pharmacological action of these compounds are due to ephedrine release incurred as metabolic by-products *in vivo*. The contrasting anti-inflammatory effects found in adrenalectomised versus intact animals suggest that these compounds mediate their anti-inflammatory effects *via* the pituitary-adrenal axis, rather than by cyclo-oxygenase inhibition *in vivo*[8].

References

1 T. G. Dekker and D. W. Oliver, S. Afr. J. Chem. *32*, 45 (1979).
2 T. G. Dekker, D. W. Oliver and A. Venter, Tetrahedron Lett. *1980*, 3101.
3 T. G. Dekker, C. J. van der Schyf, G. J. Kruger and P. H. van Rooyen, S. Afr. J. Chem. *36*, 59 (1983).
4 P. E. Eaton and B. Leipzig, J. Org. Chem. *43*, 2483 (1978).
5 S. Irwin, Science *136*, 123 (1962).
6 W. Tsukada, M. Tsubokawa, T. Masukawa, H. Kojima and A. Kasahara, Arzneim. Forsch. *28*, 428 (1978).
7 C. A. Winter, E. A. Risley and G. W. Nuss, Proc. Soc. Exp. Biol. Med. *111*, 544 (1962).
8 R. J. Gryglewski, Prostaglandin Synthetase Inhibitors, H. J. Robinson, J. R. Vane, eds., p. 32–52, Raven Press, New York 1974.

[Ph 67]

The Crystal and Molecular Structures of N4-(5-Bromosalicylidene)-N1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide

Reijo Hämäläinen, Maire Lehtinen[*)a)] and Urho Turpeinen

Division of Inorganic Chemistry, University of Helsinki, SF–00100 Helsinki 10, Finland;
a) School of Pharmacy, University of Helsinki, SF–00170 Helsinki 17, Finland
Eingegangen am 9. April 1985

The structure of the title compound was determined by X-ray analysis.

Die Kristall- und Molekularstruktur von N4-(5-Bromsalicyliden)-N1-(3,4-dimethyl-5-isoxazolyl)sulfanilamid

Die Struktur der Titelverbindung wird durch Röntgenstrukturanalyse aufgeklärt.

Medicinal compounds with *Schiff* base structure have been widely synthesized and investigated in recent years. The functional group –CH=N– of the *Schiff* bases has been shown to have considerable biological importance[1]. Many compounds with such a structure have important analgesic, anti-inflammatory, antibiotic, antimicrobial and especially anticancer activities[2-8]. Medicinal sulphonamides, having a primary amino group in their molecule, react very easily with salicylaldehyde or its derivatives[9]. Information about the exact structure of the reaction products is rather scanty, however, even though the formation reaction of the base has been utilized in many analytical procedures for medicinal sulphonamides[9-12] and many such *Schiff* bases have been found to possess good bacteriostatic properties[13-14].

Since a single crystal analysis of this kind of *Schiff* base has not yet been elucidated we have synthesized a compound from 5-bromo-salicylaldehyde and N[1]-(3,4-dimethyl-5-isoxazolyl)sulfanilamide (= sulphafurazole) and determined its crystallized structure by X-ray diffraction technique.

