DIHYDROIMIDAZOBENZOTHIADIAZINE DIOXIDES **

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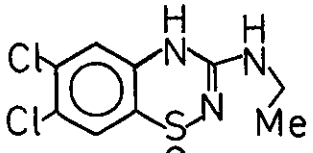
Reductive cyclization of 2-methylthio-1-(2-nitrobenzenesulfonyl)-4,5-dihydroimidazolides gave a series of 1H-2,3-dihydroimidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides, three of which were isomerized by potassium iodide to 3H-1,2-dihydroimidazo[2,1-c][1,2,4]benzothiadiazine 5,5-dioxides.

A variety of heteropolycyclic compounds whose structures embody a guanidine group has been reported to lower blood pressure;[1] among these are 3-alkylamino[1,2,4]benzothiadiazine 1,1-dioxides (e.g.,1) and tetrahydroimidazo[2,1-b]quinazolines (e.g., 2).[2,3]



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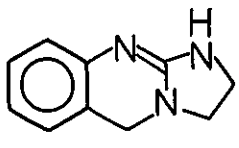

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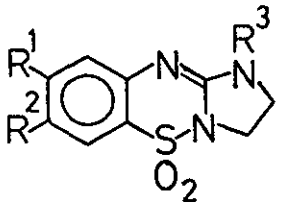
** Dedicated to Professor R.B. Woodward for the sixtieth anniversary of his birthday.

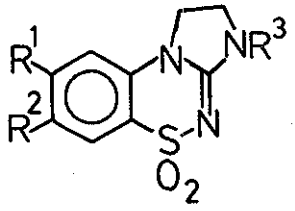
Prompted by an interest in hypertensive therapy, we have prepared two series (Tables 1 and 2) of compounds in one of which the sulfonyl group of the former (1) is embedded in the tricyclic array of the latter (2).

Table 1. 1H-2,3-Dihydroimidazo[1,2-b][1,2,4]benzothiadiazine 5,5-Dioxides.[4]



No.	Substituents			Mp (°C)
	R^1	R^2	R^3	
3	H	H	H	256-7
4	H_2N	H	H	278-9
5	MeO	H	H	313-6
6	MeO	MeO	H	290-1
7	H	NO_2	H	304-7
8	Cl	Cl	H	310-3
9	H	H	Me	134-6

Table 2. 3H-1,2-Dihydroimidazo[2,1-c][1,2,4]benzothiadiazine 5,5-Dioxides.[4]

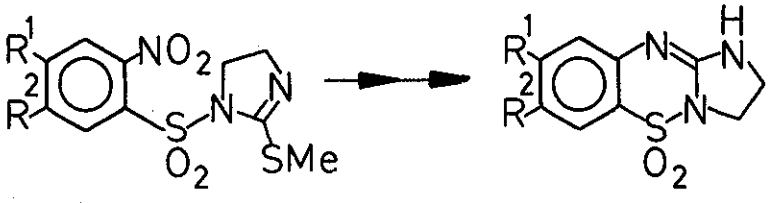


No.	Substituents			Mp (°C)
	R^1	R^2	R^3	
10	H	H	H	342-9
11	H	H	Me	297-8
12	Cl	Cl	Ac	320-5
13	H	H	Ac	300-5

The availability[5] and the structures of 2-nitrobenzenesulfonyl chlorides suggested combination of them with 2-methylthio-2-imidazoline, reduction of the nitro group of the resulting nitrobenzenesulfonyl-dihydroimidazolides, and cyclization to the

tricyclic compounds by elimination of methanethiol from the expected aminobenzenesulfonyl-dihydroimidazolides. Certain nitrobenzenesulfonyl-dihydroimidazolides were prepared, and, as expected, underwent reductive cyclization ($SnCl_2$, HCl;[6] HOAc, MeOH).

Table 3. Preparation of 1H-2,3-Dihydroimidazo-[1,2-b][1,2,4]benzothiadiazine 5,5-Dioxides.

