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Antihistamine Agents

V. Aminoalkyl Derivatives of 2-Benzylthiazole

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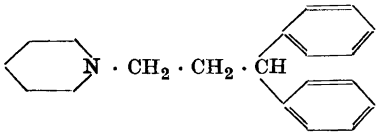
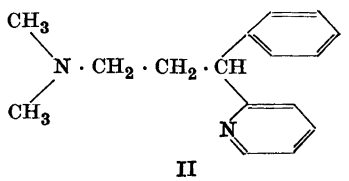
Several aminoalkyl derivatives of diphenylmethane have been reported to possess pronounced antispasmodic properties [1-3] and some of them, *e. g.* N-(γ,γ-diphenyl-propyl)-piperidine (I) have been used clinically. Replacement of a phenyl nucleus by a heterocyclic one has been carried out in the case of pyridine [4], and one of these compounds, 2-(γ-dimethylamino-α-phenyl-propyl)-pyridine (II), exerted a strong antihistaminic activity.



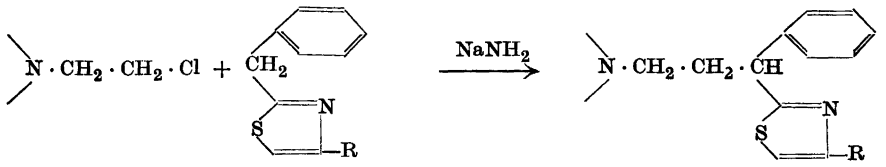
I



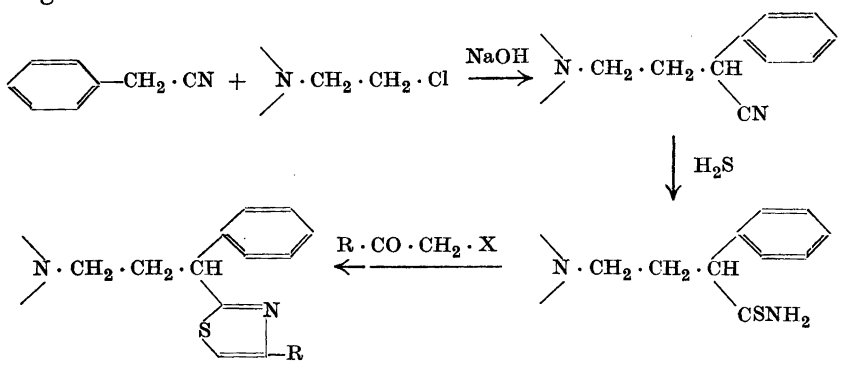
II

However, no other heterocyclic analogues appear to have been reported. As it is of great interest to study the spasmolytic and antihistaminic effect of such compounds, several derivatives of this type containing a thiazole nucleus have been prepared in this laboratory.

The thiazole compounds could be obtained by condensing the hydrochlorides of β-piperidino-, β-dimethylamino- and β-diethylaminoethyl chloride with 2-benzylthiazole and 2-benzyl-4-methylthiazole in the presence of sodium amide, two equivalents of the condensing agent being used to liberate the free aminoalkyl chloride from its hydrochloride.



They were, however, synthesised more conveniently and in better yields according to the scheme



The preparation of γ-diethylamino-α-phenylbutyronitrile by the condensation of β-diethylaminoethyl chloride and benzyl cyanide with sodium amide has been described by Eisleb [1]. The dimethyl derivative has been synthesised in the same way [5], and the piperidino compound has been prepared from γ-chloro-α-phenylbutyronitrile and piperidine [6].

Cusic showed recently [7], that sodium amide could be replaced by sodium hydroxide in a similar reaction. The basic nitriles, which were used as starting materials in the present work, were prepared in this way.

The nitriles reacted smoothly with hydrogen sulphide in ethanol at 70° to give thioamides. The reaction of the thioamides with chloroacetone, chloroacetaldehyde hydrate or ω-bromoacetophenone was best carried out in nitrobenzene as a solvent. In ethanol only ω-bromoacetophenone was reactive enough to give thiazole compounds.