Experimental Part

The *Schiff* base (melting range 471–473 K) was prepared by dissolving N[1]-(3,4-dimethyl-5-isoxazolyl)sulphanilamide (J.A. Crocq. Huizen N.H., melting range 468–471 K), by warming in absol. ethanol, and adding 5-bromo-salicylaldehyde to the clear solution. The reaction mixture was refluxed on a water bath for a few min. The product was kept in a refrigerator about two months, during which time yellow, lamellar crystals were formed. The cell dimensions were calculated, with a Nicolet P3 diffractometer using the least-squares method, from 13 centred and indexed reflections. The crystal data are: a = 15.406 (6), b = 7.257 (2), c = 16.597 (6) Å, β = 93.16 (3)°, Z = 4, V = 1853 (2) Å^3, calculated density = 1.614 Mg m^{-3}, formula weight = 450.31, monoclinic space group P2$_1$/n and linear absorption coefficient μ(MoKα) = 2.49 mm^{-1}. Intensities of 4155 reflections were collected (5 < 2θ < 53°) at room temp. using ω-scan technique and varying the scan rate from 2.0 to 25.0° min^{-1} depending upon the peak intensity. Two test reflections were checked after every 80 intensity measurements. The data were corrected for Lorentz and polarization factors. The empirical absorption correction from Ø-scan data was also applied. The molecular structure was solved by a combination of direct and Fourier methods using MULTAN 80 Program System[15] and XRAY 76[16].
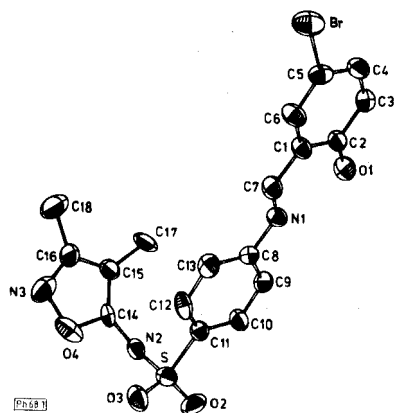

Fig. 1: ORTEP drawing and numbering sheme

The least-squares refinement, including the coordinates and anisotropic temp. factors for nonhydrogen atoms, gave the conventional R value 0.057 for 1599 reflections with $F_0 \geq 5.0\sigma$ (F_0). The function minimized in least-sqares refinement was $\Sigma w(|F_0|-|F_0|)^2$ with $w = 1/(85.0 + |F_0| + 0.008|F_0|^2)$. In the final refinement, where 10 hydrogen atoms were included with isotropic and nonhydrogen atoms with anisotropic temp. factors, the R value reached 0.047, the average shift/error ratio being 0.17. The H atoms of the methyl groups were included in the calculated positions with fixed parameters. The scattering factors for nonhydrogen and for hydrogen atoms were those proposed by *Cromer* and *Mann*[17] and by *Stewart, Davidson* and *Simpson*[18], respectively. Anomalous dispersion corrections were included for bromine. A list of the observed and calculated structure factors is obtainable on request from the authors. The molecular structure and numbering scheme are shown in Fig. 1.
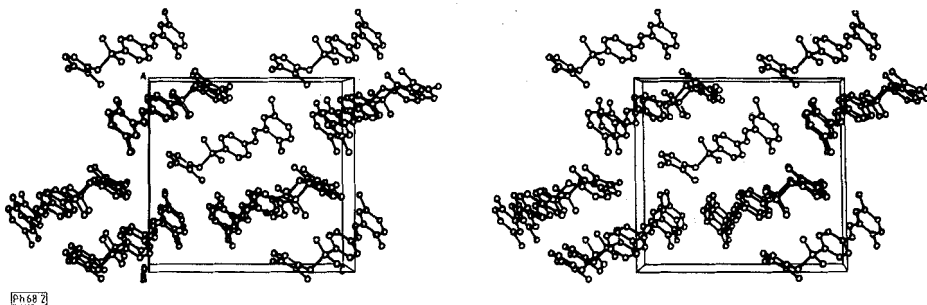

Ph 68 2

Fig. 2: Stereoview of the crystal packing

Table 1: *Fractional atomic coordinates $(x10^4$; for H atoms $x10^3)$ and equivalent isotropic thermal parameters*[19]

