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New Compounds: Synthesis of 3,4,5-Trimethoxybenzenesulfonamides

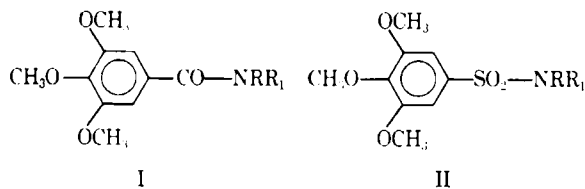## GIORGIO PIFFERI[▲] and RICCARDO MONGUZZI

Abstract ☐ Some new 3,4,5-trimethoxybenzenesulfonamides were synthesized for biological screening. The intermediate 3,4,5-trimethoxybenzenesulfonic acid was unequivocally prepared from 3,4,5-trimethoxyaniline according to the procedure of Meerwein.

Keyphrases ☐ 3,4,5-Trimethoxybenzenesulfonamides—synthesized and tested for CNS and cardiovascular effects ☐ CNS activity—synthesis and screening of 3,4,5-trimethoxybenzenesulfonamides ☐ Cardiovascular effects—synthesis and screening of 3,4,5-trimethoxybenzenesulfonamides

In connection with pharmacological research on new heterocyclic analogs of 3,4,5-trimethoxybenzamide (I) (1), it was interesting to synthesize a series of 3,4,5-trimethoxybenzenesulfonamides (II) because of their steric and electronic similarity[1].

DISCUSSION

Although numerous derivatives of 3,4,5-trimethoxybenzoic acid are of biological interest (1, 3), the SO_2 analogs (II) are unknown in the literature. The present authors ascertained that the structure of the sulfonic acid derivative VIIb was incorrectly assigned by Alimchandani (4); in fact, pyrogallol trimethyl ether (III) reacts with sulfuric acid in the experimental conditions reported (4) to give the vicinal isomer IVb. The same product was also prepared (Scheme I) by treating III with chlorosulfonic acid at room temperature and subsequent hydrolysis of the intermediate IVa to 2,3,4-trimethoxybenzenesulfonic acid (IVb). For the unequivocal synthesis of the isomer VIIb, 3,4,5-trimethoxybenzoic acid (V) was converted *via* VIa into the aniline derivative VIb (5); the latter was diazotized and the diazonium salt was decomposed with sulfur dioxide according to the method of Meerwein *et al.* (6) to afford the sulfonyl chloride VIIa. Subsequent hydrolysis gave 3,4,5-trimethoxy-
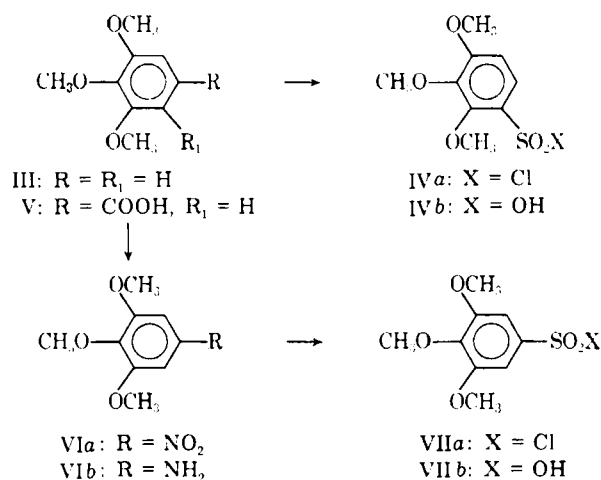
benzenesulfonic acid (VIIb), which was easily distinguished from its isomer IVb by comparison of the NMR coupling constants of the two aromatic protons in the *meta*- and *ortho*-positions, respectively (7).

To prepare the 3,4,5-trimethoxybenzenesulfonamides IIa–IIe (Table I), the sulfonyl chloride VIIa was condensed with the appropriate amine according to experimental Procedures A and B. Isoxazolidine (1), morpholine (8), and heptamethyleneimine (9) were chosen as active moieties of new CNS drugs; isopropylguanidine (10) and ε-aminocaproic acid (11) were chosen as active moieties of new cardiovascular drugs.

