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Central Nervous System Active Compounds. XV* 2-Arylisoxazol-5(2*H*)-ones

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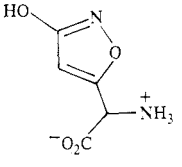
Abstract

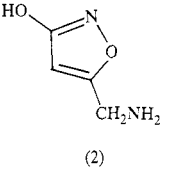
Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate has been treated with a number of chlorinated heterocycles to yield the corresponding substitution products: ethyl 2-(isoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate, ethyl 5-oxo-2-(quinolin-2-yl)-2,5-dihydroisoxazole-4-carboxylate, ethyl 5-oxo-2-(purin-2-yl)-2,5-dihydroisoxazole-4-carboxylate, ethyl 5-oxo-2-(pyrimidin-2-yl)-2,5-dihydroisoxazole-4-carboxylate, ethyl 2-(6-chlorpyridazin-3-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate, ethyl 2-(benzothiazol-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate, 2- and 6-(4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazol-2-yl)pyridine-3-carboxylic acid, ethyl 5-oxo-2-(2-phenylquinazolin-4-yl)-2,5-dihydroisoxazole-4-carboxylate and ethyl 2-(2,4-diaminotriazin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate. The compounds generally cause loss of motor control in mice, but are relatively toxic.

Introduction

Following the isolation of the central nervous system depressant isoxazoles ibotenic acid (1)[1] and muscimol (2)[2] from *Amanita muscaria* and related species, a large number of GABA agonists based on the isoxazole ring have been synthesized and tested.[3,4] We were interested in combining these desirable properties of the isoxazole ring



(1)



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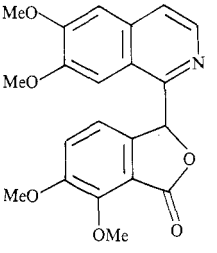

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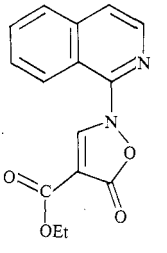

(4)

* Part XIV, *Aust. J. Chem.*, 1984, **37**, 831.

[1] Takemoto, T., Nakajima, T., and Yokobe, T., *Yakugaku Zasshi*, 1964, **84**, 1232.
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[4] See also Allan, R. D., and Johnson, G. A. R., in 'Medicinal Research Reviews' (Ed. G. de Stevens) (John Wiley: New York 1983).

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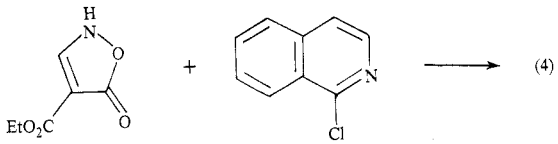
with the mild muscle-relaxing properties of the isoquinolin-1-ylphthalides such as (3),[5] and hence have investigated the synthesis of compounds of the type (4).

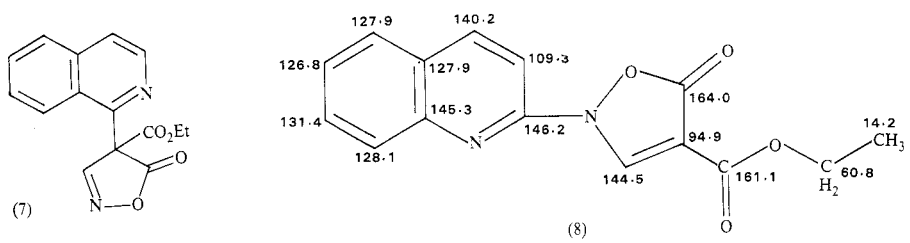
Recently several *N*-substituted isoxazol-5(2*H*)-ones such as the *N*-(cyanoethyl) derivative have been isolated from root exudates of sweet pea seedlings, where they effect protection against infection.[6] In addition, isoxazol-5(2*H*)-ones have been shown to exhibit herbicidal,[7] bactericidal[8] and anticholesteremic and hypolipemic properties.[9] Only a few instances of *N*-alkylation of isoxazol-5(2*H*)-ones have been reported,[10–13] and hence we first investigated the reaction of ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (5)[13] with 1-chloroisoquinoline (6) (Scheme 1).



