492. *Inhibitors of Flavoprotein Enzymes.*

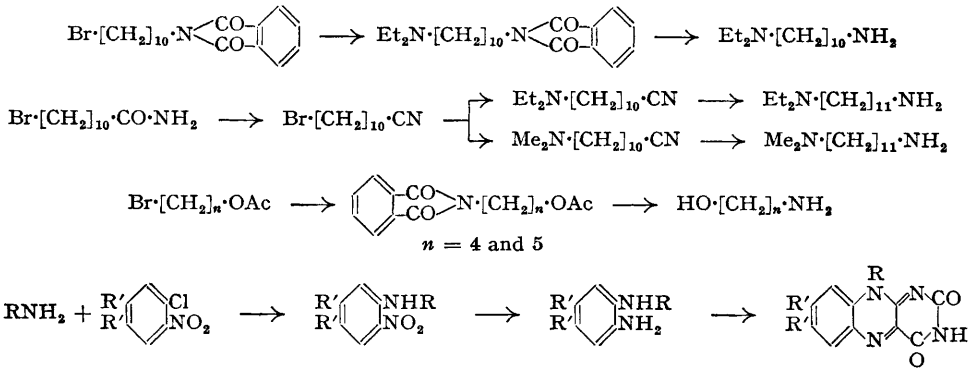
By R. B. Barlow.

Some 9-substituted 6 : 7-dichloro*iso*alloxazines and 1-substituted benziminazoles have been synthesized and tested as inhibitors of the D-amino-acid oxidase of acetone-dried pig kidney.

For several years it has been thought that molecules which have some features in common with the prosthetic group of an enzyme may inhibit it. Hellerman, Lindsay, and Bovarnick (*J. Biol. Chem.*, 1946, **163**, 553) showed that a large number of compounds, including auramine, quinine, and a number of antimalarial drugs, would inhibit the D-amino-acid oxidase of lamb kidney. The mechanism of the inhibition was not always the same—some of the compounds combined with proteins in a general way—but quinine at least appeared to compete with flavine–adenine dinucleotide (FAD) for the apoenzyme. Likewise, Singer and Kearney (*Arch. Biochem.*, 1949, **21**, 242; 1950, **27**, 348) have found that flavin analogues would inhibit the L-amino-acid oxidase of certain snake venoms. Although both enzymes have FAD as prosthetic group, the effect of a compound is not necessarily the same on each. Riboflavin, for example, is an inhibitor of the L-amino-acid oxidase but can function as prosthetic group for the D-enzyme. Dichloroflavin (Kuhn, Weygand, and Möller, *Ber.*, 1943, **76**, 1044) also inhibits the former, but is reported by Karrer and Ruckstuhl (*Bull. Schweiz. Akad. Med. Wiss.*, 1945, **1**, 236) to have no effect, even when phosphorylated, on the latter. It is remarkable, however, that both enzymes are only relatively feebly inhibited by the synthetic compounds; concentrations as high as 10^{-4}—10^{-3}M. are required.

A series of 6 : 7-dichloro-9-dialkylaminoalkyl*iso*alloxazines described in a previous paper (Barlow and Ing, *J.*, 1950, 713) had been found to inhibit the D-amino-acid oxidase of pig kidney in concentrations of this order. In place of the pyrophosphate linkage of FAD these compounds contain a basic group, and it was thought that movement of this further from the *iso*alloxazine nucleus, or replacement of it by hydroxyl, would produce more active molecules. The adenine part of FAD may also be involved in the formation of the prosthetic group–apoenzyme complex, so benziminazole and two 1-substituted benziminazoles were examined.

The compounds made are listed in Table I. They were obtained from the appropriate *o*-nitroaniline (Table II) by catalytic reduction to the *o*-phenylenediamine and treatment with alloxan or formic acid. Amino-compounds suitable for condensation with *o*-chloronitrobenzene or 2 : 4 : 5-trichloronitrobenzene were prepared by the routes shown below.



