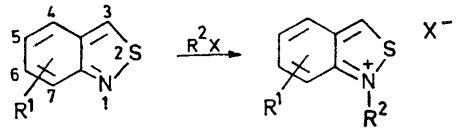
The Chemistry of 2,1-Benzisothiazoles. Part VI.[1] Quaternary Salts and their Decomposition by Base to *o*-Aminobenzaldehydes

By **Michael Davis,* Enno Homfeld,** and **K. S. Lal Srivastava,** Department of Organic Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

2,1-Benzisothiazoles react readily with dialkyl sulphates, alkyl bromides, and alkyl toluene-*p*-sulphonates at 115—120° to yield quaternary salts. Such salts are decomposed by aqueous acid or base, affording *N*-substituted *o*-aminobenzaldehydes; the parent *o*-aminobenzaldehyde can be obtained from the product of the reaction between 2,1-benzisothiazole and ethyl chloroformate. Bridged binuclear *o*-aminobenzaldehydes may also be prepared.

UNTIL recently, reports of quaternary salts of 2,1-benzisothiazoles were of 3-amino- or 3-azo-substituted derivatives only.[2-4] However, a recent paper[5] gives details of the preparation and ring-opening reactions of simple 2,1-benzisothiazole quaternary salts. The work we now describe, completed before the appearance of this paper,[5] extends the scope of such reactions.

2,1-Benzisothiazole itself (I; $R^1 = H$) and its simple derivatives afford quaternary salts (II) in good yield on direct heating with dialkyl sulphates, alkyl bromides, or alkyl toluene-*p*-sulphonates. The salts (II) are usually obtained as colourless crystalline solids by this procedure; in some cases, however, the salt is obtained as

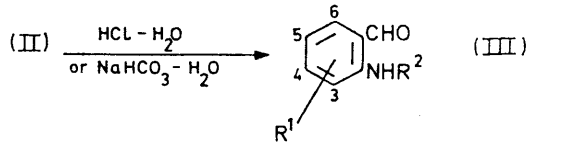


(I) (II)

an oil, and is best isolated as the orange crystalline iodide by treatment with aqueous sodium iodide solution.

The nucleophilicity (and basicity) of 2,1-benzisothiazole is less than that of, say, quinoline, and reasonably long periods of heating may be required for complete reaction. For example, the reaction with methyl toluene-*p*-sulphonate is only about 50% complete after 1 h at 100°; with 1,4-dibromobutane *ca.* 2 days heating at 116° is needed to obtain a bridged binuclear quaternary salt. We are at present examining the nucleophilic and basic strengths of 2,1-benzisothiazole and other nitrogen heterocycles in order to establish quantitative Hammett relationships.

We find that the quaternary salts (II) are rapidly



decomposed by aqueous acid or base, yielding *o*-aminobenzaldehydes (III), products not previously reported.

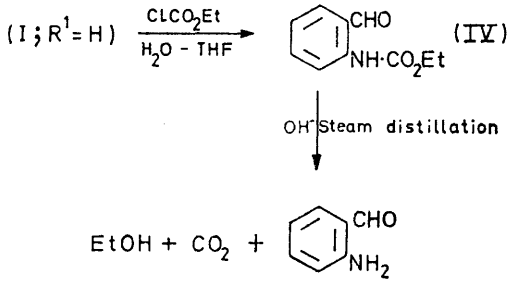
[1] Part V, M. Davis and K. S. L. Srivastava, *J.C.S. Perkin I*, 1972, 935.
[2] R. F. Meyer, B. L. Cummings, P. Bass, and H. O. J. Collier, *J. Medicin. Chem.*, 1968, **8**, 515.
[3] B.A.S.F., Neth. P. Appl. 6,608,032 (*Chem. Abs.*, 1967, **66**, 96214).
[4] Bayer, Fr. P. 1,540,834 (*Chem. Abs.*, 1970, **72**, 80338).
[5] O. Aki, Y. Nakagawa, and K. Sirakawa, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2372.

