Financial support was received from the Polish Ministry of Science and Higher Education – project R.P.II.10.

References

HOSUR, M. V. & VISWAMITRA, M. A. (1981). *Acta Cryst.* B**37**, 839–843.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

STARYNOWICZ, P. (1986). Collected Abstracts of Tenth European Crystallographic Meeting, Wrocław, Poland, p. 174.

STARYNOWICZ, P. & LIS, T. (1985). Proc. of School Symposium on Inorganic Biochemistry and Molecular Biophysics, Wrocław-Karpacz, Poland, pp. 228–229.

STARYNOWICZ, P., LIS, T. & WEICHSEL, A. (1986). Collected Abstracts, Pre-meeting Symposium on Organic Crystal Chemistry, Poznań-Rydzyna, Poland, p. 67.

Syntex (1976). *XTL/XTLE Structure Determination System*. Syntex Analytical Instruments, Cupertino, California, USA.

WALKER, N. & STUART, D. (1983). *Acta Cryst.* A**39**, 158–166.

Acta Cryst. (1987). C**43**, 1900–1905

Structure of Nedocromil Sodium: a Novel Anti-asthmatic Agent

BY ANDREW A. FREER*

Department of Chemistry, Glasgow University, Glasgow G12 8QQ, Scotland

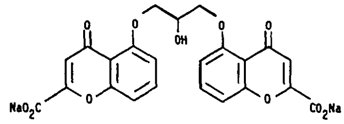
AND DAVID W. PAYLING AND JOHN L. SUSCHITZKY

Fisons plc, Pharmaceuticals Division, Bakewell Road, Loughborough, Leicestershire, LE11 0RH, England

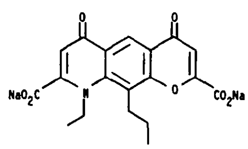
(*Received* 2 *April* 1987; *accepted* 28 *May* 1987)

Abstract. Disodium 9-ethyl-4,6-dioxo-10-propyl-4*H*,6*H*-pyrano[3,2-g]quinoline-2,8-dicarboxylate trihydrate, $C_{19}H_{15}NO_7^{2-}.2Na^+.3H_2O$, $M_r = 469{\cdot}4$, monoclinic, $P2_1/n$, $a = 21{\cdot}550\,(1)$, $b = 14{\cdot}506\,(1)$, $c = 27{\cdot}332\,(3)$ Å, $\beta = 111{\cdot}40\,(1)°$, $V = 7955{\cdot}2$ Å^3, $Z = 16$, $D_x = 1{\cdot}57$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 14{\cdot}12$ cm^{-1}, $F(000) = 3904$, $T = 291$ K, final $R = 0{\cdot}069$ for 7317 unique observed reflections. The four tricyclic units are, within experimental error, identical, with side-chain groups on N(9) and C(10) extended away from the ring system. The carboxylate group on C(2) lies almost in the same plane as the pyranoquinoline ring, whereas the group on C(8) is almost perpendicular to this ring system. Within the crystal lattice the four tricyclic rings are pseudosymmetrically related and are stacked one on top of each other up the *b* axis. Sodium ions and water molecules lie in discrete channels and do not encroach into the tricyclic ring domain.

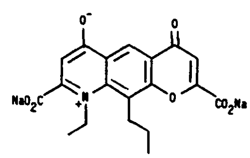
Introduction. It is now more than 17 years since the introduction of sodium cromoglycate (cromolyn sodium) (1) (Beach *et al.*, 1970) into clinical practice for the prophylactic treatment of allergic diseases, especially asthma. Much effort has been expended by more than 50 pharmaceutical companies (Sheard & Suschitzky, 1984) in an attempt to find related drugs with improved potency and efficacy. Until last year these attempts had been without success. However, workers at Fisons Pharmaceuticals have undertaken the synthesis and biological evaluation of new pyrano[3,2-g]quinoline-2,8-dicarboxylic acids with potential for the topical treatment of asthma (Cairns, Cox, Gould, Ingall & Suschitzky, 1985). The most promising member of the series was identified as nedocromil sodium (2), now marketed in the United Kingdom as Tilade®. It was therefore expedient to determine the crystal structure of (2) to ascertain the geometry of the carboxylic-acid groups and the packing mode of the sodium ions and water molecules.



(1)



(2)



(3)

Experimental. Slow cooling of a hot solution of nedocromil sodium (1 part) in isopropyl alcohol (9 parts) and water (3 parts by volume) afforded a colourless cube-shaped crystal *ca* 0·6 × 0·5 × 0·3 mm which was used in data collection, CAD-4 diffractometer. Preliminary, and subsequently detailed, Weissenberg photographs indicated crystals to be

* To whom all correspondence should be addressed.