	x	y	z	$B_{eq}/B(A^2)$
Br	3804 (1)	− 9470 (1)	829 (1)	4.70
S	1082 (2)	4941 (3)	− 1701 (4)	3.43
O (1)	1188 (4)	− 3610 (8)	1510 (4)	3.90
O (2)	668 (5)	6301 (8)	− 1228 (4)	5.17
O (3)	1830 (4)	5372 (9)	− 2126 (4)	5.05
O (4)	955 (4)	3157 (8)	− 3520 (3)	3.99
N (1)	1716 (4)	− 1761 (9)	295 (4)	2.74
N (2)	309 (4)	4252 (9)	− 2372 (4)	2.98
N (3)	1013 (6)	1507 (13)	− 3975 (5)	5.41
C (1)	2341 (5)	− 4630 (11)	724 (5)	2.75
C (2)	1772 (6)	− 4831 (11)	1366 (5)	3.06
C (3)	1853 (6)	− 6459 (12)	1840 (5)	3.55
C (4)	2467 (6)	− 7765 (12)	1688 (5)	3.81
C (5)	3013 (5)	− 7558 (11)	1052 (5)	2.99
C (6)	2955 (5)	− 6014 (11)	595 (5)	3.32
C (7)	2281 (5)	− 3073 (12)	221 (5)	3.12
C (8)	1599 (5)	− 192 (10)	− 195 (5)	2.50
C (9)	1004 (5)	1126 (11)	32 (5)	3.03
C (10)	854 (5)	2720 (11)	− 408 (5)	3.02

Forts. **Tab. 1:**

C (11)	1300 (5)	2968 (11)	− 1094 (5)	2.78
C (12)	1914 (5)	1698 (13)	− 1331 (5)	3.43
C (13)	2047 (5)	71 (11)	− 889 (5)	3.19
C (14)	484 (5)	2776 (11)	− 2883 (5)	2.48
C (15)	217 (6)	995 (11)	− 2904 (5)	3.27
C (16)	568 (6)	284 (13)	− 3607 (5)	4.03
C (17)	− 331 (8)	20 (12)	− 2317 (7)	5.23
C (18)	468 (10)	− 1656 (16)	− 3912 (8)	7.58
H (1)	122 (9)	− 249 (20)	97 (8)	13.9
H (2)	148 (5)	− 645 (11)	234 (5)	5.8
H (3)	245 (5)	− 889 (12)	191 (5)	5.4
H (4)	341 (4)	− 583 (9)	24 (4)	1.9
H (5)	274 (4)	− 288 (9)	− 21 (4)	1.5
H (6)	72 (4)	90 (9)	50 (4)	2.0
H (7)	46 (5)	359 (11)	− 30 (4)	3.7
H (8)	220 (4)	190 (9)	− 176 (4)	1.3
H (9)	247 (3)	− 91 (7)	− 109 (3)	0.5
H (10)	− 20 (7)	418 (15)	− 218 (6)	8.0
H (11)	1	− 172	− 442	6.0
H (12)	109	− 214	− 411	6.0
H (13)	27	− 263	− 347	6.0
H (14)	1	19	− 173	6.0
H (15)	− 93	82	− 230	6.0
H (16)	− 55	− 137	− 232	6.0

Table 2: *Interatomic distances (Å) and angles (°)*

Br	− C (5)	1.898 (8)	O (2)	− S	− C (11)	108.7 (4)
S	− O (2)	1.432 (7)	O (3)	− S	− N (2)	107.8 (4)
S	− O (3)	1.419 (8)	O (3)	− S	− C (11)	109.1 (4)
S	− N (2)	1.661 (8)	O (4)	− C (14) − N (2)		116.7 (7)
S	− C (11)	1.773 (8)	O (4)	− C (14) − C (15)		110.6 (7)
C (1)	− C (2)	1.423 (12)	O (4)	− N (3) − C (16)		106.1 (8)
C (1)	− C (6)	1.404 (11)	S	− C (11) − C (10)		119.3 (6)
C (1)	− C (7)	1.405 (12)	S	− C (11) − C (12)		118.9 (6)
C (2)	− C (3)	1.421 (12)	S	− N (2) − C (14)		118.7 (5)
C (2)	− O (1)	1.295 (10)	N (1)	− C (8) − C (9)		117.9 (7)
C (3)	− C (4)	1.372 (13)	N (1)	− C (8) − C (13)		122.5 (7)
C (4)	− C (5)	1.394 (13)	N (2)	− S − C (11)		104.1 (4)
C (5)	− C (6)	1.353 (12)	N (2)	− C (14) − C (15)		132.5 (7)
N (1)	− C (7)	1.300 (11)	N (3)	− O (4) − C (14)		107.3 (6)
N (1)	− C (8)	1 405 (10)	N (3)	− C (16) − C (15)		112.1 (8)
C (8)	− C (9)	1.391 (11)	C (1)	− C (2) − C (3)		117.4 (8)
C (8)	− C (13)	1.389 (12)	C (1)	− C (6) − C (5)		122.1 (8)
C (9)	− C (10)	1.380 (11)	C (1)	− C (7) − N (1)		123.7 (8)
C (10)	− C (11)	1.373 (12)	C (2)	− C (3) − C (4)		120.9 (8)
C (11)	− C (12)	1.393 (12)	C (2)	− C (1) − C (6)		119.2 (7)

