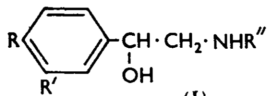
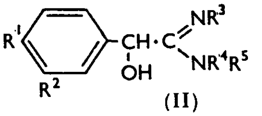
101. *Mandelamidines as Potential Bronchodilators.*

By N. W. Bristow.

Several mandelamidines were prepared by standard methods for pharmacological test, but none had pronounced bronchodilator activity.

The compounds adrenaline (I; $R = R' = OH$, $R'' = Me$), isoprenaline (I; $R = R' = OH$, $R = Pr^i$), and phenylephrine (I; $R = H$, $R' = OH$, $R'' = Me$) are well-known bronchodilators. As part of the synthetic programme of these laboratories, a series of mandelamidines (II) and the related 4 : 5-dihydroglyoxalines (III), structurally analogous to (I), has been prepared. A few of these compounds have been described in the literature, but there is no account of their pharmacological properties. None of them showed more than a slight bronchodilator activity in the guinea-pig aerosol test.


(I)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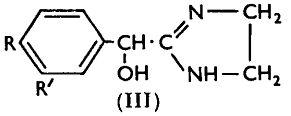
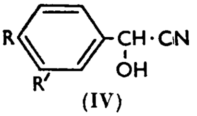

(III)

The mandelonitriles (IV) were prepared from the corresponding aldehydes by standard methods. For the nitriles (IV; $R' = Ph{\cdot}CH_2{\cdot}O$, $R = H$ or $Ph{\cdot}CH_2{\cdot}O$) the method of Butenandt and Schmidt-Thomé [1] had to be used since simpler methods failed. Treating the nitriles in ethereal solution with ethanol and dry hydrogen chloride gave the ethyl mandelimidate hydrochlorides (V), which with ammonia or an amine in ice-cold absolute ethanolic solution gave the corresponding amidines (II). When ethylenediamine was used,[2] intermediate substances, believed to be the 2-aminoethylamidines (VI), were formed. These substances were unstable, losing ammonia readily in hot ethanolic solution, and slowly in the solid state at room temperature, to give the dihydroglyoxalines, which were also formed directly in hot ethanol from the imidate hydrochlorides (cf. I.G. Farbenindustrie [3]), or from the amidinium chlorides.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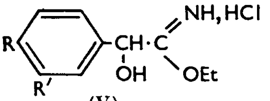
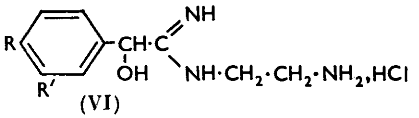

(V)


(VI)

Experimental

m-*Benzyloxybenzaldehyde*.—A mixture of *m*-hydroxybenzaldehyde (41 g., 0·33 mol.), anhydrous potassium carbonate (50 g., 0·36 mol.), benzyl chloride (50 g., 0·39 mol.), sodium iodide (2 g.), and 95% ethanol (150 c.c.) was stirred and refluxed for 4·5 hr. Water (100 c.c.) was added and the mixture was concentrated at 30 mm. to remove ethanol and benzyl chloride and poured into a mixture of N-sodium hydroxide (250 c.c.) and ice (100 g.). The solid product was crushed under the alkaline liquor and collected, washed with water, and drained. It was used in this condition for the preparation of the cyanohydrin; however, the yield of dried material in several runs was 94—100%, and the m. p. was 54° (Rapson and Robinson [4] give m. p. 54°).

3 : 4-*Dibenzyloxybenzaldehyde*.—Similarly, 3 : 4-dihydroxybenzaldehyde gave the dibenzyl ether in quantitative yield, m. p. 89° (Burton and Praill [5] give m. p. 91°).

Preparation of Ethyl Mandelimidate Hydrochlorides.—Mandelonitriles were prepared by three methods : (*a*) mandelonitrile and *m*-methoxymandelonitrile by the method of Corson

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[1] Butenandt and Schmidt-Thomé, *Ber.*, 1938, **71**, 1487.
[2] Sonn, G.P., 615,227.
[3] I.G. Farbenindustrie, B.P., 422,057.
[4] Rapson and Robinson, *J.*, 1935, 1533.
[5] Burton and Praill, *J.*, 1951, 522.