0108-2701/87/101900-06$01.50

monoclinic, $P2_1/n$ with four molecules in the asymmetric unit. Despite initial apprehension, photographic investigation and reduced-cell calculations confirm four molecules per asymmetric unit. 15 500 independent intensities, θ limit 70°, $\omega/2\theta$ scan. Two standard intensities used to monitor variations in intensity data: $<3\%$ variation observed. Least-squares techniques based on 21 reflections, $\theta > 20°$, used to refine lattice parameters. No absorption correction. h 0 to 26, k 0 to 17, l −33 to 33. Structure solution by direct-phasing techniques using *MITHRIL* (Gilmore, 1984). The correct phase set was established only after a tricyclic ring system was incorporated in *NORMAL* with random position and random orientation. 109 negative quartets were also used for both phase expansion and calculation of figures of merit (experience indicates that *ca* 100 negative quartets seems to be the optimum number). The resulting solution, clearly indicated by *PSIZERO* and *NQUEST*, gave the positions of the four tricyclic units and the eight sodium cations. Difficulty in obtaining the correct phase solution using triple phase invariants alone could be explained by the non-uniform distribution of E magnitudes caused by the pseudosymmetry of the four molecules in the asymmetric unit. Full-matrix least-squares refinement on F of coordinates and anisotropic thermal parameters for non-H atoms converged to R and wR of 0·068 and 0·078 with unit weights. During the latter stages of refinement the introduction of the correct weighting scheme was crucial to the final analysis. By using the default weighting scheme, $w = 1/\sigma^2(F_o)$, refinement converged to $R = 0{\cdot}089$, $wR = 0{\cdot}11$. Weighting analysis indicated weak reflections were badly weighted. Ultimately unit weights were used, which brought a significant improvement to the refinement and consequently to the e.s.d.'s and $\sum w\Delta^2$. It is thought that the difficulty in defining an appropriate weighting scheme lies in the pseudosymmetry within the unit cell, where in certain parity groups strong reflections dominate, and in others weak reflections. H-atom coordinates, determined from difference Fourier syntheses, were included but not refined in least-squares calculations. 7317 reflections, $I > 3{\cdot}0\sigma_I$, were used. $(\Delta/\sigma)_{max} = 0{\cdot}04$; max. and min. heights in final difference Fourier synthesis = 0·65 and −0·51 e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974). All calculations on a Gould SEL 32/27 computer using Glasgow *GX* package (Mallinson & Muir, 1985).

Discussion. Final positional and equivalent isotropic thermal parameters are given in Table 1.* Bond lengths and bond angles are given in Table 2. An *ORTEP* (Johnson, 1976) diagram, Fig. 1, illustrates the numbering scheme for the molecule.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44098 (42 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final positional parameters and equivalent isotropic thermal parameters* (Å^2)

$$U_{eq} = \tfrac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Na(1)	0·61158 (19)	0·41255 (24)	0·71940 (14)	0·039
Na(2)	0·73472 (19)	0·02456 (26)	0·70501 (14)	0·043
Na(3)	0·11254 (19)	0·32579 (25)	0·72089 (14)	0·038
Na(4)	0·76591 (19)	0·28617 (26)	0·29849 (14)	0·044