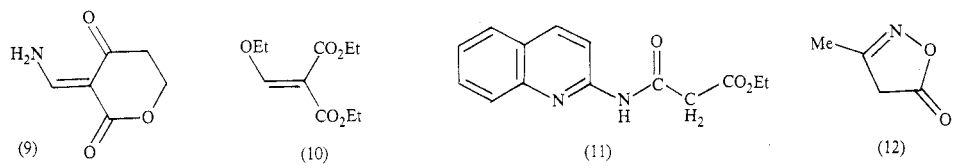
(5) (6) Scheme 1

Discussion

In view of the tautomeric nature of isoxazol-5(2*H*)-ones,[14] structures (4) and (7) were considered for the product from this reaction. The infrared spectrum of (4), and all analogous compounds described below, showed carbonyl absorptions at 1780 and 1700 cm^{-1}, and a one-proton singlet at *c.* 9·3 ppm was characteristic in the ^1H n.m.r. spectrum: such data are compatible with either structure. The ^{13}C



(7) (8)



(9) (10) (11) (12)

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[13] Claisen, L., and Haase, E., *Justus Liebigs Ann. Chem.*, 1897, **297**, 81.
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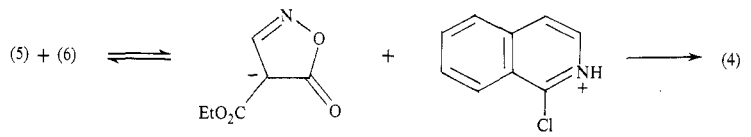

