The Crystal Structure of *dl*-Isoproterenol Sulfate Dihydrate

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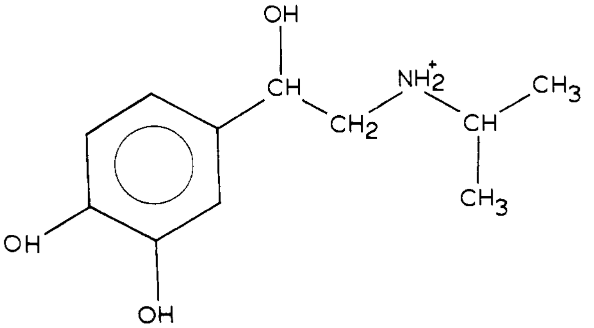
Abstract: The crystal structure of *dl*-isoproterenol sulfate dihydrate, $[3,4\text{-}(OH)_2C_6H_3CH(OH)CH_2NH_2CH(CH_3)_2]_2SO_4\cdot 2H_2O$, was determined by X-ray diffraction techniques. The compound crystallizes in the orthorhombic space group *Pbca* with $a = 26.065$, $b = 15.263$, and $c = 13.690$ Å. There are eight molecules per unit cell. The structure was solved by the symbolic addition method together with the use of Fourier syntheses and was refined by least-squares methods. The final R for the 2872 observed reflections measured with a diffractometer is 0.091. The SO_4^{2-} ion is distorted from ideal tetrahedral symmetry although the S–O bond lengths are equal (average value of 1.448 ± 0.006 Å). After a correction for thermal motion, the S–O bond lengths average 1.499 ± 0.015 Å, in agreement with the value usually found in the various sulfates. The conformations of the two independent isoproterenol molecules are identical and similar to those found in ephedrine and noradrenalin. The biological activity of all three drugs may be related to their conformations.

Isoproterenol sulfate (isoproterenol cation (I)) is a drug used in cases of heart block and in the treatment of asthma. The strong bronchodilatory action of isoproterenol sulfate is similar to that of epinephrine (adrenalin), norepinephrine (noradrenalin), and ephedrine. We undertook an investigation of isoproterenol sulfate for comparison with ephedrine[1] and noradrenalin[2] to determine if common conformational features in the three molecules could account for the similar biological activities.



I

Experimental Section

Clear, plate-like crystals of *dl*-isoproterenol sulfate,[3] $[3,4\text{-}(OH)_2C_6H_3CH(OH)CH_2NH_2CH(CH_3)_2]_2SO_4\cdot 2H_2O$, were grown from an aqueous solution. Precession and Weissenberg photographs indicated the systematic absences, $0kl$ absent if $k = 2n + 1$, $h0l$ absent if $l = 2n + 1$, and $hk0$ if $h = 2n + 1$. Therefore, the most probable space group is *Pbca*.

A second crystal with dimensions of 0.18 × 0.16 × 0.06 mm was used for the intensity measurements. The unit cell dimensions were determined by a least-squares fit of 20 measurements of the Cu Kβ (λ 1.39217 Å) 2θ value for reflections in the region of 30–50°. The final values are $a = 26.065 \pm 0.007$, $b = 15.263 \pm 0.005$, and $c = 13.690 \pm 0.004$ Å. The density calculated for eight molecules per unit cell is 1.357 g/cm^3; the value observed by flotation is 1.360 g/cm^3.

The intensity data were measured using a General Electric XRD-6 automatic diffractometer and employing the stationary-crystal–stationary-counter technique. A wide beam (takeoff angle 3.7°) of Cu Kα_1 (λ 1.54051 Å) radiation was used and a 20-sec count was taken for each reflection. A 0.35-mil nickel foil was placed at the counter window. All the unique reflections with $2\theta \leq 135°$ (Cu Kα_1) were measured first and then one-half of the hemisphere with $2\theta \leq 80°$ was remeasured, giving up to three values for most reflections. A small correction (maximum 6.5%) was applied for the decrease in intensity of the four standard reflections which were measured after every 100 reflections. A total of 4840 unique reflections was obtained after averaging equivalent reflections. The 2872 reflections which were greater than 1.2 times the background count were considered to be observed. The remaining reflections were considered to be unobserved and were entered as one-half the minimum observable intensity (0.1 times the background count) and flagged with a minus sign. The value of μ is 15.8 cm^{-1} and no absorption corrections were applied.

Structure Determination

The signs of 356 large E's were determined by the symbolic addition method.[4] The SO_4^{2-} group was easily located in an E map computed with the known phases. The two isoproterenol molecules were located by comparing the E map with a Fourier synthesis computed using phases determined by the SO_4^{2-} group. A difference Fourier synthesis computed using the two isoproterenol molecules and the SO_4^{2-} group for phasing showed three peaks, two of which were approximately one-half the height of the third. Therefore, one water molecule was assumed to be equally disordered (occupancy factor of 0.5) between the positions indicated by the two smaller peaks. The usual residual R was 0.25 at this point.