1-Methyl-5-nitro-2,1-benzisothiazolium toluene-*p*-sulphonate (II; $R^1 = 5\text{-}NO_2$, $R^2 = Me$, X = Ts) undergoes ring fission with particular ease, the aldehyde being obtained directly upon attempted recrystallization of the quaternary salt from water or aqueous ethanol. Acid-catalysed decomposition may also account for the comparatively low yields of benzyl bromide quaternary salts obtained when the reaction is carried out in ethanol heated under reflux. Under these conditions the solvent becomes slightly acidic from a slow reaction with the benzyl bromide, causing some decomposition of the slowly formed quaternary salt.

o-Aminobenzaldehydes (III) are useful synthetic intermediates, but other existing methods of synthesis are tedious and often proceed with low yields. We have used 2,1-benzisothiazole quaternary salts to prepare a number of such aldehydes, including the parent compound (III; $R^1 = R^2 = H$), functionally substituted derivatives of use as precursors of other heterocyclic systems, and a bridged binuclear aldehyde of interest in the metal ion ' template ' synthesis of macrocycles.

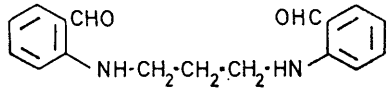
o-Aminobenzaldehyde (III; $R^1 = R^2 = H$) is readily obtained by treatment of 2,1-benzisothiazole (I; $R^1 = H$) with ethyl chloroformate in an aqueous tetrahydrofuran (THF) medium, followed by basification and steam distillation of the intermediate *o*-ethoxycarbonylaminobenzaldehyde (IV).

o-Formylphenylglycine (III; $R^1 = H$, $R^2 = CH_2{\cdot}CO_2H$) is similarly obtained from the quaternary salt produced by the reaction between 2,1-benzisothiazole and bromoacetic acid; this aldehyde is readily



cyclised to indole-2-carboxylic acid,[6] illustrating one possible heterocyclic ring synthesis.

Bridged binuclear aldehydes such as the trimethylene-bridged compound (V) are obtainable from the corresponding diquaternary salts, although the yields are not as favourable as in the case of the simple aldehydes.



(V)

Quaternary salt decomposition probably proceeds *via* attack of base on the 3-position of the salt, as the Japanese authors[5] have already suggested. The extruded sulphur usually remains dissolved in the aqueous base, although elemental sulphur is formed in the acid-catalysed decomposition. For this reason, and also because many *o*-aminobenzaldehydes are sensitive to acid (the parent compound is readily polymerised in this way) the base-catalysis procedure is preferred.

EXPERIMENTAL

Analyses were performed by the Australian Microanalytical Service, Melbourne. ^1H N.m.r. data were obtained with a Varian T-60 or A-60D instrument. I.r. spectra (liquid film or Nujol mull) were recorded on a Perkin-Elmer 257 instrument.

2,1-Benzisothiazole and substituted 2,1-benzisothiazoles were prepared as described previously.[7]

Preparation of 2,1-Benzisothiazole Quaternary Salts. General Procedure.—The benzisothiazole and the dialkyl sulphate, alkyl bromide, or alkyl toluene-*p*-sulphonate (1·1 equiv.) were heated together at 115—120° until reaction appeared complete (Table 1). Yields of crude products were generally quantitative. If the product failed to crystallise it was treated with an excess of saturated aqueous sodium iodide, thus affording the orange, highly crystalline quaternary iodide. The salts were recrystallised from ethanol containing *ca.* 5% of water. When attempts were made to recrystallise 1-methyl-5-nitro-2,1-benzisothiazolium toluene-*p*-sulphonate (II; $R^1 = 5\text{-}NO_2$, $R^2 = Me$, X = Ts) decomposition occurred and yellow needles of 2-methylamino-5-nitrobenzaldehyde (III; $R^1 = 5\text{-}NO_2$, $R^2 = Me$) were obtained.