After the experimental work had been completed, the synthesis of two of the thiazole derivatives described below was reported by Brown, Cook and Heilbron [8]. These investigators had prepared 4-methyl-2-(γ-diethylamino-α-phenylpropyl)-thiazole and 4-methyl-2-(γ-piperidino-α-phenylpropyl)-thiazole by condensing 2-benzyl-4-methylthiazole with the appropriate chloro tertiary amine in the presence of sodium amide. However, their attempts to convert γ-diethylamino-α-phenylthiobutyramide into a thiazole with chloroacetone or bromoacetal failed.

The new compounds have been tested for antihistaminic and antispasmodic activity. The tests were carried out on isolated guinea pig ileum, β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) being used as a standard *. It was found, that the highest antihistamine activity was exerted by

* Acknowledgement is made to Dr. S. Wiedling of Astra's Biological Department for performing these tests. Details will be reported elsewhere.

2-(γ-dimethylamino-α-phenylpropyl)-thiazole, which had 0.15 of the effect of Benadryl. Against barium chloride and acetyl choline, 4-methyl-2-(γ-piperidino-α-phenylpropyl)-thiazole was most potent, the activity being 1.25 and 1.8 resp. of the Benadryl activity.

EXPERIMENTAL

γ-Dimethylamino-α-phenylbutyronitrile

To a mixture of 36.0 g of powdered sodium hydroxide and 28.2 g of benzyl cyanide 43.2 g of β-dimethylaminoethyl chloride hydrochloride was added in portions. A vigorous reaction commenced and the temperature was not allowed to exceed 80°. The mixture was then heated on a water bath at 80—90° for eight hours. After cooling, the mixture was extracted with ether, the residue was dissolved in water and extracted with ether again. The combined extracts were extracted with 2 *N* hydrochloric acid, the aqueous layer was made alkaline and extracted with ether. The solvent was evaporated and the residue distilled. B. p. 90—100°/0.05 mm. Yield 17.4 g.

$C_{12}H_{16}N_2$ (188.3)	Calc.	C	76.5	H	8.56	N	14.9
	Found	»	76.6	»	8.63	»	15.0

γ-Dimethylamino-α-phenylthiobutyramide

0.25 g of sodium was dissolved in 60 ml of ethanol. 3.8 g of γ-dimethylamino-α-phenylbutyronitrile was added, the solution was cooled to — 10° and saturated with hydrogen sulphide. The mixture was then heated for seven hours at 70°. After cooling, the ethanol was evaporated at reduced pressure and the solid residue suspended in water and collected. Yield 3.6 g. After recrystallisation from ethanol the thioamide melted at 145—146° (dec.).

$C_{12}H_{18}N_2S$ (222.3)	Calc.	C	64.8	H	8.16	S	14.4
	Found	»	65.2	»	8.08	»	14.3

2-(γ-Dimethylamino-α-phenylpropyl)-thiazole

A mixture of 1.20 g of γ-dimethylamino-α-phenylthiobutyramide, 0.8 g of freshly distilled chloroacetaldehyde hydrate and 10 ml of nitrobenzene was refluxed for three hours (the refluxing temperature was 116—118°). After cooling, the reaction mixture was extracted with 100 ml of 2.5 *N* hydrochloric acid. The acid aqueous layer was then extracted with ether and made alkaline. The resulting oil was extracted with ether. An ethanolic solution of picric acid was added to the ether extract, until no more precipitate was obtained. The crude *dipicrate* (1.75 g) was recrystallised from water. M. p. 144—145°.

$C_{14}H_{18}N_2S \cdot 2\ C_6H_3N_3O_7$ (704.6)	Calc.	C	44.3	H	3.43	S	4.55
	Found	»	44.2	»	3.44	»	4.54

780 mg of the dipicrate, 30 ml of water, 5 ml of 5 *N* sodium hydroxide and 15 ml of chloroform was heated, and stirred on the water bath for one hour. The chloroform layer was separated and dried, and the solvent evaporated. The residue was distilled at 0.1 mm and 150° in the bath. Yield 205 mg of a viscous colourless oil.

