32. *The Sulphonation of Some Derivatives of Eugenol.*

By G. R. Clemo and J. H. Turnbull.

The sulphonation of "dihydroeugenol" and of its acetyl and *O*-methyl derivatives is described. The sulphonic acids obtained have been orientated by synthesis of their methyl ethers from known aminomethyldihydroeugenols.

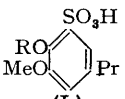
O-Methyleugenol and *O*-acetyleugenol have been shown to yield sultones on sulphonation. The mode of formation of these sultones is discussed and their structure has been established by synthesis.

The sulphonation of "dihydroeugenol" (2-methoxy-4-*n*-propylphenol) has not hitherto been fully investigated, although there is a reference to the preparation of a single unorientated dihydroeugenolsulphonic acid (D.R.-P. 487,380; *Chem. Zentr.*, 1930, II, 985).

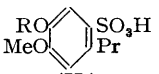
Further work on the sulphonation of dihydroeugenol is now described. Sulphonation at 0° yielded the 5-sulphonic acid (I, R = H) which was isolated as the barium salt and converted into the *p*-chlorobenzyl-ψ-thiouronium derivative (Dewey and Sperry, *J. Amer. Chem. Soc.*, 1939, **61**, 3251). The sulphonation of acetyldihydroeugenol with sulphuric acid at 0° gave similarly 5-hydroxy-4-methoxy-2-*n*-propylbenzenesulphonic acid (II, R = H).

The sulphonic acids (I and II; R = H) were methylated by boiling with methyl sulphate and aqueous potassium hydroxide giving their O-*methyl ethers* (I and II, R = Me). The latter (II, R = Me) was also obtained by sulphonation of *O*-methyleugenol.

The methylated sulphonic acids were synthesised from 5- and 6-amino-*O*-methyldihydroeugenols, and the orientation of the acids (I and II, R = H) was thereby confirmed. 3-*Nitro*-4 : 5-*dimethoxy*-n-*propylbenzene* (III) was made by methylation of 5-nitrodihydroeugenol, and gave the corresponding *amino*-compound on reduction. Treatment of the diazotised amine by Gattermann's method (*Ber.*, 1899, **32**, 1140) yielded the sulphinic acid from which the sulphonic acid (I, R = Me) was obtained by oxidation. The isomer (II, R = Me) was prepared in a similar way from the appropriate amine. All the sulphonic acids were identified as their *p*-chlorobenzyl-ψ-thiouronium salts.



(I.)



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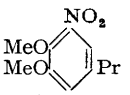


(III.)

The potassium dihydroeugenolsulphonates showed no antibacterial activity against a wide range of bacteria in inhibition tests.

Eugenol and its *O*-methyl and -acetyl derivatives show a marked difference from the corresponding dihydroeugenols in their behaviour towards sulphuric acid. Whereas the latter dissolve in the concentrated acid to give only faintly coloured solutions, the former compounds

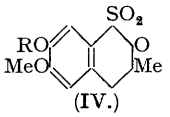
dissolve to give viscous intensely red solutions which evidently contain complex products. Hitherto no work appears to have been done on the nature of these.

Treatment of eugenol with concentrated sulphuric acid at 0° gave largely sulphonated polymers. When *O*-methyleugenol, however, was sulphonated by stirring with sulphuric acid at 0°, and the sulphonic acids were extracted with water, an amorphous mass was left from which a 5% yield of the *sultone* (IV, R = Me) was isolated. The aqueous extracts were neutralised with barium carbonate but attempts to separate the resulting amorphous mixture of barium sulphonates failed. It probably consisted largely of sulphonated polymers.

O-Acetyleugenol reacted with sulphuric acid in a similar way to methyleugenol, and the *sultone* (IV, R = H) was isolated from the sulphonation product. The substance gave a crystalline *acetate* on acetylation, and on methylation yielded the above sultone (IV, R = Me).