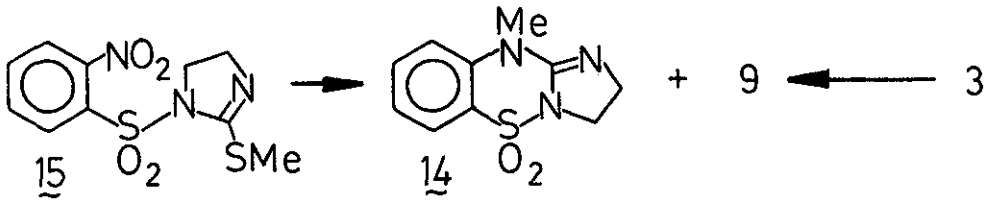


Starting Material [4]			Product	Yield (%)
R^1	R^2	Mp (°C)		
H	H	185-6	3	92
NO_2	H	168-9	4	52
MeO	H	110-3	5	83
MeO	MeO	171-2	6	71

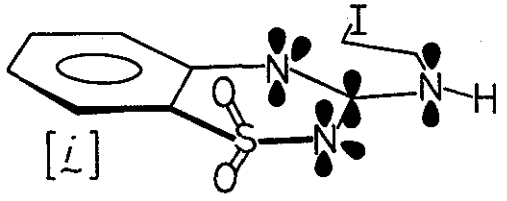
Reactions of methylthioimidazoline with 2-amino-5-nitrobenzenesulfonyl chloride, [7] and with 2-amino-4,5-dichlorobenzenesulfonyl chloride, [8] gave the corresponding aminobenzenesulfonyl-dihydroimidazolides. [9] Methanolic acetic acid converted these to 7 (59%) and 8 (74%), respectively.

Although compounds 3-8 behaved (mp, tlc, nmr) as single substances, they may be tautomeric, and therefore both N-methyl isomers of 3 were prepared for comparison. Methylation (NaH, DMF,

MeI) of 3 gave 60% of 9 and 14, mp 132-3°, [4] in a ratio of 20:1. Both isomers (9, 3%; 14, 1%) could also be obtained by treatment of 15 with trimethyl phosphite. Reaction of the anion of 3 and trimethyl phosphate, formed by initial deoxygenation ($ArNO_2$ → ArNO), may account for the observed methylations. [10]

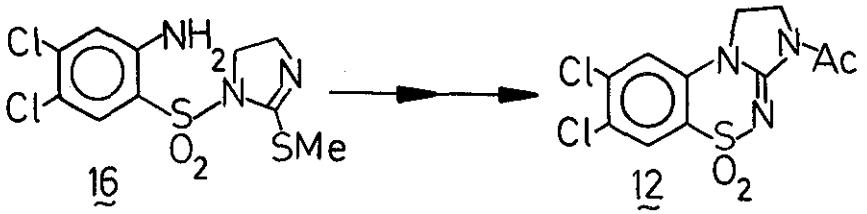


Inspection of the structure of 3 suggested that, if the bond between C-3 and N-4 could be broken by a nucleophile, re-closure of the ambident anion [i] might yield the isomer 10. When 3 was heated with potassium iodide in hexamethylphosphoric triamide (HMPA) at 200°, 10 was obtained in a yield of 86%. To confirm the structural assignments, 10 was methylated (NaH, DMF, MeI) to 11 (88%), and 9 was rearranged (75%) with iodide (HMPA, 200°) to the same (tlc, ir, nmr) product (11).



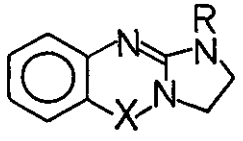
Cyclization (Ac_2O, Py, $CHCl_3$) of crude 2-methylthio-1-(2-amino-4,5-dichlorobenzenesulfonyl)-4,5-dihydroimidazolide (16) [9] gave (73%) an N-acetyldihydroimidazo[1,2-b][1,2,4]benzothiadiazine dioxide, mp 221-4°, [4,11] which was isomerized with iodide in dimethylacetamide at 166° to 12 (88%). For comparison, 10 was

acetylated (Ac_2O, Py) to 13 (86%).

