Tetrahedron Letters No.16, pp. 1467-1470, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE ABSOLUTE CONFIGURATIONS OF THE OPTICAL ISOMERS OF THE BROAD SPECTRUM ANTHELMINTIC TETRAMISOLE.

A.H.M. Raeymaekers, L.F.C. Roevens and P.A.J. Janssen

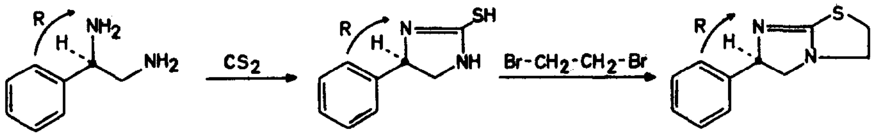
Janssen Pharmaceutica, N.V., Research Laboratoria,

Beerse, Belgium.

(Received 9 February 1967)

We wish to report upon an unambiguous stereospecific synthesis of the two optical isomers of the broad spectrum anthelmintic tetramisole (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17).

The absolute configuration of D-(-)-phenylethylenediamine I, $[\alpha]_D^{20}$ - 27.5 in benzene, is R. (18, 19, 20, 21, 22).
Its dextrorotary (+) tartrate, m.p. 222° dec., $[\alpha]_D^{20}$ + 40±2 (c: 0.8 in water) (18) reacts with carbondisulfide in alkaline water (23) to yield R-(-) 4(5)-phenyl-2-mercaptoimidazolidine II, m.p. 160-162° (24), $[\alpha]_D^{20}$ - 34±2 (c: 0.4 in methanol) (11); $C_9H_{10}N_2S$: Calcd. C, 60.64; H, 5.65; N, 15.72; Found: C, 60.28; H, 5.65; N, 15.61.

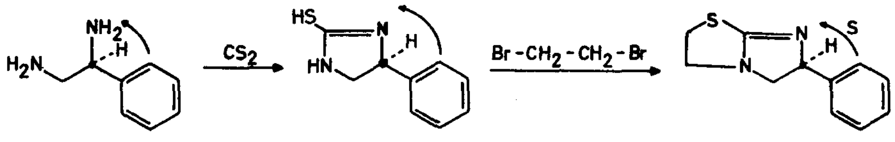


D-(-) I

D-(-) II

D-(+) or R-(+) tetramisole III

II reacts with 1,2-dibromoethane (2) in alkaline aqueous isopropanol to yield the dextrorotatory isomer of tetramisole III, i.e. R-(+)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole, isolated as the oxalate. $C_{11}H_{12}N_2S \cdot C_2H_2O_4$, Calcd.: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.96; H, 4.85; N, 9.48, m.p. 199-202°, $[\alpha]_D^{20}$ +99±2 (c: 0.5 in water).
The base is dextrorotatory in ethanol. The hydrochloride melts at 228-230°; $[\alpha]_D^{20}$ +125±2 (c : 0.7 in water).



L-(+) IV

L-(+) V

L-(-) or S-(-) tetramisole VI

Cyclisation (23) of the di-(+)-tartrate of L-(+)- or S-(+)-phenylethylenediamine IV, m.p. 179-180°; $[\alpha]_D^{20}$ +6.0 (c: 3.5 in water) (18) with carbondisulfide yields S-(+)-4(5)-phenyl-2-mercapto-imidazolidine V, m.p. 161-163°, $[\alpha]_D^{20}$ +34±2 (c: 0.4 in methanol), $C_9H_{10}N_2S$: Calcd.: C, 60.64; H, 5.65; N, 15.72; S, 17.99. Found: C, 60.63; H, 5.76; N, 15.58; S, 18.27.

1,2-dibromoethane reacts (2) with V to yield the levorotatory isomer of tetramisole VI, i.e. S-(-)-2,3,5,6-tetrahydro-6-phenyl-imidazo[2,1-b]thiazole. The oxalate melts at 200-201.5°, $[\alpha]_D^{20}$: -103±2 (c: 0.5 in water). $C_{11}H_{12}N_2S \cdot C_2H_2O_4$, Calcd.: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.11; H, 4.85; N, 9.50.
The base VI is levorotatory in ethanol. Its hydrochloride melts at 227-229°; $[\alpha]_D^{20}$ -124±2 (c: 0.9 in water).