By analogy with the corresponding dihydroeugenols, *O*-methyl- and *O*-acetyl-eugenol would be expected to undergo nuclear sulphonation to give the *o*-allylsulphonic acid (VI), which might rearrange to give a δ- or γ-sultone (IV or V). A more probable explanation of sultone formation, however, is that the allylsulphonic acid undergoes addition of sulphuric acid at the double bond in accordance with Markownikow's rule (cf. the addition of hydrogen halides to eugenol; *J.*, 1945, 533) to give the sulphuric ester (VII) which on hydrolysis (cf. Brooks and Humphrey, *J. Amer. Chem. Soc.*, 1918, **40**, 822; Burgin, Hearne, and Rust, *Ind. Eng. Chem.*, 1941, **33**, 385) and lactonisation of the hydroxy-acid would then yield a δ-sultone (IV).

O-Methyleugenol reacted with 80% sulphuric acid at 5° to give β-3 : 4-*dimethoxyphenyliso-propyl alcohol*, and a small yield of the same product was obtained by treatment of *O*-methyleugenol with 85% phosphoric acid at 80°. This result lends support to the view that a sulphonated sulphuric ester acts as an intermediate in sultone formation. Eugenol was more susceptible to polymerisation than its *O*-methyl ether, and attempts to hydrate the double bond were unsuccessful.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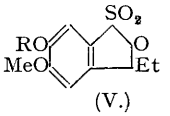
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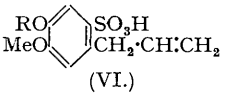
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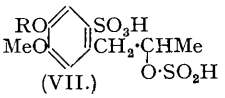
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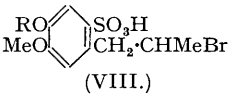
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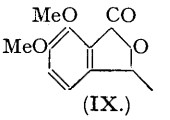
(IX.)

γ-Sultones have been described by several workers (Sachs, Wolff, and Ludwig, *Ber.*, 1904, **37**, 3253; List and Stein, *ibid.*, 1898, **31**, 1648; Marckwald and Frahne, *ibid.*, p. 1854; Shearing and Smiles, *J.*, 1937, 1348), but δ-sultones are uncommon (cf. Nilsson, *Svensk Kem. Tidskr.*, 1940, **52**, 324). The δ-sultone structure (IV) is clearly indicated by the following synthesis: β-bromodihydroeugenol methyl ether (β-3 : 4-dimethoxyphenyl*iso*propyl bromide) (Merck, D.R.-P., 274,350; *Chem. Zentr.*, 1914, I, 2079) was sulphonated to give the unstable sulphonic acid (VIII, R = Me) which lost hydrogen bromide when its aqueous solution was boiled, giving the sultone (IV, R = Me). β-Bromodihydroeugenol (*J.*, 1945, 533) was converted into the acetate, which was sulphonated with loss of the acetyl group, yielding the bromosulphonic acid (VIII, R = H). An aqueous solution of this acid lactonised on boiling to give the sultone (IV, R = H).

The eugenol sultones, unlike the physiologically active lactones of the meconine type (IX; cf. Lautenschläger, *Chem. Zentr.*, 1921, III, 1366), were found to be devoid of anthelmintic activity. The toxicity of the sultones to mice was low, but they showed no activity against *Streptococci* or against trophozoite-induced *P. gallinaceum* infection in chicks.

Experimental.

2-Hydroxy-3-methoxy-5-n-propylbenzenesulphonic (Dihydroeugenol-5-sulphonic) Acid (I, R = H).—Dihydroeugenol (10 g.) was cooled to 0°, and concentrated sulphuric acid (6·4 c.c.) was dropped in during one hour with stirring. The product was kept for 24 hours at room temperature, ice added, and the solution extracted with ether, diluted, heated to boiling, and neutralised (Congo-red) with barium carbonate. The mixture was filtered and the filtrates concentrated, the barium salt crystallising in creamy-white needles (14 g.). The *benzyl-ψ-thiouronium* derivative, prepared in aqueous solution and crystallised from 50% alcohol, formed colourless leaflets, m. p. 109—112° (Found: C, 52·2; H, 5·5. $C_{10}H_{14}O_5S,C_8H_{10}N_2S$ requires C, 52·4; H, 5·8%). The *p-chlorobenzyl-ψ-thiouronium* derivative formed colourless plates, m. p. 168—170° (Found: N, 6·1. $C_{10}H_{14}O_5S,C_8H_9N_2ClS$ requires N, 6·3%).

