John Ashby (1), D. Griffiths and D. Paton

Imperial Chemical Industries Limited, Central Toxicology Laboratory,
Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Received November 1, 1977

Reaction of 3-(2-hydroxyethylamino)benzo[d]isothiazole 1,1-dioxide (5a) with thionyl chloride gives a mixture of the expected chloroethyl derivative (5h) and the rearranged saccharin 2-(2-aminoethyl)-3-oxo-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide hydrochloride (6a). Separate treatment of the chloroethyl compound (5h) with dilute alkali gives the expected cyclization product 2,3-dihydroimidazo[1,2-b][1,2]benzisothiazole 5,5-dioxide (7a). Acidification of the liquors of the above reaction yields the ring expanded derivative 6-oxo-3,4,5,6-tetrahydro-[2H]benzo[g][1,2,5]thiadiazocine 1,1-dioxide (12f), a representative of a new ring-system. Treatment of the imidazo derivative (7a) with concentrated hydrochloric acid again yields the N-substituted saccharin (6a) which upon treatment with alkali also produces the thiadiazocine (12f). In contrast, treatment of the imidazo compound (7a) with alkali leads to attack on the sulphonamide function to give 2-(2-imidazolin-2-yl)benzenesulphonic acid (8). It is suggested that the multitude of chemical interconversions which can be induced within this series of compounds (Scheme II) can only be accounted for if two separate cyclol intermediates are invoked. Related reactions observed with variously substituted derivatives of the starting saccharin derivative (5a) are discussed as are the spectral properties and chemical reactivity of the new compounds prepared.

Many 3-substituted derivatives of saccharin have been described (2), however, very few attempts to induce intramolecular cyclization of a functionalized 3-substituent on to the adjacent, nucleophilic, ring nitrogen have been reported. The cyclodehydration of 3-(2-carboxyanilino)-benzo[d]isothiazole 1,1-dioxide (1) with acetic anhydride to give 7-oxo-7H-benzo[d]isothiazolo[3,2-c]quinazoline 5,5-dioxide, (2) (3) and the pyridine catalyzed rearrangement of 3-benzylideneaminooxybenzo[d]isothiazole 1,1-dioxide (3) to 3-oxo-2-phenyliminomethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (4) (4), are known examples of this principle.

Treatment of 3-chloro-ψ-saccharin (5) with ethanolamine yielded 3-(2-hydroxyethylamino)benzo[d]isothiazole 1,1-dioxide (5a), a known compound (6). Similarly prepared were compounds 5b-g from the appropriately substituted ethanolamines, all of which, with the exception of 1-phenylethanolamine (7) and 1-(3',4'-dichlorophenyl)ethanolamine (8), are commercially available. Our initial aim was to transform the hydroxy group of compounds 5a-g into a leaving group and carry out base assisted cyclizations as described above, thus the 2-hydroxyethylamino compound (5a) was treated with thionyl chloride under reflux. Two products were isolated

Scheme 1

15   16   17

from this reaction. The first of these was the expected chloroethyl derivative of 5a, namely, 3-(2-chloroethylamino)benzo[d]isothiazole 1,1-dioxide (5h). The second compound isolated is formulated as 2-(2-aminoethyl)-3-oxo-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide, hydrochloride (6a) consistent with its water solubility and the characteristic saccharin-type carbonyl at 1720 cm^{-1} exhibited in its ir spectrum. In the ^{1}H nmr spectrum of 6a, the two methylene groups showed two discrete resonances due to their markedly different chemical environments, whilst in contrast, these resonances in both the chloroethyl 5h and hydroxyethyl compound 5a were virtually coincident. Comments on the possible mode of formation of 6a and later unexpected compounds are made below. Upon boiling the chloro-ethyl compound 5h with 2N aqueous sodium hydroxide, the initially formed solution rapidly turned cloudy and 2,3-dihydroimidazo[1,2-b][1,2]benzisothiazole 5,5-dioxide (7a) precipitated. Upon acidification with concentrated hydrochloric acid of the warm mother liquor from the above reaction, the N-substituted saccharin (6a) was again isolated. All of the physical and spectroscopic data for the imidazo compound (7a) were consistent with the structure shown, in particular, the presence of symmetrical multiplets at δ 4.4 and 3.7 in its ^{1}H nmr spectrum.

By the careful selection of reaction conditions, it was possible to optimize the formation of the imidazo derivative (7a) to a maximum of ~ 47%, however, the amount the N-substituted saccharin (6a) formed remained constant at ~ 50%. This is consistent with 7a and 6a being formed from 5h by different mechanisms, rather than

Scheme II
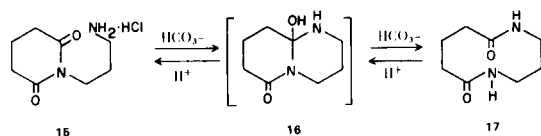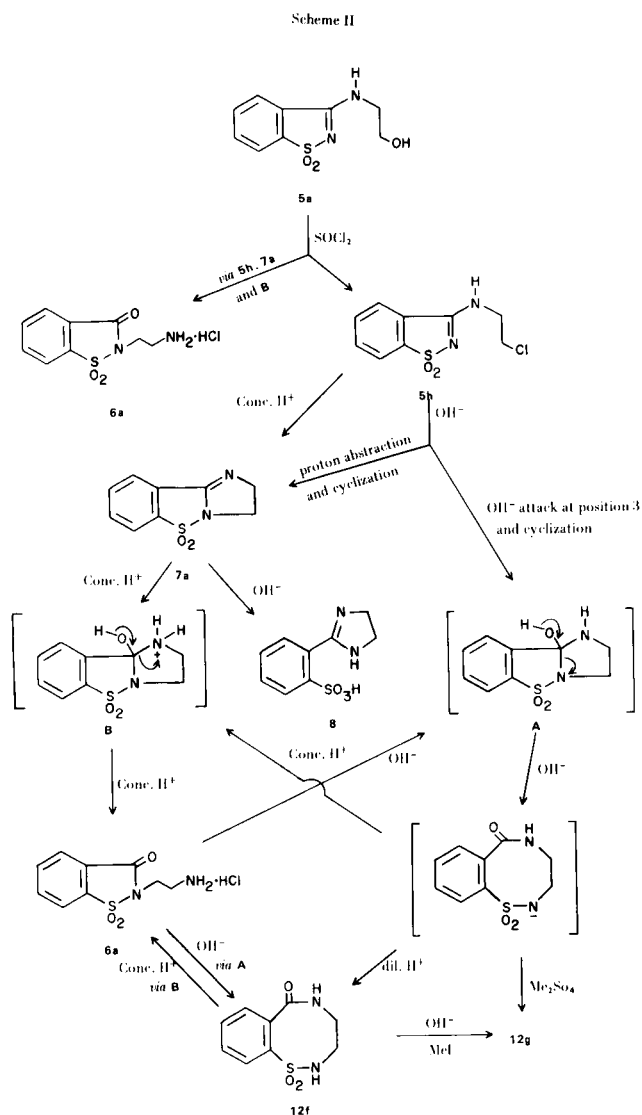
with **6a** being formed by hydroxide attack on position 9b of **7a** (Scheme II). This was confirmed by the observation that separate treatment of **7a** with boiling aqueous sodium hydroxide gave 2-(2-imidazolin-2-yl)benzenesulphonic acid **(8)** after acidification, concentration and freezing. The high solubility of the sulphonic acid **(8)** accounts for the fact that after boiling of a solution of the chloroethyl compound **(5h)** in aqueous alkali for longer than 2 minutes, dissolution of the initially precipitated imidazo derivative **(7a)** occurred leading to the production of a clear solution from which only the N-substituted saccharin **(6a)** could be isolated after acidification. As expected the imidazolinyl proton resonance of the sulphonic acid **(8)** formed a sharp singlet at δ 3.95. A refluxing solution of the soft nucleophile, cyanide ion, had no effect on the imidazo compound **(7a)**. In contrast