Na(5)	0·77586 (19)	0·29378 (25)	0·80726 (14)	0·040
Na(6)	0·4913 (2)	0·1751 (3)	0·2728 (2)	0·044
Na(7)	0·27578 (19)	0·44620 (25)	0·80514 (14)	0·039
Na(8)	0·99136 (19)	0·08989 (26)	0·27366 (15)	0·043
O*W*(101)	0·8322 (3)	0·1838 (5)	0·7765 (3)	0·039
O*W*(102)	0·6589 (3)	−0·0882 (4)	0·7115 (2)	0·037
O*W*(103)	0·3410 (3)	0·3245 (4)	0·7895 (2)	0·038
O*W*(104)	0·3291 (3)	0·1109 (5)	0·7709 (3)	0·040
O*W*(105)	0·3314 (3)	0·5519 (4)	0·7720 (2)	0·040
O*W*(106)	0·6724 (3)	0·1253 (5)	0·7345 (2)	0·039
O*W*(107)	0·1966 (3)	0·4331 (5)	0·7155 (3)	0·044
O*W*(108)	0·6968 (3)	0·3026 (5)	0·7162 (3)	0·045
O*W*(109)	0·6922 (3)	0·5049 (5)	0·7010 (3)	0·050
O*W*(110)	0·1931 (4)	0·2305 (5)	0·7036 (3)	0·053
O*W*(111)	0·5228 (3)	0·3025 (5)	0·7020 (3)	0·050
O*W*(112)	0·0223 (3)	0·4359 (5)	0·7006 (3)	0·049
O(1*A*)	0·2382 (2)	0·1033 (4)	0·4254 (2)	0·025
O(4*A*)	0·0942 (2)	0·1287 (4)	0·4876 (2)	0·031
O(6*A*)	0·2739 (3)	0·0729 (4)	0·6632 (2)	0·037
O(22*A*)	0·2133 (3)	0·0896 (4)	0·3252 (2)	0·034
O(23*A*)	0·1039 (3)	0·0885 (4)	0·3051 (2)	0·035
O(82*A*)	0·5386 (3)	0·1119 (5)	0·6992 (3)	0·046
O(83*A*)	0·5199 (3)	−0·0367 (4)	0·6802 (2)	0·041
O(1*B*)	0·7642 (2)	0·3932 (4)	0·5791 (2)	0·027
O(4*B*)	0·9064 (2)	0·3737 (4)	0·5146 (2)	0·036
O(6*B*)	0·7243 (3)	0·4015 (4)	0·3388 (2)	0·032
O(22*B*)	0·7921 (3)	0·3951 (5)	0·6804 (2)	0·043
O(23*B*)	0·9005 (3)	0·3751 (4)	0·6983 (2)	0·037
O(82*B*)	0·4689 (3)	0·3139 (4)	0·3097 (2)	0·040
O(83*B*)	0·4690 (3)	0·4680 (5)	0·3040 (3)	0·051
O(1*C*)	0·2651 (2)	0·3561 (4)	0·5806 (2)	0·029
O(4*C*)	0·4077 (3)	0·3824 (4)	0·5162 (2)	0·037
O(6*C*)	0·2274 (3)	0·3302 (4)	0·3415 (2)	0·036
O(22*C*)	0·2920 (3)	0·3450 (5)	0·6813 (2)	0·043
O(23*C*)	0·4010 (3)	0·3642 (4)	0·6998 (2)	0·036
O(82*C*)	−0·0371 (3)	0·3770 (5)	0·3080 (3)	0·048
O(83*C*)	−0·0198 (3)	0·2256 (4)	0·3222 (2)	0·041
O(1*D*)	0·7389 (2)	0·1531 (4)	0·4262 (2)	0·027
O(4*D*)	0·5940 (3)	0·1245 (4)	0·4877 (2)	0·034
O(6*D*)	0·7751 (3)	0·1414 (4)	0·6659 (2)	0·037
O(22*D*)	0·7151 (3)	0·1674 (4)	0·3265 (2)	0·038
O(23*D*)	0·6052 (3)	0·1724 (4)	0·3065 (2)	0·038
O(82*D*)	1·0313 (3)	0·0520 (4)	0·6947 (2)	0·038
O(83*D*)	1·0315 (3)	0·2059 (5)	0·7032 (2)	0·046
N(9*A*)	0·4139 (3)	0·0944 (5)	0·5951 (2)	0·028
N(9*B*)	0·5865 (3)	0·3843 (4)	0·4096 (2)	0·024
N(9*C*)	0·0873 (3)	0·3501 (4)	0·4111 (2)	0·022
N(9*D*)	0·9151 (3)	0·1292 (5)	0·5957 (2)	0·024
C(2*A*)	0·1723 (4)	0·1036 (5)	0·3942 (3)	0·025
C(3*A*)	0·1235 (4)	0·1128 (6)	0·4130 (3)	0·027
C(4*AA*)	0·2086 (4)	0·1145 (5)	0·5020 (3)	0·024
C(4*A*)	0·1375 (3)	0·1203 (5)	0·4686 (3)	0·024
C(5*A*)	0·2308 (4)	0·1088 (5)	0·5560 (3)	0·025
C(5*AA*)	0·2981 (4)	0·0977 (5)	0·5862 (3)	0·026
C(6*A*)	0·3168 (4)	0·0769 (5)	0·6420 (3)	0·026
C(7*A*)	0·3848 (4)	0·0555 (6)	0·6689 (3)	0·031
C(8*A*)	0·4306 (4)	0·0674 (6)	0·6458 (3)	0·028
C(9*AA*)	0·3463 (3)	0·1001 (5)	0·5618 (3)	0·023
C(10*A*)	0·3256 (4)	0·1023 (5)	0·5066 (3)	0·025
C(10*AA*)	0·2571 (4)	0·1075 (5)	0·4789 (3)	0·024
C(21*A*)	0·1624 (4)	0·0932 (5)	0·3362 (3)	0·024
C(81*A*)	0·5041 (4)	0·0459 (6)	0·6780 (3)	0·032
C(91*A*)	0·4667 (4)	0·1432 (6)	0·5807 (3)	0·036
C(92*A*)	0·5192 (4)	0·0820 (8)	0·5740 (4)	0·050
C(101*A*)	0·3688 (4)	0·0894 (6)	0·4740 (3)	0·027
C(102*A*)	0·3763 (4)	0·1757 (6)	0·4451 (3)	0·035
C(103*A*)	0·4172 (4)	0·1587 (7)	0·4112 (3)	0·047
C(2*B*)	0·8297 (4)	0·3852 (6)	0·6095 (3)	0·028
C(3*B*)	0·8782 (4)	0·3772 (6)	0·5899 (3)	0·031
C(4*BA*)	0·7925 (4)	0·3842 (5)	0·5018 (3)	0·025

