Syntheses of Heterocyclic Compounds. Part XV.[1] Some Imidazo[4,5-*g*]-benzoxazoles with a Polymethylene Bridge

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By pyrolysis of various polymethylene bridged benzimidazolyl azides in a mixture of polyphosphoric and acetic acid examples of the new ring system of imidazo[4,5-*g*]benzoxazole were obtained. Aspects of their ultraviolet and n.m.r. spectra are discussed.

We recently described [1] a convenient method of preparing benzoxazoles by heating certain aryl azides in a mixture of polyphosphoric and a carboxylic acid. Since one of the reaction steps involves nucleophilic substitution by an acyloxy-moiety (derived from the carboxylic acid) at a position next to the azide-group, the outcome of the oxazole cyclisation may be ambiguous when both *ortho* positions are vacant. However, ring formation could still be selective provided that one of the *ortho* positions is significantly more electron-deficient than the other. This situation is expected to occur in aromatic systems in which points of high and low electron densities are non-alternate, such as the benzene ring in benzimidazole, which has indeed yielded only one product.[1] By contrast, as we have previously shown,[1] 4-chloro-3-nitro- and 3-chloro-4-nitro-phenyl azides give both isomeric oxazoles as the positions adjacent to the azide group are of similar electron density.

To demonstrate the scope of the reaction further we prepared two series of azidobenzimidazoles, namely (II; R = H, R′ = N_3, X = $[CH_2]_2$, $[CH_2]_3$, $[CH_2]_4$, and $CH_2{\cdot}O{\cdot}CH_2$) and (II; R = N_3, R′ = H and X as before) in order to study their conversion into the imidazobenzoxazoles (III and IV). The intermediate 5-acetamido-2-nitro- and 2,4-dinitro-phenyl heterocycles (I; R = NO_2, R′ = H, R″ = NHAc, X as before) and (I; R = R′ = NO_2, R″ = H, X as before) were made by condensing the appropriate heterocyclic amines with 3-chloro-4-nitroacetanilide or 2,4-dinitrochlorobenzene. Reduction of these nitro-compounds followed by acetylation gave the 2,5- and the 2,4-diacetamidophenyl heterocycles (I; R = R″ = NHAc, R′ = H, X as before) and (I; R = R′ = NHAc, R″ = H, X as before) which were oxidatively cyclised [2] by treatment with a solution of hydrogen peroxide and formic acid to give the benzimidazoles (II; R = H, R′ = NHAc, X as before) and (II; R = NHAc, R′ = H, X as before) in good yield. Acid hydrolysis of these acetamidobenzimidazoles (II; R, R′, and X as before) was followed by diazotisation of the liberated amine and addition to a buffered aqueous sodium azide solution to obtain the required azides (II; R = N_3, R′ = H or R = H, R′ = N_3 and X as above). Their thermolysis in a mixture of acetic and polyphosphoric acid gave the imidazo[4,5-*g*]-benzoxazoles (III; X = $[CH_2]_2$, $[CH_2]_3$, $[CH_2]_4$, and $CH_2{\cdot}O{\cdot}CH_2$) and (IV; X as before). Only one product was obtained from each azide, usually in high yield. Its structure was readily assignable from the relevant n.m.r. spectrum (cf. Table 1), which showed in each case a pair of *ortho*-split doublets for the aromatic protons (cf. III and IV) thus excluding the possibility of the alternative ring-closure. The higher field doublet in compounds of type (IV) can be assigned to the aromatic proton adjacent to the imidazole ring (H_A in IV) since the proximity of the methylene ring, as is indicated by inspection of molecular models (Stuart–Briegleb), will cause shielding of this proton. No such assignment can, however, be made for the other series of compounds (III). It is of interest to note a downfield shift of 0·2 to 0·3 p.p.m. for the N–CH_2 group (α in Table 1) in compounds (III) compared with compounds (IV), which is ascribable to the inductive effect of the oxazole ring in the former. In the benzimidazoles of type (IV), where the N–CH_2 group is more distant from the oxazole ring, its influence is still noticeable, since the N–CH_2 group is downfield compared to the corresponding benzimidazole without an oxazole ring, *e.g.*, (II; R = R′ = H, X = $CH_2{\cdot}O{\cdot}CH_2$). This shows τ values of 5·92 and 5·04 for the N·$CH_2{\cdot}CH_2{\cdot}$O· and O–CH_2–⩽ groups, respectively.

The ultraviolet spectra of the imidazobenzoxazoles (IV) are similar to those of the corresponding benzimidazoles [3] (II; R = R′ = H) (cf. Table 2) except for a bathochromic shift of the lowest wavelength band from *ca.* 213 mμ to a doublet centred at *ca.* 230 mμ. No appreciable change occurs in the absorption as the number of methylene groups [X in (IV)] is increased. In the isomeric series (III), however, a new band at *ca.* 260 mμ appears and a hyperchromic effect is noticed (cf. Table 2, columns d) with a growing number of methylene groups [X in (III)].