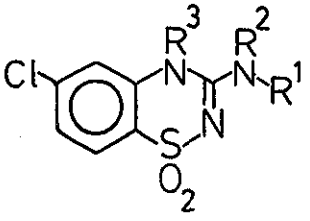


16 12

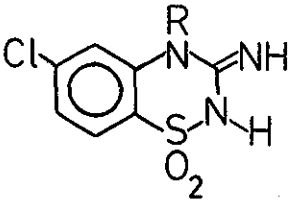
The assignments of structures to 3-9 and 14 are based on comparisons of their uv spectra and of their nmr spectra with those of model compounds, 17-20. [3] The similarities of the uv spectra and chemical shifts of the C-2 and C-3 protons imply that, in solution, 3 [13] and 9 [14] are structurally alike. The similar chemical shifts of 14 [15] and 18, which (18) was prepared unambiguously, [3] show they are related as illustrated. The downfield shift ($\nabla\delta$ = +0.54ppm) of the N-methyl group of 14 contrasted to that of 9 allows assignment of their structures and those of 3-8 as shown. Deshielding of a nearby methyl group, planar with a benzene ring, can also be observed in 20 contrasted to 19. [3]



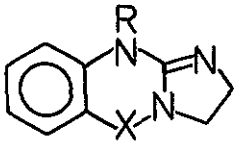
17; R=H, X=CO
19; R=Me, X=CH_2



No.	R^1	R^2	R^3
21	H	Me	Me
22	Me	Me	Me
23	Ac	Me	Me
24	Ac	Ph	H
25	Ac	Ph	Me



26, R=H
27, R=Me



18; R=Me, X=CO
20; R=Me, X=CH_2

The structures of 10-13 [16] were established by comparisons of their uv spectra with those of models 21-23. [17] The results of methylation of 26 (→ 27, 21, and 22), and of methylation of 24 (→ 25), suggest that alkylation at sulfonyl-bound nitrogen is disfavored in such systems; in this sense, these results precedent the outcomes of methylation of 10 and of the rearrangements observed in the present work. [17,18]

ACKNOWLEDGEMENT

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9 These intermediates were not characterized, but were cyclized without purification.
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11 Because of a lack of unequivocal models, [12] the structure of this derivative could not be assigned by ordinary spectral measurements.
12 The N-1 acetyl structure of the product of acetylation of 1H-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-5-one may be correct, but its assignment resulted from misinterpretation of a differential chemical shift. [3] The $\nabla\delta$-value of 0.4ppm ($CDCl_3$), attributed to anisotropy of the acetyl carbonyl, [3] may be calculated from the data of Ref. 3 on the premiss of additivity of substituent effects.
13 λ_{max} (EtOH) 265 (4.25), 306 (3.74)nm; δ (DMSO) 3.62 (m, $2H_2$), 4.08 (m, $2H_3$)ppm.
14 λ_{max} (EtOH) 270 (4.43), 307 (3.94)nm; δ (DMSO) 2.95 (s, NCH_3), 3.59 (m, $2H_2$), 4.02 (m, $2H_3$); ($CDCl_3$) 2.99, 3.48, 4.02ppm.
15 λ_{max} (EtOH) 260 (4.36), 301 (3.57)nm; δ (DMSO) 3.52 (s, NCH_3), 3.88 (s, $2H_2$ and $2H_3$); ($CDCl_3$) 3.53, 3.98 (s, $2H_2$ and $2H_3$)ppm.
16 λ_{max} (MeOH) :: 10 : 250 (4.09), 290 (3.28); 11 : 253 (4.17), 292 (3.28); 12 : 272 (4.08); 13 : 264 (3.16)nm.
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18 Compounds 3-14 were devoid of hypotensive activity.

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