et al.;[6] (*b*) *m*- and *p*-chloro- and 3 : 4-dimethoxy-mandelonitrile by Kostanecki and Lampe's method;[7] (*c*) *m*-benzyloxy- and 3 : 4-dibenzyloxy-mandelonitrile by Butenandt and Schmidt-Thomé's method.[1] The crude nitriles were dissolved in dry ether, and ethanol (1 mol.) and hydrogen chloride (1·2 mols.) were added below 10°. The solutions were stored at 0° for 24—36 hr. and the imidate hydrochlorides were collected, washed with ether, and dried *in vacuo*. There were thus obtained ethyl mandelimidate hydrochloride (56% from benzaldehyde), m. p. 125° (decomp.) (Bayer[8] gives m. p. 124—125°), methyl *m*-methoxy- (18%), m. p. 96° (decomp.) [King *et al.*[9] give m. p. 105° (decomp.)], ethyl *m*-methoxy- (34%), a waxy solid, *m*-chloro- (60%), m. p. 117° (decomp.), *p*-chloro- (65%), m. p. 115° (decomp.), 3 : 4-dimethoxy- (55%), m. p. 129° (decomp.) (Fulton and Robinson[10] give m. p. 139—140°), m-*benzyloxy*- (75%), m. p. 118° (decomp.) (Found: N, 4·5. $C_{17}H_{20}O_3NCl$ requires N, 4·4%), and 3 : 4-dibenzyloxy-mandelimidate hydrochloride (69%), m. p. 105° (decomp.).

Preparation of Amidines.—The imidate hydrochlorides were added to an ice-cooled ethanolic solution of ammonia (5 mols.) or the amine (1·04 mols.), and the amidinium chlorides were collected, after the mixture had been kept at 0° for 8—18 hr., and recrystallised, in most cases from ethanol–ether. Phenols (II; R = R′ = OH) were prepared by hydrogenating the benzyl ethers in methanol at normal temperature and pressure with palladium–charcoal. Results are summarised in the Table.

Amidinium chlorides [*hydrochlorides of* (II)].

R^1	R^2	R^3	R^4R^5	Yield (%)	M. p.	Cryst. from	Formula	Found N (%)	Required N (%)
H	H	H	H_2	57	218—219° *[a]	A †	$C_8H_{11}ON_2Cl$	15·15	15·0
H	H	C_6H_{11} [b]	H_2	56	204	B	$C_{14}H_{21}ON_2Cl$ [c]	10·7	10·4
H	MeO	H	H_2	66	190 [d]	C	$C_9H_{13}O_2N_2Cl$	13·3	12·9
H	MeO	Me	H_2	35	122—123	B	$C_{10}H_{15}O_2N_2Cl$ [e]	11·7	12·15
H	MeO	Pr^i	H_2	62	169	B	$C_{12}H_{19}O_2N_2Cl$ [f]	11·1	10·8
H	Cl	H	H_2	20	141 *	B	$C_8H_{10}ON_2Cl_2$ [g]	12·8	12·7
Cl	H	H	H_2	38	254 * [h]	A	$C_8H_{10}ON_2Cl_2$	13·0	12·7
MeO	MeO	H	H_2	50	204 *	A	$C_{10}H_{15}O_3N_2Cl$	11·7	11·4
H	Ph·CH$_2$·O	H	H_2	68	180	B	$C_{15}H_{17}O_2N_2Cl$	9·9	9·6
H	Ph·CH$_2$·O	Me	H_2	72	149—150	B	$C_{16}H_{19}O_2N_2Cl$	9·1	9·1
H	Ph·CH$_2$·O	Me	MeH	44	222	C	$C_{17}H_{21}O_2N_2Cl$	8·9	8·7
H	Ph·CH$_2$·O	H	Me_2	55	161	B	$C_{17}H_{21}O_2N_2Cl$	8·8	8·7
H	Ph·CH$_2$·O	Pr^i	H_2	81	178	B	$C_{18}H_{23}O_2N_2Cl$	8·4	8·4
H	Ph·CH$_2$·O	*n*-C_7H_{15}	H_2	73	114	B	$C_{22}H_{31}O_2N_2Cl$	7·5	7·2
H	Ph·CH$_2$·O	C_6H_{11} [b]	H_2	78	161	B	$C_{21}H_{27}O_2N_2Cl$	7·6	7·5
H	Ph·CH$_2$·O	$Et_2N·CH_2·CH_2$	H_2	81	150	B	$C_{21}H_{30}O_2N_3Cl$	10·8	10·7
Ph·CH$_2$·O	Ph·CH$_2$·O	H	H_2	56	214	A	$C_{22}H_{23}O_3N_2Cl$	6·8	7·0
Ph·CH$_2$·O	Ph·CH$_2$·O	Me	H_2	80	173	B	$C_{23}H_{25}O_3N_2Cl$	7·1	6·8
Ph·CH$_2$·O	Ph·CH$_2$·O	Pr^i	H_2	66	155	B	$C_{25}H_{29}O_3N_2Cl$	6·5	6·4
H	HO	H	H_2	88	201	B	$C_8H_{11}O_2N_2Cl$	14·0	13·8
H	HO	Me	H_2	74	215	C	$C_9H_{13}O_2N_2Cl$ [j]	13·3	12·9
H	HO	H	Me_2	84	190	C	$C_{10}H_{15}O_2N_2Cl$	11·8	12·1
H	HO	Pr^i	H_2	92	207·5	B	$C_{11}H_{17}O_2N_2Cl$	11·6	11·5
H	HO	*n*-C_7H_{15}	H_2	91	170	D	$C_{15}H_{25}O_2N_2Cl$	9·2	9·3
H	HO	C_6H_{11} [b]	H_2	62	170	B	$C_{14}H_{21}O_2N_2Cl$	9·9	9·8
HO	HO	H	H_2	74	192 *	B	$C_8H_{11}O_3N_2Cl$	12·65	12·8
HO	HO	Me	H_2	81	162	B	$C_9H_{13}O_3N_2Cl$ [k]	12·2	12·05
HO	HO	Pr^i	H_2	99	208 *	D	$C_{11}H_{17}O_3N_2Cl$ [l]	10·6	10·8