$C_{14}H_{18}N_2S$ (246.4)	Calc.	C	68.3	H	7.36	
	Found	»	68.0	»	7.33	

4-Methyl-2-(γ-dimethylamino-α-phenylpropyl)-thiazole

A. A mixture of 1.20 g of γ-dimethylamino-α-phenylthiobutyramide, 2.0 ml of chloroacetone and 10 ml of nitrobenzene was refluxed for three hours. The reaction mixture was treated as in the preceding experiment. 1.28 g of a *dipicrate* was obtained, melting at 152—153.5° after recrystallisation from water.

$C_{15}H_{20}N_2S \cdot 2\ C_6H_3N_3O_7$ (718.6)	Calc.	C	45.1	H	3.65	S	4.46
	Found	»	45.0	»	3.64	»	4.34

From 610 mg of the dipicrate 125 mg of the base boiling at 0.1 mm at a bath temperature of 150° was obtained as a colourless oil.

$C_{15}H_{20}N_2S$ (260.4)	Calc.	C	69.2	H	7.74
	Found	»	69.0	»	7.60

B. To a suspension of sodium amide, prepared from 1.3 g of sodium and liquid ammonia, in 50 ml of toluene 4.8 g of 2-benzyl-4-methylthiazole [9] and 4.0 g of β-dimethylaminoethyl chloride hydrochloride were added. The mixture was refluxed for two hours, cooled and filtered. The toluene solution was then washed with water and extracted with 1 *N* hydrochloric acid. From the extract 3.5 g of a picrate was obtained by adding an aqueous solution of picric acid. It melted after crystallisation from water at 152—154° and showed no m. p. depression with the picrate from (A).

4-Phenyl-2-(γ-dimethylamino-α-phenylpropyl)-thiazole

A solution of 1.2 g of γ-dimethylamino-α-phenylthiobutyramide and 1.1 g of ω-bromoacetophenone in 10 ml of ethanol was refluxed for half an hour. The mixture was evaporated to dryness, treated with *N* sodium hydroxide and extracted with ether. By adding an ethereal solution of oxalic acid to the extract 1.3 g of *oxalate* was obtained. M. p. 154—157° after recrystallisation from acetone.

$C_{20}H_{22}N_2S \cdot (COOH)_2$ (412.5)	Calc.	C	64.0	H	5.86
	Found	»	64.1	»	6.04

From 330 mg of the oxalate 180 mg of the base was obtained. It distilled at 0.07 mm and 190° in the bath. The colourless oil partially solidified after some weeks.

$C_{20}H_{22}N_2S$ (322.5)	Calc.	C	74.5	H	6.88
	Found	»	74.6	»	7.02

γ-Diethylamino-α-phenylbutyronitrile

From 47 g of benzyl cyanide, 60 g of sodium hydroxide and 86 g of β-diethylaminoethyl chloride hydrochloride was obtained 27.9 g of this compound. B. p. 95—105°/0.1 mm.

$C_{14}H_{20}N_2$ (216.3)	Calc.	C	77.7	H	9.32	N 13.0
	Found	»	77.8	»	9.47	» 13.3

γ-Diethylamino-α-phenylthiobutyramide

This compound was prepared from 17.3 g of γ-diethylamino-α-phenylbutyronitrile in the same way as the preceding thioamide. As it was obtained as an oil, it was converted into the hydrochloride. The crude *hydrochloride* (14.0 g) was recrystallised twice from ethanol. M. p. 199—201°. Brown, Cook and Heilbron report m. p. 187°.

$C_{14}H_{22}N_2S$ HCl (286.9)	Calc.	N	9.77	S	11.2
	Found	»	9.84	»	11.1

2-(γ-Diethylamino-α-phenylpropyl)-thiazole

3.0 g of γ-diethylamino-α-phenylthiobutyramide hydrochloride was dissolved in water, made alkaline and extracted with ether. The ether solution was dried and evaporated. The oily residue was mixed with 1.6 g of chloroacetaldehyde and 20 ml of nitrobenzene and was then refluxed for three hours. The reaction mixture was treated in the usual way. An oily *dipicrate* was obtained, which was dissolved in boiling ethanol. On cooling 2.8 g of crystals melting at 144—145° were deposited.

