Quinoxaline Precursors of Fungitoxic Benzimidazolylcarbamates: Syntheses and Photochemically-induced Transformations

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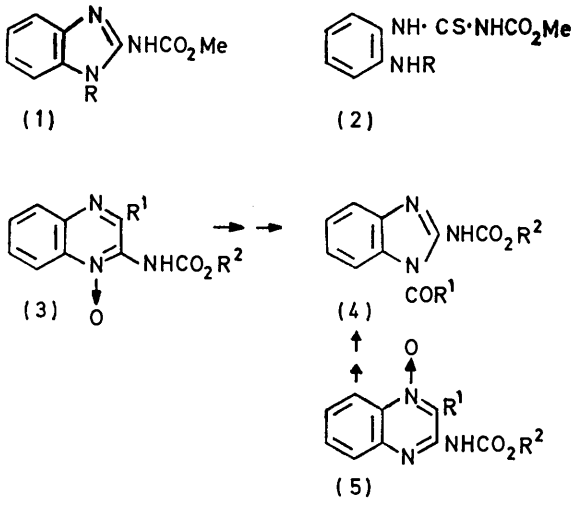
Some quinoxalin-2-ylcarbamate *N*-oxides have been synthesised and shown to undergo photochemically-induced rearrangements, in a variety of solvents, to give benzimidazoles: methyl quinoxalin-2-ylcarbamate 1-oxide gave the fungicide, methyl benzimidazol-2-ylcarbamate. In contrast, irradiation under acidic conditions resulted in the formation of methyl 3-(2-isocyanophenyl)ureidocarboxylate.

METHYL benzimidazol-2-ylcarbamate (1; R = H) is now generally regarded as the fungitoxic principle of benomyl (1; R = $CONHBu^n$), thiophanate methyl (2; R = $CS{\cdot}NHCO_2Me$), and 2-(3-methoxycarbonylthioureido)-aniline (2; R = H).[1,2] The plethora of products produced by light-induced reactions of aromatic amine *N*-oxides has been rationalised by Buchardt as involving initial oxaziridine formation and subsequent thermal reactions.[3] Utilising this approach it was envisaged that quinoxalines of the general structures (3) and (5) might rearrange to give benzimidazolylcarbamates (4).



Although it is customary to protect amines prior to oxidation,[4] we have found that 2-aminoquinoxaline itself can be oxidised with, *e.g.*, peroxymaleic acid in ethanol to give exclusively the 1-oxide. Addition of a chloroformate to the crude reaction mixture provided a simple preparation of the carbamates (3a—l) described in Table 1. A variety of 3-substituted derivatives (3m—z) have been made similarly from the appropriate 2-aminoquinoxalines. 3-Aminoquinoxalin-2(1*H*)-one, made both by reduction of its oxide [5] and by treatment of *o*-phenylenediamine with ethyl (2-*S*)-thio-oxamate, and its 1-oxide have been converted into their carbamates only in hexamethylphosphoramide.

Methyl and ethyl quinoxalin-2-ylcarbamates, their 4-oxides † and their 1,4-dioxides have been synthesised both by carbalkoxylation of the respective amines and by oxidation procedures as outlined in the flow-diagrams.

The spectral properties and chemical conversions presented below confirm the position of the *N*-oxide function in the mono-oxides, this being previously based upon the ability of only 2-aminoquinoxaline 1-oxide to dissolve in base and to form a complex with iron(III) ion,[6] and indirectly the oxide position in other compounds which can be related to the amines. Although the number of *N*-oxide functions present can be distinguished by considerable deshielding of the *peri*-proton in the n.m.r. spectrum, the presence of an adjacent oxide affects the C-3 proton only to a small extent. However the movement in the resonance position (see Experimental section) of the C-3 proton resulting from the introduction of an *N*-oxide function, β (−0·03 and −0·08 p.p.m.) and α (+0·36 and +0·31 p.p.m.) to it, are remarkably similar to those shown by pyridine and its *N*-oxide (β, −0·13 p.p.m.; α, +0·30 p.p.m.).[7] Although both ethyl quinoxalin-2-ylcarbamate 1-oxide (9; R = Et) and the corresponding 4-oxide (11; R = Et) absorb at 256 nm, only the 1-oxide forms an anion in the presence of base as evidenced by a shift to 278 nm. When heated alone to 170° or refluxed in dimethylformamide, the 1-oxide eliminated ethanol to give the fused oxadiazolone (12) in a manner analogous to the corresponding pyridine.[8] As expected, the liberation of phenol from the phenyl carbamate occurs much more readily. On dissolution of (12) in methanol, ring cleavage occurs and the carbamate (9; R = Me) is regenerated. A further indication of the position of the *N*-oxide function is given by the formation of alkyl quinoxalin-2-ylcarbamate 1-oxides from quinoxaline 1-oxide and the sodium salts of monochlorourethanes.

† For clarity, 3-substituted quinoxaline-1-oxides are named throughout as 2-substituted-4-oxides.

[1] J. W. Vonk and A. Kaars Sijpersteijn, *Pesticide Sci.*, 1971, **2**, 160, and references therein.

[2] Y. Soeda, S. Kosaka, and T. Noguchi, *Agric. and Biol. Chem. (Japan)*, 1972, **36**, 817.

[3] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 231; O. Buchardt, K. B. Tomer, and V. Madson, *Tetrahedron Letters*, 1971, 1311.

