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Thiazole Derivatives of Aminopropanes

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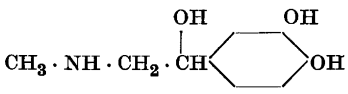
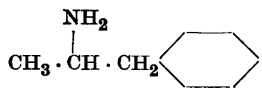
Several compounds related to adrenaline (I) possess a similar pharmacodynamic effect and some of these have been employed clinically, *e. g.* 1-phenyl-2-amino-propane (Amphetamine, II).



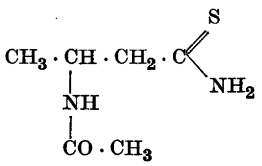
I



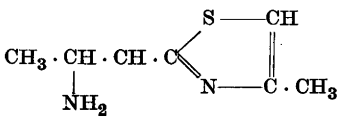
II

A large number of amphetamine derivatives have been tried and clinically used (for a review see Hartung [1]). Both the side chain and the benzene nucleus have been modified. However, no simple analogues appear to have been reported, containing a thiazole nucleus instead of a benzene nucleus. Therefore it seemed to be worth while preparing some thiazole substituted aminopropanes in order to study their potential sympathomimetic effect.

By addition of ammonia to allyl cyanide according to the method of Bruylants [2] 1-cyano-2-amino-propane was obtained. This compound was acetylated with acetic anhydride and hydrogen sulphide added to the resulting cyano compound. The 2-acetylamino-thiobutyramid (III) obtained was convertep into the thiazole derivative in the usual way by means of chloroacetone. After deacetylation 1-(4′-methyl-thiazolyl-2′)-2-amino-propane, IV, was obtained.



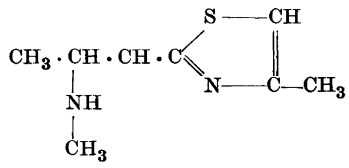
III



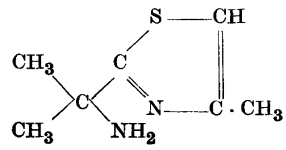
IV

The corresponding methylamino derivative V was prepared in a similar way by addition of methylamine to allyl cyanide. In this case, however, the methylamino group was benzoylated.

An isomeride of IV, 2-amino-2-(4'-methyl-thiazolyl-2')-propane, VI, was also prepared. Acetone and ammonium cyanide yielded α-amino-isobutyronitrile which after acetylation and addition of hydrogen sulphide gave α-acetylamino-thioisobutyramide [3], which with chloroacetone and subsequent deacetylation furnished VI.



V



VI

The compounds IV, V and VI have been tested according to the method of Clymer and Seifter [4]. IV and V had a certain stimulating effect on the cerebrum. However, this effect was weaker than that of II, which was used as a reference substance. IV and V however were less toxic than II. The compound VI had no stimulating effect. On the contrary it possessed a sedative effect.

EXPERIMENTAL PART

1-Cyano-2-acetylaminopropane

To 22.3 g of 1-cyano-2-amino-propane, prepared according to the method of Bruylants [2], 27.2 g of acetic anhydride was cautiously added. The mixture was cooled at intervals in ice-water. The following day it was distilled in high vacuum. The main fraction was obtained as an oil, which soon solidified. M. p. 40—45°, b. p. 190° 0.06 mm*. Yield 29.6 g.

$CH_3 \cdot CH(NH \cdot CO \cdot CH_3) \cdot CH_2 \cdot CH$	Calc.	C 57.2	H 7.93	N 22.2
	Found.	» 57.3	» 8.02	» 21.8

2-Acetylamino-thiobutyramide (III)

0.5 g of sodium was dissolved in 155 ml of ethanol. The ice-cooled solution was saturated with hydrogen sulphide to which was added 20 g of 1-cyano-2-acetylaminopropane and the mixture kept in a sealed bottle at 70° over night. The ethanol was

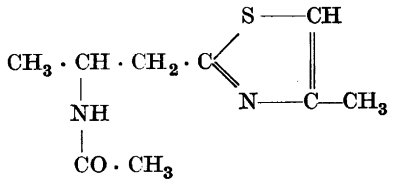
* The temperature given is the bath temperature.

distilled off at reduced pressure and the solid residue washed with petrol ether. Yield 27 g. After repeated recrystallisations from ethanol m. p. 138—140°.

$CH_3 \cdot CH(NH \cdot CO \cdot CH_3) \cdot CH_2 \cdot CSNH_2$ Calc. C 45.0 H 7.56 N 17.5 S 20.0
Found. » 45.0 » 7.58 » 17.3 » 19.3

1-(4'-Methyl-thiazolyl-2')-2-acetylamino-propane (VII)

10 g of 2-acetamido-thiopropionamide was suspended in a mixture of 6.5 g of chloroacetone and 50 ml of ethanol and the suspension shaken for 24 hours at room temperature. The clear solution was evaporated under reduced pressure. The resulting oil was distilled at 0.05 mm. After three distillations at a bath temperature of 190° 7.1 g of an almost colourless oil was obtained.



VII

Calc. N 14.0
Found. » 13.9

1-(4'-Methyl-thiazolyl-2')-2-amino-propane (IV)

11 g of the crude acetylated compound was boiled with 35 ml of hydrochloric acid for one hour. The solution was cooled and neutralized with 60 ml of 5 *N* NaOH and then extracted with chloroform. After drying the extract was evaporated and the resulting oil distilled at 130° 0.08 mm. 1.5 g of an almost colourless oil was obtained.

$C_7H_{12}N_2S$ Calc. N 17.9 S 20.5
Found » 17.7 » 20.0

Dihydrochloride. The oil was dissolved in abs. ether and the solution saturated with dry hydrogen chloride. After recrystallisation from abs. ethanol very hygroscopic crystals m. p. 178—180° were obtained.