Table 1 (*cont.*)

	x	y	z	U_{eq}
C(4*B*)	0·8634 (4)	0·3783 (6)	0·5339 (3)	0·026
C(5*B*)	0·7696 (4)	0·3874 (5)	0·4476 (3)	0·025
C(5*BA*)	0·7021 (4)	0·3914 (5)	0·4176 (3)	0·024
C(6*B*)	0·6819 (3)	0·4003 (5)	0·3602 (3)	0·023
C(7*B*)	0·6130 (4)	0·4071 (6)	0·3325 (3)	0·030
C(8*B*)	0·5685 (4)	0·3955 (5)	0·3570 (3)	0·027
C(9*BA*)	0·6538 (3)	0·3893 (5)	0·4426 (3)	0·021
C(10*B*)	0·6755 (4)	0·3931 (5)	0·4980 (3)	0·024
C(10)*BA*)	0·7446 (4)	0·3898 (5)	0·5253 (3)	0·024
C(21*B*)	0·8415 (4)	0·3853 (6)	0·6682 (3)	0·030
C(81*B*)	0·4941 (4)	0·3929 (6)	0·3209 (3)	0·034
C(91*B*)	0·5340 (4)	0·3464 (7)	0·4279 (3)	0·032
C(92*B*)	0·4829 (4)	0·4158 (6)	0·4296 (3)	0·045
C(101*B*)	0·6334 (4)	0·4095 (6)	0·5315 (3)	0·026
C(102*B*)	0·6262 (4)	0·3256 (6)	0·5630 (3)	0·034
C(103*B*)	0·5803 (4)	0·3452 (7)	0·5925 (4)	0·046
C(2*C*)	0·3308 (4)	0·3631 (5)	0·6109 (3)	0·025
C(3*C*)	0·3789 (4)	0·3737 (6)	0·5913 (3)	0·027
C(4*C*)	0·3645 (4)	0·3757 (5)	0·5352 (3)	0·027
C(4*CA*)	0·2928 (3)	0·3674 (5)	0·5028 (3)	0·023
C(5*C*)	0·2704 (4)	0·3619 (5)	0·4490 (3)	0·024
C(5*CA*)	0·2036 (4)	0·3517 (5)	0·4191 (3)	0·022
C(6*C*)	0·1840 (4)	0·3332 (5)	0·3631 (3)	0·028
C(7*C*)	0·1149 (4)	0·3159 (6)	0·3355 (3)	0·029
C(8*C*)	0·0704 (4)	0·3270 (5)	0·3595 (3)	0·025
C(9*CA*)	0·1555 (4)	0·3537 (5)	0·4441 (3)	0·025
C(10*C*)	0·1770 (4)	0·3541 (5)	0·4993 (3)	0·025
C(10*CA*)	0·2460 (3)	0·3609 (5)	0·5269 (3)	0·022
C(21*C*)	0·3425 (4)	0·3570 (6)	0·6688 (3)	0·031
C(81*C*)	−0·0031 (4)	0·3079 (6)	0·3267 (3)	0·031
C(91*C*)	0·0359 (4)	0·3970 (6)	0·4267 (3)	0·035
C(92*C*)	−0·0175 (5)	0·3348 (8)	0·4321 (4)	0·055
C(101*C*)	0·1345 (4)	0·3388 (6)	0·5324 (3)	0·029
C(102*C*)	0·1274 (4)	0·4240 (6)	0·5630 (3)	0·036
C(103*C*)	0·0805 (5)	0·4036 (7)	0·5928 (4)	0·051
C(2*D*)	0·6736 (4)	0·1528 (5)	0·3950 (3)	0·025
C(3*D*)	0·6238 (4)	0·1430 (6)	0·4138 (3)	0·027
C(4*D*)	0·6378 (4)	0·1332 (5)	0·4696 (3)	0·026
C(4*DA*)	0·7093 (3)	0·1364 (5)	0·5027 (3)	0·022
C(5*D*)	0·7312 (4)	0·1352 (5)	0·5567 (3)	0·024
C(5*DA*)	0·7984 (4)	0·1370 (5)	0·5872 (3)	0·024
C(6*D*)	0·8181 (4)	0·1406 (6)	0·6443 (3)	0·032
C(7*D*)	0·8879 (4)	0·1455 (6)	0·6733 (3)	0·031
C(8*D*)	0·9322 (4)	0·1360 (6)	0·6489 (3)	0·027
C(9*DA*)	0·8475 (4)	0·1359 (5)	0·5627 (3)	0·025
C(10*D*)	0·8260 (3)	0·1440 (5)	0·5074 (3)	0·024
C(10*DA*)	0·7573 (4)	0·1430 (5)	0·4797 (3)	0·024
C(21*D*)	0·6638 (4)	0·1655 (6)	0·3383 (3)	0·030
C(81*D*)	1·0065 (4)	0·1313 (6)	0·6852 (3)	0·033
C(91*D*)	0·9669 (4)	0·0929 (7)	0·5770 (3)	0·037
C(92*D*)	1·0191 (5)	0·1614 (8)	0·5767 (4)	0·055
C(101*D*)	0·8690 (4)	0·1605 (6)	0·4744 (3)	0·029
C(102*D*)	0·8737 (4)	0·0769 (6)	0·4421 (3)	0·034
C(103*D*)	0·9186 (5)	0·0964 (7)	0·4106 (4)	0·048