$C_{16}H_{22}N_2S \cdot 2\ C_6H_3N_3O_7$ (732.6)	Calc.	C	45.9	H	3.85
	Found	»	46.2	»	4.11

From 2.7 g of the dipicrate 550 mg of the base was obtained. It distilled at 0.1 mm and 150° in the bath.

$C_{16}H_{22}N_2S$ (274.4)	Calc.	C	70.0	H	8.08
	Found	»	70.3	»	7.99

4-Methyl-2-(γ-diethylamino-α-phenylpropyl)-thiazole

This compound was prepared from 4.0 g of γ-diethylamino-α-phenylthiobutyramide hydrochloride and 4.3 ml of chloroacetone in the same way as the preceding thiazole. 6.6 g of *dipicrate* was obtained, melting at 141—142° after crystallisation from methanol. Brown, Cook and Heilbron [8] give the m. p. 142°.

$C_{17}H_{24}N_2S \cdot 2\ C_6H_3N_3O_7$ (746.6)	Calc.	C	46.7	H	4.05
	Found	»	46.6	»	4.00

5.1 g of the dipicrate was converted into free base following the usual procedure. It boiled at 0.1 mm and 150° in the bath. Yield 0.8 g.

$C_{17}H_{24}N_2S$ (288.4)	Calc.	C	70.8	H	8.39
	Found	»	71.1	»	8.31

γ-Piperidino-α-phenylbutyronitrile

This compound was prepared in the usual way from 80 g of β-piperidinoethyl chloride hydrochloride, 41 g of benzyl cyanide and 52 g of sodium hydroxide. Yield 23.3 g, b. p. 122—125°/0.05 mm.

$C_{14}H_{20}N_2$ (228.3)	Calc.	C	78.9	H	8.83
	Found	»	78.6	»	8.80

The picrate melted at 160—161°. Anker and Cook [6] report m. p. 161°.

γ-Piperidino-α-phenylthiobutyramide

From 12.0 g of γ-piperidino-α-phenylbutyronitrile 13.0 g of the thioamide was obtained. After recrystallisation from 50 % ethanol m. p. 144—145° (dec.).

$C_{15}H_{22}N_2S$ (262.4)	Calc.	C	68.7	H	8.45	N	10.7
	Found	»	68.8	»	8.64	»	10.8

2-(γ-Piperidino-α-phenylpropyl)-thiazole

4 g of γ-piperidino-α-phenylthiobutyramide, 2.3 g of chloroacetaldehyde hydrate and 20 ml of nitrobenzene was refluxed for three hours. After the usual treatment 5.45 g of a *dipicrate* was obtained. M. p. 159—161° after recrystallisation from 50 % ethanol.

$C_{17}H_{22}N_2S \cdot 2\ C_6H_3N_3O_7$ (744.7)	Calc.	C	46.8	H	3.79
	Found	»	47.0	»	3.81

From 2.0 g of the dipicrate 0.45 g of the thiazole, boiling at 0.1 mm and 180° in the bath, was prepared.

$C_{17}H_{22}N_2S$ (286.4)	Calc.	C	71.3	H	7.74	N	9.78
	Found	»	71.4	»	7.90	»	9.71

4-Methyl-2-(γ-piperidino-α-phenylpropyl)-thiazole

This compound was prepared from 4.0 g of γ-piperidino-α-phenylthiobutyramide and 6.3 g of chloroacetone in 20 ml of nitrobenzene. The *dipicrate* (5.2 g) was recrystallised from 30 % ethanol. M. p. 184—185°. (Brown, Cook and Heilbron [8] report 180°).

$C_{18}H_{24}N_2S \cdot 2\ C_6H_3N_3O_7$ (758.7)	Calc.	C	47.5	H	3.99
	Found	»	47.1	»	3.90

2.0 g of the dipicrate was converted into free base as usually. 0.40 g was obtained, distilling at 0.1 mm and 180° in the bath.

$C_{18}H_{24}N_2S$ (300.5)	Calc.	C	72.0	H	8.05	N	9.33
	Found	»	71.6	»	8.11	»	9.19

SUMMARY

Seven aminoalkyl derivatives of 2-benzylthiazole have been prepared and tested for antihistaminic and antispasmodic activity.

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