Scheme 2

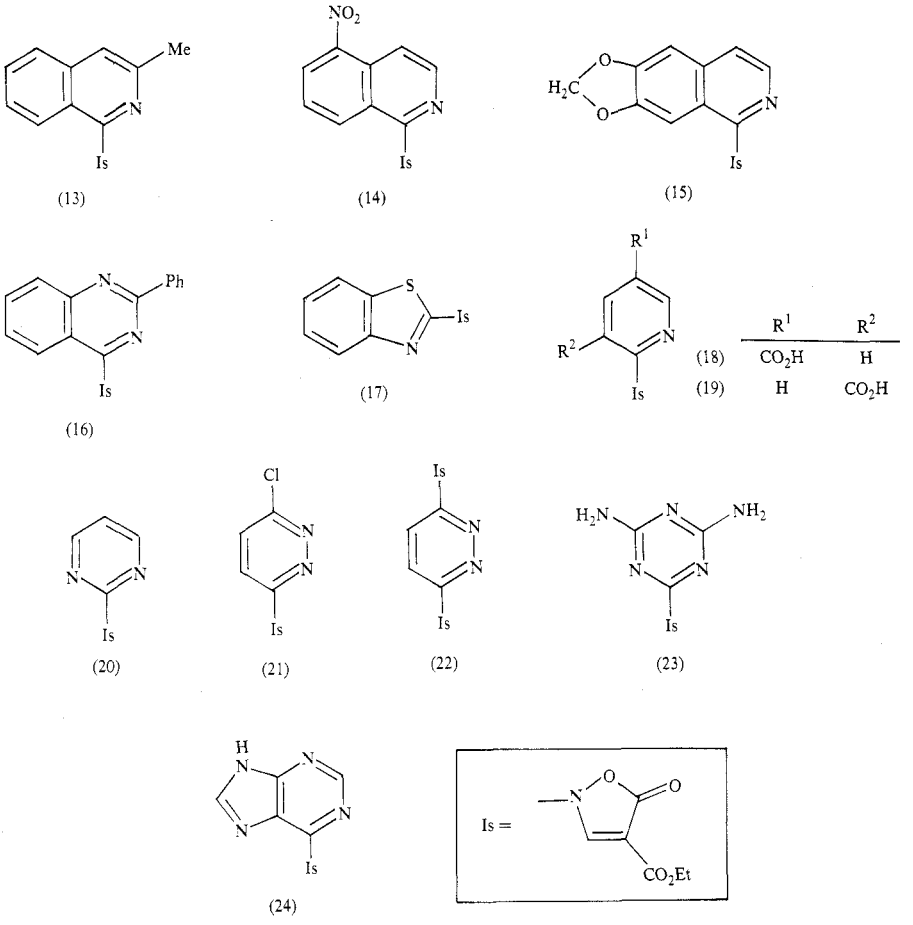

Table 1. Central nervous system activity of isoxazol-5(2*H*)-ones

Activity: L, compound causes loss of muscle control; IA, inactive below lethal dose. Dose values indicate minimum levels at which activity observed (mg/kg); LD, minimum lethal dose

Compound	Activity	Dose	LD	Compound	Activity	Dose	LD
(4)	L	35	100	(19)	IA		> 300
(13)	IA		90	(20)	L	80	200
(14)	L	45	100[A]	(21)	L	50	> 200
(8)	L	50	200[A]	(22)	L	90	> 200
(15)	L	40	200[A]	(23)	L	70	150[A]
(16)	IA		180	(24)	L	105	> 200
(17)	L	70	200				
(18)	L	130	200				

[A] Convulsions.

n.m.r. spectrum showed that all carbon atoms were sp^2-hybridized, thus excluding (7). The suggested assignments for the quinoline analogue (8) are as shown. In particular, the resonance of the quaternary carbon at C4 at 94·93 ppm is very similar to that in model compounds (9)[15] and (10), where the β-enamine or enol carbon resonates at 96·95 and 106·38 respectively. The quaternary sp^3-hybridized carbon in structure (7) would be expected to have a chemical shift of around 62 ppm. The structure of (8) was confirmed by basic hydrolysis, which allowed the isolation of the malonamide (11), whose mode of formation is delayed for a subsequent report, but which shows clearly the mode of attachment of the isoxazole ring to the quinoline moiety.

In view of the fact that 3-methylisoxazol-5(4*H*)-one (12) did not react with 1-chloroisoquinoline under similar conditions, it is assumed that the isoquinoline is sufficiently basic to form the nucleophilic anion of (5), but not of the less acidic[16] (12). The reaction in Scheme 1 is thus modified to Scheme 2. In some of the other substitution reactions described below, the use of base to generate the isoxazolinone anion was useful.

A number of analogous 2-isoquinolinylisoxazol-5(2*H*)-ones (13)–(15) were prepared by the same procedure as for (4). To gain a representative group of compounds for biological testing, the reaction was extended to the preparation of compounds (16)–(24). The poor nucleophilicity of (5) prevented reaction with any but the most reactive heterocyclic systems. Successful reaction conditions were achieved by brief heating at 130° either neat or in nitrobenzene: both (5) and the products were found to be unstable to more than 15 min under such conditions.

Biological Testing

The preliminary screening, by intraperitoneal injection into mice, was carried out as previously described,[17,18] and results are shown in Table 1.

Experimental

Experimental details have been given in previous parts of this series.

Ethyl 2-(Isoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (4)

1-Chloroisoquinoline (245 mg, 1·5 mmol) and ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (5)[13] (236 mg, 1·5 mmol) were refluxed in distilled ethanol (30 ml) for 4 h. On cooling, an off-white solid precipitated (150 mg). The solvent was removed to give additional solid material (250 mg). The combined material was recrystallized from ethyl acetate to give *ethyl 2-(isoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate* (4) (389 mg, 92%), m.p. 138° (Found: C, 63·4; H, 4·4; N, 9·8. $C_{15}H_{12}N_2O_4$ requires C, 63·4; H, 4·3; N, 9·8%). ν_{max} 1780, 1770, 1700 cm^{-1}. N.m.r. δ 9·40, s, 1H, H3; 8·75–8·38, b, 1H, ArH; 8·25, s, 1H, ArH; 8·00–7·43, m, 4H, ArH; 4·38, q, *J* 7 Hz, 2H, CH_2CH_3; 1·38, t, *J* 7 Hz, 3H, CH_2CH_3. Mass spectrum *m/e* 284.

