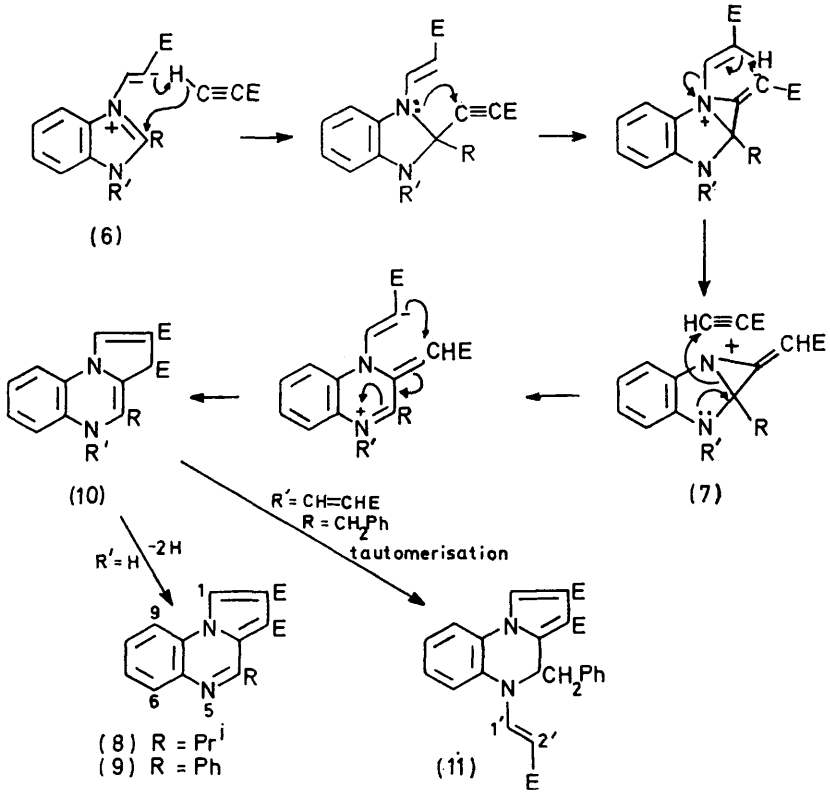
[9] R. M. Acheson and D. A. Robinson, *J. Chem. Soc.* (*C*), 1968, 1633.

[10] R. M. Acheson and M. S. Verlander, *J. Chem. Soc.* (*C*), 1969, 2311.

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

[12] M. S. Verlander, D.Phil. Thesis, Oxford 1970 (Science Catalogue no. M.S. D.Phil.d. 5086). Photocopies may be obtained without reference to the author on payment of the library's standard fees.

of the quinoxalines; one is illustrated.* The zwitterion (6), from a benzimidazole [*e.g.* (1)], could abstract the acidic proton from methyl propiolate, the resulting acetylide anion then adding at position 2. Nucleophilic attack at the triple bond as indicated would then give a new carbanion. A *cis*-elimination of the Chugaef type could then split the molecule as shown to (7) and methyl propiolate. Recombination could lead to structure (10) which by aromatisation or tautomerisation could give the two types of product observed.




## EXPERIMENTAL

The instruments and general procedures have been described previously.[2] All analyses for new compounds were within accepted limits for C, H and N [see Supplementary Publication No. SUP 20798 (3 pp.) †]. Details of the mass spectra for most of the new compounds can be obtained from the Mass Spectral Data Centre, A.W.R.E., Aldermaston. Spectra for key, and representative compounds only are tabulated; full details of these and of the chromatographic separations are available.[12]

2-(2,4,6-*Trimethylphenyl*)*benzimidazole*.—This *benzimidazole* was prepared from 2,4,6-trimethylbenzoic acid and 1,2-phenylenediamine by the method of Popp and McEwan,[13] at 200°, in 19% yield as rods (from aqueous ethanol), m.p. 253—254°, $\nu_{max.}$ 3250—2300, 1620, and 1423 $cm^{-1}$.

*Reactions of Benzimidazoles with Methyl Propiolate*.—The benzimidazole (2 g), the methyl propiolate [10] (3 g), and acetonitrile (100—150 ml) were refluxed for 5—7 days. The solvent was removed *in vacuo* and the residue chromatographed on alumina. Elution with benzene–light petroleum gave the *trans*-acrylates, which were recrystallised from methanol or hexane containing some chloroform. Use of benzene as reaction solvent gave slightly lower yields but small amounts of *cis*-acrylates were sometimes formed and were eluted before the *trans*-isomers; t.l.c. was needed for the resolution of some of the mixtures. The results are given in Table 3.