Preparation of o-Aminobenzaldehydes (III) from Quaternary Salts. General Procedure.—The salt was dissolved in the minimum volume of water and an excess of solid sodium hydrogen carbonate was added. The mixture was warmed briefly on a steam-bath, then cooled, and the aldehyde was extracted with chloroform or diethyl ether. The extract was dried and worked up in the usual way. Oily aldehydes were characterised by i.r. and n.m.r. spectra and by conversion into 2,4-dinitrophenylhydrazine derivatives. The aldehydes and derivatives are listed in Table 2.

Preparation of o-Aminobenzaldehyde from 2,1-Benzisothiazole.—2,1-Benzisothiazole (0·50 g, 3·7 mmol), ethyl chloroformate (1·7 g, 15 mmol), water (2 ml), and tetrahydrofuran (10 ml) were heated together under reflux for 3 h. Diethyl ether (15 ml) was added, and the organic layer washed with water, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from light petroleum (b.p. 40—60°) afforded *cubes* (0·47 g, 2·4 mmol, 66%) of *o*-ethoxycarbonylaminobenzaldehyde (IV), m.p. 75—76° (Found: C, 62·4; H, 5·9; N, 7·5. $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·3%), $\nu_{max.}$ 3380 (NH), 1740 (CO_2Et), and 1665 cm^{-1} (CHO).

The ester (IV) (0·45 g, 2·3 mmol) was heated under reflux in aqueous ethanolic M-potassium hydroxide (1 : 1; 40 ml) for 30 min. The solution was acidified (HCl), neutralised with solid sodium carbonate, and steam distilled. Addition of sodium chloride to the distillate (50 ml) precipitated lustrous leaflets (0·2 g, 72%) of *o*-aminobenzaldehyde, m.p. and mixed m.p. 38—39°.

Spectral data. 1-Methyl-2,1-benzisothiazolium methosulphate (II; $R^1 = H$, $R^2 = Me$, X = $MeOSO_3$) showed

[6] W. Gluud, *J. Chem. Soc.*, 1913, **103**, 1254.
[7] M. Davis and A. W. White, *Chem. Comm.*, 1968, 1547; *J. Org. Chem.*, 1969, **34**, 2985; *J. Chem. Soc.* (*C*), 1969, 2189.

TABLE 1

2,1-Benzisothiazole quaternary salts (II)

R^1	R^2	X	Time of heating (h)	M.p. (°C) *	Formula	Found (calc.) (%) C	H	N
H	Me	$MeO{\cdot}SO_3$	1	124	$C_9H_{11}NO_4S_2$	41·4(41·4)	4·2(4·2)	5·1(5·4)
H	Me	I [a]	4	178	C_8H_8INS	34·5(34·7)	2·9(2·9)	5·3(5·1)
H	CH_2Ph	Br	2	200	$C_{14}H_{12}BrNS$	54·8(54·9)	4·0(4·0)	4·3(4·6)
5-Cl	Me	I [a]	4	201	C_8H_7ClINS	30·9(30·8)	2·2(2·3)	4·2(4·5)
5-Cl	CH_2Ph	Br	4	181	$C_{14}H_{11}BrClNS$	49·0(49·3)	3·3(3·2)	4·1(4·1)
6-Cl	Me	I [a]	4	182	C_8H_7ClINS	31·0(30·8)	2·1(2·3)	4·4(4·5)
5-NO_2	Me	Ts	4	300	$C_{15}H_{14}N_2O_5S$ [b]			
H	$CH_2{\cdot}CO_2H$	Br	1	206	$C_9H_8BrNO_2S,0{\cdot}5EtOH$	40·5(40·4)	3·5(3·7)	4·9(4·7)
H	$CH_2{\cdot}CO_2H$	I [c]	1	166	$C_9H_8INO_2S$	33·4(33·7)	2·7(2·5)	4·3(4·4)
H	$CH_2{\cdot}CO_2Et$	Br	2	177	$C_{11}H_{12}BrNO_2S$	44·0(43·7)	4·1(4·0)	4·5(4·6)
H	$CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_2Ph$	I [d]	40	121	$C_{15}H_{14}INO_3S_2$	40·5(40·3)	3·3(3·2)	2·9(3·1)
H	$CH_2{\cdot}CH_2{\cdot}CH_2$	2I [e]	22	194	$C_{17}H_{16}I_2N_2S_2$	36·4(36·1)	3·0(2·9)	4·7(4·9)
H	$CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2$	2Br	42	225	$C_{18}H_{18}Br_2N_2S_2$	44·6(44·5)	3·9(3·7)	5·8(5·8)

