204°, identical (PMR, mixed melting point) to the material prepared previously by the Clemmensen route.

CONCLUSIONS

Clemmensen reduction of Mannich bases leads to a variety of products, but the reaction can still be used to prepare members of the arylpropylamine series. Catalytic hydrogenation of the low boiling fraction distilled from the crude product ensures complete saturation of the side chain and the isolation of pure aminoalkane (III). These derivatives can then be converted to phenylpropyltrimethylammonium derivatives (I, n = 3), which have potential nicotinic properties (1).

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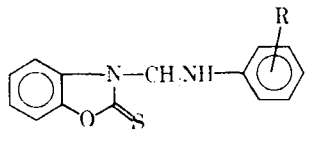
Potential Biologically Active Agents V: Synthesis and Pharmacological Screening of Substituted 3-Aminomethylbenzoxazolin-2-thiones

RAJENDRA S. VARMA

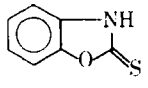
Abstract □ A series of substituted 3-aminomethylbenzoxazolin-2-thiones was synthesized and evaluated for antibacterial activity.

Keyphrases □ 3-Aminomethylbenzoxazolin-2-thiones—synthesized and screened as potential antibacterial agents □ Antibacterial agents, potential—synthesis and screening of 3-aminomethylbenzoxazolin-2-thiones □ Benzoxazolin-2-thiones, substituted—synthesized and screened as potential antibacterial agents

Benzazoles have been reported to exhibit diverse biological properties. The 2- and 3-substituted benzoxazolinone analogs have shown anticonvulsant (1) and antimicrobial (2, 3) activities. Antitubercular (4), antispasmodic (5), and antibacterial (6–9) activities have been observed for benzothiazolin-2-thione and 2-alkylmercaptobenzothiazoles. Substituted 3-aminomethylbenzothiazolin-2-thiones have displayed antimicrobial (10, 11) activity. Further antimicrobial (12, 13), diuretic (14), cancerostatic (15), antitubercular (15), hypoglycemic (16), parasympatholytic (17), and herbicidal (18) properties have been associated with benzoxazolin-2-thiones. In view of these reports, it was of interest to synthesize substituted 3-aminomethylbenzoxazolin-2-thiones (I) for biological screening. The synthesis of I was achieved by condensing benzoxazolin-2-thione (II), formaldehyde, and an amine.



I



II

BIOLOGICAL DATA

The compounds listed in Table I were screened for their inhibitory effect against *Escherichia coli* and *Staphylococcus aureus*[1] by the agar diffusion technique (19). Four compounds (I, VII, XII, and

[1] Bacterial cultures maintained at Central Drug Research Institute, Lucknow, India, were used.

Table I—Substituted 3-Aminomethylbenzoxazolin-2-thiones (I)

Compound	R	Melting Point	Molecular Formula	Analysis, % Calc.	Found	Yield, %
I[a]	4-COOH	226–228°	$C_{15}H_{12}N_2O_3S$	C 59.99	59.50	65
				H 4.02	4.30	
II[b]	4-$COOCH_3$	205–206°	$C_{16}H_{14}N_2O_3S$	C 61.13	61.50	60
				H 4.48	4.70	
				N 8.91	8.54	
III[c]	4-$COOC_2H_5$	176°	$C_{17}H_{16}N_2O_3S$	C 62.18	62.00	70
				H 4.91	5.08	
				N 8.51	8.38	
IV[d]	3-COOH	213°	$C_{15}H_{12}N_2O_3S$	C 59.99	59.70	65
				H 4.02	4.40	
				N 9.33	9.49	
V[b]	3-$COOCH_3$	182°	$C_{16}H_{14}N_2O_3S$	C 61.13	61.40	55
				H 4.48	4.74	
				N 8.91	9.10	
VI[e]	3-$COOC_2H_5$	178°	$C_{17}H_{16}N_2O_3S$	C 62.18	62.25	75
				H 4.91	5.13	
				N 8.51	8.65	
VII[f]	2-COOH	188° dec.	$C_{15}H_{12}N_2O_3S$	C 59.99	60.20	50
				H 4.02	4.38	
				N 9.33	8.89	
VIII[b]	2-$COOCH_3$	145°	$C_{16}H_{14}N_2O_3S$	N 8.91	8.30	60
IX[b]	2-$COOC_2H_5$	128–129°	$C_{17}H_{16}N_2O_3S$	C 62.18	62.80	55
				H 4.91	5.51	
X[g]	2-Thiazolyl	136–137°	$C_{11}H_9N_3OS_2$	C 50.17	50.65	45
				H 3.44	3.85	
XI[b]	4-Phenyl	186–188°	$C_{20}H_{16}N_2OS$	C 72.26	72.60	80
				H 4.85	5.15	
				N 8.42	8.01	
XII[b]	2-Phenyl	145–146°	$C_{20}H_{16}N_2OS$	N 8.42	8.04	75
XIII[h]	4-I; 2-COOH	165–166°	$C_{15}H_{11}IN_2O_3S$	C 42.27	42.45	70
				H 2.60	2.90	
				N 6.57	6.15	
XIV[i]	4-Br; 2-COOH	195–196°	$C_{15}H_{11}BrN_2O_3S$	C 47.51	47.30	60
				H 2.92	3.22	
				N 7.38	7.19	
XV[b]	2-OCH_2CH_3	130°	$C_{16}H_{16}N_2O_2S$	C 63.98	64.20	80
				H 5.37	5.59	
				N 9.33	9.25	
XVI[b]	4-COO-*n*-C_4H_9	148°	$C_{19}H_{20}N_2O_3S$	C 64.03	63.82	65
				H 5.65	5.82	
				N 7.86	7.49	
XVII[b]	4-COO-*n*-C_3H_7	178°	$C_{18}H_{18}N_2O_3S$	C 63.14	63.10	70
				H 5.29	5.52	
				N 8.18	7.78	