$C_7H_{12}N_2S \cdot 2HCl$ Calc. Cl 30.9 Found Cl 30.7

1-Cyano-2-(N-benzoyl)-methylamino-propane

55 g of sodium hydroxide was dissolved in 110 ml of water and 60 g of 1-cyano-2-methylamino-propane [2] was added to the solution. The mixture was kept below 15° and 96 g of benzoylchloride added through a dropping funnel with stirring. The resulting precipitate was collected, washed with water and recrystallised from 500 ml of hot water, the yield was 95 g. M. p. 69—71°.

$C_6H_5 \cdot CO \cdot N(CH_3) \cdot CH(CH_3) \cdot CH_2 \cdot CN$ Calc. N 13.9 Found N 13.8

2-(N-Benzoyl)-methylamido-thiobutyramide

This compound was prepared in the same manner as 2-acetamido-thiobutyramide above. From 30 g of 1-cyano-2-benzoyl-methylamino-propane 28 g of the thioamide was obtained. It was dissolved in 80 ml of boiling ethanol and to this solution 200 ml of light petroleum was added. 25 g of a crystalline material was obtained. M. p. 144—145°.

$C_{12}H_{16}ON_2S$	Calc.	N 11.8	S 13.5
	Found	» 11.6	» 13.1

1-(4'-Methyl-thiazolyl-2')-2-(N-benzoyl)-methylaminopropane

This compound was prepared in the same manner as VII. From 11.8 g of the thioamide and 8.0 g of chloroacetone in 60 ml of ethanol 13.7 g of the crude thiazolecompound was obtained. This was distilled twice at 100° 0.003 mm and 7.8 g of a light yellow oil was obtained.

$C_{15}H_{18}ON_2S$	Calc.	C 65.7	H 6.61	N 10.2	S 11.7
	Found	» 64.8	» 6.63	» 10.1	» 11.3

1-(4'-Methyl-thiazolyl-2')-2-methylamino-propane (V)

The crude benzoyl compound was boiled for six hours with a mixture of 75 ml of conc. hydrochloric acid and 50 ml of water. After cooling the benzoic acid formed (5.5 g, m. p. 121°: calc. 6.1 g) was removed by filtration. The mother liquor was made alkaline with 5 *N* NaOH and the oil which separated extracted with chloroform. After drying and evaporation of the solvent the rest was distilled. At 50° 0.05 mm 3.8 g of a light yellow oil was obtained.

$C_8H_{14}N_2S$	Calc.	N 16.5	S 18.6
	Found	» 16.5	» 18.5

Dipicrate. From ethanolic solutions of the base and picric acid. Recrystallised from ethanol. M. p. 135—136°.

$C_{20}H_{20}N_8SO_{14}$	Calc.	C 38.3	H 3.18	N 17.8	S 5.10
	Found	» 38.3	» 3.08	» 17.8	» 4.92

Dihydrochloride. By saturating an ethereal solution of the base with dry hydrogen chloride. Recrystallised from ethanol. M. p. 161—162°. The substance was very hygroscopic.

$C_8H_{16}ON_2Cl_2S$	Calc.	N 11.5	Cl 29.2
	Found	» 11.5	» 28.4

As the hydrolytic removal of the benzoyl group gave rather poor yields, the acetylated cyanocompound and thioamide were also prepared. Unfortunately the deacetylation experiments resulted in no better yields.

1-Cyano-2-(N-acetyl)-methylaminopropane

20 g of 1-cyano-2-methylamino-propane was acetylated with 20.8 g of acetic anhydride. After standing over night the mixture was distilled. 27.8 g of the acetyl compound distilled at 190° 0.1 mm. It was redistilled twice at the same temperature and pressure.

$C_7H_{12}ON_2$ Calc. N 20.0 Found N 19.3

2-(N-Acetyl)-methylamino-thiobutyramide

This was prepared in the same way as the thioamides mentioned above. From 20 g of the cyano compound 13 g thioamide was obtained. After precipitation of an ethanolic solution with light petroleum the substance had m.p. 125—126°.

$C_7H_{14}ON_2S$	Calc.	C 48.3	H 8.10	N 16.1
	Found	» 48.3	» 8.28	» 16.0

2-Acetamino-2-(4′-methyl-thiazolyl-2′)-propane

This was prepared in the same manner as the thiazole compounds mentioned above. From 3.4 g α-acetamino-thioisobutyramid [3] and 2.2 g chloroacetone 4.0 g of the thiazole was obtained. After repeated recrystallisations from acetone it had m.p. 192—195°.

$C_9H_{14}ON_2S$	Calc.	N 14.1	S 16.2
	Found	» 13.9	» 16.0

2-Amino-2-(4′-methyl-thiazolyl-2′)-propane (VI)

10 g of the acetylcompound above was boiled for one hour with 50 ml conc. hydrochloric acid. The reaction mixture was made alkaline with 5 *N* NaOH and extracted with chloroform. The residue was distilled at 130° 0.03 mm. Yield 2 g. After one redistillation the resulting oil was colourless.

$C_7H_{12}N_2S$	Calc.	C 53.8	H 7.74	N 18.9
	Found	» 53.7	» 7.63	» 17.9

Dihydrochloride. Prepared as above. M.p. 177—179°.

$C_7H_{14}N_2Cl_2S$ Calc. Cl 30.9 Found Cl 30.5

SUMMARY

Three thiazole derivatives of 2-aminopropane have been prepared and tested for sympathomimetic activity.

REFERENCES

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3. Johnson, T. B., and Gatewood, E. *J. Am. Chem. Soc.* **51** (1929) 1815.
4. Clymer, N. V., and Seifter, J. *J. Pharm. Exp. Ther.* **89** (1947) 149.

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