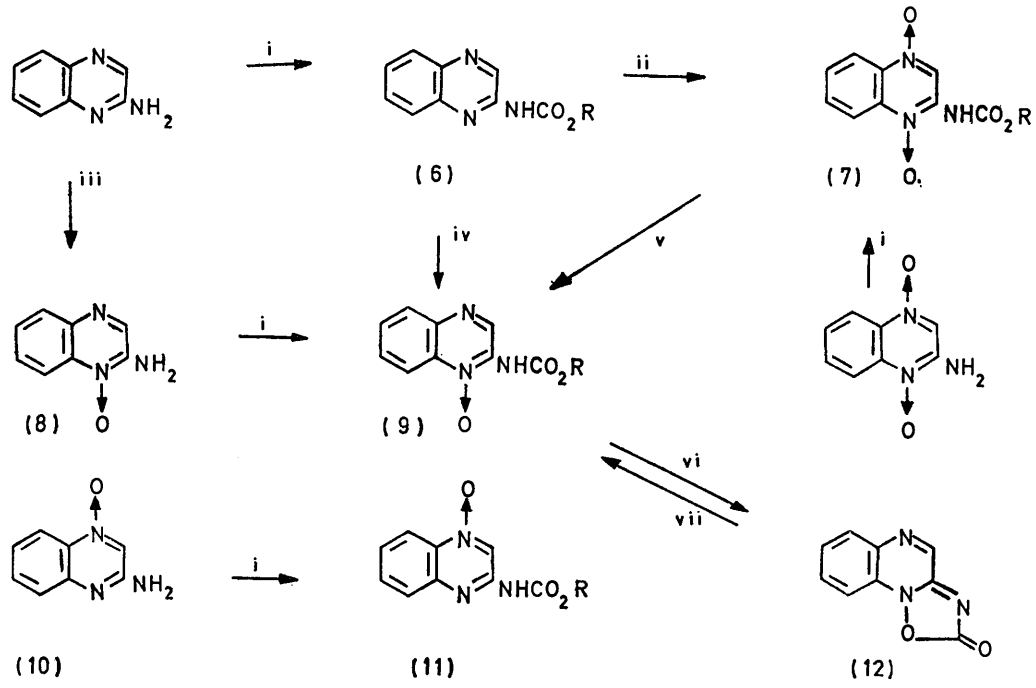
[4] For the oxidation of unprotected aminoheterocycles, see also M. Hama, S. Nomura, and T. Kawakita, *J. Pharm. Soc. Japan*, 1971, **91**, 134.

[5] G. Tennant, *J. Chem. Soc.*, 1963, 2428.

[6] A. S. Elina and L. G. Tsurul'nikova, *Zhur. obshchei Khim.*, 1963, **33**, 1544.

[7] N. S. Bhacca, H. F. Johnson, and J. N. Shoolery, 'NMR Spectra Catalog,' Varian Associates, U.S.A., 1962, Spectrum No. 96.

[8] A. R. Katritzky, *J. Chem. Soc.*, 1965, 2063.



Reagents: i, RO·CO·Cl; ii, AcO_2H in excess at 50°; iii, $HO_3C{\cdot}CH{:}CH{\cdot}CO_3H$; iv, oxidation; v, PCl_3–$CHCl_3$; vi, heat; vii, ROH.

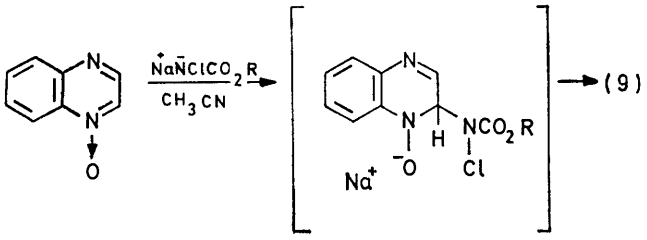
TABLE 1

Preparation of alkyl quinoxalin-2-ylcarbamate 1-oxides

Compound	R^1	R^2	Yield (%) [a]	M.p. (°) [d] (recryst. solvent)	Elemental analysis [e] Found% C	H	N	Molecular formula	Requires% C	H	N
(3a)	H	Me	25 85 [b]	188—189 (MeCN)	54·8	4·1	19·2	$C_{10}H_9N_3O_3$	54·8	4·1	19·2
(3b)	H	Et	38	126—127, 233 (EtOH)	56·4	4·9	18·1	$C_{11}H_{11}N_3O_3$	56·6	4·75	18·0
(3c)	H	Pr^i	17	119—120 (EtOH)	58·0	5·1	16·9	$C_{12}H_{13}N_3O_3$	58·3	5·3	17·0
(3d)	H	Bu^n	22	95—96 (EtOH)	59·5	5·9	16·0	$C_{13}H_{15}N_3O_3$	59·75	5·8	16·1
(3e)	H	$[CH_2]_4Me$	17	85—86 (EtOH)	61·0	6·1	15·2	$C_{14}H_{17}N_3O_3$	61·1	6·2	15·3
(3f)	H	$[CH_2]_5Me$	11	73—74 (petrol, 60—80°)	62·1	6·7	14·5	$C_{15}H_{19}N_3O_3$	62·3	6·6	14·5
(3g)	H	$CH_2{=}CH{-}CH_2$	21	118—119 (EtOH)	58·9	4·4	17·1	$C_{12}H_{11}N_3O_3$	58·8	4·5	17·1
(3h)	H	CH_2CH_2Cl	28	153—154 (EtOH)	49·7	3·7	15·5	$C_{11}H_{10}ClN_3O_3$	49·35	3·8	15·7
(3i)	H	CH_2CCl_3	30	135—136, 223—224 (petrol, 60—80°)	39·5	2·3	12·5	$C_{11}H_8Cl_3N_3O_3$	39·2	2·4	12·5
(3j)	H	CH_2Ph	27	129—130 (EtOH)	64·7	4·3	14·2	$C_{16}H_{13}N_3O_3$	65·1	4·4	14·2
(3k)	H	cyclo-C_6H_{11}	15	113—114 (EtOH)	62·8	6·0	14·7	$C_{15}H_{17}N_3O_3$	62·7	6·0	14·6
(3l)	H	Ph	28	120, 232—233 (EtOH)	63·8	4·1	14·9	$C_{15}H_{11}N_3O_3$	64·0	3·9	14·9
(3m)	Me	Et	16	108—109 (EtOH)	58·0	5·3	16·8	$C_{12}H_{13}N_3O_3$	58·3	5·3	17·0
(3n)	Cl	Me	83 [b]	261—262 (Pr^iOH)	47·4	2·8	16·4	$C_{10}H_8ClN_3O_3$	47·35	3·2	16·6
(3o)	Cl	Et	60 [b]	260 (EtOH)	49·4	4·0	15·8	$C_{11}H_{10}ClN_3O_3$	49·3	3·8	15·7
(3p)	MeO	Et	68 [b]	222—223 (EtOH)	54·5	4·95	15·8	$C_{12}H_{13}N_3O_4$	54·75	5·0	16·0
(3q)	Ph	Me	51 [b]	140, 181—182 (MeOH)	64·8	4·4	14·2	$C_{16}H_{13}N_3O_3$	65·1	4·4	14·2
(3r)	Ph	Et	68 [b]	125—126, 180—182 (EtOH)	65·7	4·8	13·6	$C_{17}H_{15}N_3O_3$	66·0	4·9	13·6
(3s)	4-MeC_6H_4	Me	65 [b]	135(sinters), 195—196 (EtOH)	65·7	4·8	13·4	$C_{17}H_{15}N_3O_3$	66·0	4·9	13·6
(3t)	4-MeC_6H_4	Et	59 [b]	130 (sinters), 195—196 (EtOH)	66·8	5·1	13·2	$C_{18}H_{17}N_3O_3$	66·85	5·3	13·0
(3u)	2,4-$Cl_2C_6H_3$	Me	81 [b]	248—250 (MeOH)	52·4	3·1	11·2	$C_{16}H_{11}Cl_2N_3O_3$	52·8	3·0	11·5
(3v)	2,4-$Cl_2C_6H_3$	Et	63 [b]	248—250 (EtOH)	53·8	3·4	10·9	$C_{17}H_{13}Cl_2N_3O_3$	54·0	3·5	11·1
(3w)	4-$NO_2C_6H_4$	Me	26 [b,c]	235—237 (MeCN)	56·1	3·9	16·1	$C_{16}H_{12}N_4O_5$	56·5	3·6	16·5
(3x)	4-$NO_2C_6H_4$	Et	31 [b,c]	236—238 (MeCN)	57·9	4·1	16·0	$C_{17}H_{14}N_4O_5$	57·6	4·0	15·8
(3y)	3-$NO_2C_6H_4$	Me	53 [b,c]	252—253 (MeCN)	56·2	3·4	16·2	$C_{16}H_{12}N_4O_5$	56·5	3·6	16·5
(3z)	3-$NO_2C_6H_4$	Et	40 [b,c]	254—255 (MeCN)	57·7	3·9	15·8	$C_{17}H_{14}N_4O_5$	57·6	4·0	15·8