to the above base assisted ring opening of imidazo derivative **7a**, protonation of the amidine function directs hydrolysis to the adjacent 9b position, thus, warming a solution of **7a** in 11N hydrochloric acid results in the formation of the N-substituted saccharin **(6a)**. This observation explains why the N-substituted saccharin **(6a)** was isolated along with the chloroethyl compound **(5h)** upon treatment of the hydroxyethyl compound **(5a)** with thionyl chloride. The hydrogen chloride generated upon cyclization of **5a** to **7a** served to catalyse the ring opening of **7a** to yield **6a**. As further confirmation of this route of formation of **6a**, separate treatment of the chloroethyl intermediate **(5h)** with 11N hydrochloric acid, under reflux for 1 hour gave a solid which both ir analysis and tlc indicated was a mixture of the imidazo tricyclic **(7a)** and the N-substituted saccharin **(6a)**.

The corresponding 2-methyl-2-hydroxyethyl compound **(5b)** reacted smoothly with thionyl chloride giving the corresponding chloroethyl compound **(5i)**, however, upon subjecting this to the same alkali treatment saccharin alone was isolated upon acidification. The formation of saccharin could be accounted for either by hydrolysis of the amidine function of the starting material **(5i)** or by rearrangement to the expected N-substituted saccharin **(6b)** (as described for **(5h)**), followed by methyl-accelerated loss of saccharin via sidechain aziridine formation (Thorpe-Ingold effect). Failure to effect cyclization of this chloroethyl compound **(5i)** led us to examine the use of the mixed reagent methanesulfonic acid-phosphorus pentoxide **(9)** for the cyclodehydration of the hydroxyethyl precursor **(5b)**. The product isolated under such conditions was the corresponding mesyloxy derivative of **5b**, namely 3-(2-mesyloxypropylamino)benzo[d]isothiazole 1,1-dioxide **(5j)**. Treatment of this material with dilute alkali gave the required 3-methyl-2,3-dihydrobenzo[d]-imidazo[2,1-b]isothiazole 5,5-dioxide **(7b)**. Again, acidification of the mother liquors from the above cyclization gave a low yield of saccharin. Similarly, this mixed reagent transformed the hydroxyethyl compound **(5a)** into the corresponding mesyloxy compound **(5k)** which with alkali gave the imidazo derivative **(7a)** in the same yield as had the chloroethyl compound **(5h)**. The 1-phenyl-2-hydroxyethyl derivative **(5c)** was similarly converted into the corresponding mesyloxy compound **(5l)** which was converted by alkali into either 2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]isothiazole 5,5-dioxide **(7c)** or the analogous N-substituted saccharin **(6c)**, depending upon the reaction conditions chosen (see Table IV).

The isomeric 2-phenyl-2-hydroxyethyl compound **(5d)** reacted smoothly with thionyl chloride giving the expected chloroethyl derivative **(5m)**, however, we were unable to isolate any products from its reaction with

Table I

Hydroxyalkyl Compounds (5a-r)

Starting Amine	Yield (%)(a)	Product	M.p. (°C)	Found (%) (Calcd. %)			Mass Spectral Fragments	Nmr (δ) 60 MHz (DMSO-d6)
				C	H	N		
Ethanolamine	71 (b)	5a	244-246 (f)					7.7-8.3 (m, aromatics and NH), 3.55-3.7 (m, CH2's)
2-Methylethanolamine	45 (b)	5b	196	48.0 (g) (48.2)	4.9 (5.2)	11.3 (11.2)	M+, M+-SO2, M+-side chain	9.4 br (m, NH), 8.3-7.8 (m, aromatics), 5.0 br, 4.0 br (m's OH & CH), 3.5 (m, CH2), 1.25 (d, CH3)
1-Phenylethanolamine	66 (b)	5c	226-228	59.3 (59.6)	4.7 (4.6)	9.0 (9.3)	M+, M+-OH, M+-CHOH	9.65 (d, NH), 8.4 (m, H-7), 7.85 (m, H-4 & H-6), 7.35 (s, phenyl), 5.25 (m, CH & OH), 3.85 (m, CH2)
2-Phenylethanolamine	51 (c)	5d	210	59.6 (59.6)	4.7 (4.6)	9.1 (9.3)	M+, M+-PhCHO	9.7 br (m, NH), 8.4-7.8 (m, fused ring aromatics), 7.3 (m, phenyl), 5.7 (d, OH), 5.0 (m, CH), 3.6 (m, CH2)
2-(3,4-Dichlorophenyl)ethanolamine	38 (d)	5e	244	48.4 (48.5)	3.2 (3.2)	7.4 (7.55)	M+, M+-SO2, M+-3,4-diClPhCHO	9.5 (m, NH), 8.1 (m, H-7), 7.8-7.2 (m, aromatics), 4.9 (m, CH), 3.6 (m, CH2)
3-Aminopropanol	89 (c)	5f	198-199	50.0 (50.0)	5.2 (5.0)	11.4 (11.65)	M+-OH, M+-CHOH, M+-CH2OH, M+-SO2	8.3-7.7 (m, aromatics), 3.6 (m, terminal CH2's), 1.85 (t, mid CH2)
5-Aminopentanol	67 (d)	5g	163-165	53.6 (53.7)	5.9 (6.0)	10.2 (10.4)	M+, M+-OH, M+-CH2OH, M+-sidechain	9.4 br (m, NH), 8.3-7.8 (m, aromatics), 3.5 (m, terminal CH2's and OH), 1.5 (m, mid CH2's)
2-Hydroxymethylaniline	81 (e)	10a	264	58.8 (58.4)	4.3 (4.2)	9.8 (9.7)	M+, M+-H2O, M+-CH2OH, M+-SO2	8.4-7.4 (m, aromatics, OH & NH), 4.66 (s, CH2)
Ethanolamine	53 (e)	5r	235-236	40.0 (39.85)	3.3 (3.3)	15.4 (15.5)	M+-CHOH, M+-CH2OH, M+-SO2	9.4 br (m, NH), 8.6 (m, aromatics), 3.7 (s, CH2's)

(a) After crystallization. (b) From ethanol-water. (c) From ethanol. (d) From acetone. (e) From acetone-water. (f) Lit. (6) m.p. 246°. (g) Hygroscopic, fits for ½H2O.