The *potassium* sulphonate, prepared from an aqueous solution of the barium salt, crystallised from water in colourless prisms, and gave a deep blue coloration with ferric chloride (Found: K, 13·6. $C_{10}H_{13}O_5SK$ requires K, 13·7%). The pH of the salt in 0·1N-aqueous solution was 6·2—6·4 (capillator method).

5-*Hydroxy*-4-*methoxy*-2-n-*propylbenzenesulphonic* (*Dihydroeugenol*-6-*sulphonic*) *Acid* (II, R = H).—*O*-Acetyldihydroeugenol (10 g.) was dropped into concentrated sulphuric acid (20 c.c.) during 3·5 hours at 0—5° with stirring. The product was worked up as in the foregoing sulphonation to afford the barium salt, which crystallised from water (charcoal) in clusters of small, creamy-white needles (8 g.). The p-*chlorobenzyl*-ψ-*thiouronium* salt formed colourless prisms, m. p. 169—170°, after sintering at 156° (Found: C, 48·2; H, 5·4. $C_{10}H_{14}O_5S,C_8H_9N_2ClS$ requires C, 48·3; H, 5·2%). The *potassium* sulphonate, prepared from the barium salt, recrystallised from water in creamy-white prisms and gave a dull blue coloration with ferric chloride (Found: K, 13·8%). The pH of its 0·1N-aqueous solution was 6·2—6·4.

Sulphonation of O-*Methyldihydroeugenol*.—Concentrated sulphuric acid (1·1 g.) was dropped into the methyl ether (1 g.) with stirring. The mixture was warmed at 60° for 7 hours, and the barium 4:5-dimethoxy-2-*n*-propylbenzenesulphonate (cf. II, R = Me) isolated as in the previous sulphonations as a white crystalline solid (1·25 g.). The benzyl-ψ-thiouronium derivative formed colourless needles, m. p. 185—187°. The p-*chlorobenzyl*-ψ-*thiouronium* derivative formed clusters of white needles, m. p. 158° (sintering at 145—148°) (Found: C, 49·9; H, 5·2; N, 6·4. $C_{11}H_{16}O_5S,C_8H_9N_2ClS$ requires C, 49·4; H, 5·5; N, 6·1%). The *potassium* salt crystallised from water in slender white prisms (Found: K, 10·9. $C_{11}H_{15}O_5SK,3H_2O$ requires K, 11·1%).

3-*Nitro*-4:5-*dimethoxy*-n-*propylbenzene* (5-*Nitromethyldihydroeugenol*) (III).—5-Nitrodihydroeugenol (3·3 g.) (Levin and Lowy, *J. Amer. Chem. Soc.*, 1933, **55**, 1995), xylene (70 c.c.), and sodium bicarbonate (12 g.) were stirred under reflux with methyl sulphate (4 c.c.) for 5 hours. The xylene solution was washed with water and sodium hydroxide solution, the xylene removed, and the residue distilled, affording a pale yellow oil (3 g.), b. p. 145—150°/2 mm. (Found: C, 58·3; H, 6·5. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7%). This *nitro*-compound (6·4 g.) was dissolved in alcohol (10 c.c.) saturated with hydrogen chloride at 0° and mixed with a solution of stannous chloride (29·4 g.) in alcohol (50 c.c.) also saturated with hydrogen chloride. After 24 hours the alcohol was removed, and water and excess of sodium hydroxide solution added; the 3-*amino*-compound, isolated by extraction with ether, distilled as a colourless oil (4 g.), b. p. 128—131°/2 mm. (Found: C, 67·0; H, 8·8. $C_{11}H_{17}O_2N$ requires C, 67·6; H, 8·8%). Its *hydrochloride* crystallised from acetone–methanol in clusters of white needles, m. p. 207° (Found: C, 56·4; H, 7·2. $C_{11}H_{17}O_2N,HCl$ requires C, 57·0; H, 7·7%). The *benzoyl* derivative crystallised from light petroleum (b. p. 40—60°) in long, silky needles, m. p. 67—69° (Found: C, 72·2; H, 7·3. $C_{18}H_{21}O_3N$ requires C, 72·4; H, 7·1%).