[a] Yields are those obtained after one recrystallisation. [b] Yields incorporating improved process, see Experimental section. [c] Oxidations carried out in ethyl acetate–ethanol for 20 h. [d] M.p.s may be those of the carbamates or the fused oxadiazolones formed on heating. Where melting, followed by resolidification and remelting, points were obvious both figures are given. [e] All compounds have n.m.r. spectra compatible with the proposed structures.

Although an initial electrophilic attack at oxygen has not been disproved, the reaction can more reasonably be regarded as a rare direct nucleophilic attack on an otherwise unactivated ring followed by elimination of hydrogen chloride from the intermediate (13).

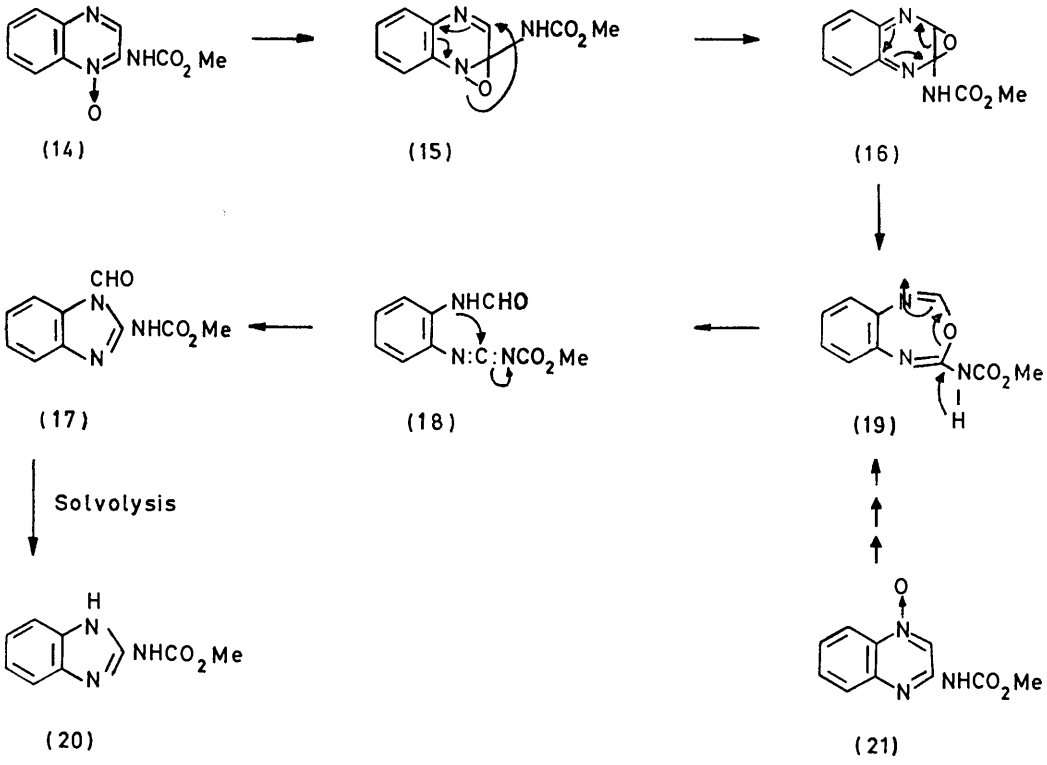


(13)

The effect of light upon the *N*-oxides has been investigated quantitatively, though briefly, in the case of methyl quinoxalin-2-ylcarbamate 1-oxide (14) and superficially for several 4-oxides, 1,4-dioxides, and 3-substituted derivatives. The 1-oxide (14) is stable for many hours in the dark, in both dichloromethane and methanol. of each, dependent chiefly upon pH and solvent, as shown in Table 2. The 4-oxide (21) also gave high yields of the benzimidazole (20) and the isocyanide (24) when irradiated with u.v. light in methanol and dichloromethane, respectively.