Table II

Reaction of Hydroxyalkyl Compounds (5) and (10) with Thionyl Chloride

Starting Alcohol	Product	Yield (%)(b)	M.p. (°C)	Found % (Calcd. %)			Mass Spectral Fragments	Nmr (δ)(f) 100 MHz
				C	H	N		
5a	5h	86 (c)	190	44.2 (44.2)	3.7 (3.7)	11.2 (11.4)	M^+, M^+-Cl, M^+-CH$_2$Cl, M^+-CHCH$_2$Cl	(g) 9.25 br (m, NH), 8.3-7.7 (m, aromatics), 3.8 (s, CH$_2$'s)
5a	6a(a)	12 (d)	279-280	41.1 (41.1)	4.4 (4.2)	10.4 (10.7)	M^+, M^+-CHNH$_2$, (M^+-CHNH$_2$)-SO$_2$	8.4, 8.1 (m, aromatics and NH$_2$), 4.04 (t, J = 6 Hz, amidic CH$_2$), 3.16 (t, J = 6 Hz, CH$_2$)
5b	5i	36 (d)	200-201	46.3 (46.4)	4.4 (4.25)	10.5 (10.8)	M^+, M^+-Cl (base), base-CHCH$_3$, base-SO$_2$	9.7 (t, J = 5 Hz, NH), 8.3-7.8 (m, aromatics, 4.48 (m, CH), 3.76 (m, CH$_2$), 1.55 (d, J = 6 Hz, CH$_3$)
5d	5m	36 (d)	175-176	55.9 (56.2)	4.1 (4.1)	8.6 (8.7)	M^+, M^+-HCl(base), base-SO$_2$, base-CHPh	9.84 (t, J = 5 Hz, NH), 8.2-7.4 (m, aromatics), 5.47 (t, J = 5 Hz, CH), 4.08 (m, CH$_2$)
5f	11	64 (c)	270-272	46.4 (46.4)	4.3 (4.3)	10.6 (10.8)	M^+, M^+-SO$_2$	9.0, 8.5 and 8.15 (m's, aromatics), 4.92 and 4.7 (t's, J = 6 Hz, terminal CH$_2$'s), 2.2 (quintuplet, J = 6 Hz, mid CH$_2$)
5g	5q	69 (c)	151-152	50.3 (50.3)	5.3 (5.2)	9.8 (9.8)	M^+, M^+-Cl, M^+-SO$_2$	9.4 br (m, NH), 8.2-7.8 (m, aromatics), 3.65-3.35 (m, terminal CH$_2$'s), 1.8-1.3 (m, mid CH$_2$'s)
5r	5s	30 (c)	228	38.0 (37.3)	3.1 (2.8)	14.2 (14.5)	M^+, M^+-Cl, M^+-CH$_2$Cl, M^+-CHCH$_2$Cl	8.8 (s, H-7; appears as singlet due to overlap with one arm of the H-5dd), 8.76 (dd, $J_{5,4}$ = 8, $J_{5,7}$ = 2 Hz, H-5), 8.47 (d, J = 8 Hz, H-4), 3.9 (s, CH$_2$'s)
5r	6e(a)	25 (d)	264	34.0 (e) (34.1)	3.5 (3.5)	13.0 (13.2)	M^+, M^+-NO$_2$, (M^+-NO$_2$)-SO$_2$	9.32 (d, J = 2 Hz, H-7), 8.76 (dd, $J_{5,4}$ = 8, $J_{5,7}$ = 1 Hz, H-5), 8.36(d, $J_{4,5}$ = 8 Hz, H-4), 8.35 br (m, NH$_2$), 4.06 (t, J = 5 Hz, amidic CH$_2$), 3.14 (t, J = 5 Hz, CH$_2$)
10a	10b	65 (c)	234-236	54.5 (54.8)	3.5 (3.6)	9.0 (9.1)	M^+, M^+-Cl (base), base-SO$_2$	(g) 8.5 br (m, NH), 7.95 and 7.5 (m's, aromatics), 4.84 (s, CH$_2$)

(a) Compounds 6a and 6f were filtered off as insoluble hydrochlorides on crystallization of crude residue from ethanol. (b) After crystallization. (c) From ethanol. For 5h, aqueous ethanol gives a distinct monohydrate, m.p. 190°. Crystallization from 100% ethanol again gives pure material. (d) From ethanol-water. (e) Hygroscopic, fits for ½ H$_2$O. (f) DMSO-d$_6$ was used as solvent, except 5h where deuteriochloroform plus one drop DMSO-d$_6$ was used. (g) Spectrum taken at 60 MHz.

alkali, although starting material was consumed. As the failure of **5m** to cyclize may be associated with the electronic nature of the carbon atom bearing the chlorine leaving group, the 2-(3,4-dichlorophenyl)hydroxyethyl compound (**5e**) was prepared in which the electron-withdrawing chlorine atoms would enhance the replaceability of the leaving group. In fact **5e** was transformed readily into the mesyloxy compound (**5n**) but this upon treatment with alkali gave an intractable mixture of products. In contrast, treatment of the unsubstituted phenyl alcohol (**5d**) under identical conditions (methanesulfonic acid/phosphorus pentoxide) resulted in the formation of the N-substituted saccharin (**6d**) (71%) as its methanesulphonate salt, together with the simple trans-dehydration product of **5d**, 3-styrylaminobenzo[d]isothiazole 1,1-dioxide (**9**) (8%). This reaction probably proceeds via the mesyloxy compound (**5p**) and its imidazo derivative (**7d**) which under the acidic reaction conditions ring opens via hydrolytic attack at the 9b position to give the N-substituted saccharin (**6d**) (as observed earlier for the acidic transformation of **7a** into **6a**). The failure of the 3,4-dichlorophenyl analogue (**5n**) to cyclize and ring open may be associated with steric strain between the sulphone group and the substituted phenyl ring, thus preventing formation of the necessary cyclol intermediate (**B**) (Scheme II). A complete resistance to cyclization was also observed for both 3-(2-chloromethylanilino)-benzo[d]isothiazole 1,1-dioxide (**10b**) and 3-(2-mesyloxy-methylanilino)benzo[d]isothiazole 1,1-dioxide (**10c**), both of which had been derived from 3-(2-hydroxymethyl-anilino)benzo[d]isothiazole 1,1-dioxide (**10a**), by the previously described methods. The hydroxymethyl compound (**10a**) was prepared as described for compounds **5a-g** using 2-hydroxymethylaniline. Failure to cyclize in these cases is probably due to the reduced acidity of the amidine proton caused by its conjugation with the phenyl ring attached to the same nitrogen atom.

Each attempt to cyclize either **10b** or **10c** resulted in re-formation of the hydroxymethyl precursor (**10a**), via simple nucleophilic replacement of the leaving group by hydroxide ion. Treatment of the mesyloxy compound (**10c**) with piperidine gave the piperidinomethyl compound (**10d**), thus confirming the above suggested mechanism.