O-*Methyldihydroeugenol*-5-*sulphonic Acid* (I, R = Me).—The foregoing amino-compound (0·5 g.) was dissolved in concentrated sulphuric acid (0·6 g.) and water (4·4 c.c.), and the cool solution diazotised by addition of sodium nitrite (0·18 g.) in water (0·9 c.c.). A cold mixture of water (1·2 c.c.) and concentrated sulphuric acid (1·2 g.) was added, and a brisk stream of sulphur dioxide passed in at 0° until a faint cloudiness began to appear. Copper powder (2 g.) was then gradually added during 40 minutes with stirring, and the mixture kept at room temperature for 2·5 hours and extracted with ether. The ethereal solution was washed with water, extracted with sodium carbonate solution, the carbonate extracts acidified (hydrochloric acid), and the sulphinic acid isolated by extraction with ether as a faintly yellow oil (0·35 g.); this was neutralised with dilute potassium hydroxide solution, the solution filtered, hydrogen peroxide (5 c.c., 100-vol.) added, and the whole evaporated to dryness on the water-bath. The residue was treated with acetone, giving the potassium salt of the sulphonic acid (I, R = Me) (0·3 g.) as a white solid. The p-*chlorobenzyl*-ψ-*thiouronium* derivative crystallised in colourless plates, m. p. 160—163° (Found: C, 49·7; H, 5·5. $C_{11}H_{16}O_5S,C_8H_9N_2ClS$ requires C, 49·4; H, 5·5%).

Methylation of Dihydroeugenol-5-*sulphonic Acid*.—Potassium dihydroeugenol-5-sulphonate (0·5 g.) was dissolved in water (5 c.c.), potassium hydroxide (0·5 g.) in water (2 c.c.) added, followed by methyl sulphate (0·5 g.), and the mixture was refluxed for 8 hours. Further additions of potassium hydroxide and methyl sulphate were made until methylation was complete (*ca.* 24 hours). The product was neutralised (hydrochloric acid) and evaporated to dryness. The residue was fractionally crystallised from water to remove potassium sulphate and gave potassium methyldihydroeugenol-5-sulphonate (0·1 g.). The *p*-chlorobenzyl-ψ-thiouronium derivative formed colourless plates, m. p. 160—163°, identical with the compound above.

O-*Methyldihydroeugenol*-6-*sulphonic Acid* (II, R = Me).—The 6-sulphinic acid, prepared from 6-amino-*O*-methyldihydroeugenol (0·5 g.) as in the case of the 5-acid (except that hydrochloric acid was used instead of sulphuric), was dissolved in baryta solution and neutralised (sulphuric acid), the solution filtered, hydrogen peroxide (4 c.c.) added, and the solution evaporated to dryness; treatment of the residue with acetone afforded the barium methyldihydro-salt of the acid (II, R = Me) (0·2 g.). The *p*-chlorobenzyl-ψ-thiouronium derivative formed white needles, m. p. 158° (after sintering at 145—147°) (Found: C, 49·8; H, 5·4%) (cf. above).

Methylation of Dihydroeugenol-6-*sulphonic Acid* (II, R = H).—The potassium salt (0·1 g.) was dissolved in water (1 c.c.), potassium hydroxide (40 mg.) and methyl sulphate (50 mg.) added, and the mixture refluxed for 2·5 hours. The product was neutralised (hydrochloric acid) and concentrated, the potassium salt of (II, R = Me) separating; it recrystallised from water in colourless needles (50 mg.). The benzyl- and the *p*-chlorobenzyl-ψ-thiouronium derivative formed colourless needles, m. p. 185° and 156° (sinters 146°), respectively, identical with the corresponding derivatives prepared above.

Sulphonation of O-*Methyleugenol*.—*O*-Methyleugenol (6 c.c.) was dropped into well-stirred concentrated sulphuric acid (15 c.c.) at 0—5° during one hour. The deep red syrup was stirred for 5 hours at room temperature and poured on ice. The mass was washed with water and sodium bicarbonate solution, the insoluble material dissolved in benzene, washed with water, dried (sodium sulphate), and the benzene removed. The residue solidified on treatment with ether to give a brown

solid (0·4 g.), which crystallised from methanol (charcoal) to give the *sultone* (IV, R = Me) of **4** : 5-dimethoxy-2-(β-hydroxy-*n*-propyl)benzenesulphonic acid in colourless prisms, m. p. 141—143° (Found : C, 51·7; H, 5·4. $C_{11}H_{14}O_5S$ requires C, 51·1; H, 5·5%).

