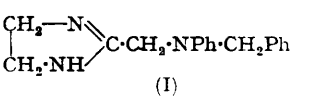
331. *2-Thymyloxymethylglyoxalines and Related Compounds as Potential Antihistamines.*

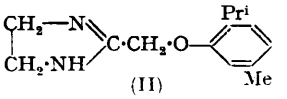
By H. Bader and J. D. Downer.

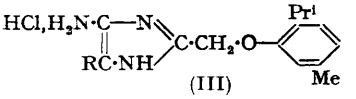
8-Thymyloxymethylcaffeine and a number of substituted 2-thymyloxymethylglyoxalines and thymyloxyacetamidines have been prepared. Some of the compounds possessed antihistamine activity.

Although histamine contains a glyoxaline ring the number of glyoxalines prepared specifically as potential antihistamines is small (Carrara, D'Amato, and Pagani, *Chimica e industria* (*Milan*), 1946, **28**, 9; Ellinger and Goldberg, *J.*, 1949, 263; Huebner, Turner, and Scholz, *J. Amer. Chem. Soc.*, 1949, **71**, 2801; 3942; Tilford, Van Campen, Jr., and Shelton, *ibid.*, p. 1885; Wright, *ibid.*, p. 2035; Ruoff and Scott, *ibid.*, 1950, **72**, 4950). Several compounds containing a dihydroglyoxaline ring have been prepared which possess con-

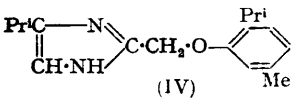
siderable antihistamine activity, including antazoline (I) and 4 : 5-dihydro-2-thymyloxymethylglyoxaline (II) (Djerassi and Scholz, *ibid.*, 1947, **69**, 1688). It was of interest therefore to examine glyoxaline analogues of (II) as potential antihistamines.

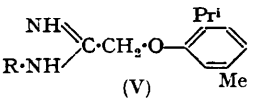

(I)


(II)


(III)

4-Amino-2-thymyloxymethylglyoxalines (III; R = Pr^i, Ph or CO_2Et) were prepared (cf. Cook, Davis, Heilbron, and Thomas, *J.*, 1949, 1071) by condensation of benzyl thymyloxyacetothioimidate hydrochloride with the appropriate α-amino-nitrile in boiling chloroform. Similarly, 4-amino-2-phenoxymethyl-5-phenylglyoxaline hydrochloride was obtained from α-aminobenzyl cyanide and benzyl phenoxyacetothioimidate hydrochloride. Good yields were obtained except in the case of (III; R = Pr^i) where much ammonium chloride was formed. With α-aminopropionitrile and benzyl thymyloxyacetothioimidate hydrochloride, ammonium chloride was formed almost quantitatively. On the other hand, α-aminoacetonitrile with the same thioimidate hydrochloride at room temperature in the presence of pyridine yielded the glyoxaline (III; R = H) (cf. Bader, Downer, and Driver, *J.*, 1950, 2775).


(IV)

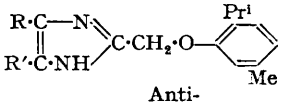

(V)

The glyoxaline (IV) was prepared by condensing benzyl thymyloxyacetothioimidate hydrochloride with 1-amino-3-methylbutan-2-one hydrochloride according to Ellinger and Goldberg's method (*loc. cit.*). A small amount of an unidentified compound, m. p. >250°, was also formed. The amino-ketone was obtained from 1-chloro-3-methylbutan-2-one by a Gabriel synthesis.

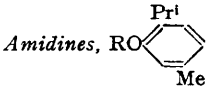
Many xanthines, including caffeine, have been found useful in the treatment of allergic conditions (Emmelin, Kahlson, and Lindstrom, *Acta physiol. scand.*, 1941, **3**, 39) and have the advantage of being non-toxic. The glyoxaline (III; R = CO_2Et) was therefore converted into 8-thymyloxycaffeine by ring-closure of its 4-methylureido-derivative, according to the method of Cook, Heilbron, Macdonald, and Mahadevan (*J.*, 1949, 1064), and methylation of the product with methyl iodide.

