Reactions of 2-Aminobenzimidazoles with Propiolic Esters and Diethyl Ethoxymethylenemalonate

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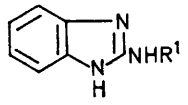
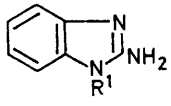
The major products of the propiolate reactions are pyrimido[1,2-*a*]benzimidazol-2-ones and those of the malonate reactions are pyrimido[1,2-*a*]benzimidazol-4-ones. The ^{1}H n.m.r., i.r., and u.v. spectra of the products are discussed.

REACTIONS of the 2-aminobenzimidazoles (I) and (II) with propiolic esters (III) can theoretically yield either



(I)

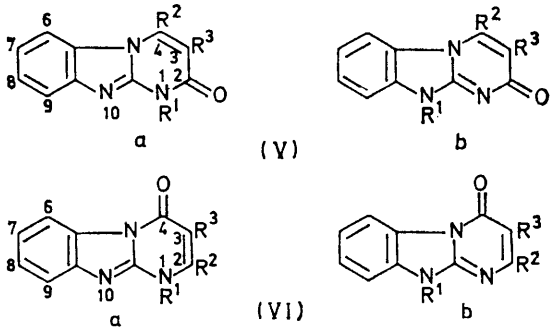


(II)

the pyrimido[1,2-*a*]benzimidazol-2-ones (V; R^3 = H) or the pyrimido[1,2-*a*]benzimidazol-4-ones (VI; R^3 = H). Similarly, reaction of the benzimidazoles with diethyl ethoxymethylenemalonate (IV) can theoretically yield either the 2-ones (V; R^2 = H, R^3 = CO_2Et) or the 4-ones (VI; R^2 = H, R^3 = CO_2Et). We have found that the 2-ones are the major products in the first reaction and the 4-ones in the second. The propiolate reactions were carried out in refluxing ethanol in the presence of catalytic quantities of tetramethylammonium hydroxide and the malonate reactions were effected in refluxing 1,2,4-trichlorobenzene. Hydrolysis of the malonate products in hydrochloric acid gave the corresponding

$R^2C{\equiv}C{\cdot}CO_2Et$ (III)

$EtO{\cdot}CH{=}C(CO_2Et)_2$ (IV)



(V) a b

(VI) a b

acids. These were decarboxylated smoothly with copper and quinoline to yield tricyclic products which were isomeric with the products from the propiolate reactions. Details of all the products are given in the Experimental section and Tables 1 and 2.

Distinction between the structures (V) and (VI) is based on ^{1}H n.m.r. data. Comparison of the data for the 2-ones (V; R^1 = R^2 = R^3 = H) (compound 1) and (V; R^1 = R^3 = H, R^2 = Ph) (compound 2) shows that there is a significant upfield shift in the signal of H-6 in the latter. This is due to shielding by the phenyl ring which would not be possible if the compound possessed the 4-one structure (VI; R^1 = R^2 = H, R^2 = Ph). Similar evidence for the 4-one structure is provided by the observation that the H-6 signals in compounds 5—11 appear at lower fields than those for H-7, H-8, and H-9 owing to deshielding of H-6 by the neighbouring carbonyl group.

Two tautomeric forms are possible for structures (V) and (VI) when R^1 = H. We have succeeded in identifying the most stable tautomer in most instances by comparison of their physical data with those of compounds 3, 4, 6, 8, 9, and 11. With the exception of compound 11, these were prepared from 1-methyl-2-aminobenzimidazole[1] or 2-methylaminobenzimidazole[2] and, therefore, possess the unequivocal structures assigned to them in Tables 1 and 2. Compound 11 was obtained by methylation of compound 7 and must possess structure (VIa) since it is hydrolysed to 2-methylaminobenzimidazole by sodium hydroxide solution.