The production of the benzimidazole (17) in solution in dry acetonitrile can be rationalised as shown in Scheme 1. Thus the initial oxaziridine (15) may undergo successive symmetry-allowed rearrangements to the oxiran (16) and the 3,1,5-benzoxadiazepine (19). The latter can be similarly derived from the 4-oxide (21). The formation of the 1-formylbenzimidazole (17) may be seen as arising *via* the carbodi-imide (18) but other mechanisms could operate. The extremely rapid methanolysis of the 1-formylbenzimidazole (17) accounts for the production of its parent (20) in methanolic solution. That the latter rather than (17) was formed in acetonitrile solution at low concentrations can be explained by the presence of trace quantities of water or an alcohol.

A novel mode of decomposition, observed when the quinoxalines (14) and (21) were irradiated under acidic conditions, may be viewed as proceeding through the



Scheme 1

Degradation was rapid using u.v. radiation even when most of the energy below 300 nm had been removed with a Pyrex filter, somewhat faster in sunlight but much slower in tungsten light. The major products formed have been shown to be the expected benzimidazoles (17) and (20) and the novel isocyanide (24) with the yield intermediates shown in Scheme 2. Although either the oxaziridine (15) or the oxadiazepine (19) could undergo ring cleavage, the isolation of the isocyanide (24) from both the 1- and 4-oxides suggests that the latter is involved. In acidic solution, this should exist as the conjugate acid (22), protonated at N-1. Ring cleavage,

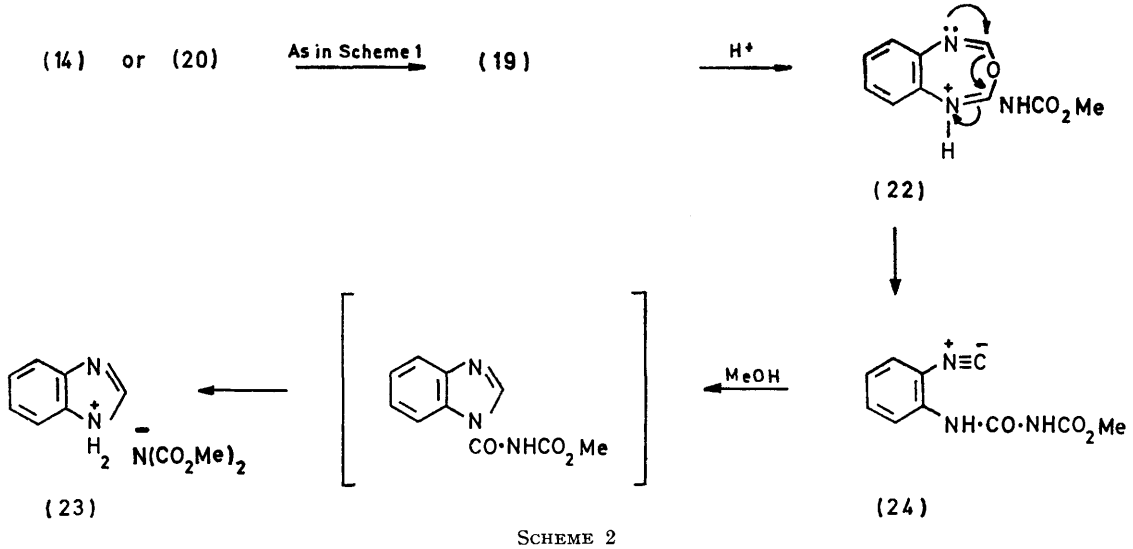
in the direction opposite to that shown by the neutral molecule, gives the isocyanide. Although not photochemically-induced, the formation of *o*-cyanophenyl isocyanide from quinazoline 3-oxide and acetic anhydride is analogous.[9] The production of isocyanide in acetonitrile containing trifluoroacetic acid and in aqueous methanol containing either sulphuric or formic acid is formic acid. The proportion of benzimidazole and isocyanide produced is dependent upon the concentration of solute and hence the acid concentration. Chemical support for the structure of the isocyanide is provided by its conversion by methanol, in the dark, into the benzimidazole salt (23). This has been unambiguously synthesised from its components.

TABLE 2

Action of light upon methyl quinoxalin-2-ylcarbamate 1-oxide (14)

Solvent	Light source	Concentration/ p.p.m. (w/v)	Time/h	Yield/% of products [b] (24)	(17)	(20)
CH_2Cl_2	none	30	94	0	0	0
MeOH	none	30	94	0	0	0
CH_2Cl_2	Tungsten	30	50	110	0	0
CH_2Cl_2	u.v.	30	3	95	0	0
CH_2Cl_2	u.v.	300	5	90	0	0
CH_2Cl_2	u.v.	3000	15	93	0	0
CH_2Cl_2–Et_3N [a]	u.v.	30	3	0	0	103 [c]
MeCN	u.v.	30	3	0	0	99 [a]
MeCN	u.v.	300	5	0	105	0
MeCN	u.v.	1000	7	0	93	0
MeCN–CF_3CO_2H [a]	u.v.	30	3	105	0	0
MeOH	tungsten	30	94	0	0	110
MeOH	u.v.	30	3	0	0	105
MeOH	u.v.	300	5	0	0	103
H_2O–MeOH [a]	u.v.	30	3	0	0	90
H_2O–MeOH [a]	u.v.	300	10	51	0	40
H_2O–MeOH [a]	sunlight	300	5	48	0	40
10^{-3}N-H_2SO_4–MeOH [a]	u.v.	30	3	81	0	0
10^{-3}N-HCO_2H–MeOH [a]	u.v.	30	3	81	0	0

[a] For solvent proportions, see Experimental section. [b] Estimated from u.v. spectra; accuracy *ca.* ±10%. [c] See text.