For almost all cases the reactions were also carried out in the absence of solvent, at 120—180° for 1½—6 h, and worked up as just described. Poorer yields were obtained, and sometimes additional products were isolated as indicated below.

Benzimidazole (no solvent) gave *methyl* cis-3-(*benzimidazol-1-yl*)*acrylate* (2) (2·5%), m.p. 95·5—96·5°, the trans-

TABLE 3

Methyl 3-(benzimidazol-1-yl)aceylates

| Compound | Yield (%) | M.p. (°C) |
|---|---|---|
| (1) | 44 | 111—112 |
| (1; 2-Me) | 47 | 88—89 |
| (1; 2-Et) | 10 | 96—97 |
| (1; 2-Pr) | 50 | 76 |
| (1; 2-Bu$^t$) | 53 | 109—110 |
| (1; 2-PhCH$_2$) [a] | 45 | 126—127 |
| (2; 2-PhCH$_2$) [a] | 5 | 81—82 |
| (1; 2-Ph$_2$CH) | 93 | 185—186 |
| (1; 2-Ph) | 64 | 150—151 |
| (1; 2-*o*-tolyl) | 69 | 120 |
| (1; 2-mesityl) | 67 | 128—129 |
| [1; 2-(1-naphthyl)] | 67 | 164—166 |
| (3) | 53 [b] | 130—131 |
| (4) | 75 [b] | 77—78 [c] |

[a] Benzene as reaction solvent. [b] Refluxed for 50—54 days. [c] From light petroleum (b.p. 40—60°)–ether.

* We thank a referee for suggesting part of this scheme.

† For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[13] F. D. Popp and W. E. McEwan. *Chem. Rev.*, 1958, **58**, 321.

*acrylate* (30%), and *methyl* 3-(2-*methoxycarbonyl*-3-*methoxycarbonylmethylpyrrolo*[1,2-a]*benzimidazol*-4-*yl*)*acrylate* (5) (10%), as needles (from methanol), m.p. 198°, $\nu_{max.}$ 1735, 1706, 1691, 1616, and 1596 $cm^{-1}$, *m/e* 370 ($M^+$, 29%) and 252 ($M^+ - 2CO_2Me$, 100). Benzimidazole in dry benzene gave 22 and 37% yields of *cis*- and *trans*-acrylates respectively; by using methanol only the *cis*-isomer (15%) could be isolated; in the reaction in acetonitrile (Table 3) an unidentified compound [crystals (from acetonitrile) (5%), m.p. 216° (Found: C, 60·7; H, 5·1; H, 9·2%)] was also isolated.

2-Ethylbenzimidazole in acetonitrile (Table 3) also gave unidentified rods (from methanol) (8%), m.p. 165—166° (Found: C, 61·2; H, 6·2; N, 8·1%).

2-Isopropylbenzimidazole, without solvent, gave the trans-*acrylate* and *dimethyl* 4-*isopropylpyrrolo*[1,2-a]*quinoxaline*-2,3-*dicarboxylate* (8) (3%), parallelepipeds (from hexane), m.p. 138—140°, solidifying to prisms, m.p. 145·5—146°, $\nu_{max.}$ 1736, 1722, and 1616 $cm^{-1}$, *m/e* 326 ($M^+$, 77%), 294 ($M^+$ — MeOH, 100), and 279 (98).

2-Benzylbenzimidazole (no solvent) gave the trans-*acrylate* (23%) and *methyl* 3-(4-*benzyl*-2,3-*bismethoxycarbonyl*-4,5-*dihydropyrrolo*[1,2-a]*quinoxalin*-5-*yl*)*acrylate* (11) (6%), parallelepipeds (from hexane–chloroform), m.p. 149—150°, $\nu_{max.}$ 1700, 1690, 1684infl, and 1623 $cm^{-1}$, *m/e* 460 ($M^+ - C_7H_7$, 100%).

2-Phenylbenzimidazole, without solvent, gave only *dimethyl* 4-*phenylpyrrolo*[1,2-a]*quinoxaline*-2,3-*dicarboxylate* (9) (3·5%), plates (from methanol), m.p. 197—198°, $\nu_{max.}$ 1745 and 1711 $cm^{-1}$.

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