Djerassi and Scholz (*loc. cit.*) found that *N*-alkyl-thymyloxyacetamidines possessed greater activity than 4 : 5-dihydro-2-thymyloxymethylglyoxaline. Similar compounds (V; R = H, Me, Pr^i, and Bu^i) were therefore prepared from the imidate hydrochlorides and excess of ammonia or the appropriate amine. The amidine (V; R = H) has been previously described (G.P. 684,945; Djerassi and Scholz, *loc. cit.*).

Pharmacological results are summarised in the annexed Table.

Glyoxalines, 

R	R′	Anti-histamine activity (γ/ml.[a])	Toxicity (mg./kg.[b])
NH_2	H	[d]	Non-toxic, 160
H	Pr^i	40	Non-toxic, 160
NH_2	Pr^i	100	Non-toxic, 160
NH·CO·NHMe	Pr^i	40	—
NH_2	Ph	d.	—
NH_2	CO_2Et	d.	—

Amidines, 

R	Anti-histamine activity (γ/ml.[a])	Toxicity (mg./kg.[b])
CH_2·C:NH·NH_2 [c]	10—15	Non-toxic, 160
CH_2·C:NH·NHMe	100	—
CH_2·C:NH·$NHPr^i$	10	Non-toxic, 160
CH_2·C:NH·$NHBu^i$	40	80
8-Thymyloxycaffeine	100	—

[a] γ of compound per ml. of solution added to the bath-liquid, equivalent to the reduction in contraction of an isolated guinea-pig gut caused by 1 γ of antazoline sulphate. [b] LD_{50}, mice. [c] Djerassi and Scholz (*loc. cit.*) give 1—10. [d] >100.

Experimental

Nitriles.—Phenoxy- and thymyloxy-acetonitriles were prepared by Djerassi and Scholz's method (*loc. cit.*).

Imidate Hydrochlorides.—The following general method, essentially that of Pinner ("Die Imido Ether"), was employed. Excess of dry hydrogen chloride was passed into a mixture of the nitrile (1 mol.) and the alcohol (1—2 mols.) at 0—5° in the diluent indicated. The resultant product was then kept (1 hr. to 3 days) at 0° until the imidate hydrochloride separated. The hydrochlorides prepared (not purified) are tabulated and where possible analyses (by titration against standard alkali).

Imidate hydrochlorides, CRR'·NH,HCl.

R	R'	Solvent	Yield (%)	M. p.	Formula	HCl (%) Found	HCl (%) Reqd.
CH_2·OPh	S·CH_2Ph	Et_2O	83	134°	—	—	—
5 : 2 : 1-$C_6H_3MePr^i$·O·CH_2–	OEt	$CHCl_3$	60	110—112 [a]	$C_{14}H_{22}O_2NCl$	13·0	13·4
,,	S·CH_2Ph	Et_2O	68	173	$C_{19}H_{24}ONSCl$	10·7	10·4

[a] Djerassi and Scholz (*loc. cit.*) give m. p. 109·5—110°.

4-*Amino*-2-*phenoxymethyl*-5-*phenylglyoxaline Hydrochloride.*—Benzyl phenoxyacetothioimidate hydrochloride (29·4 g.), α-aminobenzyl cyanide (13·6 g.), and chloroform (100 c.c.) were refluxed for 2 hr., and the precipitated solid was filtered off and washed with chloroform, to give the *glyoxaline* (23 g., 74%), m. p. 167° (unchanged by crystallisation from ethanol) (Found: C, 64·0; H, 5·8; N, 13·6; Cl, 11·6. $C_{16}H_{16}ON_3Cl$ requires C, 63·7; H, 5·35; N, 13·9; Cl, 11·75%). It is sparingly soluble in water and can be diazotised.