An abnormal reaction occurred upon warming the 3-hydroxypropyl compound (**5f**) with thionyl chloride. The product obtained was 3,4-dihydro-2H-benzo[d]-pyrimidino[2,1-b]isothiazole 6,6-dioxide (**11**). The apparent ease of cyclisation in this case may be associated with the reduced ring strain expected for compound **11** as compared with its imidazo analogue (**7a**). Moreover, the reduced ring strain in compound **11** might account for the absence of its ring-opened derivative (**6f**) in the reaction mixture (cf. the contrasting behaviour of **5a**,

Scheme II). Further, compound **11** was also stable to refluxing concentrated hydrochloric acid (cf. the contrasting behaviour of **7a** with acid, Scheme II). Reaction of the hydroxypentyl derivative (**5g**) with thionyl chloride gave the corresponding chloropentyl compound (**5q**) as sole product, which was stable to alkali under the present conditions.

An analogous sequence of reactions was carried out on 6-nitrosaccharin (10). Conversion to the known 3-chloro-6-nitrobenzo[d]isothiazole 1,1-dioxide (**4**) with thionyl chloride followed by treatment with ethanolamine gave the expected hydroxyethyl derivative (**5r**). Upon warming this material with thionyl chloride a separable mixture of the corresponding chloroethyl compound (**5s**) and the N-substituted nitrosaccharin (**6e**) was formed. Treatment of the chloroethyl compound (**5s**) with dilute alkali gave none of the expected imidazo[1,2-b][1,2]benzisothiazole. This failure to cyclize may be due to the mesomeric effect of the para-nitro function in **5s** favouring nucleophilic attack by hydroxide ion on position 3 of **5s**, thus giving the saccharin (**6e**), rather than proton abstraction and cyclization to give an imidazo derivative.

Mechanistic aspects of the mode of formation and interconversion of the above products is best considered in conjunction with the following reactions. The N-substituted saccharin (**6d**) was isolated from the mixed methanesulfonic acid/phosphorus pentoxide reagent as its methanesulfonate salt and in an attempt to form the free base we treated it with a dilute aqueous solution of sodium hydroxide. After the initial formation of a precipitate, a clear solution was re-formed. Upon acidification of this solution with dilute acid, a base soluble product was precipitated and identified as 6-oxo-3-phenyl-3,4,5,6-tetrahydro-2H-benzo[g][1,2,5]thiadaizocine 1,1-dioxide (**12a**). If instead of acidifying the above solution, dimethylsulphate was added, methylation of the acidic sulphonamide nitrogen of **12a** occurred yielding its 2-methyl analogue (**12b**). Subsequent treatment of **12b** with sodium hydride-methyl iodide under normal amide alkylation conditions produced the 2,5-dimethyl compound (**12c**). This base catalysed ring expansion was general for compounds **6a**, **c-e**, thus, the phenyl positional isomer of **6d**, namely **6c**, readily underwent ring expansion to give 6-oxo-4-phenyl-3,4,5,6-tetrahydro-2H-benzo-[g][1,2,5]thiadiazocine 1,1-dioxide (**12d**) which upon separate treatment with sodium hydroxide-dimethylsulphate gave the 2-methyl-4-phenyl derivative (**12e**). Likewise, the saccharin (**6a**) was transformed into the thiadiazocine (**12f**) or its methylated derivative (**12g**), and the nitro-substituted saccharin (**6e**) into the thiadiazocine (**12h**). Finally, the acidic nature of the N-1 sulphonamido proton in the thiadiazocine (**12a**) was further illustrated by its reaction with epichlorohydrin and dilute alkali to give the epoxide derivative (**13a**) which itself reacted

Table III

Reaction of Hydroxyalkyl Compounds with Methanesulfonic Acid-Phosphorus Pentoxide Mixture

Starting Alcohol	Product	Yield (%) (a)	M.p. (°C)	Found (%) (Theory %) C	H	N	Mass Spectral Fragments	Nmr (δ) 100 MHz (DMSO-d_6)
5a	5k	42	170 (b)	39.5 (39.5)	4.0 (4.0)	9.1 (9.2)	M^+, M^+-SO_2	9.7 br (m, NH), 8.3-7.8 (m, aromatics) 4.44 (t, J = 5 Hz, CH_2OMs), 3.8 br (t, J = 5 Hz, NHCH_2), 3.18 (s, CH_3).
5b	5j	33	174-176	(e) 40.6 (40.2)	4.5 (4.9)	8.6 (8.5)	M^+, M^+-SO_2	9.8 br (t, J = 6 Hz, NH), 8.25, 7.9 (m, aromatics), 5.0 (sym. m, CH), 3.7 (m, CH_2), 3.12 (s, SO_2CH_3), 1.44 (d, J = 6.5 Hz, CHCH_3).
5c	5l	54	150-151 (c)	50.9 (50.5)	4.4 (4.2)	6.9 (7.35)	M^+, M^+-SO_2	9.88 (d, J = 8 Hz, NH), 8.3, 7.9 and 7.4 (m's, aromatics), 5.5 br (dt, CH), 4.55 (d, J = 7 Hz, CH_2), 3.2 (s, CH_3).
5d		See experimental section						
5e	5n	82	146-148	42.7 (42.8)	3.3 (3.1)	6.2 (6.2)	M^+, M^+-SO_2	9.75 br (t, J = 6 Hz, NH), 8.2-7.6 (m, remaining aromatics), 7.85 (d, J = 9 Hz, PhH-6), 7.48 (dd, J = 9, 2 Hz, PhH-5), 5.9 (t, J = 7 Hz, CH), 3.98 br (dt, CH_2), 3.12 (s, CH_3).
10a	10c	52	224 (d)	49.9 (49.2)	3.9 (3.8)	7.6 (7.6)	M^+, M^+-SO_2	10.0 (offset NH), 8.4, 8.0 and 7.55 (m, aromatics), 5.35 (s, CH_2), 3.1 (s, CH_3).

(a) Crude yield, the products were used as such in subsequent reactions. (b) From ethanol. (c) From ethanol-water. (d) From acetone-water. (e) Hygroscopic - fits for ½H_2O.

smoothly with either isopropylamine or morpholine to give the aminopropanols 13b and 13c, respectively. Attempts to initiate intramolecular cyclization of the amidic nitrogen of 13a on to the adjacent epoxide function, with sodium hydride-DMF, to give the bridged alcohol (14) were unsuccessful despite the fact that Dreiding models showed the reaction to be sterically feasible.