When equimolar amounts of the reagents were heated at 130° for 10 min, the product was a 1 : 1 mixture of (4) and ethyl cyanoacetate, separable by preparative t.l.c.

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[16] De Sarlo, F., and Dini, G., *J. Heterocycl. Chem.*, 1967, **4**, 533.
[17] Hutchison, G. I., Prager, R. H., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2477.
[18] Kerr, D. I. B., Dennis, B. J., Breuker, E. L., Prager, R. H., Ward, A. D., and Duong, T., *Brain Res.*, 1976, **110**, 413.

Ethyl 2-(3-Methylisoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (13)

This *carboxylate*, m.p. 146–147°, was prepared by the above procedure, in 90% yield (Found: C, 64·7; H, 5·0; N, 9·6. $C_{16}H_{14}N_2O_4$ requires C, 64·4; H, 4·7; N, 9·4%). ν_{max} 1780, 1775, 1700 cm^{-1}. N.m.r. δ 9·36, s, 1H, H3; 8·66–7·20, m, 5H, ArH; 4·36, t, J 7 Hz, 2H, CH_2CH_3; 2·63, s, 3H, CH; 1·42, t, J 7 Hz, 3H, CH_2CH_3. Mass spectrum *m/e* 296.

Ethyl 2-(5-Nitroisoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (14)

This *carboxylate*, m.p. 169–170°, was prepared by the above procedure in 92% yield (Found: C, 54·4; H, 3·5; N, 12·7. $C_{15}H_{11}N_3O_6$ requires C, 54·7; H, 3·4; N, 12·7%). ν_{max} 1785, 1780, 1710, 1530, 1340 cm^{-1}. N.m.r. δ 9·53, s, 1H, H3; 9·06, d, J 9 Hz, 1H, ArH; 8·73–8·06, m, 3H, ArH; 7·93, d, J 9 Hz, 1H, ArH; 4·33, q, J 6 Hz, 2H, CH_2CH_3; 1·38, t, J 6 Hz, 3H, CH_2CH_3. Mass spectrum *m/e* 339.

Ethyl 2-(6,7-Methylenedioxyisoquinolin-1-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (15)

This *carboxylate*, m.p. 184°, was prepared by the above procedure in 54% yield (Found: C, 58·4; H, 3·9; N, 8·0. $C_{16}H_{12}N_2O_6$ requires C, 58·5; H, 3·6; N, 8·5%). ν_{max} 1784, 1710 cm^{-1}. N.m.r. δ 9·33, s, 1H, H3; 8·13, d, J 6 Hz, 1H, H3′; 7·83, s, 1H, H8′; 7·50, d, J 6 Hz, 1H, H4′; 7·16, s, 1H, H5′; 6·20, s, 2H, OCH_2O; 4·36, q, 2H, CH_2CH_3; 1·41, t, 3H, OCH_2CH_3. Mass spectrum *m/e* 328.

Ethyl 5-Oxo-2-(quinolin-2-yl)-2,5-dihydroisoxazole-4-carboxylate (8)

A mixture of 2-chloroquinoline (640 mg, 4 mmol) and (5) (620 mg, 4 mmol) in nitrobenzene (1 ml) was stirred at 140° for 10 min. The mixture was diluted with light petroleum (10 ml) and the product recrystallized from benzene/light petroleum and then ethyl acetate to give the *carboxylate* (8) (940 mg) as colourless needles, m.p. 157° (Found: C, 63·1; H, 4·6; N, 9·8%; $M^{+\cdot}$ 284·0791. $C_{15}H_{12}N_2O_4$ requires C, 63·4; H, 4·3; N, 9·8%; $M^{+\cdot}$ 284·0797). ν_{max} 1790, 1705, 1560 cm^{-1}. N.m.r. δ 9·30, s, 1H; 8·20, d, J 8 Hz, 1H; 7·4–7·8, m, 5H; 4·18, q, J 7 Hz, 2H; 1·33, t, J 7 Hz, 3H.