Imidazobenzoxazoles of type (III) and also the parent system without a polymethylene bridge [1] (V) show unusual resistance to opening of the oxazole ring since

[1] Part XIV; R. Garner, E. B. Mullock, and H. Suschitzky, *J. Chem. Soc.* (*C*), 1966, 1980.

[2] (*a*) M. D. Nair and R. Adams, *J. Amer. Chem. Soc.*, 1961, **83**, 3518; (*b*) O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1963, 4666.

[3] O. Meth-Cohn, Thesis for the Diploma of Research of the Royal Institute of Chemistry, 1961.

TABLE 1

The chemical shifts (τ values) and coupling constants for protons in the imidazo[4,5-*g*]benzoxazoles (III) and (IV) in deuteriochloroform

			Aromatics			Methylenes *					
Type	X	Me(s)	τ_A	τ_B	J_{AB} (c./sec.)	α	β	γ	δ	ε	O–CH_2–≪
(III)	$[CH_2]_2$	7·33	2·56	2·42	8·5	5·67t	(6·8—7·5m)				
(IV)	,,	7·31	2·80	2·51	8·2	5·88t	(6·7—7·6m)				
(III)	$[CH_2]_3$	7·33	2·56	2·45	8·7	5·59t	(7·87m)		6·89t		
(IV)	,,	7·33	2·78	2·49	8·8	5·87t	(7·88m)		6·86t		
(III)	$[CH_2]_4$	7·32	2·56	2·43	8·5	5·48	(7·9—8·3)			6·87	
(IV)	,,	7·31	2·79	2·47	8·5	5·77	(7·9—8·3)			6·82	
(III)	CH_2–O–CH_2	7·32	2·48	2·38	8·2	5·52 †	5·74 †				4·92s
(IV)	,,	7·30	2·76	2·46	8·5	5·77s	5·77s				4·90s

* Numbered α, β, γ, etc., from N; s, singlet; t, triplet; m, multiplet. † A_2B_2 pattern.

TABLE 2

Ultraviolet spectra of imidazo[4,5-*g*]benzoxazoles (III) and (IV), and benzimidazoles (II; R = R′ = H) in ethanol solution

		λ_{max} (mμ)						log ε					
	X	a	b	c	d	e	f	a	b	c	d	e	f
(III)	$[CH_2]_2$	225·6	231·0	251·0	258·9	274·9s	284·4	4·62	4·56	3·87	3·86	3·50	3·05
	$[CH_2]_3$	226·5	232·0	256·8	262·6	*	284·8	4·61	4·53	3·87	3·90	*	3·08
	$[CH_2]_4$	227·0	232·0	255·5	262·0	*	284·4	4·61	4·53	3·90	3·94	*	3·04
(IV)	$[CH_2]_2$	225·4	231·3	246s		277·7	287·8	4·62	4·59	3·94		3·48	3·39
	$[CH_2]_3$	227·2	233·6	248s		277·8	288·0	4·62	4·57	4·00		3·55	3·45
	$[CH_2]_4$	227·0	233·0	247s		278·9	289·0	4·65	4·60	3·99		3·54	3·46
(II) †	$[CH_2]_2$	212·4		251·3		275·2	281·6	4·45		3·69		3·70	3·72
	$[CH_2]_3$	213·1		254·6		276·2	282·4	4·42		3·71		3·71	3·73

* Band indistinctive; s, shoulder. † Ref. 3.

TABLE 3

Derivatives of *N*-phenyl heterocycles (I)

				Found (%)				Reqd. (%)	
X	R	R′	R″	M. p.	C	H	Formula	C	H
$[CH_2]_2$	NO_2	H	NHAc	141°	57·6	6·0	$C_{12}H_{15}N_3O_3$	57·8	6·1
,,	NHAc	H	NHAc	191	63·9	7·4	$C_{14}H_{19}N_3O_2$	64·3	7·3
,,	NHAc	NHAc	H	212	64·5	7·4	,,	,,	,,
$[CH_2]_3$	NO_2	H	NHAc	120	58·9	6·5	$C_{13}H_{17}N_3O_3$	59·3	6·5
,,	NHAc	H	NHAc	189	65·2	7·5	$C_{15}H_{21}N_3O_2$	65·4	7·7
,,	NHAc	NHAc	H	182	65·4	7·9	,,	,,	,,
$[CH_2]_4$	NO_2	H	NHAc	133	60·7	6·8	$C_{14}H_{19}N_3O_3$	60·6	6·9
,,	NHAc	H	NHAc	128	65·9	7·9	$C_{16}H_{23}N_3O_2$	66·4	8·0
,,	NHAc	NHAc	H	147	66·0	8·0	,,	,,	,,
CH_2·O·CH_2	NO_2	H	NHAc	202	54·6	5·7	$C_{12}H_{15}N_3O_4$	54·3	5·7
,,	NHAc	H	NHAc	196	60·4	6·9	$C_{14}H_{19}N_3O_3$	60·6	6·9
,,	NHAc	NHAc	H	167	60·3	6·9	,,	,,	,,

