Tetrahedron Letters,Vol.26,No.14,pp 1753-1756,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

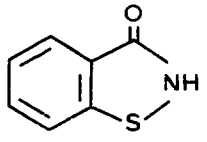
SYNTHESIS OF BUNTE SALTS FROM 1,2-BENZISOTHIAZOL-3-ONES AND VICE VERSA

A.W.R. Tyrrell

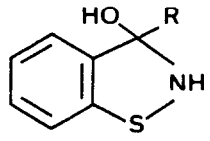
Beecham Pharmaceuticals, Biosciences Research Centre, Epsom, Surrey, England.

Summary: 1,2-Benzisothiazol-3-ones undergo ring-opening when treated with sodium hydrogen sulphite solution, giving Bunte salts, reconversion of which to benzisothiazol-3-ones can be effected with dilute alkali.

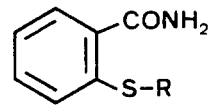
Despite a report that isothiazol-3-one underwent ring-opening on reaction with sulphite ion, giving a Bunte salt[1], Farrar[2] claimed that treatment of 1,2-benzisothiazol-3-one (1) with aqueous $NaHSO_3$ gave the adduct (2). The possibility that the Bunte salt (3) had been formed was considered by Farrar, but rejected, since treatment of the compound with cyanide ion gave a product believed to be (4). We have reinvestigated this reaction, and have also studied the action of sodium hydrogen sulphite solution on various 2-substituted 1,2-benzisothiazol-3-ones containing a tertiary amino group in the side-chain[3].



(1)



(2) R = $SO_3Na \cdot H_2O$



(3) R = $SO_3Na \cdot H_2O$

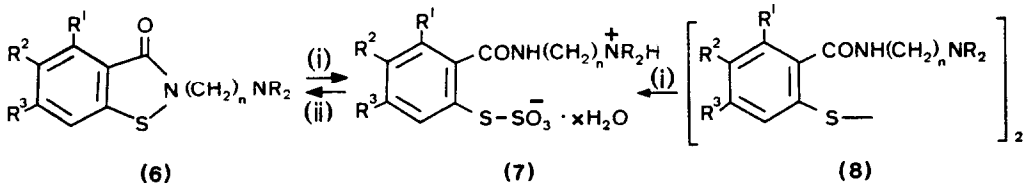
(4) R = CN

(5) R = CN

Reaction of (1) with a large excess of 30% aqueous sodium hydrogen sulphite solution (2.5h, 50-55°C) afforded a colourless solid, m.p. 135-137°C (lit.[2] m.p. not given), in 55% yield after recrystallisation (aqueous EtOH)[4]. Elemental analysis was consistent with the formula $C_7H_6NNaO_4S_2.H_2O$, and, as reported by Farrar[2], this material gave a product of m.p. ca. 145°C on treatment with cyanide ion. Physical data, however, did not accord with structure (2). Although the ir and pmr spectra of this material did not allow an unequivocal structural assigment, the ^{13}C nmr spectrum[5] (CO at δ 170.21) showed conclusively that the product was the Bunte salt (3), rather than the cyclic isomer (2). Similarly, it could be shown[6] that the product of the reaction with cyanide ion (5% aq. KCN, 5 min at room temperature) was the thiocyanate (5), rather than (4) as previously reported.

Treatment of 2-substituted 1,2-benzisothiazol-3-ones (6a-e) with 40% aqueous $NaHSO_3$ also gave Bunte salts (see Scheme and Table), but these were not simply N-substituted analogues of (3). That ring-opening to a substituted amide had occured was indicated by the ir[7] and pmr[5] spectra of the products (CONH at ca. 1630 and 3270 cm^{-1}; δ ca. 8.4, 1H, t, wholly or partially exchanges with D_2O). Elemental analysis, however, showed that sodium was absent. An explanation of these results is that the presence of a tertiary amino group in the starting material leads to the formation of Bunte salts containing a substituted ammonium cation. Such salts are zwitterionic, as shown in structure (7).