50 mg. of R-(+)-tetramisole hydrochloride III and 50 mg. of S-(-)-tetramisole hydrochloride VI were dissolved in ethanol-acetone. After cooling 75 mg. of a crystalline material is obtained, m. p. 264-265°; $[\alpha]_D^{20}$: 0 (c: 1.0 in water), which was identified as pure DL-tetramisole hydrochloride (2).

The absolute configurations of the optical isomers of tetramisole are therefor R- or D-(+) and S- or L-(-).

As an anthelmintic S-(-)-tetramisole hydrochloride is about twice as potent as racemic tetramisole hydrochloride (1) and several times more potent than R-(+)-tetramisole hydrochloride (26).

In mice and in rats the LD_{50}-values for the two isomers and for racemic tetramisole (1) are almost identical (27).

REFERENCES AND NOTES.

1. D. Thienpont, O. Vanparijs, A. Raeymaekers, J. Vandenberk, P. Demoen, F. Allewijn, R. Marsboom, C. Niemegeers, K. Schellekens, and P. Janssen, Nature, **209**, 1084 (1966).
2. A. Raeymaekers, F. Allewijn, J. Vandenberk, P. Demoen, T. Van Offenwert and P. Janssen, J. Med. Pharm. Chem., **9**, 545 (1966).
3. J. Walley, Veterinary Record, **78**, 406 (1966).
4. R. Reinecke, J. S. Afr. vet. Ass., **37**, 27 (1966).
5. J. Reinders, Tijdschr. Diergeneesk., **91**, 967 (1966).
6. P. Mesquita and H. Daher, O Hospital, **69**, 1279 (1966).
7. Nascimento Filha, M. Halsman, H. Oria and J. Campos, Rev. Inst. Med. trop. São Paulo, **8**, 143 (1966).
8. J. Pankhurst and D. Sutton, Veterinary Record, **79**, 166 (1966).
9. K. Enigk, M. Stoye and H. Bürger, Deutsche Tierärztliche Wochenschrift, **73**, 441 (1966).
10. D. Ross, Veterinary Record, **79**, 392 (1966).
11. R. Supperer and H. Pfeiffer, Deutsche Tierärztliche Wochenschrift, **73**, 513 (1966).

12. O. Nilsson and L. Sorelius, Nord. Vet. Med., **18**, 314 (1966).

13. W. Fitzsimmons, Veterinary Record, **79**, 599 (1966).

14. T. Gibson, Veterinary Record, **79**, 601 (1966).

15. L. Pouplard, Thèse, Faculté de Médecine Vétérinaire de l'Etat, Bruxelles 1966.

16. D. Bruynooghe, D. Thienpont, and O. Vanparijs, Paper presented at the thirteenth World's Poultry Congress Kiev, USSR, August 1966.

17. B. Forsyth, Austr. Veter. J., **42**, 412 (1966).

18. H. Reihlen, E. Weinbrenner and G. von Hessling, Ann. Chem., **494**, 143 (1932).

19. L. Arpesella, A. La Monna and M. Grassi, Gazz. chem. It., **85**, 1354 (1955).

20. R. Lukes, J. Kovar, J. Kloubek and K. Blaha, Chem. Listy, **51**, 1501 (1957).

21. F. Bergel and K. Harrap, J. Chem. Soc., 4050 (1961).

22. D. Neilson and D. Ewing, J. Chem. Soc., 393 (1966).

23. F. Feist and H. Arnstein, Ber., **28**, 3173 (1895).

24. Tottoli-melting point apparatus.

25. Schmidt-Haensch polarimeter after Lippich.

26. D. Thienpont and O. Vanparijs, unpublished results.

27. C. Niemegeers, unpublished results.