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SYNTHESIS OF PANTHERINE (AGARIN)

A.R. Gagneux & F. Häfliger

J.R. Geigy S.A. Basle

and

C.H. Eugster & R. Good

Department of Organic Chemistry

University of Zurich, Switzerland.

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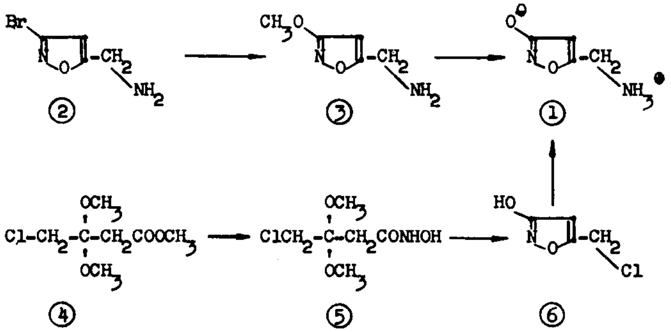
Pantherine ① has recently been described by Onda et al. (1), Takemoto et al. (2), Eugster et al. (3) as well as Bowden and Drysdale (4). The latter authors named it agarin.

We now wish to report the synthesis of pantherine via two different routes.



Refluxing a solution of 3-bromo-5-aminomethyl-isoxazole ② (5) ($\tau^{a)}$: 3.96, 1H-triplet, J∼0.5 cps; 6.05, 2H-doublet, J∼0.5 cps; 7.85, 2H-singlet disappearing on addition of D_2O) in KOH/MeOH (1:6 w/v) for 30 hours led to 3-methoxy-5-aminomethyl-isoxazole ③ b), yield 60%, b.p.$_{0,01}$ 70°, (τ: 4.22, 1H-t. J∼0.5 cps; 6.06, 3H-s.; 6.19, 2H-d. J∼0.5 cps; 8.20, 2H-s. disapp. D_2O), hydrochloride m.p. 175° dec. After hydrolysis in refluxing conc. HCl for 4 hours, evaporation of the solvent in vacuo, dissolving the residue in methanol/tetrahydrofuran 1:1, and addition of triethylamine, the zwitterion ① , m.p. 175° dec., yield 50%, crystallized. Its identity with pantherine, isolated by Eugster et al. (3), was established by thin layer- and paperchromatography, IR- and NMR-spectroscopy as well as narcosis potentiation tests c).

When methyl γ- chloro-acetoacetate (6) and methyl orthoformate were refluxed for 4 hours in abs. methanol previously saturated with dry HCl-gas, the corresponding ketal ④ , b.p.$_{12}$ 101-103°, was obtained in 65% yield. Treatment of the latter with hydroxylamine in methanol at 20° for 96 hours under N_2, evaporation of the solvent, and chromatography of the residue on a Dowex 1 X 2, 50-100 mesh ion exchanger with 2N acetic acid gave rise to 70% γ-chloro-β,β-dimethoxy-butyrohydroxamic acid ⑤ , m.p. 129-131° after sublimation at 10^{-5} Torr and 120°.

Cyclization of ⑤ was carried out in abs. acetic acid saturated with dry HCl-gas, at 20° for 16 hours. Evaporation and extraction of the residue with ether, followed by recrystallization of the ether-soluble part

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a) NMR-spectra in $CDCl_3$ were obtained on a Varian A-60 instrument using tetramethylsilane as an internal standard.

b) All new compounds gave satisfactory elemental analyses.

c) Performed by Dr. W. Theobald, J.R. Geigy S.A., Basle, Switzerland.

from acetone afforded 3-hydroxy-5-chloro-methyl-isoxazole ⑥ , m.p. 97-101° (τ: -0.47 1H-s. disapp. D_2O; 3.98, 1H-t. J~0.6 cps; 5.50, 2H-d. J~0.6 cps) pK^*_{MCS}: 7.40, eq. weight: calc. 133.5 fd. 132, in 80% yield. An essentially quantitative transformation of the chloride ⑥ in conc. aqueous NH_3 for 16 hours at 90° in an autoclave, evaporation of the solvent, and chromatography of the residue on a Dowex 50 WX 12, 50-100 mesh ion exchanger with 2% NH_3-solution completed this synthesis of pantherine ① .

REFERENCES

(1) M. Onda, H. Fukushima and M. Akagawa, Chem. Pharm. Bull. (Tokyo) **12**, 751 (1964).

(2) T. Takemoto, T. Nakajima and T. Yokobe, J. Pharm. Soc. Japan **84**, 1232 (1964).

(3) C.H. Eugster, G.F.R. Müller and R. Good, Tetrahedron Letters **23**, 1813 (1965)

(4) K. Bowden and A.C. Drysdale, Tetrahedron Letters **12**, 727 (1965)

(5) R. Fusco and S. Rossi, Rend. Ist. Lombardo Sci. Pt. I. Classe Sci. Mat. e Nat. **94A**, 729 (1960) Chem. Abstr. **57**, 16383 (1962).

(6) C.D. Hurd and J.L. Abernethy, J. Amer. Chem. Soc. **62**, 1147 (1940).