Preliminary biological testing of IIa–IIe in the Irwin (12) neuropharmacological mouse profile did not show significant signs of depression at doses up to 300 mg./kg. i.p. The complete results will be published later.

EXPERIMENTAL[²]

2,3,4-Trimethoxybenzenesulfonyl Chloride (IVa)—A solution of 5 g. (29.7 mmoles) of pyrogallol trimethyl ether (III) in 80 ml. of dry

III: R = R_1 = H
V: R = COOH, R_1 = H

IVa: X = Cl
IVb: X = OH

VIa: R = NO_2
VIb: R = NH_2

VIIa: X = Cl
VIIb: X = OH

Scheme I

I   II

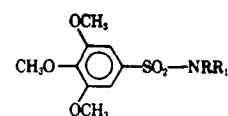[1] Actually, carbonyl and sulfonyl groups may be considered as "nonclassical isosteres" (2).

Table I—3,4,5-Trimethoxybenzenesulfonamides (II)

Com-pound	NRR₁	Method	Melting Point[a]	Yield, %	Spectral Data, cm⁻¹ νSO₂ asym.	νSO₂ sym.	Formula	Analysis, % Calc.	Found
IIa	—N (morpholine-like O ring)	B	112–113°	82	1355	1160	$C_{12}H_{17}NO_6S$	N 4.62 S 10.57	4.39 10.65
IIb	—N O	A	109–110°	83	1340	1160	$C_{13}H_{19}NO_6S$	N 4.41 S 10.10	4.26 10.39
IIc	—NH—C—NH—iso-C₃H₇ (NH)	A	147–149°	25·	1310	1150	$C_{14}H_{21}N_3O_5S$	N 12.68 S 9.68	12.64 10.07
IId	—NH—(CH₂)₅—COOH	B	158–159°	42	1320	1150	$C_{15}H_{23}NO_7S$	N 3.86 S 8.87	3.68 8.73
IIe	—N (ring)	A	108–111°	48	1330	1150	$C_{16}H_{25}NO_5S$	N 4.08 S 9.34	3.88 9.88

[a] From ethanol.

chloroform was treated dropwise at 0° with 11.5 g. (98 mmoles) of chlorosulfonic acid. The reaction mixture was stirred for 30 min. at room temperature and poured into 150 g. of crushed ice. The organic layer was separated and the mother liquor was extracted two times with 30 ml. of chloroform. The combined extracts were washed with water and dried over sodium sulfate, the solvent was removed, and the oily residue was distilled through a Claisen head to yield 1.32 g. of IVa, b.p. 165° (1.5 mm.), which crystallized from hexane to a solid, m.p. 38–39°; IR: 1350 and 1170 (SO₂ asym. and sym.) and 815 (two adjacent aromatic hydrogens) cm.⁻¹.

Anal.—Calc. for $C_9H_{11}ClO_5S$: Cl, 13.30; S, 12.02. Found: Cl, 13.86; S, 11.95.

2,3,4-Trimethoxybenzenesulfonic Acid (IVb)—A solution of 10 g. (59.5 mmoles) of pyrogallol trimethyl ether (III) in 25 ml. of 96% sulfuric acid was stirred at 25–30° for 3 hr. After cooling, water (25 ml.) was added dropwise and the solution was kept overnight in a refrigerator. The white hygroscopic precipitate was filtered and crystallized from ethyl acetate to yield 8.45 g. (57%) of IVb, m.p. 96° [lit. (4) m.p. 95–97°; IR: 3600–2150 (OH), 1190 and 1145 (SO₃ group), and 815–805 (two adjacent aromatic hydrogens) cm.⁻¹; NMR: δ(p.p.m.) 3.90 s and 4.00 s (methyl protons of methoxy groups) and 6.88 d and 7.59 d (two *ortho* aromatic protons: $J = 9.0$ Hz.).

2,3,4-Trimethoxybenzenesulfonic Acid (IVb) from IVa—A stirred suspension of 0.3 g. (1.13 mmoles) of 2,3,4-trimethoxybenzenesulfonyl chloride (IVa) in 9 ml. of water was refluxed until a solution was formed. After concentration *in vacuo*, the residue was crystallized from ethyl acetate to yield 100 mg. (36%) of IVb, identical (by mixed melting point and IR comparison) with the sample described above.