The basically substituted *iso*alloxazines were prepared from the *o*-phenylenediamines and alloxan by the action of hydrogen chloride (Kühling, *Ber.*, 1891, **24**, 2363). The exact procedure

TABLE I.

6 : 7-*Dichloro*iso*alloxazines.*

Prep.	9-Substituent.	M. p.† ‡	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
(1) *a*	$[CH_2]_{10}\cdot NEt_2,HCl$	140°	$C_{24}H_{34}O_2N_8Cl_2,2H_2O$	50·9	6·4	—	50·9	6·7	—
(2)	$[CH_2]_{10}\cdot NEt_2$ (Picrate)	180	$C_{30}H_{36}O_9N_8Cl_2,H_2O$	49·0	5·3	14·7	48·6	5·1	15·1
(3) *a*	$[CH_2]_{11}\cdot NMe_2$ (Picrate)	180	$C_{29}H_{34}O_9N_8Cl_2,H_2O$	47·8	5·0	15·0	47·9	4·95	15·4
(4) *a*, *b*	$[CH_2]_2\cdot OH$	294—296	$C_{12}H_8O_3N_4Cl_2$	43·8	2·7	17·0	44·0	2·45	17·1
(5) *a*, *b*	$[CH_2]_3\cdot OH$	268	$C_{13}H_{10}O_3N_4Cl_2,H_2O$ §	43·4	3·4	15·5	43·5	3·3	15·6
(6) *b*	$[CH_2]_4\cdot OH$	274—276	$C_{14}H_{12}O_3N_4Cl_2$	47·3	3·3	15·8	47·3	3·4	15·8
(7) *b*	$[CH_2]_5\cdot OH$	255—256	$C_{15}H_{14}O_3N_4Cl_2$	48·9	4·0	14·9	48·8	3·6	15·2

Method: *a*, HCl–MeOH; *b*, H_3BO_3–$CH_3\cdot CO_2H$. † With decomposition.

‡ Solvents used for recrystallisation of compounds were as follows: (1) ethanol; (2), (3), and (5) aqueous alcohol; (4) ethylene glycol; (6) and (7) *n*-butanol.

§ Found: H_2O, 4·98. $C_{13}H_{10}O_3N_4Cl_2,H_2O$ requires H_2O, 5·01%.

Benziminazoles.

1-Substituent.	M. p. (or b. p.).	Cryst. from:	Formula.	Found, %. C.	H.	Required, %. C.	H.
$[CH_2]_2\cdot OH$	103° (181/0·1 mm.)	C_6H_6	$C_9H_{10}ON_2$	66·5	5·83	66·7	6·17
$[CH_2]_2\cdot OH$ (Picrate)	204	$COMe_2$	$C_{15}H_{13}O_8N_5$	46·3	3·09	46·0	3·32
$[CH_2]_3\cdot NEt_2$	(142/0·05 mm.) *	—	$C_{14}H_{21}N_3$	72·4	9·02	72·7	9·09
$[CH_2]_3\cdot NEt_2,2HBr$	176	EtOH–Et_2O	$C_{14}H_{23}N_3Br_2$	42·9	5·60	42·7	5·85

* n_D^{16} 1·5462.

TABLE II.

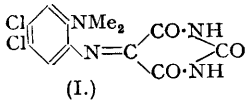
o-Nitroanilines.

