Nitration and Bromination of 3-Toluene-*p*-sulphonamidoveratrole

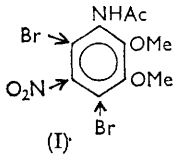
By F. Bell and A. S. Millar

3-Toluene-*p*-sulphonamidoveratrole on nitration gives a mixture of the 4-, 5-, and 6-derivatives and on dinitration mainly the 4,6-derivatative, whereas 3-acetamidoveratrole gives the 5-nitro-derivative and then a mixture of the 4,5- and 5,6-dinitro-derivatives. On bromination both give 6-bromo-derivatives. This difference between nitration and bromination is discussed.

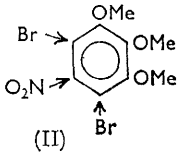
THE results obtained on electrophilic substitution of aromatic compounds already containing three substituents are often difficult to explain.[1] 3-Acetamidoveratrole resembles 1,2,3-trimethoxybenzene both on nitration and bromination, as in (I) [2] and (II),[3] and collectively these results might suggest that the steric requirements of the nitronium ion were greater than those of the species responsible for bromination.[4] When, however, 3-toluene-*p*-sulphonamidoveratrole (III) was mononitrated the 5-derivative was only a minor product, and on dinitration the 4,6-derivative was isolated in over 50% yield. This would suggest that the principal determining factor is salt formation under the acid conditions. Salt formation would be greatest with the acetamido-group, less with the methoxyl group even in a sterically open position, and least with the toluene-*p*-sulphonamido-group. The bromination of 3-acetamidoveratrole, which is conducted in acetic acid or

[1] M. J. S. Dewar, *J. Chem. Soc.*, 1949, 463.
[2] C. S. Gibson, J. L. Simonsen, and M. G. Rau, *J. Chem. Soc.*, 1917, **111**, 69; J. L. Simonsen and M. G. Rau, *Ibid.*, 1918, **113**, 782; H. Vermeulen, *Rec. Trav. chim.*, 1929, **48**, 971.
[3] M. Kohn and S. Grun, *Monatsh.*, 1925, **46**, 85; M. Kohn and E. Gurewitsch, *Monatsh.*, 1928, **49**, 179.
[4] P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 1956, 36; 1957, 131.

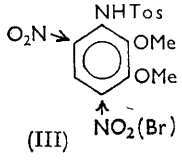
chloroform, would allow the –NHAc group to exercise its normal strong *o*-*p*-directing action, but this would



(I)



(II)



(III)

be largely suppressed by the strong nitric acid used for the nitration.

EXPERIMENTAL

N.m.r. spectra (60 Mc./sec.) are for solutions in deuterochloroform, with tetramethylsilane as internal standard; the authors are indebted to Mr. B. Semple, B.Sc., for their determination.

3-Aminoveratrole was prepared by the sequence: *o*-vanillin ⟶ *o*-veratraldehyde ⟶ *o*-veratric acid ⟶ *o*-veratroyl chloride ⟶ *o*-veratramide ⟶ 3-aminoveratrole (benzoyl derivative, m. p. 107°; lit.,[2] 107°). **3**-*Toluene*-p-*sulphonamidoveratrole* formed needles, m. p. 109°, from ethanol (Found: C, 58·6; H, 6·0. $C_{15}H_{17}NO_4S$ requires C, 58·6; H, 5·5%).

Nitration of 3-*Toluene*-p-*sulphonamidoveratrole*.—(*a*) A mixture of nitric acid (3 c.c., *d*, 1·5) and acetic acid (15 c.c.) was added dropwise to a solution of the compound (6 g.) in acetic acid (30 c.c.) at room temperature. After 1 hr. slight crystallisation occurred and a little water was added. The crop (1·5 g., m. p. 150—160°) formed needles, m. p. 164—165°, of the 5-*nitro*-derivative from ethanol (Found: C, 51·7; H, 5·1. $C_{15}H_{16}N_2O_6S$ requires C, 51·1; H, 4·6%). The filtrate on further dilution gave material which after fractional crystallisation from ethanol gave the 6-*nitro*-derivative in prisms, m. p. 134° (Found: C, 51·0; H, 4·3%) and the 4-*nitro*-derivative in needles, m. p. 62—64° (Found: C, 51·6; H, 4·9%). Hydrolysis of these derivatives by solution in cold sulphuric acid gave respectively 3-amino-5-nitroveratrole, m. p. 103° (lit., 105—106°), acetyl-derivative, m. p. 173° (lit., 172—173°); 3-*amino*-6-*nitroveratrole*, prisms, m. p. 93°, from chloroform–light petroleum (Found: C, 48·6; H, 4·9. $C_8H_{10}N_2O_4$ requires C, 48·5; H, 5·1%), *acetyl*-derivative, prisms m. p. 114—115°, from ethanol (Found: C, 49·8; H, 4·8. $C_{10}H_{12}N_2O_5$ requires C, 50·0; H, 5·0%); and 3-*amino*-4-*nitroveratrole*, prisms, m. p. 87—89° (large depression in m. p. on admixture with the 6-nitro-isomeride) from ethanol (Found: 48·9; H, 5·2%).