After four full-matrix least-squares cycles using individual isotropic thermal parameters, R was 0.16. A 3 × 3 and 6 × 6 block approximation was used for six least-squares cycles using anisotropic thermal parameters and R was reduced to 0.11.

A difference Fourier synthesis indicated positions for all the hydrogen atoms in both isoproterenol molecules. Two block diagonal least-squares cycles in which the hydrogen atom contributions were included but their parameters were not varied reduced R to 0.095. Four additional least-squares cycles in which the hydrogen positional parameters and an individual isotropic thermal parameter were varied reduced R to 0.091. The improvement in R was not significant and since the shifts at this point were less than 0.3 of an estimated standard deviation for any parameter,

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(1) D. C. Phillips, *Acta Crystallogr.*, 7, 159 (1954).

(2) D. Carlström and R. Bergin, *ibid.*, 23, 213 (1967).

(3) Purchased from the Aldrich Chemical Co.

(4) The computer programs FAME, MAGIC, LINK, and SYMPL written by R. B. K. Dewar, A. Stone, and E. Fleischer, University of Chicago, Chicago, Ill., were used to carry out this method.

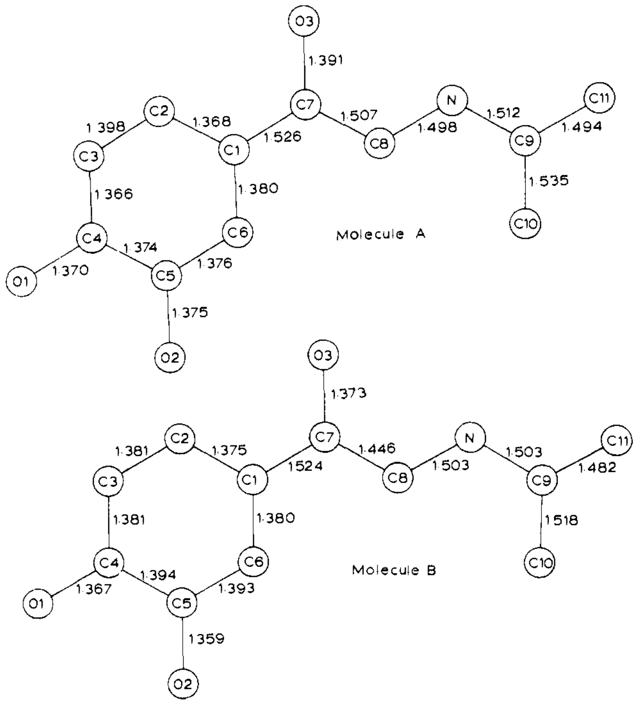

Figure 1. Atomic numbering and bond lengths in the two isoproterenol molecules.

Table I. Final Positional Parameters (×10[4]) of Nonhydrogen Atoms and Their Estimated Standard Deviations in Parentheses

Atom	$x\ (\sigma_x)$	$y\ (\sigma_y)$	$z\ (\sigma_z)$
CA-1	1807 (3)	4653 (4)	1459 (4)
CA-2	1414 (3)	4685 (4)	799 (5)
CA-3	1491 (3)	5042 (4)	−130 (5)
CA-4	1962 (3)	5354 (4)	−393 (5)
CA-5	2354 (2)	5321 (4)	277 (4)
CA-6	2282 (3)	4975 (4)	1195 (4)
CA-7	1761 (3)	4267 (4)	2484 (5)
CA-8	1996 (3)	3365 (4)	2504 (5)
CA-9	2398 (3)	2322 (4)	3726 (5)
CA-10	2365 (4)	2084 (5)	4813 (6)
CA-11	2317 (4)	1538 (5)	3091 (6)
OA-1	2062 (2)	5714 (3)	−1290 (3)
OA-2	2826 (2)	5629 (3)	−14 (3)
OA-3	1256 (2)	4197 (4)	2806 (4)
NA	1998 (2)	3017 (3)	3528 (4)
CB-1	195 (3)	3291 (5)	1174 (5)
CB-2	72 (3)	3823 (5)	398 (5)
CB-3	330 (3)	3742 (4)	−478 (5)
CB-4	715 (3)	3127 (4)	−588 (5)
CB-5	824 (3)	2561 (5)	183 (5)
CB-6	566 (3)	2653 (5)	1067 (5)
CB-7	−60 (3)	3448 (5)	2160 (5)
CB-8	−434 (3)	2780 (5)	2392 (6)
CB-9	−996 (3)	2225 (5)	3779 (6)
CB-10	−1121 (4)	2445 (7)	4834 (6)
CB-11	−1461 (3)	2098 (6)	3171 (7)
OB-1	1010 (2)	3045 (3)	−1408 (3)
OB-2	1202 (2)	1961 (4)	31 (4)
OB-3	274 (2)	3509 (6)	2932 (5)
NB	−653 (2)	2938 (4)	3392 (4)
OW-1	3925 (4)	538 (6)	4040 (6)
OW-2	4605 (5)	601 (8)	2833 (10)[a]
OW-3	4915 (6)	967 (10)	4909 (13)[a]
S	1128 (1)	148 (1)	1789 (1)
O-4	1482 (2)	785 (4)	1381 (4)
O-5	804 (2)	558 (4)	2496 (5)
O-6	805 (3)	−224 (5)	1039 (4)
O-7	1400 (3)	−565 (3)	2254 (4)

[a] Disordered.