SCHEME 2

thus explained. Dichloromethane is known to contain hydrochloric acid, and this leads to the formation of isonitrile. Addition of triethylamine to the solvent caused reversion to the benzimidazole pathway with the production of the benzimidazole (20). The presence of trace quantities of water or alcohols may again explain the non-appearance of the 1-formyl derivative (17). Photolysis in aqueous methanolic solution is more complex since solvolysis of the acylbenzimidazole liberates

The action of sunlight on 30 p.p.m. methanolic solutions of compounds (3c—m, p—z) also resulted in a rapid breakdown to benzimidazoles but the dioxides (7; R = Me or Et), and possibly the 3-chloro-derivatives (3n) and (3o), apparently follow a different course. No products have been identified.

Methyl quinoxalin-2-ylcarbamate 1-oxide (14) is the most fungitoxic of the compounds described against the

[9] T. Higashino, *Chem. and Pharm. Bull.* (*Japan*), 1961, **9**, 635.

majority of organisms and has an activity spectrum and level comparable with those of benomyl (1; R = CONHBu^n).[10] On root application to cucumbers, it is translocated into the leaves without decomposition but, on exposure of the leaves to light, the benzimidazole (1; R = H) is present.[11] During use as a seed-dressing against soil and seed-borne fungal pathogens and as post-harvest treatments, it was found not to be active if the test was conducted in the absence of light,[12] supporting the contention that activity is due to the production of methyl benzimidazol-2-ylcarbamate (1; R = H).

EXPERIMENTAL

I.r., u.v., and n.m.r. spectra were obtained on Perkin-Elmer 237, 137, and R10 instruments respectively. Mass spectroscopy was carried out both at Jealott's Hill and I.C.I. Pharmaceuticals Division, Alderley Park. Microanalyses were performed both at Jealott's Hill and by Dr. F. B. Strauss, Oxford. M.p.s were determined on a Gallenkamp apparatus. T.l.c. employed Eastman Chromatographic Sheets, silica gel No. 6060, and either ether or 20% methanol in ether as eluants. Irradiations were carried out with u.v. (Hanovia Fluorescence 16 lamp) and tungsten (Osram, 60 W) light and sunlight (July), all filtered through Pyrex glass.

Methyl and Ethyl Quinoxalin-2-ylcarbamate (6; R = Me *and* Et).—A solution of ethyl chloroformate (5·5 g) in chloroform (40 ml) was added to a solution of 2-aminoquinoxaline [13] (2·9 g) in pyridine (20 ml), maintaining the temperature of the mixture below 10°. After the addition was complete, the mixture was left at 20° for 3 days then poured into ice–water, acidified with 2N-hydrochloric acid, and extracted with chloroform. The extracts were washed, dried, and evaporated to give a yellow solid which was recrystallised from ethanol to give *ethyl quinoxalin-2-ylcarbamate* (1·62 g), m.p. 159—160° (Found: C, 60·9; H, 5·2; N, 19·9. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·35%), τ ($CDCl_3$) 0·14 (1H, s), 1·06br (1H, s), 1·8 (1H, m), 2·2 (3H, m), 5·66 (2H, q), and 8·70 (3H, t). The methyl carbamate was prepared similarly in 30% yield, m.p. 194—195° (from ethanol) (Found: C, 59·7; H, 4·25; N, 20·6. Calc. for $C_{10}H_9N_3O_2$: C, 59·1; H, 4·5; N, 20·7%) (lit.,[14] m.p. 188—190°).

Methyl and Ethyl Quinoxalin-2-ylcarbamate 1-Oxide (9; R = Me *and* Et).—(*a*) 2-Aminoquinoxaline 1-oxide [15] (2·0 g) was dissolved in hexamethylphosphoramide (25 ml) with heating and the solution was cooled rapidly to 20° Pyridine (1·0 g) was added, the solution cooled to 10°, and ethyl chloroformate (1·36 g) added dropwise with stirring. The mixture was left at 20° overnight then poured into ice–water to give a pale-yellow precipitate of *ethyl quinoxalin-2-ylcarbamate 1-oxide* (1·75 g, 60%), m.p. 127—129° (from ethanol) (Found: C, 56·4; H, 4·9; N, 18·1. $C_{11}H_{11}N_3O_3$ requires C, 56·6; H, 4·75; N, 18·0%), τ ($CDCl_3$) 0·11 (1H, s), 0·55 (1H, m), 1·4 (1H, m), 1·8 (1H, m), 2·2 (2H, m), 5·65 (2H, q), and 8·64 (3H, t), M^+ 233, $\lambda_{max.}$ (MeOH) 256 nm (ε 60,000). The methyl carbamate was prepared similarly in 50% yield, m.p. 188—189° (from acetonitrile or ethanol) (Found: C, 54·8; H, 4·1; N, 19·2. Calc. for $C_{10}H_9N_3O_3$: C, 54·8; H, 4·1; N, 19·2%), τ [$CDCl_3$–$(CD_3)_2SO$] 0·2 (1H, s), 1·4 (1H, m), 2·0 (3H, m), and 6·08 (3H, s), M^+ 219, $\lambda_{max.}$ (MeOH) 256 nm (ε 55,000) (lit.,[14] m.p. 178—179°).

(*b*) Hydrogen peroxide (22·2 ml; 30% w/v) and maleic anhydride (5·45 g) were added to a solution of ethyl quinoxalin-2-ylcarbamate (12·0 g) in acetic acid (110 ml). After standing overnight at 20°, the mixture was poured into ice–water and the precipitate was removed by filtration and dried (8·5 g). T.l.c. indicated the presence of starting material, its 1-oxide, and 1,4-dioxide. Although the desired 1-oxide was the major component, it could be isolated pure only by repeated fractional crystallisation. The corresponding methyl carbamate was prepared similarly but purification again proved difficult. The use of *m*-chloroperbenzoic or peracetic acid was not successful.

(*c*) The general procedure for carbamate production, described below, has been successfully applied to the methyl and ethyl carbamates.

(*d*) Phosphorus trichloride (1·1 g) was added, with stirring, to a solution of ethyl quinoxalin-2-ylcarbamate 1,4-dioxide (1·0 g) in chloroform (25 ml). After 10 min, the solvent was removed and the residue twice recrystallised from ethanol giving ethyl quinoxalin-2-ylcarbamate 1-oxide (0·41 g), m.p. 124—126°.