The general aspects of all of the above transformations will be considered using the 2-hydroxyethyl compound (5a) as a model, although the comments made should apply equally to all of the substituted examples described above. The ring expansion of the aminoethyl saccharin (6a) to the thiadiazocine (12f) has a close precedent in the work of Rapoport (11) in which 1-(3-aminopropyl)-perhydropyridine-2,6-dione hydrochloride (15) was converted via the cyclol (16) into the 10-membered alicycle perhydro[1,5]diazecine-6,10-dione (17) by the action of sodium bicarbonate. The sequence was reversible [17→15] under the influence of dilute acid (Scheme I) and likewise, treatment of the thiadiazocine (12f) with concentrated acid gave the saccharin (6a). A drop in the frequency of the carbonyl absorption was observed upon conversion of the piperidione (15) to the 10-membered amide (17) (1720 to 1650 cm^{-1}, respectively). A similar change is observed in passing from the saccharin (6a) (1735 cm^{-1}, C=O) to the thiadiazocine (12f) (1640 cm^{-1}, C=O), and the latter frequency is as expected for a large ring cis enforced amide (12). The infrared spectrum of the thiadiazocine (12f) also showed two sharp NH absorptions at ~ 3100 cm^{-1} (-SO_2NH) and ~ 3300 cm^{-1} (-CONH-). These absorptions were lost, in sequence, upon mono- and dimethylation of, for example, 12a (producing 12b and 12c, respectively).

Scheme II illustrates the formation of the thiadiazocine (12f) from the saccharin (6a), along with the other interconversions mentioned earlier. We are forced to postulate two distinct cyclol intermediates, the first (A) is that generated under basic conditions and the second (B), is that generated under acidic conditions, and therefore shown protonated. The former generates the thiadiazocine ring system, the latter, an N-substituted saccharin. It is interesting to note that the partial formation of the saccharin (6a) from the hydroxyethyl compound (5a) (via 5h, 7a and B) stops at the tricyclic stage (11) when using the propanol (5f) and no chloropropyl compound is detected. As can be seen from Scheme II, acidification of the thiadiazocine anion can yield different products depending upon the concentration of the acid used. Unless care is taken a mixture of the saccharin derivative and the protonated thiadiazocine is formed, as a solid. However, separate treatment of this mixture with concentrated acid yields the pure saccharin derivative.
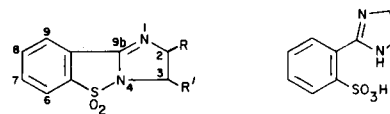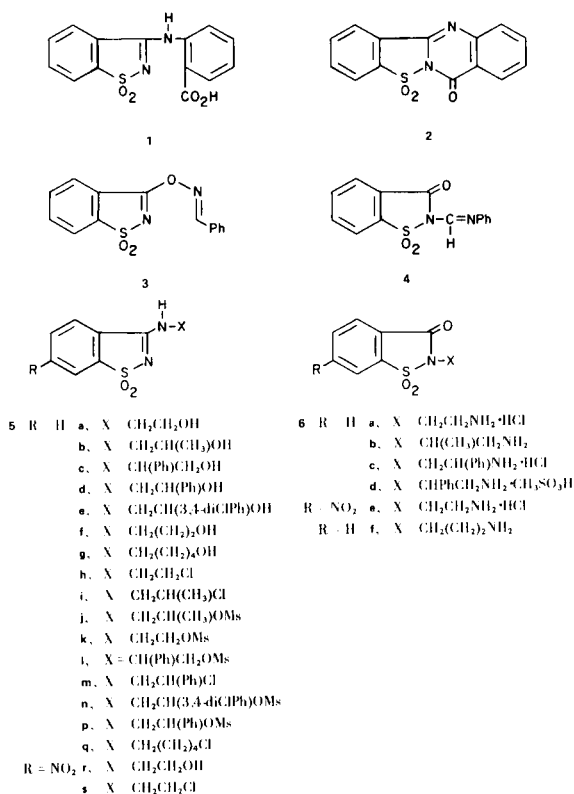
When considering the ring expansion of a substituted N-aminoethyl saccharin such as 6d, the question of the

site of attack of the sidechain amino group becomes important. In the case of **6d**, attack on the adjacent amide would yield what is in fact the observed thiadiazocine product (**12a**) whilst attack on the sulphonamide function would yield its phenyl positional isomer (**12d**). Clear evidence for the formation of **12a** is obtained from the ^{1}H nmr spectrum of the derived dimethyl compound (**12c**) where the sulphonamido-methyl resonance occurs at δ 2.13, which is shielded by ca. 0.4 ppm compared to this resonance in the des-phenyl thiadiazocine (**12f**). This shielding is consistent with the methyl group in question being positioned above the plane of the adjacent phenyl ring (13) (Figure 1). Moreover, the conformation

Figure 1
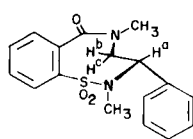
H(a)-H(b)   90°

imposed upon the eight membered ring in order to achieve this proximity also imposes a 90° angle between H-a and H-b (Figure 1) (Dreiding Models) and in fact zero coupling is observed between these protons (see Table V). The above shielding effect was even more marked in the case of the N-ethylthiadiazocine (**12i**), prepared from the parent compound (**12a**) and diethylsulphate, where the resonance of the ethyl CH$_3$ group appeared broadened
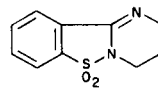

at δ 0.5. As further confirmation of the structure of the phenyl isomers, the ^{1}H nmr resonance of the amidic NH in the thiadiazocine (**12a**) appears as a triplet at δ 8.3 whilst this resonance in the isomer (**12d**) appears as a doublet at δ 8.58 consistent in each case with their respective chemical environments.

EXPERIMENTAL

Table IV

Treatment of Chloroalkyl and Mesyloxyalkyl Compounds (5) with Alkali

Starting Material	Reaction Conditions Temp. (°C)	Time (min.)	Yield (%)(a)	Product	M.p. (°C)	Found (%) (Theory %) C	H	N	Mass Spectral Fragments	Nmr (δ) 100 MHz (b)
5k	60	1.0	2.8 (c)							
	100	0.5	49 (e)	7a	196	52.0 (51.9)	4.0 (3.8)	13.2 (13.5)	M⁺, M⁺-SO₂	8.2-7.8 (m, aromatics), 4.4 (m, CH₂), 3.7 (m, CH₂).
5h	100	0.5	47 (d)							
	100	2.0	51 (e)	6a	See Table II for physical data on this compound.					
5j	65	0.5	21	7b	134-136	54.1 (54.0)	4.6 (4.5)	12.5 (12.6)	M⁺, M⁺-CH₃, M⁺-SO₂	8.2-7.9 (m, aromatics), 4.8-3.7 (m, CHCH₂), 1.45 (d, J = 6 Hz, CH₃).
	65	0.5	25							
5i	100	2.0	80	Saccharin (f)	226-228	45.6 (45.9)	3.1 (2.75)	7.7 (7.65)	M⁺	
5l	80	2.0 (g)	66	7c	118-120	63.6 (63.4)	4.5 (4.2)	9.5 (9.9)	M⁺, M⁺-SO₂	(i) (deuteriochloroform) 8.2-7.8 (m, fused ring aromatics), 7.4 (s, phenyl), 5.8 (t, CH), 4.0 (m, CH₂).
	100	2.0	23	6c	237-239	53.2 (53.2)	4.2 (4.4)	8.3 (8.3)	M⁺-PhCHNH₂, then -SO₂. PhCHNH₂ (Base)	(i) 8.3-7.9 (m, fused ring aromatics), 7.4 (m, phenyl), 4.6 (m, CH), 4.2 (m, CH₂).
10b	25	5.0	50	10a						
10c	100	1.0	25							
5n	100	3.0	-----	h						

(a) After recrystallization from ethanol. (b) DMSO-d_6 as solvent except where stated otherwise. (c) Although the 60° experiment was reproducible the 100° reaction sometimes failed to give any precipitate of 7a, but this was rare. (d) Acidification of the liquors in this case gave starting material (5h) irrespective of the acid employed. This observation eliminates the possibility of 3-aziridinyl formation with subsequent ring opening with chloride to give 5h. (e) No initial precipitation of 7a was observed in this case (7 equivalents of sodium hydroxide used). The most reliable source of 6a is via the reaction of thionyl chloride with 5a (see Table II). (f) Isolated after acidification. (g) Precipitated oily solid extracted into ethyl acetate, removal of the solvent gave the crude product which was crystallized. (h) Oily intractable mixture containing some alcohol (5e) (by ir). (i) Spectrum taken at 60 MHz.