4-*Amino*-2-*thymyloxymethylglyoxaline Hydrochloride.*—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.), chloroform (60 c.c.), pyridine (2·5 c.c.), and aminoacetonitrile (1·6 g.) were mixed in the above order and shaken under nitrogen for 15 min. Ethanolic hydrogen chloride (20 c.c. of 8·7%) was added to the cold solution with stirring, and the mixture diluted with ethyl acetate (2 vol.) and left at 0°. The precipitate (6·3 g., 75%), m. p. 170° (decomp.), recrystallised from methanol (charcoal) as needles of 4-*amino*-2-*thymyloxymethylglyoxaline hydrochloride*, m. p. 170° (decomp.) (Found: C, 59·95; H, 7·05; N, 14·7; Cl, 12·5. $C_{14}H_{20}ON_3Cl$ requires C, 59·65; H, 7·15; N, 14·9; Cl, 12·6%). It is readily soluble in warm water and can be diazotised.

4-*Amino*-5-iso*propyl*-2-*thymyloxymethylglyoxaline Hydrochloride.*—Benzyl thymyloxyacetothioimidate hydrochloride (7·5 g.), α-amino*iso*valeronitrile (2·1 g.), and chloroform (20 c.c.) were refluxed for 3 hr., the mixture was filtered, and the filtrate diluted with ether (200 c.c.) and kept at 0° for 30 min. The crystals that had separated were triturated with ethanol (25 c.c.) at 0° and the undissolved ammonium chloride was filtered off. The filtrate was diluted with ether (80 c.c.) and kept overnight. Recrystallisation of the solid (1·5 g.), so obtained, from ethanol–ethyl acetate gave colourless needles of 4-*amino*-5-iso*propyl*-2-*thymyloxymethylglyoxaline hydrochloride*, m. p. 157° (Found: C, 62·7; H, 8·2; N, 12·8; Cl, 10·95. $C_{17}H_{26}ON_3Cl$ requires C, 63·0; H, 8·1; N, 13·0; Cl, 10·95%). Light absorption (ethanol): $\lambda_{max.}$ 2710 Å, ε 6300. It gave a red dye on diazotisation and coupling with β-naphthol.

4-N'-*Methylureido*-5-iso*propyl*-2-*thymyloxymethylglyoxaline.*—Methyl *iso*cyanate (4·5 c.c.) was added in three portions at 0° to the preceding glyoxaline hydrochloride (3 g.) in pyridine (15 c.c.), and the mixture warmed at 100° for 20 min. after each addition. The resultant mixture on dilution with ethanol (20 c.c.) and water (30 c.c.) yielded 4-N'-*methylureido*-5-iso*propyl*-2-*thymyloxymethylglyoxaline* (2·2 g.), which recrystallised from 50% aqueous ethanol as colourless needles, m. p. 156° (Found: C, 66·05; H, 7·95; N, 16·7. $C_{19}H_{28}O_2N_4$ requires C, 66·2; H, 8·2; N, 16·3%).

4-*Amino*-5-*phenyl*-2-*thymyloxymethylglyoxaline Hydrochloride.*—Benzyl thymyloxyacetothioimidate hydrochloride (20 g.), α-aminobenzyl cyanide (7·7 g.), and chloroform (90 c.c.) were refluxed for 3·5 hr., and the solid formed (17 g., 80%), m. p. 176°, was collected and crystallised from methanol (250 c.c.), to give colourless needles of 4-*amino*-5-*phenyl*-2-*thymyloxymethylglyoxaline hydrochloride*, m. p. 183° (decomp.) (Found: C, 67·0; H, 6·75; N, 11·4; Cl, 10·05. $C_{20}H_{24}ON_3Cl$ requires C, 67·1; H, 6·75; N, 11·7; Cl, 9·9%). It gave a red dye on diazotisation and coupling with β-naphthol.

