Volume 221, number 2, 325-326 FEB 05107 September 1987

S-configuration of (+)-primaquine by X-ray analysis of the urea obtained with *R*-(+)-1-phenylethylisocyanate

Qian-Sheng Yu, Arnold Brossi* and Judith L. Flippen-Anderson

**Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892* and *Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375-5000, USA*

Received 28 July 1987

The *S*-configuration for (+)-primaquine prepared from the racemate by chemical resolution was established by solid-state X-ray analysis of the (+)-1-phenylethylurea obtained with *R*-(+)-1-phenylethylisocyanate.

(+)-Primaquine; X-ray analysis; Structure determination

1. INTRODUCTION

Primaquine used as a racemate is the most commonly used tissue schizontocide in malaria chemotherapy [1]. Optical resolution of racemic material with TAPA afforded the optically active isomers [2] which showed, when compared in vitro in an assay measuring tissue schizontocidal activity, similar potency to the racemate [3]. The absolute configuration of (+)-primaquine prepared by the published chemical resolution procedure has now been determined indirectly by X-ray analysis of the urea obtained with *R*-(+)-1-phenylethylisocyanate.

2. MATERIALS AND METHODS

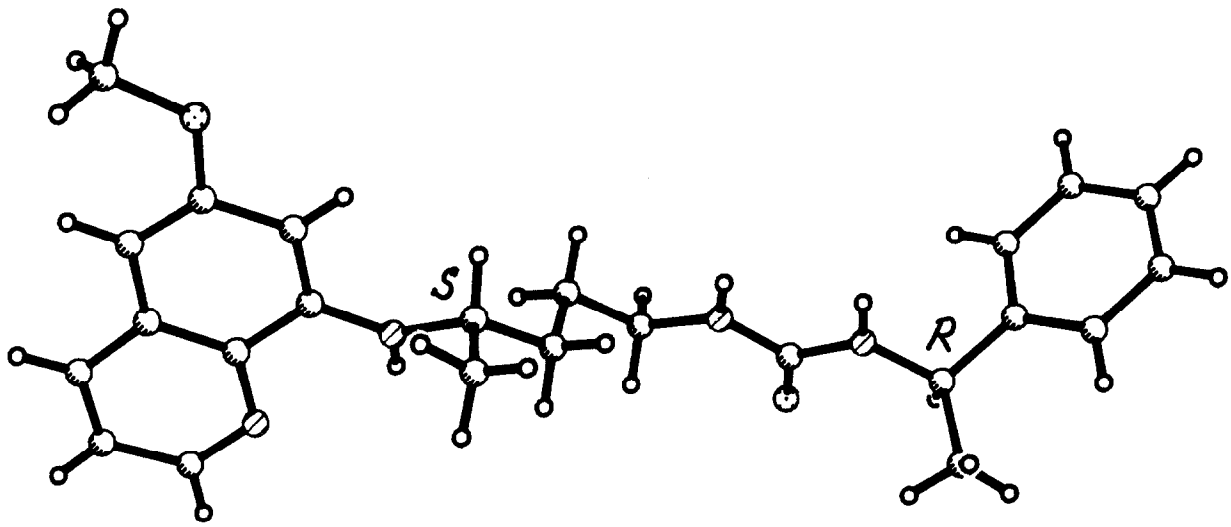
(+)-Primaquine was prepared according to the published procedure [2] [We thank Dr P. Buchs from SAPEC, S.A., Fine Chemicals, Barbengo, Lugano, Switzerland, for a sample of (+)-primaquine diphosphate prepared by the procedure of Carroll et al. [2]: m.p. 180–182°C; $[\alpha]_D^{20}$ + 27.8° (c = 1, H_2O); free base $[\alpha]_D^{22}$ + 51.8° (c = 1, CH_3OH)]. Optically active *R*-(+)-1-phenylethylisocyanate of >98% optical purity is commercially available. Reaction of (+)-primaquine base [2], prepared from the (+)-diphosphate salt in the usual way, afforded when reacted with *R*-(+)-1-phenylethylisocyanate in ether crystalline *N*-(1-phenylethyl)carbamoylprimaquine: m.p. 154–155°C; MS (CI) 407 (M^+ + 1); $[\alpha]_D^{22}$ + 32.9° (c = 1, $CHCl_3$); $C_{24}H_{30}N_4O_2$ (406.52); Calcd. C, 70.90; H, 7.44; N, 13.79%; Found C, 70.90; H, 7.46; N, 13.76%. X-ray analysis of this urea, using the *R*-configuration of the methyl group in the urea portion as a reference point [4], allowed determination of the methyl group at C1′ in (+)-primaquine as having the *S* configuration.

Correspondence address: Q.-S. Yu, Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892,USA

2.1. *X-ray analysis*

The crystals are orthorhombic, space group $P2_12_12_1$, with a = 9.353(2), b = 7.992(2) and c = 29.837(6) Å, V = 2230.2(7) Å^3, Z = 4, d_{calc} = 1.21 Mg·m^{-3}, λ (CuKa) = 1.54178 Å, μ = 0.59 mm^{-1}, $F(000)$ = 872, T = 295 K, final R = 0.053, wR = 0.049 for 1175 independent observed reflections. The goodness-of-fit parameter was 1.33 and the final difference map was featureless. Results of the X-ray study are shown in fig.1 [Tables of coordinates and bond lengths and angles have been

Published by Elsevier Science Publishers B.V. (Biomedical Division)
00145793/87/$3.50



deposited with the Crystallographic Data Centre, Cambridge University, University Chemical Lab., Cambridge, England]. There are two intermolecular hydrogen bonds in which both N atoms in the urea act as donors to the carbonyl oxygen of a neighboring molecule (N...O distances are 2.95 and 3.01 Å).

3. CONCLUSIONS

Salts of amines prepared with acids containing heavy atoms often do not give good crystals suitable for determining absolute configurations by X-ray diffraction analysis. It is found that ureas, formed from primary or secondary amines with optically active 1-phenylethylisocyanates, are amenable to making such assignments by indirectly establishing the relative configuration of the chiral substituent present in the amine to that of the methyl group of established absolute configuration introduced with the optically active isocyanate [5].

ACKNOWLEDGEMENT

This work was supported in part by the UNO/World Bank/WHO Special Program for Research and Training in Tropical Diseases.

REFERENCES

[1] Schmidt, L.H. (1969) Ann. Rev. Microbiol. 23, 427.
[2] Carroll, F.I., Berrange, B. and Linn, C.P. (1978) J. Med. Chem. 21, 325.
[3] Brossi, A., Millet, P., Landau, I., Bembenek, M.E. and Abell, C.W. (1987) FEBS Lett. 214, 291–294.
[4] Cairns, T.L. (1941) J. Am. Chem. Soc. 63, 871.
[5] Chrzanowska, M., Schönenberger, B., Brossi, A. and Flippen-Anderson, L. (1987) Helv. Chim. Acta, in press.