(*e*) A mixture of quinoxaline 1-oxide (1·46 g), methyl chlorocarbamate [16] (2·30 g), sodium carbonate (1·1 g), and acetonitrile (50 ml) was refluxed for 2 h, cooled, and poured into ice–water. The precipitate (0·35 g), m.p. 180—182°, was recrystallised from ethanol to give methyl quinoxalin-2-ylcarbamate 1-oxide, m.p. 190°. The ethyl carbamate was obtained similarly in 17% yield.

Methyl and Ethyl Quinoxalin-2-ylcarbamate 4-Oxide (11; R = Me *and* Et).—A solution of 2-aminoquinoxaline 4-oxide [17] (1·0 g) in pyridine (10 ml) was treated dropwise with a solution of ethyl chloroformate (2·0 g) in chloroform (20 ml) maintaining the temperature of the reaction mixture below 10°. After addition was complete, the mixture was left for 1 h at 10° and 2 h at 20°. It was then poured into ice–water, acidified with 2N-hydrochloric acid, and extracted with chloroform. The extracts were washed, dried, and evaporated to give a residue which was recrystallised from petroleum (b.p. 80—100°) to give *ethyl quinoxalin-2-ylcarbamate 4-oxide* (0·56 g), m.p. 128—130° (Found: C, 56·3; H, 4·9; N, 18·0. $C_{11}H_{11}N_3O_3$ requires C, 56·6; H, 4·75; N, 18·0%), τ ($CDCl_3$) 0·50 (1H, s), 1·4 (1H, m), 1·9 (1H, m), 2·2 (3H, m), 5·67 (2H, q), and 8·68 (3H, t), $\lambda_{max.}$ (MeOH) 256 nm. *Methyl quinoxalin-2-ylcarbamate 4-oxide* was prepared similarly in 33% yield; m.p. 182—183°, again at 254° (decomp.) after solidification (from toluene); purification required chromatography (silica gel, chloroform–ether) (Found: C, 55·0; H, 4·0; N, 19·1. $C_{10}H_9N_3O_3$ requires C, 54·8; H, 4·1; N, 19·2%), τ ($CDCl_3$) 0·50 (1H, s), 1·5 (2H, m), 2·2 (3H, m), and 6·15 (3H, s).

Methyl and Ethyl Quinoxalin-2-ylcarbamate 1,4-Dioxide (7; R = Me *and* Et).—(*a*) 2-Aminoquinoxaline 1,4-dioxide [6] (1·30 g) was dissolved in hexamethylphosphoramide (20 ml) by heating and the solution cooled to 20°. Pyridine (0·58 g)

[10] G. M. Farrell, personal communication.
[11] R. J. Hemingway, personal communication.
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was added, the solution cooled to 10°, and ethyl chloroformate (0·80 g) was added dropwise with stirring. The mixture was left at 20° overnight, then poured in ice–water (100 ml) to give a yellow precipitate of *ethyl quinoxalin-2-ylcarbamate* 1,4-*dioxide* (0·97 g), m.p. 187—188° (from ethanol) (Found: C, 52·7; H, 4·6; N, 16·6. $C_{11}H_{11}N_3O_4$ requires C, 53·0; H, 4·45; N, 16·9%), τ ($CDCl_3$) 0·42 (1H, s), 0·4 (1H, m), 1·3 (2H, m), 2·1 (2H, m), 5·62 (2H, q), and 8·64 (3H, t), $\lambda_{max.}$ (MeOH) 236 and 273 nm. *Methyl quinoxalin-2-ylcarbamate* 1,4-*dioxide* was prepared similarly in 33% yield, m.p. 198—199° (from ethanol) (Found: C, 51·3; H, 4·0; N, 18·0. $C_{10}H_9N_3O_4$ requires C, 51·1; H, 3·9; N, 17·9%), τ [$CDCl_3$–$(CD_3)_2SO$] 0·5 (1H, s), 1·4 (2H, m), 2·1 (3H, m), and 6·05 (3H, s).

(*b*) A mixture of ethyl quinoxalin-2-ylcarbamate (15·0 g), anhydrous sodium acetate (3·2 g), and peracetic acid (38%; 60 ml) was heated at 50—60° for 3 days. It was then cooled and diluted with water (200 ml) to give a precipitate (9·09 g) which was recrystallised from ethanol to give the dioxide (7·1 g), m.p. 186—188°. The methyl carbamate was obtained similarly in 50% yield.

Oxidation of 2-Aminoquinoxaline.—A solution of diperoxymaleic acid was prepared by dissolving freshly ground maleic anhydride (2·5 g) in an ice-cold solution of ethanol (125 ml) and hydrogen peroxide (30% w/v; 5 ml). A solution of 2-aminoquinoxaline (3·63 g) in ethanol (50 ml) was added and the mixture stirred for 30 min and filtered to remove a salt or complex of 2-aminoquinoxaline. Although t.l.c. showed the filtrate to contain the desired 1-oxide and no unoxidised material or its 4- and 1,4-oxides, evaporation and recrystallisation from propan-2-ol gave only impure 1-oxide, m.p. 160—164°. Despite this failure, addition of chloroformates to the filtrate gave carbamates as described below.

Inclusion of an acid-binding agent, *e.g.* sodium hydrogen carbonate, to continuously regenerate 2-aminoquinoxaline from the by-product successfully prevented removal of a considerable proportion of starting material from the reaction sphere.[18] Thus oxidation of 2-aminoquinoxaline in ethanol with maleic anhydride (2 mol. equiv.), hydrogen peroxide (30% w/v; 3·4 mol. equiv.), and sodium hydrogen carbonate (4·6 mol. equiv.), charged simultaneously, resulted in an 85% yield of methyl quinoxalin-2-ylcarbamate 1-oxide, following removal of solids and treatment of the filtrate with methyl chloroformate (1 mol. equiv.). This contrasts with the 25% yield obtained initially.