Table V

Benzo[g][1,2,5]thiadiazocines from N-Substituted Saccharins (6) and their Alkylation Products

Starting Material	Reaction with Alkali Temp. (°C)	Time (min.)	Yield (%)	Product	M.p. (°C)(a)	Found (%) (Theory %) C	H	N	Mass Spectral Fragments	Nmr (δ) 100 MHz (DMSO-d6)
6a	80	2.0	66	12f	218	47.4 (47.8)	4.3 (4.4)	12.2 (12.4)	M+, M+-NHCH2, M+-SO2	8.15 (m, CONH), 7.98-7.5 (m, aromatics and SO2NH), 3.3-2.7 (m, CH2-CH2).
6c	100	1.0	37	12d	199-201	57.5 (b) (57.9)	4.7 (4.8)	8.8 (9.0)	M+, M+-PhCHNH2, PhCHNH2	8.58 (d, J = 10 Hz, CONH), 8.0-7.5 (m, fused ring aromatics and SO2NH), 7.3 (s, Ph), 4.25 [m, (with J = 10 Hz coupling to CONH apparent) C-4H], 3.6-3.2 br (m, CH2).
6d	25	1.0	92	12a	242-244	59.8 (59.6)	4.7 (4.6)	9.2 (9.3)	M+, M+-SO2	8.3 (t, J = 7 Hz, CONH), 8.0-7.5 (m, fused ring aromatics and SO2NH), 7.32 (s, Ph), 4.55 br, (t, J (apparent) = 4 Hz, C-3H), 32.8 br (d, J = 4 Hz after deuterium oxide added, CH2).
6e	100	1.0	36	12h	251	38.3 (b) (38.6)	3.6 (3.6)	14.9 (15.0)	M+, M+-SO2, (M+-SO2)-NHCH2	8.55 (d, J (10,8) = 2 Hz, C-10 H), 8.5 (dd, J (8,7) = 10 Hz, J (8,10) = 2 Hz, C-8 H), [due to overlap these two resonances appear as a singlet at 8.55 and a doublet (J = 2 Hz) at 8.45; combined integral 3H], 8.06 [t, (or coalesced dd) J = 6 Hz, CONH], 7.8 (d, J (7,8) = 10 Hz, C-7H, 3.6-2.8 (m, CH2-CH2).
6a	see experimental section		44	12g	246	49.9 (50.0)	5.0 (5.0)	11.5 (11.66)	M+, M+-CH3NCH2, M+-SO2	8.2 br (m, NH), 7.95-7.6 (m, aromatics), 3.6-3.0 (m, CH2's), 2.62 (s, CH3).
6a or 12a	←		63	12b	208-210	60.7 (60.7)	5.2 (5.1)	8.7 (8.7)	M+, M+-SO2, (M+-SO2)-NCH3	8.2 (t, J = 7 Hz, CONH), 7.9-7.6 (m, fused ring aromatics), 7.36 (s, Ph) 5.05 br (t, CH), 4.45 (dt J (CH2CH) = 7 Hz, J (CH2NH) = 4 Hz, CH2), 2.13 (s, shielded CH3).

Compound	Yield	m.p.	C	H	N	MS	^{1}H NMR
12e	48	212-215(a)	60.8 (60.9)	5.1 (5.1)	8.9 (8.9)	M^+, M^+-NCH$_3$, (M^+-NCH$_3$)-SO$_2$	8.0 br (NH), 7.7 (s, Ph), 7.4-7.2 br (m, fused ring aromatics), 4.4 (m, CHPh), 3.3 br (m, CH$_2$), 2.8 (s, CH$_3$).
12f	25	220-222	59.8(b) (60.2)	5.3 (5.6)	7.9 (8.3)	M^+, M^+-SO$_2$, (M^+-SO$_2$)-Et, M^+-CH$_2$NHCHO	8.0-7.5 (m, fused ring aromatics), 7.35 (s, Ph), 5.0 br (s, CHPh), 3.5 br (m, ring CH$_2$), 2.8 br (m, ethyl CH$_2$), 0.5 br (m, ethyl CH$_3$).
12c	68(c)	180-182(c)	61.7 (61.8)	5.5 (5.5)	8.3 (8.5)	M^+, M^+-SO$_2$	7.8 (m, fused ring aromatics), 7.38 (s, Ph), 5.2 (d, J (H(c)-H(a)) = 7 Hz, H(a): see fig. 1), 3.9 (dd, J (H(b)-H(c)) = 16 Hz, J (H(a)-H(c)) = 7 Hz, H(c)), 3.6 (d, J (H(c)-H(b)) = 16 Hz, H(b)), 3.0 (s, CONCH$_3$), 2.1 (s, SO$_2$NCH$_3$).
12d, 6d, 12b	\{ see experimental section \}						

(a) After recrystallization from ethanol. (b) Slightly hygroscopic fits for ½H$_2$O. (c) Recrystallized from ethyl acetate-light petroleum.

cm^{-1}; compounds 7a-d and 11, an intense band at 1660 cm^{-1} (protonated) or 1670 cm^{-1} (unprotonated) and compounds 12a-h, a sometimes broadened, but always intense absorption at 1660-1640 cm^{-1}. 2-Methylethanolamine, 1-phenylethanolamine, 2-phenylethanolamine, 3-aminopropan-1-ol and 5-aminopentan-1-ol were obtained from Aldrich Chemical Co. Ltd., Gillingham, Dorset, England and 2-aminobenzylalcohol from Fluka AG Buchs., Switzerland. These amines were used as purchased.

Preparation of the Hydroxyalkyl Compounds (5a-g): General Comments.

A solution of the appropriate amine (0.05 mole) in toluene (~50 ml.) was added to a mixture of 3-chloro-ψ-saccharin (0.05 mole) and triethylamine (0.05 mole) in toluene (~ 300 ml.) and the mixture stirred at room temperature for 4 hours. The liquors were decanted, and the oily deposit washed with water to give the crude product, which was then crystallised (see Table I).

Reaction of the Hydroxyalkyl Compounds (5a,b,d,f,g,r) and (10a) with Thionyl Chloride: General Comments.

