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An unambiguous synthesis of a number of 3-coumaryl phenyl sulfones or sulfoxides have been described which were obtained by the oxidation of the corresponding sulfides with hydrogen peroxide. The sulfides were prepared by the Perkin-Ogialoro reaction of *o*-hydroxyaldehyde with the sodium salt of different *S*-phenyl thioacetic acids. The sulfones did not exhibit any appreciable antituberculous activity in the preliminary screening tests.

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In a previous communication (2) we have described the synthesis of several 4-coumaryl phenyl sulfones, some of which showed fairly good antituberculous activity in the preliminary screening tests. The above sulfones were obtained by the oxidation of 4-coumaryl phenyl sulfides prepared by the condensation of 3-bromocoumarin with

thiophenols in the presence of pyridine. The present paper describes the synthesis of 3-coumaryl phenyl sulfones by an unambiguous route, starting from 3-coumaryl phenyl sulfides. The latter were synthesised in 60-80% yields by the application of the Perkin-Ogialoro reaction on salicylaldehyde and β -resorcyaldehyde, which were condensed

Table I

Compound No.	R ₁	R ₂	R ₃	R ₄	X	M.p. °C	Molecular formula	Analysis			
								Calcd.		Found	
							C	H	C	H	
Ia	H	H	H	H	S	125-126	C ₁₅ H ₁₀ O ₂ S	70.86	3.93	70.53	4.12
Ib	H	H	H	H	SO ₂	214-215 (5)	C ₁₅ H ₁₀ O ₄ S	62.93	3.49	62.76	3.60
IIa	CH ₃	H	H	H	S	116	C ₁₆ H ₁₂ O ₂ S	71.64	4.47	71.66	4.75
IIb	CH ₃	H	H	H	SO ₂	207-208 (5)	C ₁₆ H ₁₂ O ₄ S	64.00	4.00	64.00	4.30
IIIa	H	CH ₃	H	H	S	76-77	C ₁₆ H ₁₂ O ₂ S	71.64	4.47	71.28	4.49
IIIb	H	CH ₃	H	H	SO ₂	181-182	C ₁₆ H ₁₂ O ₄ S	64.00	4.00	64.31	4.21
IVa	H	H	H	OCOCH ₃	S	180	C ₁₇ H ₁₄ O ₄ S	65.38	3.84	65.37	4.06
IVb	H	H	H	OCOCH ₃	SO ₂	235-236	C ₁₇ H ₁₂ O ₆ S	59.30	3.66	59.38	3.46
Va	H	H	H	OH	S	226-228	C ₁₅ H ₁₀ O ₃ S	66.66	3.70	66.54	4.01
Vb	H	H	H	OH	SO ₂	273	C ₁₅ H ₁₀ O ₅ S	59.60	3.31	59.73	3.60
VIa	CH ₃	H	H	OCOCH ₃	S	191-192	C ₁₆ H ₁₄ O ₄ S	66.25	4.29	66.35	4.19
VIb	CH ₃	H	H	OCOCH ₃	SO ₂	233-234 (5)	C ₁₆ H ₁₄ O ₆ S	60.33	3.91	60.55	3.93
VIIa	CH ₃	H	H	OH	S	196-197	C ₁₆ H ₁₄ O ₃ S	67.60	4.22	67.38	4.31
VIIb	CH ₃	H	H	OH	SO ₂	238-239 (5)	C ₁₆ H ₁₂ O ₅ S	60.75	3.79	60.49	4.00
VIIIa	H	H	Cl	H	S	163-164	C ₁₅ H ₉ ClO ₂ S	62.43	3.12	62.08	3.29
VIIIb	H	H	Cl	H	SO ₂	242	C ₁₅ H ₉ ClO ₄ S	56.16	2.81	56.15	2.63
IXa	H	CH ₃	H	OCOCH ₃	S	156-157	C ₁₆ H ₁₄ O ₄ S	66.25	4.29	66.20	4.26
IXb	H	CH ₃	H	OCOCH ₃	SO	205-206	C ₁₆ H ₁₄ O ₅ S	63.15	4.09	63.22	4.24
Xa	H	CH ₃	H	OH	S	207-208	C ₁₆ H ₁₂ O ₃ S	67.60	4.22	67.47	4.45
Xb	H	CH ₃	H	OH	SO	254-255	C ₁₆ H ₁₂ O ₄ S	64.00	4.00	64.11	4.01
XIa	CH ₃	H	Cl	H	S	184	C ₁₆ H ₁₁ ClO ₂ S	63.47	3.63	63.22	3.71
XIb	CH ₃	H	Cl	H	SO	244	C ₁₆ H ₁₁ ClO ₄ S	60.28	3.45	60.00	3.34
XIIa	H	CH ₃	Cl	H	S	131-132	C ₁₆ H ₁₁ ClO ₂ S	63.47	3.63	63.25	3.66
XIIb	H	CH ₃	Cl	H	SO	210-211	C ₁₆ H ₁₁ ClO ₄ S	60.28	3.45	60.48	3.43
XIIIa	H	CH ₃	H	H	S	125-127	C ₂₀ H ₁₄ O ₂ S	75.47	4.40	75.25	4.60
XIIIb	H	CH ₃	H	H	SO	205-206	C ₂₀ H ₁₄ O ₃ S	71.85	4.20	71.85	4.20
XIVa	H	H	H	H	S	179	C ₁₉ H ₁₂ O ₂ S	75.00	4.00	75.08	4.14
XIVb	H	H	H	H	SO ₂	235-236	C ₁₉ H ₁₂ O ₄ S	68.42	3.65	68.26	3.97
XVa	CH ₃	H	H	H	S	162-163	C ₂₀ H ₁₄ O ₂ S	75.47	4.40	75.58	4.82
XVb	CH ₃	H	H	H	SO ₂	253-254	C ₂₀ H ₁₄ O ₄ S	68.57	4.00	68.82	4.26