* M. p. with decomp. † A = EtOH, B = EtOH–Et_2O, C = EtOH–EtOAc, D = MeOH–Et_2O.
[a] Bayer[8] gives m. p. 214°. [b] *cyclo*Hexyl. [c] Found: Cl^-, 13·1. Reqd.: Cl^-, 13·2%. [d] King *et al.*[9] give m. p. 190°. [e] Found: Cl^-, 15·6. Reqd.: Cl^-, 15·4%. [f] Found: Cl^-, 13·7. Reqd.: Cl^-, 13·7%. [g] Found: Cl^-, 16·6. Reqd.: Cl^-, 16·1%. [h] Rule[11] gives m. p. 252—253° (decomp.). [j] Found: C, 50·2; H, 6·1. Reqd.: C, 49·9; H, 6·0%. [k] Found: Cl^-, 15·5. Reqd.: Cl^-, 15·2%. [l] Found: Cl^-, 13·8. Reqd.: Cl^-, 13·6%.

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[6] Corson, Dodge, Harris, and Yeaw, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 336.
[7] Kostanecki and Lampe, *Ber.*, 1909, **42**, 827.
[8] Bayer, *J. prakt. Chem.*, 1885, **31**, 382.
[9] King, King, and Muir, *J.*, 1946, 5.
[10] Fulton and Robinson, *J.*, 1933, 1463.
[11] Rule, *J.*, 1918, **113**, 3.

4 : 5-*Dihydro-2-α-hydroxybenzylglyoxalinium Chloride.*—Ethyl mandelimidate hydrochloride (10·75 g.) was added to a solution of anhydrous ethylenediamine (3·6 c.c.) in absolute ethanol (50 c.c.) below 5°. The mixture began to crystallise almost immediately; after 1 hr. at 0° the product was filtered off, washed with ethanol, and dried *in vacuo*. N-(2-*Aminoethyl*)*mandelamidinium chloride* (8·8 g.) was thus obtained as plates, m. p. 172—184° (dependent on the rate of heating) (Found: N, 18·3; Cl^-, 14·9. $C_{10}H_{16}ON_3Cl$ requires N, 18·3; Cl^-, 15·5%). The compound slowly evolved ammonia in the cold. It was recrystallised from ethanol, a slight excess of 3N-alcoholic hydrogen chloride being added, to give 4 : 5-dihydro-2-α-hydroxybenzylglyoxalinium chloride (6·3 g., 60%) as prisms, m. p. 219—221° (Found: N, 13·3. Calc. for $C_{10}H_{13}ON_2Cl$: N, 13·2%) (Tilford *et al.*[12] give m. p. 224—226°). When prepared by the method of I.G. Farbenindustrie[3] the dihydroglyoxalinium chloride was obtained in 45% yield, m. p. 219—223°, after recrystallisation from ethanolic hydrogen chloride.