Ethyl 4-*Amino*-2-*thymyloxymethylglyoxaline*-5-*carboxylate Hydrochloride.*—Benzyl thymyloxyacetothioimidate hydrochloride (30 g.), chloroform (50 c.c.), and ethyl α-aminocyanoacetate

(15 g.) were refluxed for 4 hr. A small quantity of ammonium chloride was removed and the filtrate evaporated to dryness *in vacuo*. The residue was triturated with ethanol (2·2 c.c.), diluted with ether, and filtered. The solid (24·8 g., 81·8%), m. p. 150°, crystallised from ethanol, to give *ethyl 4-amino-2-thymyloxymethylglyoxaline-5-carboxylate hydrochloride*, m. p. 154° (Found: C, 57·7; H, 6·95; N, 11·9. $C_{17}H_{24}O_3N_3Cl$ requires C, 57·7; H, 6·85; N, 11·9%). The base, m. p. 146°, could be obtained by trituration of the hydrochloride with aqueous sodium carbonate solution.

8-*Thymyloxymethylcaffeine*.—Methyl *iso*cyanate (13·5 g.) was added in three portions at 0° to the preceding glyoxaline hydrochloride (16·9 g.) in pyridine (30 c.c.), and the mixture gently refluxed for 20 min. after each addition. The pyridine was removed *in vacuo*, the crude methylureido-derivative dissolved in aqueous sodium hydroxide (300 c.c. of 10%) at 60°, water (300 c.c.) added, and a small amount of insoluble material (not examined) removed. Ethanol (600 c.c.) was added to the filtrate which was then neutralised with 30% aqueous acetic acid and kept at 0° overnight. The xanthine (4·2 g., 27%), m. p. 256°, which had separated was purified by dissolution in aqueous ethanolic sodium hydroxide and precipitation with acetic acid, to give *1-methyl-8-thymyloxymethylxanthine*, m. p. 256° (Found: N, 17·15. $C_{17}H_{20}O_3N_4$ requires N, 17·05%). The xanthine (2 g.) and methyl iodide (5 g.) in aqueous sodium hydroxide (30 c.c. of 5%) were heated at 100—110° for 2 hr. The gum (1·82 g.) formed was removed and dissolved in chloroform (charcoal), the solution concentrated to 10 c.c., and ether added until the solution became faintly turbid. After 1 hr. at 0° the precipitate (0·21 g.), m. p. 250° (mainly unchanged xanthine), was removed. The filtrate was kept for 2 hr. at 0° and the solid (0·52 g., 24%), m. p. 154°, that had separated was crystallised from chloroform–ether, to give colourless plates of *8-thymyloxymethylcaffeine*, m. p. 154° (Found: C, 63·2; H, 6·55; N, 15·9. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 6·9; N, 15·7%). It gave a positive murexide colour.

1-Amino-3-methylbutan-2-one Hydrochloride.—1-Chloro-3-methylbutan-2-one (29 g.), potassium phthalimide (25 g.), and dry xylene (25 c.c.) were heated under reflux at 120—130° for 1 hr., the xylene and unchanged chloride were removed by steam-distillation, and the residue was cooled and filtered. The crude solid (35 g., 64%), m. p. 82—90°, was crystallised from ethanol (200 c.c.), to give colourless needles of *3-methyl-1-phthalimidobutan-2-one* (31 g.), m. p. 102° (Found: C, 67·35; H, 5·95; N, 6·05. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·65; N, 6·05%). This (25 g.) was suspended in aqueous hydrochloric acid (275 c.c. of 30%) and refluxed for 8 hr. The phthalic acid was then removed and the solution evaporated *in vacuo* at 50°. The residue was recrystallised from 50% ethanol–ether (120 c.c.) to give colourless plates of *1-amino-3-methylbutan-2-one hydrochloride* (13 g., 90%), m. p. 164° (Found: C, 43·25; H, 8·85; N, 10·2; Cl, 25·85. $C_5H_{12}ONCl$ requires C, 43·6; H, 8·8; N, 10·2; Cl, 25·8%).