Substituents in positions: 4.	5.	*N*-.	M. p.†	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
(1) Cl	Cl	$[CH_2]_{10}\cdot NEt_2,HClO_4$	80°	$C_{20}H_{34}O_6N_3Cl_3,H_2O$	45·0	6·8	7·9	44·8	6·7	7·84
(2) Cl	Cl	$[CH_2]_{11}\cdot NMe_2$	40	$C_{19}H_{31}O_2N_3Cl_2$	56·6	7·5	—	56·5	7·7	—
(3) Cl	Cl	$[CH_2]_{11}\cdot NMe_2$ (Picrate)	88	$C_{25}H_{34}O_9N_6Cl_2$	47·5	5·3	—	47·4	5·4	—
(4) Cl	Cl	$[CH_2]_{11}\cdot NEt_2,HClO_4$	70	$C_{21}H_{36}O_6N_3Cl_3$	47·3	6·95	—	47·4	6·8	—
(5) Cl	Cl	$[CH_2]_2\cdot OH$	143	$C_8H_8O_3N_2Cl_2$	38·2	3·4	—	38·2	3·2	—
(6) Cl	Cl	$[CH_2]_3\cdot OH$	99	$C_9H_{10}O_3N_2Cl_2$	40·9	3·8	10·7	40·7	3·8	10·6
(7) Cl	Cl	$[CH_2]_4\cdot OH$	73	$C_{10}H_{12}O_3N_2Cl_2$	43·2	4·3	10·2	43·0	4·3	10·0
(8) Cl	Cl	$[CH_2]_5\cdot OH$	92	$C_{11}H_{14}O_3N_2Cl_2$	45·2	4·8	—	45·0	4·8	—
(9) H	H	$[CH_2]_3\cdot NEt_2,HCl$ *	179—180	$C_{13}H_{22}O_2N_3Cl_2$	54·4	7·8	—	54·4	7·7	—
(10) H	H	$[CH_2]_2\cdot OH$	72	$C_8H_{10}O_3N_2$	53·0	5·4	—	52·7	5·5	—

* Obtained by Kipnis, Weiner, and Spoerri (*J. Amer. Chem. Soc.*, 1944, **66**, 1446) as picrate, m. p. 122—123°.

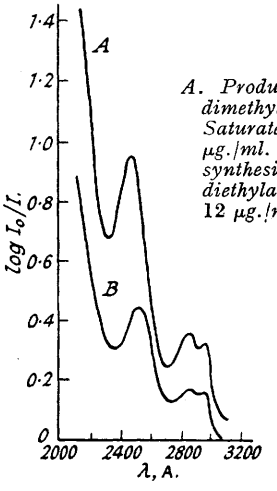
† Compound (2) was crystallised from petrol (b. p. 40—60°), (3) from ethanol–acetone, (5) from methanol, and the others from ethanol.

was the same as that previously described (Barlow and Ing, *loc. cit.*) but the yields of these long-chain substances were very low. No pure 6 : 7-dichloro-9-11′-diethylamino-*n*-undecyl*iso*alloxazine could be isolated either as hydrochloride or as picrate. In several experiments a second product was formed which, in one instance, could be purified. It was less soluble in alcohol than the corresponding *iso*alloxazine and much lighter in colour, and had a completely different absorption spectrum in ultra-violet light. It may be an " anil " such as those obtained by Kühling (*Ber.*, 1893, **26**, 540), Kühling and Käselitz (*Ber.*, 1906, **39**, 1314), Kuhn and Reinemund (*Ber.*, 1934, **67**, 1932), and Tishler, Wellman, and Ladenburg (*J. Amer. Chem. Soc.*, 1945, **67**, 2165). In order to investigate this point, 4 : 5-dichloro-2-dimethylaminoaniline was treated with alloxan dissolved in acetic acid. The product was recrystallized from ethanol and had an ultra-violet absorption spectrum similar to that of the second product of the *iso*alloxazine synthesis. Unfortunately, analysis showed that the former is not the anil (I) because it contains an extra molecule of water which cannot be removed by drying.



(I.)

Attempts to prepare these basically substituted *iso*alloxazines by Kuhn and Weygand's method (*Ber.*, 1935, **68**, 1282)—acetic acid as solvent, boric acid as catalyst—gave only intractable tars. The 6 : 7-di-chloro-9-ω-hydroxy-*n*-alkyl*iso*alloxazines, however, were best made by this means. The 2′-hydroxyethyl and 3′-hydroxypropyl compounds were obtained in moderate yield when the condensation was performed in methanolic hydrogen chloride, but only a very little of the 4′-hydroxybutyl and 5′-hydroxyamyl homologues could be isolated in a pure state. By the use of Kuhn and Weygand's method, these four *iso*alloxazines were obtained in excellent yield.