Ethyl 3-Oxo-3-(quinolin-2-ylamino)propanoate (11)

(i) The isoxazol-5(2*H*)-one (8) (500 mg) was dissolved in 20% aqueous sodium hydroxide (10 ml), and kept at 20° for 10 h. The reaction mixture was neutralized and the product collected. The product was partitioned between aqueous sodium carbonate and dichloromethane, the organic phase yielding the *propanoate* (200 mg) after recrystallization from acetone/water, m.p. 153°, identical with that of the authentic sample prepared below (Found: $M^{+\cdot}$ 258·1001. $C_{14}H_{14}N_2O_3$ requires $M^{+\cdot}$ 258·1004).

(ii) 2-Aminoquinoline (210 mg, 1·5 mmol) and diethyl malonate (320 mg, 2 mmol) were heated at 180° for 3 h. The solid product (200 mg) was recrystallized from aqueous acetone as colourless needles, m.p. 153° (Found: C, 65·5; H, 5·5; N, 11·2. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·5; N, 10·9%). ν_{max} 3250, 1735, 1675, 1600 cm^{-1}. N.m.r. δ 7·1–8·2, m, 7H (ArH, NH); 4·13, q, J 8 Hz, 2H; 3·47, s, 2H; 1·23, t, J 8 Hz, 3H.

Ethyl 5-Oxo-2-(2-phenylquinazolin-4-yl)-2,5-dihydroisoxazole-4-carboxylate (16)

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (236 mg, 1·5 mmol) and 4-chloro-2-phenylquinazoline (360 mg, 1·5 mmol) were refluxed in a mixture of dichloromethane (20 ml) and triethylamine (3 drops) for 10 h. The cooled mixture was washed with water, dried and evaporated, and the product crystallized from ethyl acetate to give the *carboxylate* (16) as colourless needles, m.p. 191° (Found: C, 66·6; H, 4·3; N, 11·3%; $M^{+\cdot}$ 361·1059. $C_{20}H_{15}N_3O_4$ requires C, 66·5; H, 4·2; N, 11·6%; $M^{+\cdot}$ 361·1062). ν_{max} 1785, 1705, 1610 cm^{-1}. N.m.r. δ 9·47, s, 1H; 7·3–8·6, m, 9H; 4·30, q, J 8 Hz, 2H; 1·42, t, J 8 Hz, 3H.

Ethyl 2-(Benzothiazol-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (17)

A mixture of 2-chlorobenzothiazole (510 mg, 3 mmol) and (5) (470 mg, 3 mmol) was heated at 130° for 15 min. When cold, the mixture was dissolved in dichloromethane and washed with water and evaporated. The product (880 mg) was recrystallized from ethyl acetate to give the *carboxylate*

(17) (500 mg), m.p. 174° (dec.) (Found: C, 54·1; H, 3·5; N, 9·9%; $M^{+\cdot}$ 290·0355. $C_{13}H_{10}N_2O_4S$ requires C, 53·8; H, 3·5; N, 9·7%; $M^{+\cdot}$ 290·0361). ν_{max} 1800 (infl.), 1790, 1705, 1560 and 1520 cm^{-1}. N.m.r. δ 9·00, s, 1H; 7·3–7·8, m, 4H; 4·25, q, *J* 7 Hz, 2H; 1·32, t, *J* 7 Hz, 3H.

The mother liquors contained ethyl cyanoacetate (100 mg), identified by direct spectral comparison.