2-(p-*Chloro-α-hydroxybenzyl*)-4 : 5-*dihydroglyoxalinium Chloride.*—When ethylenediamine (10 c.c.) was added to *p*-chloromandelamidinium chloride (8·8 g.) there was a vigorous reaction with copious evolution of ammonia. When this reaction had subsided the mixture was refluxed with ethanol (45 c.c.) for 1 hr., cooled, and diluted with ether (100 c.c.). 2-(p-*Chloro-α-hydroxybenzyl*)-4 : 5-*dihydroglyoxaline–ethylenediammonium chloride double salt* (8·7 g.; m. p. 132—134°) was collected after 2 hr. at 0° and recrystallised from ethanol–ether (charcoal) to give rhombs (5·1 g., 52%), m. p. 138—140° (Found: N, 16·1; Cl^-, 20·8. $C_{12}H_{21}ON_4Cl_3$ requires N, 16·3; Cl^-, 20·7%). The double salt was dissolved in hot ethanol (40 c.c.), and a slight excess of ethanolic hydrogen chloride was added. Ethylenediammonium chloride was filtered off. The filtrate was concentrated to 15 c.c. and ether was added slowly, precipitating the *dihydroglyoxalinium chloride* as thin rhombs (1·4 g., m. p. 178°) (Found: N, 11·5; Cl^-, 14·4. $C_{10}H_{12}ON_2Cl_2$ requires N, 11·3; Cl^-, 14·4%).

2-(m-*Benzyloxy-α-hydroxybenzyl*)-4 : 5-*dihydroglyoxalinium Chloride.*—When prepared by the method used for the *p*-chloro-compound (above), this *dihydroglyoxalinium chloride* was obtained as thin rhombs, m. p. 198°, in 66% yield (Found: N, 8·6. $C_{17}H_{19}O_2N_2Cl$ requires N, 8·8%) [free *base*, plates, m. p. 156—162° (Found: C, 72·1; H, 6·5; N, 10·2. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9%)]. When prepared by adding ethyl *m*-benzyloxymandelimidate hydrochloride to ice-cold ethanolic ethylenediamine (1·1 mols.), N-(2-*aminoethyl*)-m-*benzyloxymandelamidinium chloride* was obtained as the initial product as plates, m. p. 151—173° (Found: N, 12·1; Cl^-, 10·4. $C_{17}H_{22}O_2N_3Cl$ requires N, 12·5; Cl^-, 10·6%). Recrystallisation from ethanolic hydrogen chloride–ether converted this into the dihydroglyoxalinium chloride (59%), m. p. 195—197°.

2-(3 : 4-*Dibenzyloxy-α-hydroxybenzyl*)-4 : 5-*dihydroglyoxaline.*—Treating the mandelimidate hydrochloride with ice-cold ethanolic ethylenediamine (1·3 mols.), followed by two recrystallisations of the crude product from 95% ethanol, afforded 2-(3 : 4-*dibenzyloxy-α-hydroxybenzyl*)-4 : 5-*dihydroglyoxaline* (21%) as plates, m. p. 160—161° (Found: C, 74·0; H, 6·15; N, 7·25. $C_{24}H_{24}O_3N_2$ requires C, 74·2; H, 6·2; N, 7·2%). The method of I.G. Farbenindustrie[3] gave only 3 : 4-*dibenzyloxymandelamide* (66%) as prisms, m. p. 119°, from 95% ethanol (Found: C, 71·7; H, 5·7; N, 4·2. $C_{22}H_{21}O_4N$ requires C, 72·7; H, 5·8; N, 3·9%), readily hydrolysed to 3 : 4-*dibenzyloxymandelic acid* (76%), obtained as needles, m. p. 137°, from ethyl acetate (Found: C, 72·4; H, 5·2; N, 0·0. $C_{22}H_{20}O_5$ requires C, 72·5; H, 5·5%).

4 : 5-*Dihydro-2-*(*α : 3 : 4-trihydroxybenzyl*)*glyoxalinium Chloride.*—Hydrogenation (palladium–charcoal) of the dibenzyl ether in methanol containing one equivalent of hydrogen chloride afforded 4 : 5-dihydro-2-(α : 3 : 4-trihydroxybenzyl)glyoxalinium chloride (64%) as needles, m. p. 174—175°. I.G. Farbenindustrie[3] give m. p. 174—176°.

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[12] Tilford, Van Campen, and Shelton, *J. Amer. Chem. Soc.*, 1949, **71**, 1885.