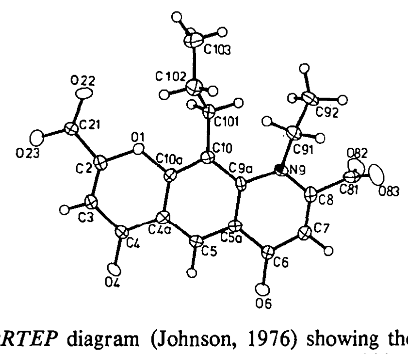


Fig. 1. *ORTEP* diagram (Johnson, 1976) showing the numbering scheme with vibrational ellipsoids at 50% probability level.

Table 2. *Bond lengths* (Å) *and angles* (°)

	Molecule *A*	Molecule *B*	Molecule *C*	Molecule *D*
O(1)–C(2)	1·364 (9)	1·357 (9)	1·360 (9)	1·354 (9)
O(1)–C(10a)	1·366 (9)	1·373 (9)	1·374 (9)	1·376 (9)
O(4)–C(4)	1·228 (9)	1·224 (9)	1·226 (10)	1·221 (9)
O(6)–C(6)	1·257 (9)	1·253 (9)	1·275 (10)	1·268 (10)
O(22)–C(21)	1·240 (9)	1·234 (10)	1·241 (10)	1·249 (10)
O(23)–C(21)	1·238 (9)	1·247 (10)	1·266 (10)	1·261 (10)
O(82)–C(81)	1·221 (11)	1·258 (12)	1·238 (11)	1·254 (11)
O(83)–C(81)	1·240 (11)	1·227 (12)	1·240 (11)	1·229 (12)
N(9)–C(8)	1·357 (10)	1·355 (10)	1·364 (9)	1·368 (10)
N(9)–C(9a)	1·410 (10)	1·403 (9)	1·417 (10)	1·409 (10)
N(9)–C(91)	1·509 (11)	1·499 (10)	1·489 (10)	1·482 (10)
C(2)–C(3)	1·336 (11)	1·343 (11)	1·337 (11)	1·354 (11)
C(2)–C(21)	1·527 (11)	1·528 (11)	1·511 (11)	1·497 (11)
C(3)–C(4)	1·442 (11)	1·445 (11)	1·449 (11)	1·451 (11)
C(4)–C(4a)	1·473 (11)	1·460 (11)	1·478 (11)	1·476 (10)
C(5)–C(4a)	1·376 (10)	1·380 (10)	1·372 (10)	1·375 (10)
C(4a)–C(10a)	1·410 (11)	1·405 (11)	1·394 (10)	1·398 (10)
C(5)–C(5a)	1·393 (11)	1·386 (11)	1·379 (10)	1·384 (10)
C(6)–C(5a)	1·460 (10)	1·471 (10)	1·456 (10)	1·460 (11)
C(5a)–C(9a)	1·426 (10)	1·438 (10)	1·435 (11)	1·443 (10)
C(6)–C(7)	1·413 (11)	1·403 (11)	1·424 (11)	1·424 (12)
C(7)–C(8)	1·363 (11)	1·368 (11)	1·354 (11)	1·358 (11)
C(8)–C(81)	1·538 (11)	1·546 (12)	1·534 (11)	1·547 (11)
C(10)–C(9a)	1·408 (10)	1·414 (10)	1·408 (11)	1·415 (10)
C(10)–C(10a)	1·393 (11)	1·401 (11)	1·404 (10)	1·397 (10)
C(10)–C(101)	1·517 (11)	1·525 (11)	1·521 (11)	1·528 (11)
C(91)–C(92)	1·500 (13)	1·505 (13)	1·511 (14)	1·504 (14)
C(101)–C(102)	1·521 (12)	1·532 (12)	1·532 (12)	1·525 (12)
C(102)–C(103)	1·514 (12)	1·511 (12)	1·539 (13)	1·539 (13)
C(2)–O(1)–C(10a)	120·5 (6)	119·9 (6)	119·1 (6)	119·9 (6)
C(8)–N(9)–C(9a)	120·2 (7)	120·3 (6)	119·4 (6)	119·3 (6)
C(8)–N(9)–C(91)	117·2 (7)	116·1 (6)	117·5 (6)	116·5 (6)
C(9a)–N(9)–C(91)	120·3 (7)	122·3 (6)	120·6 (6)	122·5 (6)
O(1)–C(2)–C(3)	123·0 (7)	123·3 (7)	123·4 (7)	123·2 (7)
O(1)–C(2)–C(21)	111·7 (6)	112·4 (6)	111·9 (7)	111·9 (7)
C(3)–C(2)–C(21)	125·3 (7)	124·3 (7)	124·7 (7)	124·9 (7)
C(2)–C(3)–C(4)	121·5 (7)	121·2 (7)	121·9 (7)	121·3 (7)
C(4)–C(4a)–C(5)	122·9 (7)	122·3 (7)	121·9 (7)	122·0 (7)
C(4)–C(4a)–C(10a)	120·0 (7)	120·7 (7)	120·0 (7)	120·3 (7)
C(5)–C(4a)–C(10a)	116·9 (7)	117·0 (7)	118·0 (7)	117·6 (7)
O(4)–C(4)–C(3)	123·6 (7)	123·0 (7)	123·2 (7)	122·9 (7)
O(4)–C(4)–C(4a)	121·5 (7)	122·3 (7)	122·9 (7)	122·9 (7)
C(3)–C(4)–C(4a)	114·8 (7)	114·6 (7)	113·9 (7)	114·2 (7)
C(4a)–C(5)–C(5a)	121·5 (7)	121·7 (7)	121·7 (7)	121·3 (7)
C(5)–C(5a)–C(6)	118·3 (7)	118·2 (7)	118·9 (7)	118·4 (7)
C(5)–C(5a)–C(9a)	119·8 (7)	120·2 (7)	119·6 (7)	120·3 (7)
C(6)–C(5a)–C(9a)	121·6 (7)	121·6 (7)	121·4 (7)	121·3 (7)
O(6)–C(6)–C(5a)	121·4 (7)	121·2 (7)	120·8 (7)	121·5 (7)
O(6)–C(6)–C(7)	123·2 (7)	123·6 (7)	123·4 (7)	122·8 (7)
C(5a)–C(6)–C(7)	115·2 (7)	115·2 (7)	115·8 (7)	115·7 (7)
C(6)–C(7)–C(8)	121·3 (7)	121·4 (7)	120·8 (7)	120·7 (7)
N(9)–C(8)–C(7)	122·9 (7)	123·6 (7)	124·1 (7)	124·4 (7)
N(9)–C(8)–C(81)	118·5 (7)	120·2 (7)	118·5 (7)	119·5 (7)
C(7)–C(8)–C(81)	118·5 (7)	116·1 (7)	117·3 (7)	116·1 (7)
N(9)–C(9a)–C(5a)	117·0 (7)	117·0 (6)	117·3 (7)	117·8 (7)
N(9)–C(9a)–C(10)	122·8 (7)	123·4 (7)	122·7 (7)	123·1 (7)
C(5a)–C(9a)–C(10)	120·1 (7)	119·6 (7)	119·9 (7)	119·1 (7)
C(9a)–C(10)–C(10a)	116·4 (7)	116·3 (7)	116·5 (7)	116·6 (7)
C(9a)–C(10)–C(101)	127·1 (7)	127·7 (7)	127·1 (7)	127·7 (7)
C(10a)–C(10)–C(101)	116·2 (7)	115·7 (7)	116·2 (7)	115·6 (6)
O(1)–C(10a)–C(4a)	120·1 (7)	120·1 (7)	121·4 (6)	120·9 (7)
O(1)–C(10a)–C(10)	115·1 (7)	115·0 (7)	114·6 (6)	114·4 (6)
C(4a)–C(10a)–C(10)	124·8 (7)	124·9 (7)	123·9 (7)	124·7 (7)
O(22)–C(21)–O(23)	126·8 (7)	127·4 (7)	126·0 (7)	125·3 (7)
O(22)–C(21)–C(2)	117·0 (7)	117·0 (7)	116·7 (7)	117·2 (7)
O(23)–C(21)–C(2)	116·1 (7)	115·6 (7)	117·3 (7)	117·6 (7)
O(82)–C(81)–O(83)	128·7 (8)	128·7 (8)	129·2 (8)	129·2 (8)
O(82)–C(81)–C(8)	115·8 (8)	115·6 (8)	115·1 (8)	115·9 (8)
O(83)–C(81)–C(8)	115·5 (8)	115·4 (8)	115·7 (8)	114·7 (8)
N(9)–C(91)–C(92)	115·3 (8)	114·5 (8)	115·3 (8)	115·3 (8)
C(10)–C(101)–C(102)	114·1 (7)	114·7 (7)	114·1 (7)	113·6 (7)
C(101)–C(102)–C(103)	112·3 (8)	111·7 (8)	110·4 (8)	111·5 (8)

There is pronounced pseudosymmetry within the crystal structure corresponding to a pseudo-cell with base vectors of (100), ($0\frac{1}{2}0$), ($0\frac{1}{4}\frac{1}{2}$) to give $Z = 4$. This pseudosymmetry is, on the whole, so exact that several upper-layer Weissenberg photographs were closely scrutinized to ensure the space-group absences were correct and, along with reduced-cell calculations, confirmed 16 molecules in the unit cell of space group $P2_1/n$.