A. Product from 4 : 5-*dichloro*-2-*dimethylaminoaniline and alloxan. Saturated solution in water,* ca. 50 μg./ml. *B. Second product in synthesis of* 6 : 7-*dichloro*-9-10′-*diethylamino*-n-*decyl*isoalloxazine, 12 μg./ml. *in water.*

The synthesis of the benziminazoles presented no difficulty.

The compounds were tested on the D-amino-acid oxidase of acetone-dried pig kidney. The substrate was DL-methionine. This enzyme, unlike Singer and Kearney's L-amino-acid oxidase (*loc. cit.*), appears to be unaffected by phosphate. There was no appreciable difference in the rate of oxidation of the substrate when the phosphate buffer normally used was replaced by a borate buffer of the same pH. On the other hand, experiments suggested that the inhibitory activity of 10^{-3}M-solutions of 6 : 7-dichloro-9-5′-diethylamino-*n*-pentyl*iso*alloxazine hydrochloride (Barlow and Ing, *loc. cit.*) was slightly potentiated (25—50%) by phosphate. This effect could not be detected when the inhibitor was more dilute; 10^{-4}M-solutions inhibited the enzyme to a small but definite extent irrespective of the presence of phosphate. A similar small effect was shown by solutions of 6 : 7-dichloro-9-10′-diethylamino-*n*-decyl*iso*alloxazine hydrochloride, and of the 5′-hydroxy-*n*-amyl and 4′-hydroxy-*n*-butyl compounds, which were in the region of 10^{-4}M. This concentration is the maximum which can be achieved in these experiments for the last two, and the 3′-hydroxy-*n*-propyl and 2′-hydroxyethyl compounds are even less soluble. This low order of activity at the maximum solubility may account for Karrer and Ruckstuhl's report (*loc. cit.*) that dichloroflavin is inactive. Such a small effect would lie within the limits of error of their experiments. The inactivity of the calcium salt of dichloroflavin phosphate, which is presumably reasonably soluble in water, would seem to be indisputable.

Benziminazole and the substituted benziminazoles were all virtually inactive at concentrations as high as 10^{-2} to 2×10^{-3}M.

From these results it appears that alteration of the nature of the 9-substituent of these 6 : 7-dichloro*iso*alloxazines makes little difference to their powers of inhibiting this D-amino-acid oxidase. Coupled with the inactivity of the benziminazoles, this suggests that FAD is held on to this particular apoenzyme mainly by the *iso*alloxazine nucleus.

Experimental.

(Analyses are by Mr. J. M. L. Cameron and Miss H. H. Kennaway. All m. p.s are uncorrected.)

Dialkylaminoalkylamines and Amino-alcohols.—10-*Bromo*-n-*decylphthalimide* was prepared by heating decamethylene dibromide (5 mols.) with potassium phthalimide (2 mols.) for 3 hours at 160—180°. Excess of dibromide was distilled off in a vacuum, and the residue shaken with water and recrystallized from ethanol. This solid was extracted in a Soxhlet apparatus with light petroleum (b. p. 40—60°). The material which separated from the petroleum in the extraction flask was filtered off and recrystallized from this solvent; it had m. p. 59° (yield 20%, based on the amount of dibromide used) (Found: N, 4·1. $C_{18}H_{24}O_2NBr$ requires N, 3·8%). The bromodecylphthalimide was heated with diethylamine (2·5 mols.) under reflux for 4 hours. Excess of diethylamine was distilled off, and the residue treated with aqueous sodium carbonate (1 mol.) and extracted with chloroform. 10-Diethylamino-*n*-decylphthalimide was obtained as an oil after removal of the chloroform and, without further purification, was decomposed with hydrazine hydrate (1 mol.) followed by excess of concentrated hydrochloric acid. The phthalylhydrazide was filtered off, and the filtrate evaporated to dryness. The residue was dissolved in a small amount of water, made strongly alkaline with solid potassium hydroxide, and extracted with benzene. The extract was dried and distilled. The yield of 10-*diethylamino*-n-*decylamine*, b. p. 157—160°/7 mm., n_D^{16} 1·4585, was 66% (Found: N, 11·8. $C_{14}H_{32}N_2$ requires N, 11·9%).