(*b*) Nitric acid (5 c.c., *d*, 1·5) in acetic acid (10 c.c.) was added to the compound (5 g.) in acetic acid (25 c.c.) at 70°. After ¼ hr. the mixture was cooled and the crop recrystallised from ethanol to yield the 4,6-*dinitro*-derivative as needles, m. p. 152—154° (4·0 g.) (Found: C, 45·5; H, 4·3. $C_{15}H_{15}N_3O_8S$ requires C, 45·3; H, 3·8%); no pure material could be obtained from the filtrate. This dinitro-compound was hydrolysed by solution in cold concentrated sulphuric acid to give 3-*amino*-4,6-*dinitroveratrole* as yellow plates (ethanol), m. p. 129° (Found: C, 39·3; H, 4·2. $C_8H_9N_3O_6$ requires C, 39·5; H, 4·2%). It gave an *acetyl*-derivative, m. p. 139—141° (needles, ethanol) (Found: C, 42·7; H, 4·3. $C_{10}H_{11}N_3O_7$ requires C, 42·1; H, 3·9%).

3-Aminonitroveratroles (τ values)

Position of nitro-groups	Nuclear protons		Amino protons	Methoxy protons	
4	2·05	3·62 doublets $J \sim 9$	3·62	6·05	6·13
5	2·68	2·76 doublets $J \sim 2$	5·8	6·08	
6	2·3	3·5 doublets $J \sim 9$	5·35	6·02	6·10
4, 5	3·22		3·88	6·0	6·03
4, 6	1·30		3·1	5·91	6·0
5, 6	2·69		5·45	6·02	

Nitration of 5-*Nitro*-3-*toluene*-p-*sulphonamidoveratrole*.—Fuming nitric acid (1·7 c.c.) mixed with acetic acid (1·7 c.c.) was added to a warm solution of the compound (1·7 g.) in acetic acid (8·5 c.c.). After a short time the mixture was set aside to cool, filtered from the crop (0·7 g., m. p. 198—201°) and then slightly diluted to yield a further crop (0·5 g., m. p. *ca.* 170°). The first crop yielded the 5,6-*dinitro*-derivative as prisms, m. p. 199—201°, from acetic acid (Found: C, 45·8; H, 3·6. $C_{15}H_{15}N_3O_8S$ requires C, 45·3; H, 3·8%), and the second crop the 4,5-*dinitro*-derivative as needles, m. p. 188°, from acetic acid (Found: C, 45·8; H, 3·6%). Both compounds were readily hydrolysed in cold sulphuric acid to give respectively 3-amino-5,6-dinitroveratrole, m. p. 141—143° (lit., 141—142°) and 3-amino-4,5-dinitroveratrole, m. p. 122—123° (lit., 112—113°). The bases on acetylation gave the respective acetyl-derivatives, m. p. 182—184° (lit., 178—179°), insoluble in dilute sodium hydroxide, and m. p. 242° (decomp.) (lit. 241° decomp.), easily soluble in dilute sodium hydroxide solution.

Bromination of 3-*Toluene*-p-*sulphonamidoveratrole*.—*N*-Bromosuccinimide (0·73 g.) was added to a solution of the compound (1·25 g.) in pyridine. After 1 hr. the mixture was decomposed by dilute hydrochloric acid and the precipitated oil separated by decantation. After several recrystallisations from ethanol the 6-*bromo*-derivative was obtained as needles, m. p. 123—126° (0·35 g.), (Found: C, 46·9; H, 3·9. $C_{15}H_{16}BrNO_4S$ requires C, 46·6; 4,4·1%) slowly hydrolysed by cold concentrated sulphuric acid to 3-amino-6-bromoveratrole, acetyl-derivative prismatic needles, m. p. 75—77° (lit., 78°).[2] Bromination by bromine in acetic acid gave an even less favourable result.

HERIOT-WATT COLLEGE,
EDINBURGH.

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