Alkyl Quinoxalin-2-ylcarbamate 1-Oxides (3).—*General method.* An ethanolic solution of 2-aminoquinoxaline 1-oxide was prepared by oxidation of 2-aminoquinoxaline with peroxymaleic acid as described above. A chloroformate (1 mol. equiv. based upon 2-aminoquinoxaline) was added dropwise over 15 min. and stirring continued for a further 1 h. The products, isolated by filtration with partial evaporation, cooling, and dilution with water as necessary, are shown in Table 1.

2-Aminoquinoxalines substituted at C-3 were made by literature methods: methyl-,[19] chloro-,[20] methoxy-,[21] aryl.[22] The improved technique, incorporating sodium hydrogen carbonate, was used for most of the 3-substituted compounds (see Table 1). A solution of the amine (0·01 mol) in ethanol (50 ml) and sodium hydrogen carbonate (3·5 g) was added to a solution of maleic anhydride (2·0 g) and hydrogen peroxide (30% w/v; 3·2 ml) in ethanol (50 ml) and the mixture was stirred for 3 h. It was then filtered, the solids washed well with ethanol, and the combined filtrates treated with either ethyl or methyl chloroformate. After several hours, the products, shown in Table 1, were obtained by filtration with partial evaporation and addition of water if necessary.

Ethyl 3-Oxo-3,4-dihydroquinoxalin-2-ylcarbamate 1-Oxide.—3-Aminoquinoxalin-2(1*H*)-one 4-oxide [5] (2·64 g) was dissolved in hexamethylphosphoramide (30 ml) by heating and the solution cooled rapidly to 20°. Pyridine (1·18 g) was added, the solution cooled to 10°, and ethyl chloroformate (1·62 g) was added dropwise. The solution was stirred at 20° for 20 h, then poured into ice–water (150 ml). The resultant yellow precipitate (3·04 g) was recrystallised with difficulty from ethanol to give *ethyl 3-oxo-3,4-dihydroquinoxalin-2-ylcarbamate 1-oxide*, instantaneous m.p. 280° (decomp.) (Found: C, 52·8; H, 4·4; N, 17·0. $C_{11}H_{11}N_3O_4$ requires C, 53·0; H, 4·45; N, 16·9%).

Ethyl 3-Oxo-3,4-dihydroquinoxalin-2-ylcarbamate.—3-Aminoquinoxalin-2(1*H*)-one was made both by reduction of its oxide,[5] and by reaction of *o*-phenylenediamine with ethyl (2-*S*)-thio-oxamate. Thus a solution of *o*-phenylenediamine (20 g) and ethyl (2-*S*)-thio-oxamate [23] (25 g) in dry ethanol (380 ml) was refluxed for 6 h. On cooling a precipitate (14·0 g; m.p. >330°) was obtained which was identical by i.r. spectroscopy with authentic material. A portion (4·0 g) was dissolved in hexamethylphosphoramide (50 ml) by heating and the solution cooled rapidly to 20°. Pyridine (8·0 g) was added, the solution cooled to 10°, and ethyl chloroformate (12·0 g) added dropwise. The solution was stirred for 3 days, then poured into ice–water. The resultant precipitate was recrystallised from acetonitrile to give *ethyl 3-oxo-3,4-dihydroquinoxalin-2-ylcarbamate* (3·68 g), m.p. 189—190° (Found: C, 56·5; H, 4·7; N, 18·1. $C_{11}H_{11}N_3O_3$ requires C, 56·6; H, 4·75; N, 18·0%).

[1,2,4]-*Oxadiazolo*[2,3-a]*quinoxalin-2-one* (12).—(*a*) Ethyl quinoxalin-2-ylcarbamate 1-oxide (1·0 g) was heated at 170° for 30 min, then cooled and triturated with hot acetone. The insoluble material (0·50 g), m.p. 226—227°, was recrystallised from dimethylformamide to give [1,2,4]-*oxadiazolo*[2,3-a]*quinoxalin-2-one* (0·32 g), m.p. 234° (Found: C, 58·1; H, 2·95; N, 22·5. $C_9H_5N_3O_2$ requires C, 57·75; H, 2·7; N, 22·5%), τ [$(CD_3)_2SO$] 0·65 (1H, s) and 1·9 (4H, m), M^+ 187, $\lambda_{max.}$ (MeOH) 237sh (ε 20,700) and 257 nm (19,700). After 2 days, in the dark, the methanolic solution showed $\lambda_{max.}$ (MeOH) 256 nm (ε 50,000) indicating essentially complete conversion into methyl quinoxalin-2-ylcarbamate 1-oxide.

(*b*) A mixture of ethyl quinoxalin-2-ylcarbamate 1-oxide (4·0 g) and dimethylformamide (5 ml) was refluxed vigorously for 30 min, then poured into ether (200 ml) to give the tricyclic compound (1·39 g), m.p. 234°.

(*c*) Phenyl quinoxalin-2-ylcarbamate 1-oxide (3·0 g) was heated at 130—160° and 14 mmHg. The distillate (0·93 g, 93%; m.p. 40°) was identified as phenol by i.r. spectroscopy and mixed melting-point. The solid residue (1·9 g), m.p. 225—226°, was recrystallised from dimethylformamide to give material with m.p. 234—235°.