3,4,5-Trimethoxynitrobenzene (VIa)—Compound VIa was prepared from 3,4,5-trimethoxybenzoic acid (V) and 70% nitric acid according to the method of Hughes *et al.* (5), m.p. 96–98° (from ethanol).

3,4,5-Trimethoxyaniline (VIb)—Compound VIb was obtained by catalytic reduction at room temperature of 3,4,5-trimethoxynitrobenzene (VIa) in the presence of 5% palladium-on-charcoal, m.p. 111–112° [lit. (5) m.p. 113–114°].

3,4,5-Trimethoxybenzenesulfonyl Chloride (VIIa)—To 320 ml. of concentrated hydrochloric acid was added, at 70° with stirring, 40 g. (0.218 mole) of 3,4,5-trimethoxyaniline (VIb). The mixture was stirred at the same temperature for 10 min. and, after cooling to 0°, a solution of 15.2 g. (0.22 mole) of sodium nitrite in 30 ml. of water was added dropwise. The solution was then stirred at 0° for 15 min. and added dropwise with caution to a saturated solution of sulfur dioxide in 480 ml. of glacial acetic acid containing 4.8 g. of cuprous chloride. At the end of addition, the mixture was stirred at room temperature for 3 hr., poured into cold water, and extracted four times with 1 l. of dichloromethane. The combined organic extracts were washed with cold water and dried over calcium chloride, and the solvent was evaporated. The solid residue was recrystallized twice from hexane to yield 11.84 g. (20.5%) of VIIa, m.p. 82–85°;

IR: 1370 and 1175 (SO₂ asym. and sym.), and 835 (two *meta* aromatic hydrogens) cm.⁻¹.

Anal.—Calc. for $C_9H_{11}ClO_5S$: C, 40.55; H, 4.16; Cl, 13.30; S, 12.02. Found: C, 40.59; H, 4.29; Cl, 13.46; S, 12.22.

3,4,5-Trimethoxybenzenesulfonic Acid (VIIb)—A stirred suspension of 0.9 g. (3.37 mmoles) of 3,4,5-trimethoxybenzenesulfonyl chloride (VIIa) in 30 ml. of water was refluxed until solution. After evaporation *in vacuo*, the solid residue was crystallized from nitroethane to yield 0.5 g. (60%) of VIIb as a very hygroscopic material, m.p. 147–149°. The mixed melting point with IVb was depressed. IR: 3700–2100 (OH), 1160 and 1130 (SO₃ group), and 835 (two *meta* aromatic hydrogens) cm.⁻¹; NMR: δ(p.p.m.) 3.83 s and 3.95 s (methyl proton of methoxy groups) and 7.20 s (two *meta* aromatic protons).

Anal.—Calc. for $C_9H_{12}O_6S$: C, 43.54; H, 4.87; S, 12.91. Found: C, 42.80; H, 5.21; S, 13.50.

3,4,5-Trimethoxybenzenesulfonamides (II)—*Procedure A*—A solution of 12 mmoles of 3,4,5-trimethoxybenzenesulfonyl chloride (VIIa) in 15 ml. of dichloromethane was added at room temperature to a stirred solution of 27 mmoles of the appropriate base in 80 ml. of the same solvent. The mixture was refluxed for 3 hr., cooled at room temperature, and washed successively with diluted hydrochloric acid, a saturated sodium bicarbonate solution, and water. The organic extracts were dried over sodium sulfate and evaporated *in vacuo*, and the solid residue crystallized (Table I).

Procedure B—A solution of 15 mmoles of 3,4,5-trimethoxybenzenesulfonyl chloride (VIIa) in 15 ml. of dichloromethane was added at room temperature to a stirred solution of 15 mmoles of the appropriate base hydrochloride and 34 mmoles of triethylamine in 80 ml. of the same solvent. The mixture was stirred for 1 hr. at room temperature and refluxed for 3 hr. After cooling, it was washed with diluted hydrochloric acid and water and dried over sodium sulfate. The solvent was evaporated and the residue was crystallized (Table I).