The i.r. spectra of compounds 1, 2, and 3 (KBr) show amide I absorption bands at *ca.* 1680 whereas the corresponding absorption for compound 4 is at 1630 cm^{-1}. The absorptions for compounds 5 and 6 are at *ca.* 1680 cm^{-1}. Esters 7 and 8 possess weak carbonyl bands at 1650 whereas ester 11 absorbs strongly at 1670 cm^{-1}. These absorptions show that compounds 1 and 2 exist predominantly as the 2(1*H*)-ones (Va) and compounds 5 and 7 as the 4(10*H*)-ones (VIb) in the solid state. The absorptions of compounds 4—9 are similar to those of the corresponding pyrimido[2,1-*b*]benzothiazol-2

[1] L. Joseph, *J. Medicin. Chem.*, 1963, **6**, 601.
[2] P. N. Craig and J. R. E. Hoover, B.P. 1,111,957.

and 4-ones [3] and of various substituted pyrimidinones.[4] The amide I band of compound **1** in dimethyl sulphoxide solution is in approximately the same position as in pressed KBr. This shows that compound **1** exists mainly as the 2(1*H*)-one (Va) in solution as well as in the solid state.

The u.v. spectra of compounds **7** and **8** are similar to each other and sufficiently different from that of compound **11** to show that compound **7** exists mainly as the 4(10*H*)-one (VIb) in solution. The u.v. spectra of compounds **4** and **7** are similar to those of the corresponding pyrimido[2,1-*b*]benzothiazol-2 and 4-ones.[3]

Similarly, the following were prepared: 4-*phenylpyrimido*-[1,2-a]*benzimidazol*-2(1H)-*one* (46%), m.p. >300° (Found: C, 73·8; H, 4·4; N, 16·2. $C_{16}H_{11}N_3O$ requires C, 73·6; H, 4·2; N, 16·1%); 1-*methylpyrimido*[1,2-a]*benzimidazol*-2(1H)-*one* (56%), m.p. 178° (Found: C, 66·0; H, 4·7; N, 21·3. $C_{11}H_9N_3O$ requires C, 66·3; H, 4·55; N, 21·1%); 10-*methylpyrimido*[1,2-a]*benzimidazol*-2(10H)-*one* (31%), m.p. 274° (Found: C, 66·1; H, 4·6; N, 20·8. $C_{11}H_9N_3O$ requires C, 66·3; H, 4·55; N, 21·1%).

Ethyl 4,10-*Dihydro*-4-*oxopyrimido*[1,2-a]*benzimidazole*-3-*carboxylate*.—A mixture of 2-aminobenzimidazole (80 g), diethyl ethoxymethylenemalonate (112 ml), and 1,2,4-trichlorobenzene (500 ml) was heated under reflux and the ethanol which formed was separated by use of a fractionating column. When the theoretical amount of ethanol (70 ml) had been collected, the solution was allowed to cool. The crystals were filtered off and recrystallised from dimethylformamide to give the ester as white *needles* (146 g, 95%), m.p. >280° (Found: C, 60·6; H, 4·4; N, 16·6. $C_{13}H_{11}N_3O_3$ requires C, 60·7; H, 4·3; N, 16·3%).

Ethyl 4,10-*Dihydro*-10-*methyl*-4-*oxopyrimido*[1,2-a]*benzimidazole*-3-*carboxylate* was similarly prepared from 2-amino-1-methylbenzimidazole [1] and diethyl ethoxymethylenemalonate as white crystals (97%), m.p. 190° (Found: C, 61·7; H, 5·0; N, 15·5. $C_{14}H_{13}N_3O_3$ requires C, 62·0; H, 4·8; N, 15·5%).