Forts. **Tab. 2:**

C (12) – C (13)	1.400 (12)	C (2)	– C (1)	– C (7)	120.3 (7)
N (2) – C (14)	1.402 (10)	C (3)	– C (4)	– C (5)	121.0 (8)
C (14) – C (15)	1.356 (11)	C (4)	– C (5)	– C (6)	119 3 (8)
C (14) – O (4)	1.344 (10)	C (6)	– C (1)	– C (7)	120.5 (8)
N (3) – O (4)	1.420 (11)	C (7)	– N (1)	– C (8)	127.2 (7)
N (3) – C (16)	1.294 (13)	C (8)	– C (9)	– C (10)	121.8 (8)
C (15) – C (16)	1.409 (13)	C (8)	– C (13)	– C (12)	119.0 (7)
C (15) – C (17)	1.501 (15)	C (9)	– C (8)	– C (13)	119.7 (7)
C (16) – C (18)	1.501 (15)	C (9)	– C (10)	– C (11)	118.1 (8)
		C (10)	– C (11)	– C (12)	121.8 (7)
Br – C (5) – C (6)	121.3 (7)	C (11)	– C (12)	– C (13)	119.5 (8)
Br – C (5) – C (4)	119.3 (6)	C (14)	– C (15)	– C (16)	103.9 (8)
O (1) – C (2) – C (1)	122.1 (7)	C (14)	– C (15)	– C (17)	127.8 (8)
O (1) – C (2) – C (3)	120.5 (8)	C (15)	– C (16)	– C (18)	125.8 (9)
O (2) – S – O (3)	121.2 (4)	C (16)	– C (15)	– C (17)	128.3 (8)
O (2) – S – N (2)	104.5 (4)	C (18)	– C (16)	– N (3)	122.1 (10)

Table 3: *Equations of the least-squares planes, deviations (Å) of some atoms from these planes and angles (°) between the planes*. (Atoms indicated with an asterisk were omitted from the calculation of the planes).

Plane (1) $12.3386\,x - 1.9148\,y + 8.1753\,z = -2.2966$

O (4)	– .008	C (16)	– .005
N (3)	.008	N (2)*	– .075
C (14)	.005	C (17)*	– .010
C (15)	.000	C (18)*	– .008

Plane (2) $9.7419\,x + 3.3486\,y + 9.7337\,z = 1.4375$

C (1)	– .002	Br*	– .095
C (2)	.001	O (1)*	– .019
C (3)	– .004	N (1)*	– .069
C (4)	.009	C (7)*	– .029
C (5)	– .010	C (8)*	– .134
C (6)	.007		

Plane (3) $10.7245\,x + 3.3630\,y + 8.4497\,z = 1.4815$

C (8)	.004	S*	– .097
C (9)	.000	O (2)*	.317
C (10)	.004	O (3)*	.491
C (11)	– .014	N (1)*	.016
C (12)	.018		
C (13)	– .013		

Angles (°) between planes: 1 and 2   44.0
                              1 and 3   43.1
                              2 and 3   5.6

Discussion: The molecule is bent into a V-shape through the sulphur atom, and the oxygen atoms O(2) and O(3) are directed outwards with an angle of 121.2(4)°. The distances of S–N and S–C are 1.661 (8) and 1.773 (8) Å, respectively.