The alcohols were dissolved in thionyl chloride (1 g. per 1 ml.) and after the initial exotherm the solution was refluxed for 10 minutes. The excess thionyl chloride was removed under vacuum and the crude residue crystallised (see Table II).

Preparation of the Mesyloxyalkyl Compound (5a-e) and (10a): General Comments.

The appropriate alcohol (0.025 mole) was added to a solution of phosphorus pentoxide (0.1 mole) in methanesulphonic acid (1.0 mole) and the resulting solution stirred at room temperature for 2 hours. The solution was then added dropwise to ice-water maintaining the temperature below 25°. The resultant crude product was collected and washed with water and then cold ethanol (see Table III).

The Abnormal Reaction of 3-(β-Hydroxy-β-phenethylamino)benzo-[d]isothiazole 1,1-Dioxide (5d) with a mixture of Methanesulfonic Acid-Phosphorus Pentoxide.

The alcohol (5d) (17.5 g., 0.058 mole) was added in one portion to a solution of phosphorus pentoxide (32.6 g., 0.23 mole) in methanesulphonic acid (220 g., 2.3 moles) and the resulting solution stirred at room temperature for 2 hours. The solution was then added to water (400 ml.) maintaining the temperature below 25°. The pale yellow precipitate of 3-styryl-aminobenzo[d]isothiazole 1,1-dioxide (9) was collected, washed with water and recrystallised from ethanol-water (1:1) (1.8 g., 8%), m.p. 270°; ^{1}H nmr: δ 8.35, 7.95 and 7.4(m's, aromatics), 7.58 (d, J = 14 Hz, amidine CH) and 6.72 (d, J = 14 Hz, CHPh); ms: m/e 284 (M$^+$), 220 (M$^+$ -SO$_2$), 194 (M$^+$ -CHPh) and 181 (M$^+$ -CHCHPh).

Anal. Calcd. for C$_{15}$H$_{12}$O$_2$N$_2$S: C, 63.4; H, 4.2; N, 9.9. Found: C, 63.4; H, 4.4; N, 9.2.

Upon standing the above aqueous liquors over a chloroform layer for 12 hours, a precipitate of the N-substituted saccharin (6d) was obtained (as its methanesulfonate salt) which was collected, washed with water and air dried (16.4 g., 71%), m.p. 224° (unchanged upon recrystallization from ethanol); ^{1}H nmr: δ 8.25 (m, fused ring aromatics and NH$_2$), 7.45 (m, Ph), 5.5 (dd, J = 10 Hz and 4 Hz, CHPh), 4.05 and 3.65 (m's, CH$_2$'s: the non-equivalence of the two CH$_2$ protons is probably due to hydrogen bonding of the adjacent NH$_2$ with the saccharin carbonyl) and 2.32(s,CH$_3$ anion); ms: m/e 272.0361 (M$^+$ -CH$_2$NH$_2$, requires 272.0381), 209.0807 (272-SO$_2$, requires 209.0840) and 180.0802 (209-HCO, requires 180.0813).

Anal. Calcd. for $C_{15}H_{14}O_3N_2 \cdot CH_3SO_3H$: C, 48.2; H, 4.5; N, 7.0. Found: C, 48.3; H, 4.6; N, 6.9.

Treatment of the Chloroalkyl or Mesyloxyalkyl Compounds (5h-l,n) and (10b,c) with Dilute Alkali: General Comments.

A suspension or solution of the appropriate chloride or mesyloxy compound in 2N aqueous sodium hydroxide (2 equivalents) was rapidly heated with a bunsen burner to a given temperature for a given time (see Table IV). The solution was then rapidly cooled and any precipitated imidazo derivative filtered, washed with water and recrystallized. The liquors were then acidified with an excess of concentrated hydrochloric acid, heated at 80° for 3 minutes and cooled. After freezing, any N-substituted saccharin derivative formed was filtered, washed with ethanol and recrystallized (see Table IV).

In the case of the N-substituted saccharin (6a), two alternative syntheses were possible. Warming a solution of either the imidazo compound (7a) or the thiadiazocine (12f) with concentrated hydrochloric acid at 80° for 5 minutes followed by cooling gave the saccharin (6a) ($\sim$50% in each case), identified by comparison with an authentic sample.

Preparation of the Benzo[g][1,2,5]thiadiazocines (12a,d,f,h) from the N-Substituted Saccharins (6): General Comments.

A solution of the appropriate saccharin (6d,c,a or e) in 2N aqueous sodium hydroxide (2.2 equivalents) was warmed as described in Table V. Upon cooling, the solution was acidified with 2N hydrochloric acid and the product collected and washed with water (see Table V).

Preparation of the 2-Methylbenzo[g][1,2,5]thiadiazocines (12g, b,e and i).

Method a.

Dimethyl sulphate (2.7 g., 0.027 mole) was added in two portions to a solution of the N-substituted saccharin (6a) (0.6 g., 0.003 mole) in 2N sodium hydroxide (10 ml., 0.02 mole) at 60° and the resulting solution maintained at 60° for 0.5 minute. Upon cooling, the crystalline product was collected and washed with water (see Table V). The N-ethyl thiadiazocine (12i) was prepared as above from the saccharin (6d) except that diethyl sulphate was used in place of dimethyl sulphate.

Method b.

A solution of the thiadiazocine (12a) (50 mg.) in 2N sodium hydroxide (6 ml.) was added to an excess of methyl iodide (6 ml.) in ethanol (3 ml.) and the two phase system stirred at room temperature for 3 days. The mixture was evaporated *in vacuo*, and the resultant solid washed successively with 2N sodium hydroxide, saturated aqueous sodium thiosulphate and water. The remaining solid was crystallized from ethanol to give a low yield of the methylthiadiazocine (12b), identified by comparison with the previous sample (Method a).

2,5-Dimethyl-6-oxo-3-phenyl-3,4,5,6-tetrahydro-2H-benzo[g]-[1,2,5]thiadiazocine 1,1-Dioxide (12c).

The thiadiazocine (12b) (1.2 g., 0.0038 mole) was added to a suspension of sodium hydride (80% in oil, 0.69 g., 0.023 mole) in dry DMF (20 ml.) and the mixture stirred at room temperature for 15 minutes. Methyl iodide (0.7 ml., 0.0114 mole) was then added and the stirring continued for a further 1 hour when the mixture was added dropwise to water (50 ml.). The crude product (12c) was collected and washed with water and then light petroleum, (see Table V; recrystallization of the crude product did not affect its m.p.).

2-(2,3-Epoxypropyl)-6-oxo-3-phenyl-3,4,5,6-tetrahydro-2H-benzo-[g][1,2,5]thiadiazocine 1,1-Dioxide (13a).

(a) From the N-Substituted Saccharin (6d).

Epichlorohydrin (2.34 ml., 0.03 mole) was added to a solution of 6d (3.0 g., 0.0075 mole) in aqueous sodium hydroxide (0.9 g., 0.0225 mole in 25 ml.) and the mixture stirred at room temperature for 4 hours. The product was collected and washed with water (1.8 g., 70%), m.p. 188-190°; ^{1}H nmr (DMSO-d_6 + deuteriochloroform): δ 8.1-7.6 (m, fused ring aromatics), 7.4 (s, Ph), 5.2 br (m, C-3 H), 3.8 br and 3.0 (m's CH and CH_2's); ms: m/e 358 (M$^+$), 294 (M$^+$-SO$_2$).