4-iso*Propyl-2-thymyloxymethylglyoxaline*.—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.) was added portion-wise during 10 min. to a solution of sodium (0·84 g.) in dry ethanol (35 c.c.) with stirring at −10° to −5° in an atmosphere of nitrogen. After 15 min. a solution of the above amino-ketone hydrochloride (3·93 g.) in ethanol (70 c.c.) was added, during 30 min., at −5°. The mixture was stirred at −5° for 1 hr., then kept at room temperature for 24 hr. Sodium (0·42 g.), dissolved in ethanol (25 c.c.), was then added at −5° and the mixture left for 4 days at room temperature. Sodium chloride (2·7 g., 85%) was removed and the solution evaporated *in vacuo* at 50° to leave a yellow oil. To this, ethanolic hydrogen chloride (40 c.c. of 5%) was added followed by ether (100 c.c.) and unchanged thioimidate hydrochloride (1·6 g.) thus precipitated was removed. The remainder was diluted with ether (350 c.c.) and kept at 0° overnight. The solid (0·3 g.) which had separated was crystallised from methanol–ether, to give colourless crystals of a *substance*, decomp. >250° (Found: C, 48·2; H, 8·9; N, 14·3; Cl, 27·4. $C_{16}H_{35}N_4Cl_3$ requires C, 49·25; H, 9·05; N, 14·4; Cl, 27·3%). It gave no Pauly reaction and was not further examined. The main filtrate was evaporated *in vacuo* at 40°, and the yellow oily residue diluted with water (150 c.c.) and steam-distilled to remove toluene-ω-thiol (2 g.). The non-volatile residue was extracted with ether and the ethereal extract evaporated *in vacuo* to give a gum (4·5 g.). This was rubbed with warm water, made alkaline with dilute aqueous sodium carbonate, and extracted into chloroform. Removal of the chloroform gave a gum (4 g.) which crystallised (charcoal) from ethanol (75 c.c.)–water (70 c.c.) (or benzene–light petroleum), to give colourless prisms of 4-iso*propyl-2-thymyloxymethylglyoxaline* (2·5 g.), m. p. 97° (Found: C, 74·6; H, 9·1; N, 10·0. $C_{17}H_{24}ON_2$ requires C, 74·95; H, 8·9; N, 10·3%). Light absorption (ethanol): $\lambda_{max.}$ 2735 Å, ε 1900. It gave a positive Pauly reaction.

Thymyloxyacetamidine Hydrochloride.—Benzyl thymyloxyacetothioimidate hydrochloride (10 g.) and ethanolic ammonia (55 c.c. of 10%) were shaken until homogeneous and the solution

kept at room temperature for 6 days. Ammonia was removed *in vacuo*, and the residue treated with ethanolic hydrogen chloride (20 c.c. of 8%) and cautiously diluted with ether to 250 c.c., whereupon a small amount of ammonium chloride was precipitated. This was filtered off and the solution kept overnight at 0°; thymyloxyacetamidine hydrochloride (3·0 g.) separated. A further crop (3·1 g.) was obtained by concentration of the mother-liquor. It recrystallised from methanol–ether as needles, m. p. 185° (Djerassi and Scholz, *loc. cit.*, give m. p. 185—185·5°) (Found: C, 59·5; H, 7·7; N, 11·6; Cl, 14·6. Calc. for $C_{12}H_{19}ON_2Cl$: C, 59·35; H, 8·0; N, 11·55; Cl, 14·6%).