Table II. Final Thermal Parameters of Nonhydrogen Atoms with Their Estimated Standard Deviations in Parentheses[a]

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
CA-1	20 (1)	34 (3)	49 (4)	−6 (3)	9 (4)	−5 (6)
CA-2	20 (1)	43 (4)	63 (4)	−7 (4)	10 (4)	−8 (7)
CA-3	19 (1)	45 (4)	63 (4)	−13 (4)	−6 (4)	1 (7)
CA-4	20 (1)	38 (3)	54 (4)	−11 (4)	1 (4)	16 (6)
CA-5	15 (1)	43 (3)	61 (4)	−9 (3)	3 (4)	1 (6)
CA-6	21 (1)	34 (3)	52 (4)	−13 (4)	8 (4)	8 (6)
CA-7	17 (1)	52 (4)	69 (5)	−2 (4)	30 (4)	37 (7)
CA-8	26 (2)	45 (4)	46 (4)	−2 (4)	4 (4)	2 (7)
CA-9	27 (2)	42 (4)	74 (5)	7 (4)	−6 (5)	12 (7)
CA-10	40 (2)	59 (5)	74 (6)	7 (5)	14 (6)	27 (8)
CA-11	38 (2)	47 (4)	104 (7)	5 (5)	10 (7)	−11 (9)
OA-1	24 (1)	58 (3)	62 (3)	−19 (3)	−8 (3)	35 (5)
OA-2	19 (1)	76 (3)	65 (3)	−24 (3)	−3 (3)	42 (5)
OA-3	32 (1)	82 (4)	103 (5)	−3 (3)	17 (4)	12 (6)
NA	20 (1)	46 (3)	47 (3)	−9 (3)	6 (3)	5 (5)
CB-1	17 (1)	53 (4)	80 (5)	2 (4)	21 (4)	−1 (8)
CB-2	17 (1)	48 (4)	87 (5)	5 (4)	19 (5)	2 (8)
CB-3	16 (1)	46 (4)	76 (5)	5 (4)	12 (4)	4 (7)
CB-4	22 (1)	42 (3)	68 (5)	4 (4)	21 (5)	1 (7)
CB-5	23 (1)	50 (4)	81 (5)	21 (4)	30 (5)	29 (8)
CB-6	22 (1)	61 (4)	76 (5)	14 (4)	24 (5)	33 (8)
CB-7	23 (2)	77 (5)	76 (6)	−15 (5)	24 (5)	−20 (9)
CB-8	31 (2)	84 (6)	69 (5)	−32 (5)	38 (5)	−31 (9)
CB-9	22 (2)	60 (4)	83 (5)	−4 (4)	21 (5)	20 (8)
CB-10	33 (2)	98 (6)	95 (7)	−13 (7)	44 (7)	1 (9)
CB-11	22 (2)	99 (6)	116 (7)	−35 (5)	−13 (6)	35 (12)
OB-1	34 (1)	59 (3)	72 (3)	17 (3)	43 (4)	13 (5)
OB-2	38 (1)	77 (3)	119 (5)	61 (4)	62 (5)	86 (7)
OB-3	24 (1)	221 (8)	114 (6)	−44 (5)	22 (4)	−81 (11)
NB	22 (1)	64 (4)	78 (4)	−12 (3)	26 (4)	1 (7)
OW-1	78 (3)	141 (6)	140 (7)	−50 (8)	−33 (8)	−45 (11)
OW-2	42 (3)	60 (7)	174 (14)	22 (8)	23 (11)	64 (16)
OW-3	34 (3)	113 (11)	234 (18)	3 (9)	39 (12)	126 (23)
S	22 (1)	54 (1)	49 (1)	−5 (1)	2 (1)	−4 (2)
O-4	25 (1)	70 (3)	108 (4)	2 (3)	15 (4)	50 (6)
O-5	40 (2)	84 (4)	109 (5)	−9 (4)	56 (5)	−72 (8)
O-6	40 (2)	151 (6)	91 (4)	−34 (5)	−34 (5)	−54 (9)
O-7	41 (2)	62 (3)	113 (5)	13 (4)	−21 (5)	37 (6)

[a] The temperature factor is of the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$. The values are multiplied by 10[4].

the refinement was terminated. The final positional and thermal parameters are given in Tables I, II, and III.[5]

The quantity $\Sigma w(|F_o| - |F_c|)^2$ was minimized in the least-squares calculations. The weighting scheme used was: $\sqrt{w} = F_o/3F_{\min}$ if $F_o < 3F_{\min}$; $\sqrt{w} = 1$ if $3F_{\min} \leq F_o \leq 5F_{\min}$; $\sqrt{w} = 5F_{\min}/F_o$ if $5F_{\min} < F_o$; $\sqrt{w} = 0$ if $F_o < 0$ (unobserved reflections), where $F_{\min}$ was 8.0. The scattering factor curves were taken from the International Tables for X-ray Crystallography.[6]

The atomic numbering and the bond lengths in the two independent molecules of isoproterenol are given in Figure 1. The bond lengths and angles in the sulfate ion and the bond angles in the isoproterenol molecule are given in Table IV. The angles involving the hydrogen atoms were chemically reasonable and, therefore, were not included in Table IV.