they are recovered after prolonged treatment with sulphuric acid at 100°. Potassium nitrate in sulphuric acid causes mono-nitration in (III; X = $[CH_2]_3$) with fission of the oxazole ring, whilst the oxazole (V) gives a mononitro-compound without cleavage.

EXPERIMENTAL

Polyphosphoric acid was commercial tetraphosphoric acid (Albright and Wilson) containing 80—85% of phosphorus pentoxide.

5-*Acetamido*-2-*nitro*-N-*phenyl Heterocycles*.—3-Chloro-4-nitroacetanilide (15 g.), prepared by nitration of *m*-chloroacetanilide as described,[4] condensed in quantitative yield with pyrrolidine, piperidine, hexahydroazepine, or morpholine (15 ml.) during 5 hr. on a steam-bath to give the 5-acetamido-2-nitro-*N*-phenyl heterocycles after trituration with hot water. The products, listed in Table 3, were purified by crystallisation from benzene.

2,5-*Diacetamido*-N-*phenyl Heterocycles*.—The nitro-compounds above (15 g.) dissolved in ethanol (200 ml.) were reduced with hydrogen and Raney nickel under 5 atm. at room temperature during 2—3 hr. After filtering the solution the solvent was removed under reduced pressure and the amino-compound immediately acetylated. The products are listed in Table 3.

2,4-*Diacetamido*-N-*phenyl Heterocycles*.—The 2,4-dinitro-*N*-phenyl derivatives of pyrrolidine, piperidine, hexahydroazepine, and morpholine were reduced as described above. The diamines were distilled *in vacuo* before acetylation. Products are listed in Table 3.

Oxidative Cyclisation to Benzimidazoles.—The 2,4- and 2,5-diacetamido-*N*-phenyl heterocycles (6 g.) reacted with 98% formic acid (24 ml.) and 30% hydrogen peroxide (12 ml.) during 10 min. on a steam-bath. The acetamidobenzimidazole derivatives listed in Table 4 precipitated on pouring the reaction mixture into ice–water and making slightly alkaline.

Azido-benzimidazoles.—The acetamido-benzimidazoles (4 g.) were hydrolysed by heating with hydrochloric acid (20

[4] R. E. Lutz, P. S. Bailey, T. A. Martin, and J. M. Salisbury, *J. Amer. Chem. Soc.*, 1946, **68**, 1324.

ml.) for 0·5 hr. After dilution with water (80 ml.) the reaction mixture was cooled to 0—5° and sodium nitrite (1·3 g.) was added. The reaction mixture was then added to a solution of sodium azide (1·1 g.) and sodium acetate (7 g.) in water (30 ml.). On neutralising the solution (ammonia solution, *d* 0·88) the azide precipitated. Products are listed in Table 5. The azides were thermally stable up to 145—150° and could be sublimed *in vacuo* at 100—130°.

Imidazo[4,5-g]*benzoxazoles.*—The azido-compound (2·0 g.) was added to a mixture of acetic acid (20 ml.) and polyphosphoric acid (20 g.). The temperature of the stirred reaction mixture was raised during 0·5 hr. until the acetic acid refluxed (*ca.* 140°) and maintained for a further 2 hr. After cooling, the reaction mixture was diluted with ice–water and basified with ammonia solution (*d* 0·88) whence the product precipitated. The products, listed in Table 6, were purified by sublimation *in vacuo* at 200° and by crystallisation from light petroleum (b. p. 100—120°).

Nitration and Ring-opening Experiments.—(*a*) 2-Methylimidazo[4,5-g]benzoxazole [1] (V) (0·2 g.) and sulphuric acid (*d* 1·84, 2·0 ml.) were heated at 100° for 1 hr. On pouring into ice–water and neutralising with ammonia solution (*d* 0·88) starting material was precipitated.

(*b*) 8,9-Dihydro-2-methyl-7*H*-pyrrolo[1,2-*i*]imidazo[4,5-*g*]-benzoxazole or 7,8,9,10-tetrahydro-2-methylpyrido[1,2-*i*]-imidazo[4,5-*g*]benzoxazole, when treated as in (*a*), were recovered.