Table 3. *Positions of selected atoms* (Å × 10^3) *illustrating the pseudosymmetry of the anion*

		x	y	z	Pseudo-translation
O(1)	*A*	238	103	425	
	B	236	607	421	I
	C	235	856	919	II
	D	239	347	926	III
N(9)	*A*	414	094	595	
	B	414	616	590	I
	C	413	850	1089	II
	D	415	371	1096	III
C(2)	*A*	172	104	394	
	B	170	615	391	I
	C	169	863	889	II
	D	174	347	895	III
C(6)	*A*	317	077	642	
	B	318	600	640	I
	C	316	833	1137	II
	D	318	359	1144	III
C(103)	*A*	417	159	411	
	B	420	655	408	I
	C	419	904	907	II
	D	419	404	911	III
O(22)	*A*	213	090	325	
	B	208	605	320	I
	C	208	845	819	II
	D	215	333	826	III
O(83)	*A*	520	−037	680	
	B	531	532	696	I
	C	520	726	1178	II
	D	532	294	1203	III

The atoms *B*, *C* and *D* are derived, respectively, from the coordinates in Table 1 by the transformations $-x, -y, -z$; $\frac{1}{2}-x, \frac{1}{2}+y, 1+(\frac{1}{2}-z)$; $1-(\frac{1}{2}+x), \frac{1}{2}-y, \frac{1}{2}+z$.

The pseudo relationships among atoms *A*, *B*, *C* and *D* are then given by the following transformations: (I) $x, \frac{1}{2}+y, z$; (II) $x, \frac{3}{4}+y, \frac{1}{2}+z$; (III) $x, \frac{1}{4}+y, \frac{1}{2}+z$.

The ring pseudosymmetry amongst the four pyranoquinoline anions is displayed in Table 3 where the ring atoms conform to the additional lattice points at (0, $\frac{1}{2}$, 0), (0, $\frac{3}{4}$, $\frac{1}{2}$) and (0, $\frac{1}{4}$, $\frac{1}{2}$). This pseudosymmetry only breaks down at the periphery of the anions where the carboxylate oxygens start to differ significantly from their pseudo locations. Evidence for this sub-cell is also enhanced by comparing reflection parity groups and their intensities, where reflections with k odd have intensities of approximately half the value of those with k even.

The four tricyclic units are, within experimental error, identical with side-chain groups on N(9) and C(10) fully extended away from the ring system. The two carboxylate groups are in differing orientations to the pyranoquinoline ring. At position 2 the acid function is in the same plane as the major ring component [dihedral angle between planes defined by O(1), C(2), C(3), C(4), C(4a), C(10a) and C(21), O(22), O(23) is 3·7 (4)°], whilst, owing to steric hinderance by the ethyl group on N(9), the carboxy acid at C(8) is tilted to almost 90° from the adjacent ring system [dihedral angle between planes defined by C(5a), C(6), C(7), C(8), N(9), C(9a) and C(81), O(82), O(83) is 92·1 (6)°]. Many of the *potent* antiallergy compounds that have previously been reported are dicarboxylic acids. The majority of these [notably benzodipyrans, pyridoquinolines, bis(oxamic acids) and quinolinyloxamic acids] share a common geometry with the pyranoquinoline described here, and this suggests a stereochemical role for both carboxylate groups. It has been shown (Cairns, Cox, Gould, Ingall & Suschitzky, 1985) that a second acid function is not essential for activity. However, it may serve to promote receptor affinity by binding at an auxiliary site on the cromoglycate receptor. Molecular graphics analysis (Cairns, Cox, Gould, Ingall & Suschitzky, 1985) suggests that sodium cromoglycate may readily adopt a conformation in which the two acid functions are disposed in a spatial relationship similar to that found in the pyranoquinolines and that this may be an important conformation at the cromoglycate receptor site. The short N(9)—C(8) bond, 1·361 (10) Å, suggests conjugation between N(9) and the carbonyl group C(6)=O(6), implying a resonance contribution from structure (3). Hence, elongation of the C(6)=O(6) bond, 1·263 (10) Å, compared with its C(4)=O(4) neighbour, 1·225 (9) Å, suggests that the carbonyl oxygen O(6) may be involved in electrostatic interactions with Na ions and water molecules.

Within the crystal lattice the four pyranoquinoline anions are stacked one on top of each other up the *b* axis at approximately $\frac{1}{4}$, $\frac{3}{4}$ along the *a* axis and 0, $\frac{1}{2}$, 1 along the *c* axis. This is shown in the stereoview of the unit cell in Fig. 2.

The sodium cations and water molecules lie in discrete channels in the unit cell, running throughout the length of the *a* axis at approximately $\frac{1}{4}$, $\frac{3}{4}$ along the *c* axis and do not encroach into the tricyclic ring domain (Fig. 3). The pseudosymmetry already described for the anion moiety is also to be found among the sodium cations and water molecules. In this instance the extra symmetry allows Na ions and water molecules to be

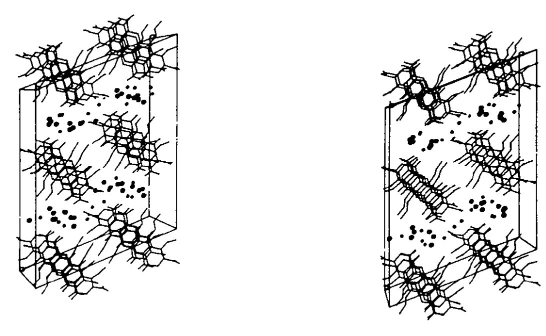


Fig. 2. Stereoview of unit-cell contents looking down the *b* axis. Smaller spheres are sodium ions.