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(5) Observed and calculated structure factors (multiplied by 10) for isoproterenol sulfate dihydrate are deposited as Document No. NAPS-01166 with the ASIS National Auxiliary Publication Service, c/o CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and remitting $2.00 for microfiche or $5.00 for photocopies. Advanced payment is required. Make checks or money orders payable to: CCMIC–NAPS.

(6) "International Tables for X-ray Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1962, p 202.

Table III. Parameters of the Hydrogen Atoms and Their Estimated Standard Deviations in Parentheses

Atom	Bonded to	$x\ (\sigma_x) \times 10^3$	$y\ (\sigma_y) \times 10^3$	$Z\ (\sigma_z) \times 10^3$	B, Å^2	Atom	Bonded to	$x\ (\sigma_x) \times 10^3$	$y\ (\sigma_y) \times 10^3$	$Z\ (\sigma_z) \times 10^3$	B, Å^2
HA-1	CA-2	110 (3)	451 (5)	94 (5)	5.7 (1.3)	HB-1	CB-2	−19 (2)	435 (5)	40 (5)	4.6 (1.6)
HA-2	CA-3	124 (3)	506 (5)	−59 (5)	5.5 (1.4)	HB-2	CB-3	20 (2)	416 (4)	−104 (4)	3.4 (2.0)
HA-3	CA-6	256 (3)	501 (5)	172 (5)	4.6 (1.8)	HB-3	CB-6	64 (3)	219 (5)	161 (5)	5.4 (1.3)
HA-4	CA-7	183 (2)	481 (4)	311 (4)	4.6 (1.4)	HB-4	CB-7	−18 (3)	427 (6)	223 (6)	9.7 (0.7)
HA-5	CA-8	186 (2)	292 (4)	205 (4)	2.5 (2.2)	HB-5	CB-8	−69 (4)	322 (7)	192 (7)	12.7 (0.5)
HA-6	CA-8	246 (2)	350 (4)	230 (4)	3.7 (2.0)	HB-6	CB-8	−33 (4)	206 (7)	212 (7)	13.8 (0.4)
HA-7	CA-9	279 (2)	270 (4)	343 (5)	4.6 (1.5)	HB-7	CB-9	−76 (3)	160 (5)	385 (6)	7.6 (1.0)
HA-8	CA-10	262 (3)	157 (5)	496 (5)	6.4 (1.2)	HB-8	CB-10	−141 (4)	183 (6)	523 (7)	11.9 (0.6)
HA-9	CA-10	241 (3)	268 (5)	528 (5)	7.0 (1.1)	HB-9	CB-10	−134 (3)	302 (5)	488 (6)	8.2 (0.9)
HA-10	CA-10	192 (3)	184 (4)	488 (5)	5.2 (1.5)	HB-10	CB-10	−74 (3)	243 (6)	516 (6)	8.3 (1.0)
HA-11	CA-11	247 (3)	91 (5)	334 (5)	7.5 (1.1)	HB-11	CB-11	−179 (3)	153 (6)	359 (6)	11.1 (0.6)
HA-12	CA-11	194 (3)	118 (5)	326 (6)	7.8 (0.9)	HB-12	CB-11	−175 (3)	271 (6)	303 (7)	11.1 (0.7)
HA-13	CA-11	246 (3)	183 (5)	244 (6)	7.9 (1.0)	HB-13	CB-11	−141 (3)	197 (5)	236 (6)	8.8 (0.9)
HA-14	OA-1	182 (3)	563 (4)	−177 (5)	5.1 (1.5)	HB-14	OB-1	96 (3)	367 (6)	−185 (6)	10.0 (0.7)
HA-15	OA-2	294 (3)	564 (6)	68 (7)	10.0 (0.7)	HB-15	OB-12	124 (3)	160 (6)	45 (6)	9.3 (0.7)
HA-16	OA-3	119 (3)	480 (1)	332 (6)	9.3 (0.7)	HB-16	OB·3	64 (3)	362 (5)	294 (6)	6.8 (1.0)
HA-17	NA	166 (2)	281 (4)	369 (4)	3.1 (2.0)	HB-17	NB	−80 (3)	350 (6)	346 (6)	7.8 (0.9)
HA-18	NA	208 (3)	353 (5)	400 (5)	5.8 (1.2)	HB-18	NB	−30 (3)	299 (6)	377 (6)	8.1 (0.9)