(*c*) 2-Methylimidazo[4,5-*g*]benzoxazole (0·75 g.), sulphuric acid (*d* 1·84, 4 ml.), and potassium nitrate (0·45 g.) were left for 16 hr. at 20—25°. When worked up as in (*a*) starting material (0·5 g.) was recovered. Chloroform extraction of the acidified filtrate gave a *mononitro-derivative* (0·1 g.), yellow needles from ethanol, decomp. 300° (Found: C, 49·4; H, 3·2. $C_9H_6N_4O_3$ requires C, 49·5; H, 2·8%). When treated at 100° for 1 hr. the yield of nitro-compound was increased to 50%.

(*d*) 7,8,9,10-Tetrahydro-2-methylpyrido[1,2-*i*]imidazo-[4,5-*g*]benzoxazole (2·0 g.), sulphuric acid (*d* 1·84, 20 ml.), and potassium nitrate (1·0 g.) were treated at 20—25° for 16 hr. After cooling, the reaction mixture was poured on to ice–water and neutralised with ammonia solution (*d* 0·88). Chloroform extraction gave a mixture from which starting material was obtained by trituration with acetone, leaving a *mononitro-derivative* of 6-acetamido-1,2,3,4-tetrahydro-5-hydroxypyrido[1,2-*a*]benzimidazole (0·8 g.), m. p. 235° (decomp.); ν max. (in Nujol): 3460 (OH), 3280 (NH), 1660 and 1540 cm.$^{-1}$ (amide I and II) (Found: C, 53·8; H, 4·9. $C_{13}H_{14}N_4O_4$ requires C, 53·8; H, 4·9%).

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[5] Belgian Patent, 618,235/1962.
[6] K. H. Saunders, *J. Chem. Soc.*, 1955, 3275.

TABLE 4

Acetamido derivatives of the benzimidazoles (II)

X	R	R′	Yield (%)	M. p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H	Lit. (m. p.)
$[CH_2]_2$.....	H	NHAc	91	236°	66·6	6·0	$C_{12}H_{13}N_3O$	67·0	6·1	260—262° [5]
,, ...	NHAc	H	43	256	66·5	6·1	,,	,,	,,	—
$[CH_2]_3$.....	H	NHAc	84	238	67·6	6·6	$C_{13}H_{15}N_3O$	68·1	6·6	—
,, ...	NHAc	H	60	222	—	—	,,	,,	,,	220 [6]
$[CH_2]_4$.....	H	NHAc	66	222	69·2	7·1	$C_{14}H_{17}N_3O$	69·1	7·0	—
,, ...	NHAc	H	58	252	—	—	,,	—	—	254—255 [6]
$CH_2{\cdot}O{\cdot}CH_2$...	H	NHAc	67	258	61·8	5·9	$C_{12}H_{13}N_3O$	62·3	5·7	—
,, ...	NHAc	H	17	210	62·0	5·8	,,	,,	,,	—

TABLE 5

Azido-benzimidazoles (II)

X	R	R′	M. p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
$[CH_2]_2$.....	H	N_3	150° *	60·3	4·6	$C_{10}H_9N_5$	60·3	4·6
,, ...	N_3	H	136	60·1	4·4	,,	,,	,,
$[CH_2]_3$.....	H	N_3	128	61·9	5·2	$C_{11}H_{11}N_5$	61·9	5·2
,, ...	N_3	H	102	61·3	5·0	,,	,,	,,
$[CH_2]_4$.....	H	N_3	98	63·3	5·7	$C_{12}H_{13}N_5$	63·4	5·8
,, ...	N_3	H	108	63·7	5·6	,,	,,	,,
$CH_2{\cdot}O{\cdot}CH_2$.....	H	N_3	136	55·5	4·1	$C_{10}H_9N_5O$	55·8	4·2
,, ...	N	H	147 *	55·9	4·6	,,	,,	,,

* Decomposition point.

TABLE 6

Imidazo[4,5-*g*]benzoxazoles of types (III) and (IV) obtained by decomposition of the azides listed in Table 5

Type	X	Yield (%)	M. p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
(III)	$[CH_2]_2$	75	226°	67·4	5·2	$C_{12}H_{11}N_3O$	67·6	5·2
(IV)	,,	81	221	67·4	5·4	,,	,,	,,
(III)	$[CH_2]_3$	75	196	68·8	6·3	$C_{13}H_{13}N_3O$	68·7	6·2
(IV)	,,	61	188	68·8	5·7	,,	,,	,,
(III)	$[CH_2]_4$	61	176	69·7	6·3	$C_{14}H_{15}N_3O$	69·7	6·3
(IV)	,,	66	137	70·0	6·6	,,	,,	,,
(III)	$CH_2{\cdot}O{\cdot}CH$	30	189	62·9	4·5	$C_{12}H_{11}N_3O_2$	62·9	4·8
(IV)	,,	30	200	62·5	5·0	,,	,,	,,