The shortest distance between a methyl carbon C(17) and a plane of the benzene ring is 3.787 Å. The C–N bond length in the functional group –CH = N– is 1.300 (11) Å, which is the usual value and was also found in our earlier *Schiff* base compounds[20,21].

The packing of molecules in the unit cell is zigzaging, such that the planes of the furazole ring and the bromosubstituted benzene ring of the neighbouring molecule (equivalent position 1/2–x, 1/2+y, 1/2–z) form an angle of only 15.7°. The shortest intermolecular contact, and also a hydrogen bond, is O(1)–N(2^i) = 2.818 (11) Å (i = –x,–y,–z), where O(1)···H(10) = 1.99 (11) and H (10)–N(2) = 0.86 (11) Å and the angle O(1)···H(10)–N(2) = 164°.

References

1   S. Patai, Ed., The Chemistry of Carbon-nitrogen Double Bond, Interscience Publishers Inc., New York 1970.

2   G. Pala, A. Donetti, A. Mantegani, G. Coppi, E. Marazzi-Uberti and B. Lumachi, Eur. J. Chem. Chim. Ther. *6*, 10 (1971).

3   F. Sparatore, G. Pirisino, M. C. Alamanni, P. Manca-Dimich and M. Satta, Boll. Chim. Farm. *117*, 638 (1978).

4   R. Rips, N. Lachaize, O. Albert and M. Dupont, Eur. J. Chem. Chim. Ther. *6*, 126 (1971).

5   N. M. Omar, H. H. Farag and N. Mahfouz, Arch. Pharm. Chemi. Sci. Ed. 7, 163 (1979).

6   C. Rufer, H. J. Kessler and E. Schröder, J. Med. Chem. *14*, 94 (1971).

7   J. D. Modi, S. S. Sabnis and C. V. Deliwala, J. Med. Chem. *13*, 935 (1970).

8   E. M. Hodnett and P. D. Mooney, J. Med. Chem. *13*, 786 (1970).

9   M. Lehtinen, Ann. Acad. Sci. Fenn. Ser. A. 2, *1981* 194.

10   H. Bräuniger and H. Duda, Pharm. Zentralhalle Dtschl. *97*, 305 (1958).

11   J. L. Colaizzi, Am. J. Pharm. Educ. *30*, 187 (1966).

12   L. V. Kononenko, V. D. Bezuglyi, V. N. Dmitrieva, J. Gen. Chem. USSR *38*, 2087 (1968); C. A. *70*, 25201z (1969).

13   M. D. Aptekar, E. P. Trailina and I. A. Savich, J. Gen. Chem. USSR *42*, 2545 (1972); C.A. *78*, 79089c (1973).

14   K. Lal, Acta Chim. Acad. Sci. Hung. *99*, 281 (1979); C.A. *91*, 113228c (1979).

15   P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declecq and M. N. Woolfson, MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Univs. of York, England, and Louvain, Belgium, 1980.

16   J. M. Stewart, P. A. Machin. C. Dickinson, H. L. Ammon, H. Heck and H. Flack, The XRAY 76 System. Tech. Rep. TR–446. Computer Science Center, Univ. of Maryland, College Park, Maryland 1976.

17   D. T. Cromer and J. B. Mann, Acta Crystallogr. *A24*, 321 (1968).

18   R. F. Stewart, E. R. Davidson and W. T. Simpson, J. Chem. Phys. *42*, 3175 (1965).

19   W. C. Hamilton, Acta Crystallogr. *12*, 609 (1959).

20   R. Hämäläinen, M. Ahlgrén, U. Turpeinen and M. Rantala, Acta Chem. Scand. *A32*, 235 (1978).

21   K. Korhonen, R. Hämäläinen and U. Turpeinen, Acta Crystallogr. *C40*, 1175 (1984).

[Ph 68]