ω-Bromo-*n*-undecenoamide (Goldberg and Kelly, *J.*, 1947, 1369) was dehydrated by mixing it with an equal weight of phosphoric oxide and warming it to 140—150° in an oil-bath. If this temperature was exceeded or maintained for more than a few minutes, the yield of nitrile was appreciably reduced. The fused mass was allowed to cool, and treated with water. The resulting nitrile was extracted with a large volume of light petroleum (b. p. 40—60°), and the extract dried and distilled. The product (70%) was obtained colourless by redistillation, with b. p. 180—181°/9 mm., n_D^{18} 1·4738 (Found: C, 53·7; H, 7·8. Calc. for $C_{11}H_{20}NBr$: C, 53·7; H, 8·1%). Goldberg and Kelly (*loc. cit.*) record b. p. 158—164°/4 mm. The nitrile was heated under reflux for 4 hours with a large excess of a 33% solution of dimethylamine in alcohol. The mixture was concentrated and treated with aqueous sodium carbonate (1 mol.). The ω-*dimethylamino*-n-*undecenonitrile* was extracted with chloroform. The extract was dried and twice distilled; the product (60%) had b. p. 159—160°/9 mm., n_D^{17} 1·4500 (Found: N, 12·7. $C_{13}H_{26}N_2$ requires N, 13·3%). The corresponding *diethylamino-nitrile* was prepared in the same way with anhydrous diethylamine instead of the dimethylamine solution; it had b. p. 174°/6 mm., n_D^{14} 1·4540 (yield, 80—90%) (Found: C, 75·8; H, 12·6. $C_{15}H_{30}N_2$ requires C, 75·6; H, 12·6%).

The nitriles were dissolved in saturated solutions of ammonia in methanol and ethanol, respectively, and reduced at 120° with hydrogen under high pressure and Raney nickel catalyst. The catalyst and solvent were removed and the diamines twice distilled. 11-*Dimethylamino*-n-*undecylamine*, b. p. 156—158°/5·5 mm., n_D^{17} 1·4548, was obtained in 50% yield (Found: N, 12·8. $C_{13}H_{30}N_2$ requires N, 13·1%), and the *diethylamino*-compound, b. p. 162—164°/5·5 mm., n_D^{17} 1·4572, in 80% yield (Found: N, 11·4. $C_{15}H_{34}N_2$ requires N, 11·6%).

In exactly the same way, ethylene cyanohydrin, dissolved in methanolic ammonia, was reduced to 3-aminopropan-1-ol, b. p. 184—186°, in 75% yield. Henry (*Ber.*, 1900, **33**, 3169) records b. p. 187—188°. 4-Amino-*n*-butanol and 5-amino-*n*-pentanol were obtained from the corresponding ω-bromoalkyl acetates. These were heated with potassium phthalimide (1 mol.) at 180° for 3 hours. Unchanged bromoalkyl acetate was distilled off in steam, and the solid residue was recrystallized from ethanol. The first crop consisted of high-melting material and the phthalimidoalkyl acetates were obtained by concentration of the mother-liquors. They were recrystallized from ethanol. The yield of 4-*phthalimido*-n-*butyl acetate*, m. p. 59·5°, was 50% (Found: C, 64·2; H, 5·5; N, 5·4. $C_{14}H_{15}O_4N$ requires C, 64·3; H, 5·75; N, 5·4%), and that of 5-*phthalimido*-n-*amyl acetate*, m. p. 43°, was 33% (Found: N, 5·3. $C_{15}H_{17}O_4N$ requires N, 5·1%).