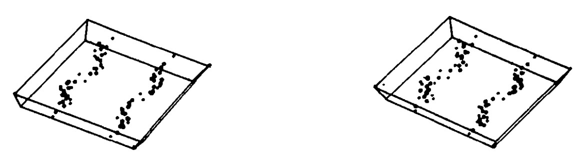


Fig. 3. Stereoview of unit cell showing only sodium ions and water molecules.

interchanged, *e.g.* Na(3), O*W*(102), O*W*(103) can be obtained from Na(1) and Na(4), O*W*(109), O*W*(110) from Na(2) *etc.* Although the degree of fit for the interchanged Na ions is very close the water molecules, just as with the atoms at the periphery of the anion, deviate to a greater extent from this pseudosymmetry.

Each Na ion is coordinated by five O atoms (Table 4) derived from either adjacent water molecules or oxygens of the acid groups or the carbonyl on C(6) with an average Na···O distance of 2·400 (7) Å. From thermogravimetric (TG) and differential scanning calorimetric (DSC) analyses it was noted that two-thirds of the water molecules were lost over the range 344–410 K (loose bound) while the remaining water molecules (hard bound) were not released until a temperature range of 438–492 K was attained. It was therefore interesting to look at the intermolecular bonding network to ascertain if indeed differing bonding environments could be allocated to the water molecules. Table 5 shows an analysis of the bonding environment for the 12 water molecules.

This shows clearly that the water molecules fall into three groups of four: (i) 101, 104, 105, 106; (ii) 102, 103, 111, 112; (iii) 107, 108, 109, 110. Which group of four are the hard-bound waters is difficult to determine unambiguously. Group (i) shares four common characteristics in a unique environment whereby each water molecule is in the proximity of only one sodium ion, one water molecule, atom O(82) of the acid group which lies perpendicular to the ring system and atom O(6) of the ketone on C(6). On the other hand group (ii) waters could be hard bound because they associate exclusively with strongly charged atoms (Na^+, carboxylate$^-$) *via* two lone pairs and two H atoms, or, indeed, group (iii) waters are candidates since they associate with five nearby atoms, not four like the others. The authors would be grateful if anyone could advance a convincing argument as to which group is really hard bound.

Throughout the molecule the temperature parameters are noticeably smaller than would otherwise be expected for data collected at room temperature, which suggests a rather rigid packing arrangement. TG and DSC information predicts phase transformations at higher temperatures (as both types of water are involved). These transformations would probably result in a disordered structure based on the sub-cell already discussed.

Thanks are due to Dr Richard Marsh for his useful comments on the pseudosymmetry, to Dr Gerald Steele for thermal analytical results, and to Mr Michael D. Baker for the crystals.

Table 4. *Sodium coordination distances* (Å)

	Waters (O*W*)		Acid oxygens		Carbonyl oxygens	
Na(1)	(108)	2·458 (8)	23*A*	2·407 (6)		
	(109)	2·389 (8)	83*B*	2·371 (8)		
	(111)	2·402 (8)				
Na(2)	(102)	2·364 (7)				
	(106)	2·321 (7)	22*A*	2·315 (7)	(6*D*)	2·334 (4)
	(109)	2·492 (8)				
Na(3)	(107)	2·434 (8)	22*D*	2·402 (4)		
	(110)	2·396 (8)				
	(112)	2·419 (8)	83*D*	2·385 (4)		
Na(4)	(103)	2·356 (8)				
	(104)	2·325 (8)	23*D*	2·315 (4)	(6*B*)	2·352 (7)
	(110)	2·505 (8)				
Na(5)	(101)	2·339 (8)	22*A*	2·324 (7)	(6*C*)	2·431 (4)
	(102)	2·388 (7)				
	(108)	2·453 (7)				
Na(6)	(112)	2·811 (8)	83*A*	2·443 (7)		
			23*B*	2·366 (7)		
			82*B*	2·379 (7)		
			22*D*	2·286 (4)		
Na(7)	(103)	2·391 (7)	23*D*	2·307 (4)	(6*A*)	2·440 (7)
	(105)	2·325 (7)				
	(107)	2·429 (7)				
Na(8)	(111)	2·776 (8)	23*A*	2·259 (7)		
			22*C*	2·331 (4)		
			83*C*	2·434 (4)		
			82*D*	2·350 (4)		

Table 5. *Intermolecular distances* (Å) *involving the* 12 *water molecules*

O*W*	101	102	103	104	105	106
Na	(5), 2·339 (8)	(2), 2·364 (7) (5), 2·388 (7)	(4), 2·356 (8) (7), 2·391 (7)	(4), 2·325 (8)	(7), 2·325 (7)	(2), 2·321 (7)
O*W*	(109), 2·761 (10)			(107), 2·693 (10)	(110), 2·773 (10)	(108), 2·707 (9)
Acid oxygens	(82*B*), 2·748 (9)	(83*A*), 2·897 (9) (22*B*), 2·762 (8)	(23*C*), 2·768 (6) (83*C*), 2·891 (7)	(82*C*), 2·688 (7)	(82*D*), 2·759 (6)	(82*A*), 2·692 (8)
Carbonyl oxygens	(6*D*), 2·884 (6)			(6*A*), 2·798 (8)	(6*B*), 2·899 (8)	(6*C*), 2·799 (6)