Table IV. Bond Lengths and Angles

In the sulfate ion			
Bond	Distance, Å	Angle	Deg
S-O(4)	1.454 (6)	O(4)-S-O(5)	108.5 (3)
S-O(5)	1.450 (7)	O(4)-S-O(6)	111.1 (4)
S-O(6)	1.444 (7)	O(4)-S-O(7)	111.2 (3)
S-O(7)	1.445 (6)	O(5)-S-O(6)	108.5 (4)
		O(5)-S-O(7)	109.9 (4)
		O(6)-S-O(7)	107.7 (4)

In the isoproterenol molecules					
	In molecule			In molecule	
Bond, Å	A	B	Angle	A	B
C(2)-H(1)	0.88 (7)	1.06 (7)	C(1)-C(2)-C(3)	120.5 (6)	120.3 (7)
C(3)-H(2)	0.92 (7)	1.06 (6)	C(2)-C(3)-C(4)	120.4 (6)	120.6 (6)
C(6)-H(3)	1.02 (7)	1.04 (7)	C(3)-C(4)-C(5)	118.7 (6)	119.2 (6)
C(7)-H(4)	1.20 (6)	1.30 (7)	C(4)-C(5)-C(6)	121.4 (6)	119.7 (7)
C(8)-H(5)	0.99 (6)	1.15 (9)	C(5)-C(6)-C(1)	119.9 (6)	120.1 (7)
C(8)-H(6)	1.25 (6)	1.19 (10)	C(6)-C(1)-C(2)	119.1 (6)	120.0 (7)
C(9)-H(7)	1.24 (6)	1.14 (8)	C(6)-C(1)-C(7)	116.7 (6)	120.7 (6)
C(10)-H(8)	1.05 (7)	1.31 (8)	C(2)-C(1)-C(7)	124.6 (6)	119.3 (6)
C(10)-H(9)	1.12 (8)	1.05 (8)	C(3)-C(4)-O(1)	123.2 (6)	124.0 (6)
C(10)-H(10)	1.22 (7)	1.09 (8)	C(5)-C(4)-O(1)	118.1 (6)	116.7 (6)
C(11)-H(11)	1.08 (8)	1.34 (8)	C(6)-C(5)OO(2)	121.2 (6)	123.5 (6)
C(11)-H(12)	1.14 (8)	1.22 (9)	C(4)-C(5)-O(2)	117.4 (5)	116.7 (6)
C(11)-H(13)	1.06 (8)	1.14 (8)	C(1)-C(7)-O(3)	113.3 (6)	114.6 (7)
O(1)-H(14)	0.92 (7)	1.13 (9)	C(1)-C(7)-C(8)	109.8 (5)	112.1 (7)
O(2)-H(15)	1.00 (9)	0.80 (9)	C(8)-C(7)-O(3)	108.0 (6)	107.8 (7)
O(3)-H(16)	1.17 (9)	0.96 (7)	C(7)-C(8)-N	110.0 (5)	110.1 (7)
N-H(17)	0.96 (6)	0.95 (8)	C(8)-N-C(9)	114.7 (5)	115.5 (6)
N-H(18)	1.03 (7)	1.06 (8)	N-C(9)-C(10)	106.5 (6)	107.6 (6)
			N-C(9)-C(11)	111.1 (6)	112.4 (6)
			C(10)-C(9)-C(11)	111.5 (6)	112.8 (7)

Discussion of the Structure

The S–O bond distances in the sulfate ion vary from 1.444 to 1.454 Å. The mean value is shorter than most of the values given in a recent tabulation of the dimensions of the SO_4^{2-} ion.[7] However, a correction for thermal motion using the riding model[8] gave S–O distances from 1.482 to 1.518 Å, with an average of 1.499 ± 0.015 Å. The corrected S–O bond lengths are in the upper range of the tabulated values;[7] however, many of the quoted distances are not corrected for thermal motion.

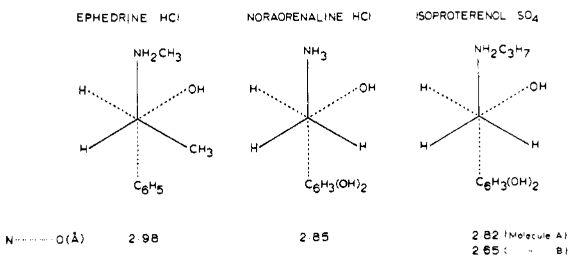

Figure 2. The conformation about the C–C bond of the ethyl side chain in isoproterenol compared with the corresponding conformations in ephedrine and noradrenaline.

The O–S–O angles in the sulfate ion vary from 107.7 to 112.4 ± 0.4° and the differences are statistically

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(7) G. R. Andretti, L. Cavalca, and A. Musatti, *Acta Crystallogr., Sect. B*, **24**, 683 (1968).

(8) W. R. Busing and H. A. Levy, *ibid.*, 17, 142 (1964).