with the sodium salts of different S-phenyl thioacetic acids to give 3-(phenylthio)-2H-1-benzopyran-2-ones (Ia-IIIa) with the former aldehyde and 7-acetoxy-3-(phenylthio)-2H-1-benzopyran-2-ones (IVa, VIa, IXa) with the latter. The reaction was further extended to 5-chlorosalicylaldehyde affording 6-chloro-3-(phenylthio)-2H-1-benzopyran-2-ones (VIIIa, XIa, XIIa) and 2-hydroxy-1-naphthaldehyde (3) when 2-(phenylthio)-3H-naphtho[2,1-b]pyran-3-ones (XIIIa-XVa) were obtained.

The spectral data of Ia shows ms: m/e 254 (M⁺); uv (methanol): λ max nm (log ϵ), 230 (4.65), 275 (4.01), 335 (4.17); ir (potassium bromide): ν max cm⁻¹ 1720 (C=O, lactone). In the nmr spectrum (carbon tetrachloride), besides a multiplet at δ 7.2 to 7.6 for the aromatic protons, a clear single for one proton was observed at δ 6.8. This was assigned to the C-4 proton, which in coumarin and 7-methoxycoumarin, appears around δ 7.7. The upfield shift in the case of Ia was attributed to the +I effect of the sulfur atom at the 3-position.

Coumaryl phenyl sulfones were prepared in 60-70% yields by oxidising the corresponding sulfides with hydrogen peroxide (30%) in acetic acid at room temperature. A typical sulfone Ib showed uv (methanol): λ max nm (log ϵ) 280 (3.85), 310 (4.29); ir (potassium bromide): ν max cm⁻¹ 1715 (C=O, lactone) and 1320, 1135 (-SO₂). Some of the sulfides (IXa-XIIIa) could be oxidised only to the sulfoxide stage even with an excess of the oxidising agent or with acidified potassium permanganate solution (4). Further oxidation of the sulfoxides (IXb-XIIIb) also failed to occur. The structures of the sulfoxides were evident from their analytical and spectral data. Thus, compounds IXb-XIIIb showed ms: m/e (M⁺) 342, 300, 318-320, 318-320 and 334, respectively. Compound XIb showed ir (potassium bromide): ν max cm⁻¹ 1730 (C=O, lactone) and 1050 of (-SO).

EXPERIMENTAL

The screening for antitubercular activity of the sulfones and sulfoxides were carried out against highly virulent H₃₇Rv strains of *Mycobacterium tuberculosis var. hominis*. The sulfones and sulfoxides showed the tuberculostatic activity in the range of 100-200 $\mu\text{g./cm}^3$ as compared to that of streptomycin taken as 1 and INH as 0.04.

3-Coumaryl Phenyl Sulfides.

General Procedure.

A mixture of *o*-hydroxyaldehyde (0.02 mole) and dry sodium S-phenylthioacetate (0.04 mole) in excess of acetic anhydride (0.15 mole) was refluxed at 170-180° for 6-7 hours. It was then cooled, poured over crushed ice and left overnight when a brownish solid separated, which was filtered, and washed thoroughly with aqueous sodium bicarbonate and water. It was crystallised from acetic acid in all cases except in the case of compound IIIa, which was crystallised from benzene-petroleum ether.

In the case of β -resorcyraldehyde, the 7-acetoxy compounds which were obtained first were hydrolysed by refluxing them with 2:1 alcoholic hydrochloric acid to afford the corresponding 7-hydroxy-3-(phenylthio)-2H-1-benzopyran-2-ones (Va, VIIa, Xa), which crystallised from acetic acid.

Oxidation.

To a coumaryl phenyl sulfide (500 mg.) in glacial acetic acid (10 ml.) was added hydrogen peroxide (6 ml., 30%) with constant shaking and the reaction mixture was kept at room temperature for 48-72 hours when a crystalline solid separated. All the sulfones and sulfoxides were crystallised from acetic acid.

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REFERENCES AND NOTES

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- (2) J. R. Merchant, A. S. Gupta, P. J. Shah and S. S. Shirali, *Chem. Ind.*, **10**, 351 (1979).
- (3) K. C. Pandya and T. A. Vahidy, *Proc. Indian Acad. Sci.*, **6a**, 181 (1937).
- (4) R. W. Bost and J. E. Everett, *J. Am. Chem. Soc.*, **62**, 1752 (1940).
- (5) J. Troger and E. Nolte, *J. Prakt. Chem.*, **103**, 163 (1921); J. Troger and R. Dunkel, *ibid.*, **104**, 311 (1922).