6-(4-Ethoxycarbonyl-5-oxo-2,5-dihydroisoxazol-2-yl)pyridine-3-carboxylic Acid (18)

Equimolar amounts of 6-chloronicotinic acid and (5) were heated in nitrobenzene at 140° for 10 min. The cooled reaction mixture was diluted with light petroleum, the precipitate washed well, and the *carboxylic acid* (65%) recrystallized from water as pale yellow needles, m.p. 224° (dec.). The reaction appears to have occurred immediately on solution of the reagents. There was no reaction between the reagents after 3 h at 65° in tetrahydrofuran (Found: C, 51·6; H, 3·5; N, 10·1%; $M^{+\cdot}$ 278·0546. $C_{12}H_{10}N_2O_6$ requires C, 51·8; H, 3·6; N, 10·1%; $M^{+\cdot}$ 278·0539). ν_{max} 1770, 1700, 1675, 1600, 1580, 1560 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 9·55, s, 1H; 8·87, d, *J* 3 Hz, 1H; 8·40, dd, *J* 8 Hz, 3 Hz, 1H; 7·53, d, *J* 8 Hz, 1H; 4·43, q, *J* 7 Hz, 2H; 1·32, t, *J* 7 Hz, 3H.

2-(4-Ethoxycarbonyl-5-oxo-2,5-dihydroisoxazol-2-yl)pyridine-3-carboxylic Acid (19)

The *carboxylic acid* (19) was prepared as above (68%), 1·5 equiv. of (5) being used. The product was recrystallized from water as colourless needles, m.p. 170°. The use of tetrahydrofuran or dimethylformamide as a solvent for the reaction was unsatisfactory (Found: C, 51·7; H, 3·3; N, 9·8%; $M^{+\cdot}$ 278·0541. $C_{12}H_{10}N_2O_6$ requires C, 51·8; H, 3·6; N, 10·1%; $M^{+\cdot}$ 278·0539). ν_{max} 2600–3200, br, 1790, 1770, 1750, 1730, 1705 (infl.) 1695 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 9·33, s, 1H; 8·50, dd, *J* 2 Hz, 5 Hz, 1H; 8·17, dd, *J* 2 Hz, 8 Hz, 1H; 7·43, dd, *J* 5 Hz, 8 Hz, 1H; 4·27, q, *J* 7 Hz, 2H; 1·30, t, *J* 7 Hz, 3H.

Ethyl 5-Oxo-2-(pyrimidin-2-yl)-2,5-dihydroisoxazole-4-carboxylate (20)

Equimolar quantities of (5) and 2-chloropyrimidine were heated neat as for the preparation of the benzothiazole (17). In ethanol as used for (4), there was no reaction. The crude product consisted of (20) and ethyl cyanoacetate in the ratio of 7·9 to 1. Recrystallization from ethyl acetate gave the off-white *carboxylate* (20), (62%), m.p. 165° (Found: C, 51·4; H, 3·9; N, 17·9; $M^{+\cdot}$ 235·0591. $C_{10}H_9N_3O_4$ requires C, 51·1; H, 3·9; N, 17·9%; $M^{+\cdot}$ 235·0593). ν_{max} 1780, 1690, 1615 cm^{-1}. N.m.r. δ 9·18, s, 1H; 8·55, d, *J* 5 Hz, 2H; 7·13, t, *J* 5 Hz, 1H; 4·28, q, *J* 8 Hz, 2H; 1·33, t, *J* 8 Hz, 3H.