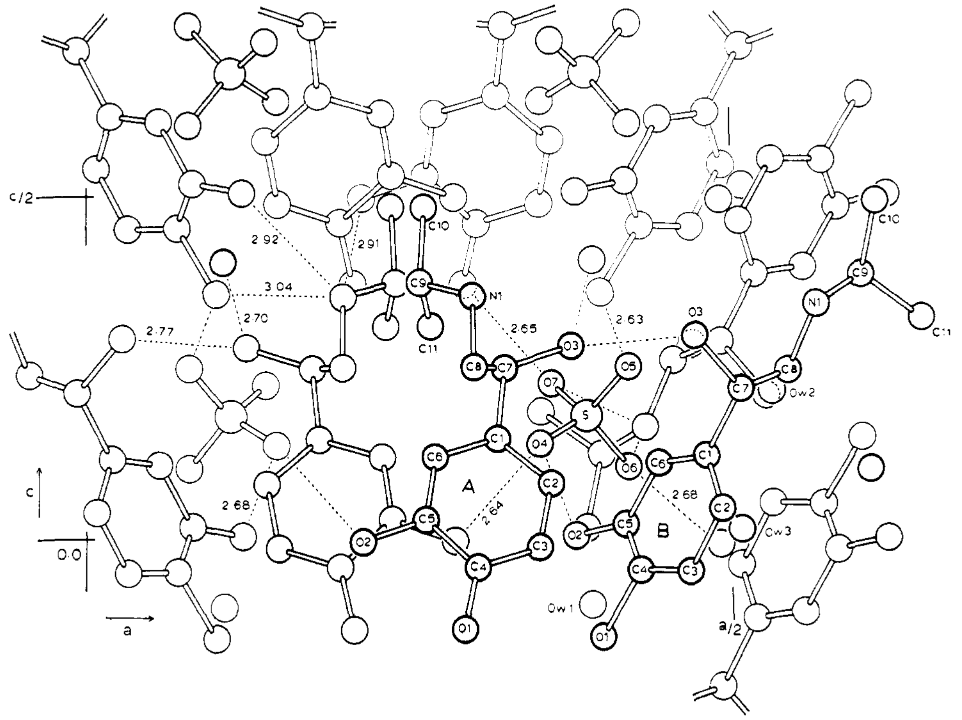

Figure 3. The packing of the molecules projected on the 010 plane. The broken lines indicate the hydrogen bonds.

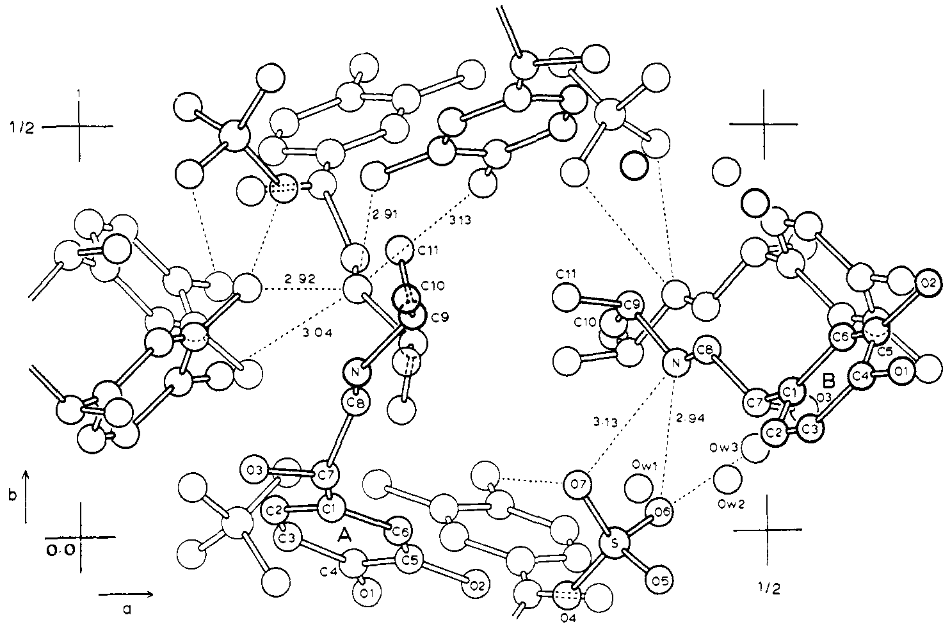

Figure 4. A view down the *c* axis illustrating the molecular packing, with the hydrogen bonds shown by broken lines.

significant. Angular distortions are present in almost all sulfates reported to date.[7] Presumably crystal packing and hydrogen bonding cause angular distortions in the SO_4^{2-} group, and in the crystalline state, the concept of an ideal tetrahedron for SO_4^{2-} must be abandoned.

There are two molecules of isoproterenol in the asymmetric unit; therefore, we have two measurements of the molecular dimensions. The bond distances are given in Figure 1 and except for C(7)–C(8), none of the chemically equivalent bonds is statistically different. The difference of 0.061 Å between the C(7)–C(8) bonds in the two molecules is significant (t_0 = 4.0).[9] The value of 1.446 Å found in molecule B is shorter than a normal C–C bond but no satisfactory explanation is possible.