Sulphonation of O-*Acetyleugenol.*—*O*-Acetyleugenol (7·4 g.) was added to stirred concentrated sulphuric acid (18 c.c.) at 5—10° during 30 minutes. After being stirred at 5—10° for 4 hours, the deep red product was poured on ice, and the mass washed with water and bicarbonate solution, and dried on a porous tile. The brown solid was powdered and extracted with boiling benzene. The extracts deposited a crystalline solid which recrystallised from methanol (charcoal) to give the *sultone* (IV, R = H) (" eugenol sultone ") as large colourless plates which fell to a powder after drying at 100° (0·4 g.), m. p. 166—168° [Found : C, 49·4; H, 4·8; S, 13·2; *M* (Rast), 228. $C_{10}H_{12}O_5S$ requires C, 49·1; H, 4·9; S, 13·1%; *M*, 244]. It was soluble in dilute sodium hydroxide solution. The *acetyl* derivative crystallised from benzene–light petroleum (b. p. 100—120°) in small white needles or colourless prisms, m. p. 167—169° depressed to 130—140° by the unacetylated compound (Found : C, 50·4; H, 5·0. $C_{12}H_{14}O_6S$ requires C, 50·3; H, 4·9%).

Methylation of the Sultone (IV).—The sultone (0·1 g.) was dissolved in acetone (2 c.c.), anhydrous potassium carbonate (0·11 g.) added, and the mixture refluxed with methyl sulphate (0·1 g.) for 4 hours. The acetone was removed, and the residue diluted with water; an oil separated which solidified to a white solid (0·1 g., m. p. 140—142°). This recrystallised from methanol in large colourless plates, m. p. 141—142°, identical with the sultone (IV, R = Me) above.

Action of 80% *Sulphuric Acid on* O-*Methyleugenol.*—Methyleugenol (4 c.c.) was dropped into a well-stirred mixture of water (5 c.c.) and concentrated sulphuric acid (8·7 c.c.) at 5° during two hours. Stirring was continued for a further 4 hours, ice-water was added, and the product heated to 90° for one hour. The mixture was cooled, extracted with ether, the extracts washed (sodium bicarbonate) and dried, the ether removed, and the residue distilled; it gave a colourless oil (1·85 g.), b. p. 138—140°/2 mm., which solidified on treatment with light petroleum. It crystallised from ether–light petroleum (b. p. 40—60°) to give β-**3** : 4-*dimethoxyphenylisopropyl alcohol* in white leaflets (1·5 g.), m. p. 43—45° (Found : C, 67·1; H, 8·3. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%), which dissolved in concentrated sulphuric acid giving a deep red solution.

" *Methyleugenol Sultone* " (IV, R = Me).—β-**3** : 4-Dimethoxyphenyl*iso*propyl bromide (0·5 g.) was slowly mixed with concentrated sulphuric acid (0·5 g.) at 0°. After 16 hours at room temperature, ice-water was added, unsulphonated material removed by extraction with ether, and the clear aqueous solution of the bromo-2-sulphonic acid (VIII, R = Me) so obtained was refluxed for 5 minutes. An oil separated which solidified on cooling (0·42 g.) and crystallised from methanol in colourless plates, m. p. 141—142°, identical with the sultone described above.

" *Eugenol Sultone* " (IV, R = H).—" β-Bromodihydroeugenol " (2 g.) in pyridine with acetic anhydride and acetyl chloride formed the *O*-acetyl compound as a colourless oil (1·7 g.), b. p. 142—146°/2 mm. This (0·5 g.) was mixed with concentrated sulphuric acid (0·5 g.) at 0° and the product worked up after 16 hours as in the previous sulphonation to give a clear aqueous solution of the sulphonic acid (VIII, R = H). When this was boiled for 2 minutes an oil separated which solidified on cooling (0·25 g.) and crystallised from methanol in colourless plates which fell to a powder after drying at 100°, m. p. 166—167°, identical with " eugenol sultone " described above.

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