Light-induced Transformations.—(*a*) *Methyl quinoxalin-2-*

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ylcarbamate 1-*oxide* (14). Solutions of the quinoxaline in the following solvents were prepared having the concentrations shown in Table 2: acetonitrile (dried over molecular sieves), acetonitrile containing 0·03% trifluoroacetic acid, methanol, dichloromethane, dichloromethane containing 0·05% triethylamine, methanol–water, methanol–10^{-3}N-aqueous sulphuric acid, and methanol–10^{-3}N-aqueous formic acid. The aqueous solutions were prepared by dissolving the quinoxaline in methanol and diluting with the second component to give a final methanol concentration of 6%. Solutions were irradiated with u.v. light, through a Pyrex filter, for periods of time indicated in the Table. Selected samples were stored in the dark, or exposed to tungsten light or to sunlight as shown. Estimates of products were made by comparison of the u.v. spectra of the solutions with those of the pure products, methyl 3-(2-isocyanophenyl)ureidocarboxylate, methyl 1-formyl-benzimidazol-2-ylcarbamate, and methyl benzimidazol-2-ylcarbamate in the appropriate solvent. The yields given in Table 2 are accurate to *ca.* 10%. Although in some cases measurements were made after intermediate periods of time only the full-term results are reported. U.v. irradiations in dichloromethane, acetonitrile, methanol, methanol–water, and methanol–10^{-3}N-sulphuric acid were completed by isolation of the respective products as follows. (i) A solution of the quinoxaline (3·0 g) in dichloromethane (1 l) was irradiated for 15 h, then evaporated to dryness. The residue (3·0 g), m.p. 117—120°, was recrystallised from toluene to give *methyl* 3-(2-*isocyanophenyl*)*ureidocarboxylate* (2·27 g), m.p. 125—126° (decomp.) (Found: C, 54·5; H, 4·0; N, 18·9. $C_{10}H_9N_3O_3$ requires C, 54·8; H, 4·1; N, 19·2%), τ [$(CD_3)_2SO$] −0·85br (1H), −0·55 (1H, s), 0·7 (1H, m), 2·6 (3H, m), and 6·20 (3H, s), M^+ 219, $\lambda_{max.}$ (MeOH) 247 nm (ε 14,000), $\nu_{max.}$ (Nujol) 2120 cm^{-1}.

(ii) A solution of the quinoxaline (200 mg) in dry acetonitrile (200 ml) was irradiated for 7 h then evaporated to dryness. The residue (200 mg) was recrystallised from acetonitrile to give *methyl* 1-*formylbenzimidazol*-2-*ylcarbamate* (120 mg), m.p. 278—285° (decomp.) (Found: C, 54·6; H, 4·15; N, 19·2. $C_{10}H_9N_3O_3$ requires C, 54·8; H, 4·1; N, 19·2%), τ [$(CD_3)_2SO$] 0·37 (1H, s), 2·0 (1H, m), 2·7 (4H, m), and 6·26 (3H, s), M^+ 219, $\lambda_{max.}$ (CH_3CN) 294 (ε 16,300) and 288sh nm (14,700).

(iii) A solution of the quinoxaline (300 mg) in methanol (1 l) was irradiated for 5 h, then evaporated to dryness. The residue was recrystallised from ethanol to give methyl benzimidazol-2-ylcarbamate (220 mg), m.p. 327—332° (decomp.), with i.r. and u.v. spectra identical with those of authentic material [lit.,[24] m.p. 338° (decomp.)], $\lambda_{max.}$ (MeOH) 288 (ε 14,100), 282 (12,800), 252sh (8800), and 244 nm (11,600).

(iv) A solution of the quinoxaline (300 mg) in hot methanol (60 ml) was added to water (940 ml), then irradiated for 10 h. It was extracted three times with chloroform and the extracts evaporated to give a solid (220 mg), m.p. 120—125° (decomp.). Recrystallisation from toluene, with hot filtration, gave methyl 3-(2-isocyanophenyl)ureidocarboxylate (100 mg), m.p. 123—126° (decomp.). The aqueous solution was evaporated *in vacuo* to give a solid (50 mg). Recrystallisation from ethanol gave methyl benzimidazol-2-ylcarbamate (40 mg), m.p. 328—330° (decomp.).

(v) A solution of the quinoxaline (30 mg) in hot methanol (60 ml) was added to 10^{-3}N-sulphuric acid (940 ml), then irradiated for 3 h. It was extracted thoroughly with chloroform and the extracts were evaporated to give a solid (25 mg). Recrystallisation from toluene gave methyl 3-(2-isocyanophenyl)ureidocarboxylate (18 mg), m.p. 124° (decomp.).

(*b*) *Methyl quinoxalin*-2-*ylcarbamate* 4-*oxide* (21). (i) A solution of the quinoxaline (300 mg) in dichloromethane (100 ml) was irradiated with u.v. light for 15 h. The u.v. spectrum showed a 90% conversion into isocyanide. The solution was evaporated and the residue recrystallised from toluene to give methyl 3-(2-isocyanophenyl)ureidocarboxylate (115 mg), m.p. 125° (decomp.), identical with the material obtained from the 1-oxide above.

(ii) A solution of the quinoxaline (300 mg) in methanol (1 l) was irradiated with u.v. light for 5 h. The u.v. spectrum showed a 100% conversion into a benzimidazole. The solution was evaporated and the residue recrystallised from ethanol to give methyl benzimidazol-2-ylcarbamate (195 mg), m.p. 326—330° (decomp.), identical with the material obtained from the 1-oxide above.

(*c*) *Other quinoxalines.* Solutions of compounds (3c—m, p—z) (30 p.p.m.) were irradiated in methanol for 3 h. U.v. spectra suggested a high yield of methyl (or ethyl) benzimidazol-2-ylcarbamates in all cases. The dioxides (7) apparently gave no benzimidazole when treated similarly and results using the 3-chloro-derivatives (3n and o) were inconclusive. No attempt was made to isolate the products.

Benzimidazolium Bismethoxycarbonylamide (23).—(*a*) A solution of methyl 3-(2-isocyanophenyl)ureidocarboxylate (50 mg) in methanol (50 ml) was allowed to stand at 20° for 4 days. The solvent was removed *in vacuo* and the residue recrystallised from ether–petroleum (b.p. 40—60°) to give the *benzimidazolium bismethoxycarbonylamide* (25 mg), m.p. 124—126° (Found: C, 52·1; H, 5·0; N, 17·1. $C_{11}H_{13}N_3O_4$ requires C, 52·6; H, 5·2; N, 16·7%), τ ($CDCl_3$) 1·5br (2H, s), 1·78 (1H, s), 2·2 (2H, m), 2·7 (2H, m), and 6·38 (6H, s), $\nu_{max.}$ (Nujol) 3250 and 1785 cm^{-1}.

(*b*) A solution of benzimidazole (1·20 g) and dimethyl 2-azamalonate [25] (1·30 g) in acetone (100 ml) was left at 20° for 10 min, then evaporated to dryness. The residue was triturated with a small volume of ether to give the salt (1·95 g), m.p. 124—126°, identical by i.r. and u.v. spectroscopy and by mixed m.p. with the material prepared above.

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