The side chains in both molecules are fully extended. The distances (excluding C(7)–C(8) in molecule B) are in good agreement with the corresponding values in noradrenaline hydrochloride.[2] In fact the C–N bond is longer than a normal C–N bond but agrees well with the mean value reported[10] for the $C\text{–}NH_3^+$ bond distance. The conformation about the C(7)–C(8)

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(9) D. W. J. Cruickshank and A. P. Robertson, *Acta Crystallogr.*, **6**, 698 (1953).

(10) T. Hahn, *Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem.*, **109**, 438 (1957).

Table V. Least-Squares Planes and Deviations from the Plane[a]

Atom	In molecule A	B
C-1	**0**	**15**
C-2	**−2**	**−9**
C-3	**4**	**−8**
C-4	**−3**	**20**
C-5	**0**	**−14**
C-6	**2**	**−3**
C-7	−24	143
O-1	6	112
O-2	−26	−2
	Parameters of the Plane[b]	
$A \times 10^4$	−2569	6873
$B \times 10^4$	9040	6538
$C \times 10^4$	3419	3163
D, Å	5.893	4.126

[a] Deviations ($\times 10^3$) in boldface type indicate atoms which were used to define the plane. [b] Equation of the plane in the form: deviations (Å) = $AX + BY + CZ + D$ with X, Y, Z the coordinates of the atom in ångströms with respect to a, b, and c.

Table VI. Hydrogen Bonds

Bond D–H···A[a]	Position of A	D–H, Å	H···A, Å	D···A, Å	D–H···A angle, deg
OA(1)–HA(14)···O(7)	$x, \frac{1}{2} - y, z - \frac{1}{2}$	0.91	1.74	2.648 (8)	173
OA(2)–HA(15)···O(4)	$\frac{1}{2} - x, \frac{1}{2} + y, z$	1.00	1.80	2.638 (7)	140
OB(1)–HB(14)···O(5)	$x, \frac{1}{2} - y, z - \frac{1}{2}$	1.13	1.51	2.626 (8)	168
OB(2)–HB(15)···O(4)	x, y, z	0.80	1.89	2.678 (8)	168
OW(3)···O(6)	$\frac{1}{2} - x, -y, \frac{1}{2} + z$			2.683 (17)	
NB–HB(17)···O(6)	$-x, \frac{1}{2} + y, \frac{1}{2} - z$	0.95	2.06	2.938 (10)	153
NB–HB(17)···O(7)	$-x, \frac{1}{2} + y, \frac{1}{2} - z$	0.95	2.33	3.129 (8)	142
NA–HA(17)···OB(1)	$x, \frac{1}{2} - y, \frac{1}{2} + z$	0.96	2.15	3.045 (8)	155
NA–HA(17)···OB(2)	$x, \frac{1}{2} - y, \frac{1}{2} + z$	0.96	2.22	2.922 (8)	130
NA–HA(18)···OA(1)	$\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$	1.03	2.56	3.133 (7)	115
NA–HA(18)···OA(2)	$\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$	1.03	1.89	2.910 (7)	173
OB(3)–HB(16)···OA(3)	x, y, z	0.96	1.85	2.772 (9)	160
OA(3)–HA(16)···OW(1)	$\frac{1}{2} - x, \frac{1}{2} + y, z$	1.17	1.53	2.696 (10)	176
NB–HB(18)···OB(3)	x, y, z	1.06	2.04	2.646 (9)	113

[a] Donor–hydrogen···acceptor. D–H at x, y, z.

bond in isoproterenol is given in Figure 2 together with the corresponding conformations in ephedrine hydrochloride[1] and noradrenaline hydrochloride.[2] Only one of the optical isomers is shown for each molecule in Figure 2 since the activity of *d*- and *l*-ephedrine is about the same.[11] The common feature in all three cases is that the amino and hydroxyl groups are cis and relatively close (the N–O distances vary from 2.65 to 2.98 Å). Since all three compounds have strong central nervous system activity, the above conformation may be of prime importance. Recent studies[12] of similar molecules support the hypothesis of the importance of the conformation and indicate that the conformation is retained in solution. The lack of dependence of the activity on the optical isomer suggests that hydrogen bonding involving HO···NH or HN···OH may play an important role in the biological action of these drugs. Additional structural studies are in progress to test this hypothesis.

The least-squares planes through the benzene rings are given in Table V. The O-1, O-2, and C-7 atoms in molecule A are not significantly out of the plane, while in molecule B, O-1 and C-7 are both significantly out of the plane of the ring. These deviations from planarity are presumably due to slightly different hydrogen bonding schemes in the two molecules.

The arrangements of the isoproterenol molecules, the sulfate ion, and the water molecules are illustrated in Figures 3 and 4. The hydrogen bonds are shown as dotted lines in the two figures. The distances and angles in the various hydrogen bonds are tabulated in Table VI. The phenol groups in both molecules form O–H···O hydrogen bonds to the sulfate ion. The mean O···O distance of 2.647 Å indicates a fairly strong hydrogen bond. The nitrogen atom of molecule B (NB) has two short N···O (sulfate) contacts, 2.938 and 3.129 Å, suggesting a bifurcated hydrogen bond. A water OW-3 also appears to be hydrogen bonded to the sulfate ion; however, since the hydrogen atoms on the water molecules could not be located in the difference Fourier synthesis, these hydrogen bonds are less certain. The final result is that all the oxygen atoms of the sulfate ion act as receptors for hydrogen bond formation.