[a] Recrystallized from ethanol. IR (μ): 2.95 (NH), 3.4 (OH, broad), and 5.92 (C=O). [b] Recrystallized from ethanol. [c] Recrystallized from ethanol. IR (μ): 2.95 (NH) and 5.92 (C=O). [d] Recrystallized from ethanol. IR (μ): 2.95 (NH), 3.4 (OH, broad), and 5.90 (C=O). [e] Recrystallized from ethanol. IR (μ): 2.95 (NH) and 5.85 (C=O). [f] Recrystallized from acetone. [g] Recrystallized from methanol. The compound is 3-(*N*-2-thiazolylaminomethyl)-benzoxazolin-2-thione. IR (μ): 3.12 (NH). [h] Recrystallized from methyl ethyl ketone. IR (μ): 2.97 (NH), 3.3 (OH, broad), and 5.97 (C=O). [i] Recrystallized from ethyl acetate.

XIII) showed inhibition against both organisms. Compounds III, V, VI, VIII, X, and XV were only effective against *E. coli*.

EXPERIMENTAL[2]

Benzoxazolin-2-thione was prepared by a published procedure (20). Esters of aminobenzoic acids were obtained by refluxing a mixture of appropriate alcohol, thionyl chloride, and the aminobenzoic acid for several hours.

The synthesis of the substituted 3-aminomethylbenzoxazolin-2-thiones (I) was conducted as follows. Compound II (1.51 g., 0.01 mole) and the amino compound (0.01 mole) were suspended in 20 ml. of boiling ethanol. To this suspension, 2 ml. of 37% formalin was added. The reaction mixture was warmed on a steam bath for 5 min. and then set aside at room temperature overnight. The solid product thus deposited was filtered, washed with petroleum ether (60–80°), and recrystallized from a suitable solvent.

The analyses, melting points, and other pertinent data are recorded in Table I.

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

GIORGIO PIFFERI▲ and RICCARDO MONGUZZI

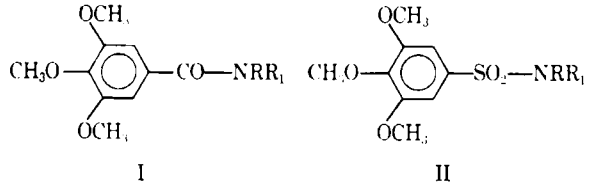
Abstract □ Some new 3,4,5-trimethoxybenzenesulfonamides were synthesized for biological screening. The intermediate 3,4,5-trimethoxybenzenesulfonic acid was unequivocally prepared from 3,4,5-trimethoxyaniline according to the procedure of Meerwein.

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 VII*b* 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 IV*b*. The same product was also prepared (Scheme I) by treating III with chlorosulfonic acid at room temperature and subsequent hydrolysis of the intermediate IV*a* to 2,3,4-trimethoxybenzenesulfonic acid (IV*b*). For the unequivocal synthesis of the isomer VII*b*, 3,4,5-trimethoxybenzoic acid (V) was converted *via* VI*a* into the aniline derivative VI*b* (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 VII*a*. Subsequent hydrolysis gave 3,4,5-trimethoxybenzenesulfonic acid (VII*b*), which was easily distinguished from its isomer IV*b* by comparison of the NMR coupling constants of the two aromatic protons in the *meta*- and *ortho*-positions, respectively (7).



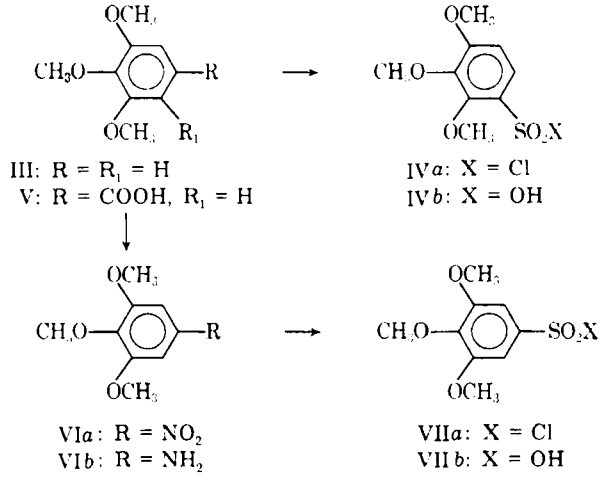
I II

To prepare the 3,4,5-trimethoxybenzenesulfonamides II*a*–II*e* (Table I), the sulfonyl chloride VII*a* 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 II*a*–II*e* 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 (IV*a*)—A solution of 5 g. (29.7 mmoles) of pyrogallol trimethyl ether (III) in 80 ml. of dry



Scheme I

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

[2] All melting points are uncorrected. IR spectra were recorded as mineral oil mulls with a Perkin-Elmer IR 157. A Varian Associates model A-60 NMR spectrometer was used to determine the proton magnetic resonance spectra. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as a standard reference, and D_2O was used as the solvent.