* Decomp.

[a] From toluene-*p*-sulphonate salt. [b] Decomposed to aldehyde on attempted recrystallisation. [c] From bromide salt. [d] From benzenesulphonate salt. [e] From dibromide salt.

TABLE 2

Aldehydes (III) and 2,4-dinitrophenylhydrazones from 2,1-benzisothiazole quaternary salts

R^1	R^2	M.p. (°C)	Formula	Found (calc.) (%) C	H	N
H	Me	267 [a]	$C_{14}H_{13}N_5O_4$	53·1(53·3)	4·2(4·1)	22·0(22·2)
H	CH_2Ph	251 [a]	$C_{20}H_{17}N_5O_4$	61·2(61·4)	4·4(4·4)	18·1(17·9)
5-Cl	Me	287 [a]	$C_{14}H_{12}ClN_5O_4$	48·3(48·1)	3·6(3·4)	20·3(20·0)
5-Cl	CH_2Ph	286 [a]	$C_{20}H_{16}ClN_5O_4$	56·7(56·4)	3·9(3·8)	16·6(16·5)
H	$CH_2{\cdot}CO_2H$ [b]	170 [c]	$C_9H_9NO_3$	60·2(60·3)	5·2(5·1)	7·8(7·8)
5-NO_2	Me	129	$C_8H_8N_2O_3$	53·2(53·3)	4·5(4·5)	15·7(15·6)
H	$CH_2{\cdot}CH_2{\cdot}CH_2$	85 [d]	$C_{17}H_{18}N_2O_2$			

[a] M.p., formula, and analytical data refer to 2,4-dinitrophenylhydrazone. [b] $NaHCO_3$ solution brought to pH 7 before extraction of aldehyde. [c] Lit.,[8] 176—177°. [d] Identical (i.r., t.l.c.) with authentic sample.[9]

δ (D_2O) 3·80 (s, MeO), 4·48 (s, MeN), 7·53—8·30 (m, aromatic H), and 10·20 (s, 3-H). *o*-Methylaminobenzaldehyde (III; R^1 = H, R^2 = Me) showed δ (CCl_4) 3·0 (s, Me), 6·6—7·5 (m, aromatic H), and 9·88 (s, CHO); $\nu_{max.}$ at 3355 (NH), 2825 and 2750 (CH of CHO), and 1670 cm^{-1} (CO). *o*-Formylphenylglycine (III; R^1 = H, R^2 = $CH_2{\cdot}CO_2H$) displayed δ ($CDCl_3$) 2·55 (s, CH_2), 5·0br (NH), 6·9 (s, aromatic H), and 9·51 (s, CHO).

We thank Dr. D. St. C. Black, Monash University, for an authentic sample of the bridged binuclear aldehyde (V), and the Department of Education and Science, Canberra, and La Trobe University for research scholarships (to E. H. and K. S. L. S.).

[3/831 *Received*, 17*th April*, 1973]

[8] W. Gluud, *Ber.*, 1915, **48**, 420.
[9] D. St. C. Black, personal communication.