No precipitate of the phthalylhydrazide salt of the amine was formed unless these phthalimido-compounds were treated with 2 mols. of hydrazine hydrate, for the first molecule hydrolyses the acetate group. After the addition of a slight excess of concentrated hydrochloric acid and separation of the phthalylhydrazide, the filtrates were concentrated in a vacuum. They were then dissolved in water, made alkaline to litmus, and subjected to continuous extraction with benzene. The amino-alcohols are exceedingly soluble in water and not very soluble in benzene or ether. It was not feasible to precipitate them from the aqueous layer by saturating it with solid potassium hydroxide, so it was necessary to continue the extraction for several days. The yield of 4-amino-*n*-butan-1-ol, b. p. 95°/5 mm., n_D^{19} 1·4625, was 33% after 7 days (Found: C, 53·6; H, 12·6. Calc. for $C_4H_{11}ON$: C, 53·9; H, 12·4%). Henry (*loc. cit.*) records b. p. 206°/776 mm. That of 5-amino-*n*-pentan-1-ol, m. p. 29°, b. p. 107°/10 mm., n_D^{17} 1·4610, was 50% after 14 days. Putochin and Lissizin (*Ber.*, 1926, **59**, 629) record m. p. 27—28°, b. p. 221—222°, n_D^{17} 1·4618.

2-*Nitro- and* 4 : 5-*Dichloro*-2-*nitro*-N-ω-*dialkylaminoalkyl- and* -N-ω-*hydroxyalkyl-anilines*.—These *compounds* were all prepared by heating the appropriate amino-compound with a solution of *o*-chloronitrobenzene or 2 : 4 : 5-trichloronitrobenzene (10% excess) and pyridine (1 mol.) in toluene under reflux for 5—12 hours. The toluene and any unused pyridine were distilled off in a vacuum and the residue was extracted with benzene and the extract concentrated. Compounds (5), (10), and (6) (Table II) were not very soluble in this solvent and crystallized out. They were recrystallized from ethanol. The first two were a very deep red, the last was orange. The orange-coloured solutions of the remaining compounds were poured on alumina columns and washed through with benzene. The hydroxyalkyl and dimethylaminoundecyl compounds were all obtained as orange needles from benzene or alcohol but the diethylaminoalkyl compounds could only be isolated as perchlorates. They are listed in Table II together with their m. p.s and the analytical results. The yields of pure material were usually 30—40%.

The iso*Alloxazine Condensation.*—The *o*-nitroanilines were dissolved in dry methanol (basically-substituted ones which had been isolated as salt were first converted into the free base) and reduced with hydrogen and Raney nickel at room pressure and temperature. The catalyst was filtered off, and the filtrate was either treated with dry hydrogen chloride in the manner already described (Barlow and Ing, *loc. cit.*), or, if the boric acid method was to be used, concentrated in a vacuum. In the latter instance, the procedure was the same as that described by Kuhn, Weygand, and Möller (*loc. cit.*). The basically-substituted compounds were isolated from the products of the reaction in methanolic hydrogen chloride by addition of ether in the usual way. When the 6 : 7-dichloro-9-ω-hydroxyalkyl*iso*alloxazines were prepared by this method, they gradually separated from the reaction mixture and were filtered off and recrystallized. In the experiments with boric acid and acetic acid, they came out of solution during the reaction and were left, together with boric acid, when the acetic acid was distilled off. To make sure of the complete elimination of boric acid, the *iso*alloxazines were boiled with water (in which they are not very soluble) before being finally filtered off. They were dried and recrystallized. The yields of pure material were as high as 40—60% when this method was used.