Reaction of 3,6-Dichloropyridazine with Ethyl 5-Oxo-2,5-dihydroisoxazole-4-carboxylate (5)

(i) Equimolar quantities of 3,6-dichloropyridazine[19] and (5) were refluxed in ethanol for 3 h. On cooling, *ethyl 2-(6-chloropyridazin-3-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate* (21) (75%) crystallized, and was recrystallized from ethyl acetate/light petroleum as colourless crystals, m.p. 166° (Found: C, 44·9; H, 2·9; N, 15·6; $M^{+\cdot}$ 269·0208. $C_{10}H_8ClN_3O_4$ requires C, 44·65; H, 3·0; N, 15·6%; $M^{+\cdot}$ 269·0203). ν_{max} 1790, 1700, 1575, 1550 cm^{-1}. N.m.r. δ 9·37, s, 1H; 7·58, s, 2H; 4·32, q, *J* 7 Hz, 2H; 1·37, t, *J* 7 Hz, 3H. When the procedure used for the preparation of (17) was adopted, the yield was 66%.

(ii) When 2 equiv. of (5) were used and the ethanolic solution refluxed overnight, or better, the reagents were heated neat at 130° for 15 min, the product was the *bis adduct* (22). It was purified by washing with dichloromethane and recrystallization from dimethylformamide/benzene as pale yellow needles, m.p. 210° (dec.) (Found: $M^{+\cdot}$ 390·0809. $C_{16}H_{14}N_4O_8$ requires $M^{+\cdot}$ 390·0817). ν_{max} 1775, 1765 (infl.), 1750 (infl.), 1705, 1560 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 9·53, s, 2H; 7·98, s, 2H; 4·03, q, *J* 7 Hz, 4H; 1·37, t, *J* 7 Hz, 6H.

Ethyl 2-(2,4-Diaminotriazin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (23)

2-Choro-4,6-diamino-1,3,5-triazine (290 mg; 2 mmol) and (5) (310 mg, 2 mmol) were heated in nitrobenzene (4 ml) at 140° for 15 min. The cooled mixture was diluted with light petroleum,

[19] Coad, P., Coad, R. A., Clough, S., Hyepock, J., Salisbury, R., and Wilkins, C. L., *J. Org. Chem.*, 1963, **28**, 218.

and the product washed with cold sodium bicarbonate solution, and recrystallized from dimethylformamide/water (1 : 1) to yield the *carboxylate* (23) as pale yellow needles, m.p. 280° (dec.) (400 mg) (Found: C, 40·4; H, 3·8; N, 31·9; $M^{+\cdot}$ 266·0768. $C_9H_{10}N_6O_4$ requires C, 40·6; H, 3·8; N, 31·6%; $M^{+\cdot}$ 266·0764). ν_{max} 1780, 1765, 1705, 1650, 1625, 1590 cm^{-1}. N.m.r. δ 9·13, s, 1H; 7·05, br s, 4H, exch; 4·23, q, *J* 7 Hz, 2H; 1·28, t, *J* 7 Hz, 3H.

Ethyl 5-Oxo-2-(purin-6-yl)-2,5-dihydroisoxazole-4-carboxylate (24)

6-Chloropurine (100 mg) and (5) (250 mg) were heated in nitrobenzene (4 ml) at 140° for 15 min. The mixture was cooled, diluted with light petroleum (5 ml) and the product (200 mg) washed with dichloromethane and dilute hydrochloric acid, and then recrystallized from dimethylformamide to give the colourless *carboxylate* (24) m.p. >220° (dec.) (Found: C, 47·6; H, 3·3; N, 25·8%; $M^{+\cdot}$ 275·0647. $C_{11}H_9N_5O_4$ requires C, 48·0; H, 3·3; N, 25·5%; $M^{+\cdot}$ 275·0654). ν_{max} 1790, 1725, 1700, 1635, 1620 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 9·77, s, 1H; 8·58, s, 1H; 8·50, s, 1H; 4·20, q, *J* 7 Hz, 2H; 1·28, t, *J* 7 Hz, 3H.

Unsuccessful Reactions

The isoxazole-4-carboxylate (5) failed to give more than traces of the desired product, by using any of the above preparative methods, with 2-bromopyridine, 2,5-dibromo-1,3,4-thiadiazole and 2-chloropyrazine. In the latter case decomposition occurred at the higher temperatures.

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