TABLE 1

Pyrimido[1,2-*a*]benzimidazol-2(1H)-ones (Va)

Compound no.	R^1	R^2	R^3	ν [a]	^{1}H N.m.r. data [b] 3-H	4-H	6-H	7-H	8-H	9-H	U.v. spectra [c]
1	H	H	H	1680 [e]	6·13	8·71	← 7·2—8·1 →				211(112), 237(175),[d] 248(106), 263(453), 283(610)
2	H	Ph	H	1675	6·83	—	6·65	← 7·29—7·9 →			212(581), 239(576), 297(198)
3	Me	H	H	1670	6·15	8·02	← 7·1—7·8 →				212(209), 227(128),[d] 248(230), 263(130),[d] 290(91)

Pyrimido[1,2-*a*]benzimidazol-2(10H)-one (Vb)

4	Me	H	H	*ca.* 1630	6·37	8·08	← 7·3—7·7 →				215(215), 237(327), 303(122)

[a] Frequency of amide I band (KBr) in cm^{-1}. [b] δ at 60 MHz; solvent $CDCl_3$ unless otherwise stated. [c] $\lambda_{max.}$/nm (ε × 10^{-2}) in MeOH. [d] Shoulder. [e] This frequency was the same for a solution in dimethyl sulphoxide.

TABLE 2

Pyrimido[1,2-*a*]benzimidazol-4(10H)-ones (VIb)

Compound no.	R^1	R^2	R^3	ν [a]	^{1}H N.m.r. data [b] 2-H	3-H	6-H	7-H	8-H	9-H	U.v. spectra
5	H	H	H	1678	7·99 [e]	6·03	8·47	← 7·3—7·75 →			228(214), 250(116),[d] 321(104), 331(111)
6	Me	H	H	1690	7·92	6·08	8·52	← 7·1—7·5 →			228(230), 250(125),[d] 324(128), 337(140)
7	H	H	CO_2Et	1650	8·67 [e]		8·50	← 7·3—7·6 →			220(241), 243(163),[d] 264(74), 275(54),[d] 331(186), 342(182)
8	Me	H	CO_2Et	1653	8·78 [f]		8·63	← 7·2—7·7 →			217(282), 240(154), 267(48), 276(44), 326(214), 343(205)
9	Me	H	CO_2H	1645	9·22 [g]		8·80	← 7·8—8·0 →			218(255), 241(149), 269(46), 334(169), 344(156) [d]
10	Ac	H	CO_2Et	1700	8·75		8·52 [h]	7·4—7·5 [h]		8·37 [h]	210(242), 231(176), 265(52) [d] 273(36), 334(195), 342(191) [d]

Pyrimido[1,2-*a*]benzimidazol-4(1H)-one (VIa)

11	Me	H	CO_2Et	1670	8·40		8·57	← 7·3—7·9 →			228(254), 240(233), 329(100)

[a–d] As in Table 1. [e] Solvent $(CD_3)_2SO$. [f] Solvent $CDCl_3$–$(CD_3)_2SO$. [g] Solvent $CF_3{\cdot}CO_2H$. [h] Symmetrical pattern.

Acetylation of ester **7** with acetic anhydride gave a compound whose n.m.r. and u.v. spectra show that it is the 10-acetyl derivative.

EXPERIMENTAL

The i.r. spectra were determined with a Perkin-Elmer 457, the u.v. spectra with a Unicam SP 800, and the n.m.r. spectra with a Varian A-60 instrument.

Pyrimido[1,2-a]*benzimidazol*-2(1H)-*ones*.—Ethyl propiolate (5·0 g) and aqueous 25% tetramethylammonium hydroxide (3 drops) were added to a hot solution of 2-aminobenzimidazole (6·6 g) in ethanol (100 ml). The solution was heated under reflux for 6 h, cooled, and filtered yielding white crystals (5·1 g, 56%), m.p. >300° (from dimethylformamide–water) of *pyrimido*[1,2-a]*benzimidazol*-2(1H)-*one* (Found: C, 64·8; H, 4·0; N, 22·9. $C_{10}H_7N_3O$ requires C, 64·9; H, 3·8; N, 22·7%).

[3] D. W. Dunwell and D. Evans, *J. Chem. Soc.* (*C*), 1971, 2094.
[4] A. R. Katritzky, 'Physical Methods in Heterocyclic Chemistry,' Academic Press, New York and London, 1963, vol. II, p. 252; 1971, vol. IV, p. 349 and references therein.