The Benziminazole Condensation.—The *N*-substituted *o*-phenylenediamines, obtained as oils by reduction of the nitro-compounds in the manner described above, were boiled with anhydrous formic acid (70 ml. per 10 millimol. of compound) under reflux for 4—6 hours. The formic acid was distilled off under vacuum. The basically-substituted benziminazole was treated with ammonia solution (*d* 0·88) until alkaline, and extracted with benzene; the alcoholic compound was dissolved in methanol, heated with a trace of sodium methoxide for 1 hour on a water-bath, concentrated, diluted with water, and extracted with chloroform. The extracts were dried and twice distilled in a high vacuum. The yields of pure material were 20—30%.

The *compounds* are listed in Table I together with the analytical results, etc.

The second product formed in the preparation of the basically-substituted *iso*alloxazines was less soluble in alcohol. The compound isolated in the synthesis of the 10′-diethylamino-*n*-decyl*iso*-alloxazine was obtained crystalline by addition to the reaction mixture of a suitable amount of ether. It was recrystallized from alcohol and had m. p. (sinters) 181°, (decomp.) 206°.

The product of the reaction of alloxan with 4 : 5-dichloro-2-dimethylaminoaniline was prepared by heating equimolar quantities in glacial acetic acid 50 ml. per 10 millimol.) on a water-bath for 1 hour. The solution, which had become a deep brown, was left overnight. The acetic acid was distilled off under vacuum, and the residue recrystallized from alcohol until it was colourless (4 times). It did not melt below 300° (Found: C, 41·8; H, 3·2. $C_{12}H_{10}O_3N_4Cl_2$ requires C, 43·7; H, 3·0. $C_{12}H_{12}O_4N_4Cl_2$ requires C, 41·5; H, 3·5%). It was only very slightly soluble in water and its solutions had a greenish fluorescence. The *compound* did not lose weight when dried for 4 hours at 120°/0·5 mm.

Manometric Experiments.—The tests were performed in Warburg manometers at 37·5° with pure oxygen in the gas phase. The centre well contained 0·3 ml. of N-sodium hydroxide. The buffer (1·0 ml.; pH 7·4) and the inhibitor solution (0·4 ml.) were placed in the main compartment, and the substrate (0·4 ml. of 0·1M-DL-methionine) in the side-bulb. The enzyme (0·2 ml. of a buffered extract of the acetone-dried pig-kidney powder) was added at zero hour and gassing was begun. The flasks were equilibrated for 10 minutes before the substrate was tipped in. The time that the enzyme and inhibitor were in contact (usually 20—35 minutes) was noted but did not appear to be connected with the result. Included in each experiment were a thermobarometer and blanks containing (i) buffer and enzyme, (ii) buffer, enzyme, and inhibitor, and (iii) buffer, enzyme, and substrate only.

Results.—Effect of phosphate.

Molar concn. of phosphate:	$1·3 \times 10^{-2}$.	$1·3 \times 10^{-3}$.	$1·3 \times 10^{-4}$.	0.
Oxygen uptake after 15′ (mm.³) (duplicates)	112	112	115	111
	106	117	112	118

Effect of inhibitors.

6 : 7-Dichloro*iso*alloxazines.

9-Substituent.	Molar concn.	Mean % inhibition after 15′.	No. of expts.
$[CH_2]_{10}$·NEt_2,HCl	10^{-4}	12	3
$[CH_2]_5$·OH	10^{-4}	16	4
$[CH_2]_4$·OH	$1·6 \times 10^{-4}$	17	4
$[CH_2]_3$·OH	5×10^{-5}	3	2
$[CH_2]_2$·OH	$1·3 \times 10^{-5}$	5	2

Benziminazoles.

1-Substituent.	Molar concn.	Mean % inhibition after 15′.	No. of expts.
H	8×10^{-3}	9	1
$[CH_2]_3$·NEt_2,2HBr	2×10^{-3}	12	2
$[CH_2]_2$·OH	2×10^{-3}	9	2

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