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COMMUNICATIONS

Sulfamate Sweeteners: A Reappraisal

Keyphrases ☐ Sulfamates, alicyclic—hydrolysis rate constants determined from polar and steric parameters, equation ☐ Cyclamates, alicyclic—hydrolysis rate constants determined from polar and steric parameters, equation ☐ Sweeteners, alicyclic sulfamates—hydrolysis rate constants determined from polar and steric parameters, equation

Sir:

There is evidence from feeding experiments that *in vivo* conversion of the nonnutritive sweeteners, the cyclamates [sodium cyclohexylsulfamate (I) and calcium cyclohexylsulfamate (II)] gives cyclohexylamine (1–4), which is considered to be responsible for the induction of tumors (4). These and other experiments (5–7) resulted in a ban since 1970 on the use of cyclamates in foodstuffs, beverages, and pharmaceuticals. No work appears to have been published on the nature of the metabolic conversion of cyclamate to cyclohexylamine. However, it is possible that the ease of metabolism to primary amine may be correlative with the hydrolytic stability of the sulfamate.

We derived a Taft-Pavelich-type equation (Eq. 1) which correlates the hydrolytic rate constants (measured under identical conditions) for cleavage of the nitrogen–sulfur bond with polar (σ^*) and steric (E_s) parameters for a large number of aromatic, aliphatic, and alicyclic sulfamates (8) and is of the form:

$$\log k = 2.35\Sigma\sigma^* - 1.0037\Sigma E_s + 0.6971 \qquad (Eq. 1)$$

Further tests on Eq. 1 indicate that it reproduces log *k* values to within an average of 12%. The *k* values are reproduced to within 26% on average. For Compound I, the *k* value was reproduced with an accuracy of 5%.

By using Eq. 1, it is possible to predict the hydrolytic stability of unsynthesized sulfamates (whose σ^* and E_s values are known). Equation 1 could thus act as a guide to the choice of sulfamates that might be more resistant to *in vivo* conversion to primary amines than are I and

II. Such sulfamates may lack carcinogenic or cocarcinogenic activity because of the possibility of a lower conversion to amine. A second criterion in choosing sulfamates is that they have a comparable degree of sweetness to I and II. Audrieth and Sveda (9) showed that the retention of the sulfamate function, $-NHSO_3^-$, and the presence of a reduced ring (*e.g.*, cyclohexyl) appear to be essential for sweetness in sulfamates. Later results substantiated these findings and extended them to exclude ring substitution in the reduced ring since such compounds tend to be tasteless or to leave a bitter aftertaste (10–12). These criteria for sweetness should be met by Compounds III. In fact, sodium cyclopentylsulfamate (III, *n* = 3)(10), sodium cycloheptylsulfamate (III, *n* = 5), and sodium cyclooctylsulfamate (III, *n* = 6)(11) are extremely sweet.

Equation 1 predicts that the cycloheptyl compound (estimated $\sigma^* = -0.10$, $E_s = -1.10$)[1] will hydrolyze almost 3 times more rapidly than I or II, the cyclopentylsulfamate ($\sigma^* = -0.20$, $E_s = -0.51$) will hydrolyze 2.5 times more slowly, and the unprepared cyclobutyl (III, *n* = 2) compound (estimated $\sigma^* = -0.28$, $E_s = -0.06$) will hydrolyze 11 times more slowly. Compound IV, *N*-(α-cyclohexylmethyl)sulfamate ($\sigma^* = -0.06$, $E_s = -0.98$) is predicted to hydrolyze 2.5 times more rapidly than I or II. Cyclopropylsulfamate (III, *n* = 1) was prepared (10), but its sweetness was not assessed. Polar and steric parameters are not available for this compound or for cyclooctylsulfamate.

These observations suggest that an examination of the percent metabolism to primary amine and the

III   IV

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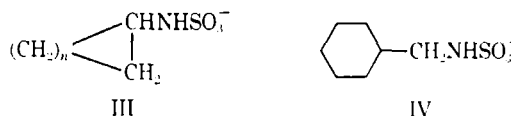
[1] Polar and steric parameters were taken from K. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1966, pp. 414, 415. The σ^* values for the cycloheptylsulfamate and cyclobutylsulfamate were estimated from an examination of the values for cyclohexylsulfamate (−0.15), cyclopentylsulfamate (−0.20), and *tert*-butylsulfamate (−0.3).