The nitrogen atom of molecule A (NA) forms four close contacts with the phenolic oxygens of both molecules. However, the angles in two cases NA–HA(17)–OB(2) of 130° and NA–HB(18)–OA(1) of 115° appear too small for hydrogen bonds.[13] The OH group on the side chain of molecule B [OB(3)–HB(16)] forms an O–H···O bond to OA(3), the OH group on the side chain of molecule A. In turn, the OA(3)–HA(16) group forms a hydrogen bond to a water molecule OW-(1). The net result is an extensive network of intermolecular hydrogen bonds in the crystal.

One short intramolecular contact involves NB–HB-(18) which does not form any intermolecular hydrogen bonds and OB-3 which does not accept any intermolecular hydrogen bonds. Although the N···O distance

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(11) G. Lanciault and H. H. Wolf, *J. Pharm. Sci.*, **54**, 84 (1965), and references therein.

(12) P. S. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafr'ee, *J. Med. Chem.*, 11, 12 (1968), and references therein.

(13) J. Donohue in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, p 443.

of 2.650 Å is reasonable, the small angle of 113° suggests that a hydrogen bond does not exist. However, the N···O distance of 2.65 Å is shorter than that found in molecule A, lending credence to the idea of an attractive force between NB and OB-3.

All the intermolecular distances less than 3.9 Å were computed and surveyed but no unusually short contacts (other than hydrogen bonds) were found.

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Photochemistry of Electron-Transport Quinones. II.[1] Model Studies with Plastoquinone-1

[2,3-Dimethyl-5-(3-methylbut-2-enyl)-1,4-benzoquinone]

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Abstract: A number of photoproducts have been characterized from near-uv irradiation of plastoquinone-1 (**1**, $n = 1$) under several conditions. In benzene or isopropyl alcohol under oxygen the naphthoquinone **2**, the novel tricyclic peroxide **3**, and the benzofuranone **7** were formed. In the same solvents but under nitrogen, irradiation afforded **2**, the chromenol (**9a**, $n = 0$), and the benzoxepin **10**. Two additional photoproducts isolated from irradiation in isopropyl alcohol under nitrogen were the isomeric spiroenones **13** (A and B). These oxidized dimers were not only interconvertible upon treatment with triethylamine but also gave rise to the pyranoxanthene **18**. Irradiation in methanol or aqueous acetonitrile under nitrogen resulted in formation of the dihydrobenzofurans **4a** and **c** in addition to **10** and, in methanol, **2**. The characterization of these photoproducts will facilitate future studies on the photochemistry of the photosynthetic electron-transport quinones.

Electron-transport quinones located in membranous cellular substructures such as mitochondria and chloroplasts which perform, respectively, respiratory and photosynthetic functions, are redox components of electron-transport chains. The loss or diminution of some biological functions, such as growth, oxidative phosphorylation, and photosynthesis following ultraviolet irradiation of cells, has been attributed[3] to photochemical disruption of electron transport, the photolabile electron-transport quinones being the most likely targets for the radiation.

Considerable evidence[4] has accumulated that plastoquinone-9 (PQ-9, **1**, $n = 9$) is an essential transport quinone in photosynthetic processes. Far-uv irradiation of autotrophic cells leads to destruction of PQ-9 and the concomitant loss of several partial photosynthetic reactions.[5] The more energetic radiations in the 300-nm region of sunlight reaching the earth can also modify plastoquinone-9. Therefore, autotrophic cells must have evolved mechanisms for protecting plastoquinones from the harmful radiations, or alternatively, if the quinones are destroyed, evolved processes for their restoration.

These considerations prompted our initiation of studies to unravel the *in vitro* and *in vivo* photochemistry of PQ-9. There appears to be only one report on photodamage to PQ-9 *in vitro*, that of Eck and Trebst,[6] who prepared a PQ-9 dimer by irradiating the quinone as a thin film. They isolated the same dimer—one in which the quinone ring of one molecule has added to one of the nine double bonds of a second molecule—from horse chestnut leaves but were uncertain whether it occurred naturally or was an artifact of the isolation procedure.

Because of the limited availability of PQ-9 and other naturally occurring plastoquinones, we chose to study a model quinone PQ-1[7] (**1**, $n = 1$), which has the main structural features of the plastoquinones except for the presence of only one isoprene unit in the side chain. We expected that characterization of PQ-1 photoproducts, the subject of this report, would greatly facilitate our projected studies of the naturally occurring plastoquinones.

Results

Near-Uv Irradiation of Plastoquinone-1 under Oxygen. Following irradiation of PQ-1 (**1**, $n = 1$) in dry benzene

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