The same amidine was obtained by the method of Partridge and Short (*J.*, 1947, 390), by heating thymyloxyacetonitrile (18 g.) and ammonium thiocyanate (29 g.) at 180° for 90 min. with vigorous stirring. After cooling, the product was boiled with water (40 c.c.) and poured on ice (40 g.) and aqueous sodium hydroxide (30 c.c. of 10%). The oily suspension was extracted into ether (400 c.c.), the extract washed, and the product re-extracted with 10% hydrochloric acid (3 × 50 c.c.). On concentration of the extract to 250 c.c. *in vacuo*, the amidine hydrochloride (7 g.) separated.

N-*Methyl-α-thymyloxyacetamidine Hydrochloride*.—A mixture of benzyl thymyloxyacetothioimidate hydrochloride (15 g.) and methylamine (20 g.) in methanol (100 c.c.) was kept at room temperature for 6 days. The excess of methylamine was then removed at room temperature, ethanolic hydrogen chloride (35 c.c. of 10%) added, followed by ether (300 c.c.), and the solution kept at 0° for 1 hr. Methylamine hydrochloride which had deposited was removed, ether (200 c.c.) added to the filtrate, and the latter kept at 0° for 3 hr. N-*Methyl-α-thymyloxyacetamidine hydrochloride* (5·4 g.) separated as prisms, m. p. 173° (unchanged by crystallisation from ethanol–ether) (Found: N, 10·2; Cl, 13·7. $C_{13}H_{21}ON_2Cl$ requires N, 10·9; Cl, 13·8%). Concentration of the mother-liquor to small volume and dilution with ether gave a further crop (4·6 g.), m. p. 166° (total yield, 91%).

N-iso*Propyl-α-thymyloxyacetamidine Hydrochloride*.—A solution of *iso*propylamine (8 c.c.) and benzyl thymyloxyacetothioimidate hydrochloride (10 g.) in dry methanol (40 c.c.) was kept at room temperature for 5 days, the excess of amine removed, and the solution concentrated *in vacuo* at 25° to *ca.* 20 c.c. Ethanolic hydrogen chloride was then added and the solution diluted with ether (120 c.c.) until just turbid. The solid (2·5 g.), m. p. 114°, which separated after several days was crystallised from ethanol–ether, to give colourless needles of N-iso*propyl-α-thymyloxyacetamidine hydrochloride*, m. p. 115° (Found: N, 10·1; Cl, 12·75. $C_{15}H_{25}ON_2Cl$ requires N, 9·8; Cl, 12·45%).

N-iso*Butyl-α-thymyloxyacetamidine Hydrochloride*.—*iso*Butylamine (10 g.), benzyl thymyloxyacetothioimidate hydrochloride (15 g.), and dry ethanol (150 c.c.) were mixed at 0° and the clear solution kept under nitrogen for 1 week. Most of the excess of amine was removed by concentration *in vacuo* to small volume, ethanolic hydrogen chloride (75 c.c. of 7%) added, and the mixture again concentrated to small volume at 30°. Ethyl acetate (100 c.c.) was added, followed by ether (*ca.* 300 c.c.) until the solution was just cloudy; it was then kept at 0° overnight. *iso*-Butylamine hydrochloride that had separated was removed, the filtrate evaporated to an oil *in vacuo* at 30°, water (200 c.c.) added, and the suspended toluene-ω-thiol extracted with ether. Dissolved ether was removed from the aqueous layer, potassium carbonate (20 g.) added, and the crude *amidine* (12·8 g.) isolated by extraction with chloroform. This was triturated with ethanolic hydrogen chloride (25 c.c. of 3%) and the hygroscopic colourless needles of N-iso*butyl-α-thymyloxyacetamidine hydrochloride* (5 g.) m. p. 93° (unchanged by crystallisation from ethanol–ether), were collected (Found: N, 9·7; Cl, 11·9. $C_{16}H_{27}ON_2Cl$ requires N, 9·35; Cl, 11·95%).

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BEECHAM RESEARCH LABORATORIES, LTD.,
BROCKHAM PARK, BETCHWORTH, SURREY.

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