SCHEME



(6) (7) (8)

Reagents: (i) 40% aq. $NaHSO_3$; (ii) aq. NaOH

	n	NR_2	R^1	R^2	R^3	x
a	2	$-NEt_2$	Me	H	Me	0
b	2		H	H	H	0
c	3		H	H	H	1
d	2		H	OMe	OMe	0
e	4		H	OMe	OMe	1.5

TABLE

Bunte salts formed from 2-substituted 1,2-benzisothiazol-3-ones (6) and aqueous $NaHSO_3$ solution

Compound[a]	Yield[b] (%)	m.p. (C°)
(7a)	59	219-220
(7b)	60	188-190
(7c)	60	159-163 dec.
(7d)	68	215-217 dec.
(7e)	83	162-164

[a] Satisfactory spectral and analytical data were obtained for all compounds

[b] Yields, which were not optimised, are those obtained after the product had been recrystallised from EtOH-H_2O

Bunte salts (7) are reconverted into the corresponding 1,2-benzisothiazol-3-one (6) on treatment with dilute alkali: for example (6d), m.p. 138.5-140°, was obtained in 65% yield from (7d) and 5% aqueous NaOH (20 min, room temperature). This general reaction has proved useful, since we have found that Bunte salts (7) can also be synthesized by treating 2,2'-dithiodibenzamides (8) with aqueous $NaHSO_3$ [for example, (7b) was prepared in 47% yield from the dihydrochloride salt[8] of (8b)]. It is therefore possible to obtain 1,2-benzisothiazol-3-ones of type (6) from 2,2'-dithiodibenzamides (8) via Bunte salts (7) - a process which, because of its mildness, has advantages over existing routes[9] to (6) in certain instances. The preparation of 2-substituted 4,6-dimethoxy-1,2-benzisothiazol-3-ones by this procedure is described elsewhere[3].

Bunte salts (7) were found to be similar to the corresponding 1,2-benzisothiazol-3-ones (6) in their ability to inhibit collagen - and ADP-induced platelet aggregation in human platelet-rich plasma *in vitro*[3,10].

References and Notes

1. W.D. Crow and N.J. Leonard, J. Org. Chem., 30, 2660 (1965).

2. W.V. Farrar, Z. Naturforschung, 29b, 693 (1974); Chem. Abstr., 82, 72853w (1975).

3. K.H. Baggaley, P.D. English, L.J.A. Jennings, B. Morgan, B. Nunn and A.W.R. Tyrrell, J. Med. Chem., in press.

4. A preliminary investigation of this reaction was carried out with assistance from G.M. Hearn.

5. All nmr spectra (^1H and ^{13}C) were obtained in $(CD_3)_2SO$ unless otherwise noted, with Me_4Si as internal standard.

6. The structure of (5), m.p. 145.5-147.5°C (decomp.), was deduced from ^{13}C nmr [CO at δ 168.69 in $(CD_3)_2SO$-$CDCl_3$], ir (SCN at 2155; CO at 1675 cm^{-1}) and mass spectra (strong peak at M-NH_2). Found: C, 53.77; H, 3.39; N, 15.53; S, 17.97. $C_8H_6N_2OS$ requires C, 53.91; H, 3.39; N, 15.72; S, 17.99%.

7. Infrared spectra were obtained using KBr discs. All the Bunte salts described give a strong band in the region 1010-1030 cm^{-1}.

8. The dihydrochloride of (8b) was prepared by treating 2,2'-dithiodibenzoyl chloride with N-(2-aminoethyl)piperidine in a manner analogous to that described in Ger. Offen. 2656227 (1978); Chem. Abstr., 89, 109123f (1978). The product had m.p. 250-255°C dec. (from aq. EtOH). Found: C, 55.61; H, 6.88; N, 9.03; S, 10.67; Cl, 11.83. $C_{28}H_{40}Cl_2N_4O_2S_2$ requires C, 56.08; H, 6.72; N, 9.34; S, 10.69; Cl, 11.83%.

9. M. Davis, Advances in Heterocyclic Chemistry, 14, 43 (1972).

10. K.H. Baggaley (Beecham Group), Ger. Offen. 2652201 (1977); Chem. Abstr., 87, 117847u (1977).

The author thanks Drs. K.H. Baggaley, R.S. Oliver, and A.T. Ainsworth for helpful discussions; Dr. B. Nunn for carrying out the biological testing; and Mrs. A.M. Rogers for typing the manuscript.

(Received in UK 31 January 1985)