Anal. Calcd. for $C_{18}H_{18}O_4N_2S \cdot \frac{1}{2}H_2O$: C, 58.9; H, 5.1; N, 7.6. Found: C, 59.2; H, 5.1; N, 7.5.

(b) From the Parent Thiadiazocine (12a).

The procedure was as above except that the saccharin (6d) was replaced by the thiadiazocine (12a) and only 2 equivalents of sodium hydroxide used, (yield 62%, product identical to that described above).

Reaction of 2-(2,3-Epoxypropyl)-6-oxo-3-phenyl-3,4,5,6-tetrahydro[2H]benzo[g][1,2,5]thiadiazocine 1,1-Dioxide (13a) with Amines.

(a) With Isopropylamine.

A solution of the above epoxide (13a) (1.1 g., 0.003 mole) in a mixture of isopropylamine (8 ml.) and water (10 ml.) was refluxed for 1 hour. The residue formed upon evaporation *in vacuo* was dissolved in 2N hydrochloric acid (10 ml.) and the aqueous solution extracted with chloroform. The aqueous phase was poured onto a mixture of ice and 18N sodium hydroxide and the resultant gummy precipitate extracted into ethyl acetate (2 x 25 ml.). Evaporation of the combined ethyl acetate extracts gave an oil which was crystallised from ethyl acetate-light petroleum (1:1) to give 2-(2-hydroxy-3-isopropylaminopropyl)-6-oxo-3-phenyl-3,4,5,6-tetrahydro[2H]benzo[g][1,2,5]thiadiazocine 1,1-dioxide (13b) (0.3 g., 23%), m.p. 106-108° dec.; ^{1}H nmr: poorly resolved spectrum but aromatic (δ $\sim$7.5) to isopropyl (δ $\sim$0.8) ratio as expected; ms: m/e 416 (M$^+$-1), 402 (M$^+$-CH$_3$), 358 (M$^+$-NHPr^i), 302 (M$^+$-aminopropanol sidechain), 238 (302-SO$_2$).

Anal. Calcd. for $C_{21}H_{27}O_4N_3S$: C, 60.4; H, 6.5; N, 10.1. Found: C, 59.9; H, 6.5; N, 9.8.

(b) With Morpholine.

A solution of the epoxide (13a) (7.9 g., 0.022 mole) and morpholine (7.8 g., 0.088 mole) in 1-propanol (150 ml.) was refluxed for 18 hours. The reaction was processed as above. The product, 2-(2-hydroxy-3-morpholinopropyl)-6-oxo-3-phenyl-3,4,5,6-tetrahydro[2H]benzo[g][1,2,5]thiadiazocine 1,1-dioxide (13c) was precipitated from 18N sodium hydroxide, collected, washed with water and recrystallized from ethanol (4.3 g., 44%), m.p. 154°; ^{1}H nmr: δ 8.0-7.3 (m, aromatics and CONH), 4.8 br (m, C-3H), 4.0-2.5 br (m, remaining protons apart from -:), 2.2 br (m, CH$_2$N's); ms: m/e 445 (M$^+$), 401 (M$^+$-CH$_2$CH$_2$O), 381 (M$^+$-SO$_2$).

Anal. Calcd. for $C_{22}H_{27}O_5N_3S$: C, 59.25; H, 6.1; N, 9.2. Found: C, 59.3; H, 6.2; N, 9.2.

Treatment of 2,3-Dihydroimidazo[1,2-b][1,2]benzoisothiazole 5,5-Dioxide (7a) with Sodium Hydroxide.

A solution of 7a (0.3 g., 0.0014 mole) in 2N sodium hydroxide (8 ml.) was refluxed for 3 minutes, acidified with 11N hydrochloric acid and concentrated *in vacuo* to $\sim$1 ml. After cooling, the product, 2-(2-imidazolinyl)phenylsulphonic acid (8) was col-

lected and washed with ice-cold water (0.5 ml.) (0.25 g., 76%), m.p. 323-325°; ^{1}H nmr: (60 MHz) 10.5 (s, NH), 7.9-7.6 (m, aromatics), 3.95(s, CH_2CH_2); ms: m/e 226 (M^+), 208 (M^+-H_2O), 145 (M^+-SO_3H).

Anal. Calcd. for $C_9H_{10}O_3N_2S$: C, 47.8; H, 4.4; N, 12.4. Found: C, 47.9; H, 4.5; N, 12.2.

3-(2-Piperidinomethylanilino)benzisothiazole 1,1-Dioxide (10d).

A solution of the mesyloxy compound (10c) (0.92 g., 0.0025 mole) and piperidine (2.2 g., 0.025 mole) in ethanol (10 ml.) was refluxed for 4 hours when the crystalline product was filtered and recrystallized from ethanol (0.25 g., 28%), m.p. 238-240°; ^{1}H nmr (DMSO-d_6 + trifluoroacetic acid): δ 9.2 br (m, NH), 8.4, 7.9 and 7.55 (m's, aromatics), 4.4 (s, CH_2), 3.5-2.8 (m, 4H, CH_2NCH_2) and 1.8 [m, 6H, -$(CH_2)_3$-]; ms: m/e 355 (M^+), 291 (M^+-SO_2), 271 (M^+-piperidine), 207 (291-piperidine, base peak).

Anal. Calcd. for $C_{19}H_{21}O_2N_3S$: C, 64.2; H, 5.9; N, 11.8. Found: C, 64.0; H, 5.9; N, 11.7.

Acknowledgement.

REFERENCES AND NOTES

(1) To whom all correspondence should be addressed.

(2) H. Hettler, in "Advances in Heterocyclic Chemistry", Vol. 15, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1973, p. 234.

(3) E. Stephen and H. Stephen, *J. Chem. Soc.*, 490 (1957).

(4) H. Hettler and H. Neygenfund, *Chem. Ber.*, 103, 1397 (1970).

(5) Japanese Patent 72 01926; *Chem. Abstr.*, 76, P153734 (1972).

(6) H. Hettler, *Z. Anal. Chem.*, 220, 9 (1966).

(7) F. Hein and F. Meier, *Z. Anorg. Allg. Chem.*, 376, 296 (1970); *Chem. Abstr.*, 73, 87296 (1970).

(8) H. E. Glynn and W. H. Linnell, *Q. J. Pharm. Pharmacol.*, 5, 480 (1932).

(9) P. E. Eaton, G. R. Carlson and J. T. Lee, *J. Org. Chem.*, 38, 4071 (1973).

(10) N. C. Rose, *J. Heterocyclic Chem.*, 6, 745 (1969).

(11) G. I. Glover, R. B. Smith and H. Rapoport, *J. Am. Chem. Soc.*, 87, 2003 (1965).

(12) von K. Stich and H. G. Leeman, *Helv. Chim. Acta*, 46, 1151 (1963).

(13) J. S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, 79, 846 (1957).