O*W*	107	108	109	110	111	112
Na	(3), 2·434 (8) (7), 2·429 (7)	(1), 2·458 (8) (5), 2·453 (7)	(1), 2·388 (8) (2), 2·492 (8)	(3), 2·396 (8) (4), 2·505 (8)	(1), 2·402 (8) (8), 2·776 (8)	(3), 2·419 (8) (6), 2·811 (8)
O*W*	(104), 2·693 (10) (110), 2·954 (10)	(106), 2·707 (10) (109), 2·961 (10)	(101), 2·761 (10) (108), 2·961 (10)	(105), 2·773 (10) (107), 2·954 (10)		
Acid oxygens	(23*C*), 2·852 (7)	(22*B*), 2·907 (9)	(22*B*), 2·894 (9)	(23*C*), 2·935 (7)	(22*C*), 2·754 (7) (82*A*), 2·791 (10)	(23*B*), 2·749 (9) (82*C*), 2·754 (7)

References

BEACH, J. E., BLAIR, A. M. J. N., CLARKE, A. J., COX, J. S. G., KING, J., LEE, T. B., LOVEDAY, D. E. E., MOSS, G. F., ORR, T. S. C., RITCHIE, J. T. & SHEARD, P. (1970). *Adv. Drug Res.* **5**, 115–121.

CAIRNS, H., COX, D., GOULD, K. J., INGALL, A. H. & SUSCHITZKY, J. L. (1985). *J. Med. Chem.* **28**, 1832–1842.

GILMORE, C. J. (1984). *J. Appl. Cryst.* **17**, 42–46.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

MALLINSON, P. R. & MUIR, K. W. (1985). *J. Appl. Cryst.* **18**, 51–53.

SHEARD, P. & SUSCHITZKY, J. L. (1984). *Progress in Medicinal Chemistry*, Vol. 21, edited by G. P. ELLIS & G. B. WEST. Amsterdam: Elsevier.

Acta Cryst. (1987). C**43**, 1905–1908

Synthesis and Structure of Bis(orotato)dioxouranium(VI) Pentahydrate

BY D. MENTZAFOS, NICK KATSAROS AND A. TERZIS*

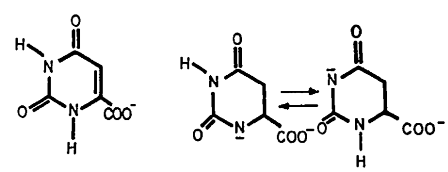
Nuclear Research Center 'Demokritos', 153 10 Aghia Paraskevi, Attiki, Greece

(*Received* 14 *July* 1986; *accepted* 2 *June* 1987)

Abstract. Dioxobis(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinecarboxylato)uranium(VI) pentahydrate, $[UO_2(C_5H_3N_2O_4)_2].5H_2O$, $M_r = 670{\cdot}29$, monoclinic, $C2/c$, $a = 16{\cdot}167$ (4), $b = 10{\cdot}384$ (2), $c = 10{\cdot}866$ (3) Å, $\beta = 97{\cdot}62$ (2)°, $V = 1808{\cdot}0$ (7) Å^3, $Z = 4$, $D_m = 2{\cdot}51$, $D_x = 2{\cdot}462$ Mg m^{-3}, λ(Mo $K\bar{\alpha}$) = 0·71069 Å, $\mu = 86{\cdot}5$ cm^{-1}, $F(000) = 1264$, $T = 295$ (2) K, final $R = 0{\cdot}022$, $wR = 0{\cdot}029$ for 1533 observed reflections with $F_o \geq 5{\cdot}0\sigma(F_o)$. The U atom is seven-coordinate and has a pentagonal-bipyramidal coordination. The orotate ion acts as a monodentate ligand through the carboxylate group.

Introduction. Orotic acid is a key compound involved in the *de nuovo* biosynthesis of pyrimidine bases of nucleic acids in living organisms (Leberman, Kornberg & Simms, 1955; Genchev, 1970; Lehninger, 1970). The overall process of enzymatic phosphoribosylation of orotic acids from phosphoribosyl pyrophosphate ultimately requires an unsubstituted N(1) nitrogen atom (Victor, Greenberg & Sloan, 1979). Metal ions make orotic acid available in the form of its reactive N(3)H dianion where N(1) is unsubstituted, thus contributing to the phosphoribosylation at the N(1) site (Sander, Wright & McCormick, 1965). It is also known to display bacteriostatic and cytostatic properties (*Small Medical Encyclopedia*, 1967).

Orotic acid, besides being biologically important, is also an interesting potentially multidentate ligand, since coordination may occur through the two N atoms of the pyrimidine ring, the two carbonyl oxygens and the carboxylic group. However, complexity of the pyrimidine system results also from pH changes. Between pH 3 and 9 orotic acid is present in aqueous solutions mainly as the orotate anion (I). N(3)H with N(1) unsubstituted is obtained by abstraction of a second proton (pK = 9·45) and, according to previous observations on related uracil anion systems, should be present together with the N(1)H tautomer (II) (Psoda, Kazimierczak & Shugar, 1974; Bensaude, Aubard, Dreyfus, Dodin & Dubois, 1978).



(I) (II)

Although the crystal structures of orotic acid monohydrate (Takusagawa & Shimada, 1973) and ammonium orotate monohydrate (Solbakk, 1971) are known, very few structural studies of metal complexes with this ligand have been published. Crystal data of the complexes diammine(orotato)copper(II) (Mutikainen & Lumme, 1980) and tetraaqua(orotato)nickel(II) hydrate (Sabat, Zglinska & Jerowska-Trzebiatowska, 1980) indicate that complexation stabilizes the N(3)H tautomer and coordination to the metal occurs *via* carboxylate oxygen and the N(1) atom as chelation sites. The crystal structures of two complexes of 5-nitroorotic acid with Cu^{II} have also been reported recently (Arrizabalaga, Castan & Daham, 1983).

Experimental. The title complex was obtained by mixing aqueous solutions of sodium orotate and uranyl nitrate in a 2:1 molar ratio. Upon evaporation of the

* To whom all correspondence should be addressed.

0108-2701/87/101905-04$01.50