4,10-*Dihydro*-10-*methyl*-4-*oxopyrimido*[1,2-a]*benzimidazole*-3-*carboxylic Acid*.—A suspension of the foregoing ester (15 g) in concentrated hydrochloric acid (200 ml) was heated under reflux for 2 h and cooled. The white solid was filtered off and recrystallised from dimethylformamide to yield white crystals of the *acid* (10 g, 74%), m.p. >300° (Found: C, 59·0; H, 3·5; N, 17·5. $C_{12}H_9N_3O_3$ requires C, 59·2; H, 3·7; N, 17·3%).

4,10-Dihydro-4-oxopyrimido[1,2-*a*]benzimidazole-3-carboxylic acid was prepared in a similar manner, but owing to its insolubility, an analytical sample was not prepared. This compound (1 g) was decarboxylated by heating with copper (500 mg) in quinoline (5 ml). The mixture, on cooling, was diluted with ether. The solid produced was filtered off and extracted with hot ethanol–water. On cooling, white crystals of *pyrimido*[1,2-a]*benzimidazol*-4(10H)-*one* (500 mg., 62%), m.p. 290° (Found: C, 65·2; H, 3·6; N, 22·8. $C_{10}H_7N_3O$ requires C, 64·9; H, 3·8; N, 22·7%), were formed.

10-*Methylpyrimido*[1,2-a]*benzimidazol*-4(10H)-*one* was similarly prepared from 10-methyl-4,10-dihydropyrimido-[1,2-a]benzimidazole-3-carboxylic acid as white needles (49%), m.p. 192° (Found: C, 66·2; H, 4·5; N, 20·8. $C_{11}H_9NO$ requires C, 66·3; H, 4·5; N, 21·1%).

Ethyl 10-*Acetyl*-4,10-*dihydro*-4-*oxopyrimido*[1,2-a]*benzimidazole*-3-*carboxylate*.—A solution of ethyl 4,10-dihydro-4-oxopyrimido[1,2-*a*]benzimidazole-3-carboxylate (2 g) in acetic anhydride (50 ml) was heated under reflux for 2 h, then evaporated to dryness. The residue was crystallised from toluene–petroleum to yield *needles* (1·2 g, 52%), m.p. 181° (Found: C, 60·1; H, 4·5; N, 13·9. $C_{15}H_{13}N_3O_4$ requires C, 60·2; H, 4·4; N, 14·0%).

Ethyl 1,4-*Dihydro*-1-*methyl*-4-*oxopyrimido*[1,2-a]*benzimidazole*-3-*carboxylate*.—A mixture of ethyl 4,10-dihydro-4-oxopyrimido[1,2-*a*]benzimidazole-3-carboxylate (2 g), methyl iodide (10 ml), potassium carbonate (2 g), and dry dimethylformamide (40 ml) was stirred at room temperature for 1 hr, then evaporated to dryness. Chromatography of the residue over silica gel (elution with chloroform–ether) yielded long *needles* (1 g, 47%), m.p. 244° (Found: C, 62·1; H, 4·8; N, 15·6. $C_{14}H_{13}N_3O_3$ requires C, 62·0; H, 4·8; N, 15·5%).

2-*Methylaminobenzimidazole*.[2]—A solution of ethyl 1,4-dihydro-1-methyl-4-oxopyrimido[1,2-*a*]benzimidazole-3-carboxylate (5 g) in 2N-sodium hydroxide (100 ml) was heated under reflux for 24 h. The solution was neutralised; the oil produced was separated and crystallised from chloroform–carbon tetrachloride to give 2-methylaminobenzimidazole (300 mg, 11%), m.p. 192° (Found: C, 65·2; H, 6·2; N, 28·4. $C_8H_9N_3$ requires C, 65·3; H, 6·2; N, 25·5%).

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