

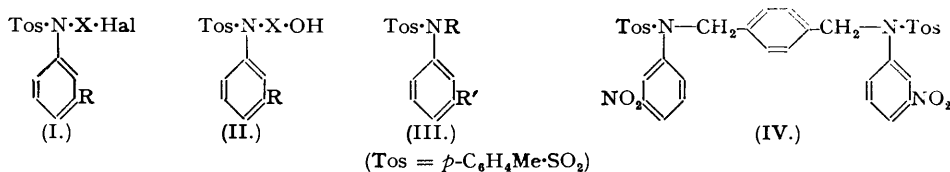
40. *The Preparation of Some Toluene-*p*-sulphonanilide Derivatives.
A Note on the Reactivity of Ethylene Chlorohydrin.*

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The preparation of some *N*-alkyl- and *N*- ω -halogenoalkyl-toluene-*p*-sulphonanilides is described. It is suggested that the low reactivity of ethylene chlorohydrin towards the toluene-*p*-sulphonanilide ion ($\overset{\ominus}{\text{N}}\text{R}_2$) is due to intramolecular hydrogen bonding.

THE preparation and optical activation of *N*-benzenesulphonyl-*N*-2-hydroxyethyl-8-nitro-1-naphthylamine has recently been reported by Glazer, Harris, and Turner (*J.*, 1950, 1753). In

connection with the synthesis of this compound, the reactivity of toluene-*p*-sulphonanilide and toluene-*p*-sulphon-*m*-nitroanilide towards various halogeno-compounds became of interest: it was hoped to hydrolyse *N*- ω -halogenoalkylsulphonanilides (I) to the corresponding alcohols (II). In no case, however, did the hydrolysis succeed.

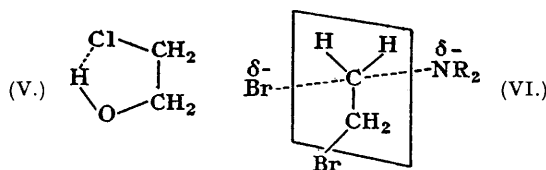


N-Benzyltoluene-*p*-sulphon-*m*-nitroanilide (III; R = Ph·CH₂, R' = NO₂) was obtained by boiling under reflux the sodium salt of toluene-*p*-sulphon-*m*-nitroanilide with benzyl chloride in dry ethanol. Its structure was confirmed by synthesis from *N*-benzyl-*m*-nitroaniline and toluene-*p*-sulphonyl chloride. The ease of this reaction suggested the possibility of obtaining *N*-*p*-hydroxymethylbenzyltoluene-*p*-sulphon-*m*-nitroanilide (II; X = ·CH₂·C₆H₄·CH₂·, R = NO₂) through the corresponding bromide. However, treatment of the sodium salt of toluene-*p*-sulphon-*m*-nitroanilide with *p*-xylylene dibromide in dry methanol or ethanol or in ethanol-acetone yielded *NN'*-*p*-xylylenebis(toluene-*p*-sulphon-*m*-nitroanilide) (IV).

N-2-Bromoethyltoluene-*p*-sulphonanilide (I; X = ·CH₂·CH₂·, R = H) and its *m*-nitro-derivative were prepared by heating the sodium salt of the sulphonanilide with ethylene dibromide in dry ethanol. The deactivating effect of the *m*-nitro-group was shown by the greater time of reaction needed to obtain the same yield. *N*-2-Methylallyltoluene-*p*-sulphonanilide (III; R = ·CH₂·CMe·CH₂·, R' = H) and its *m*-nitro-derivative were obtained by the same method, the greater reactivity of 2-methylallyl chloride leading to higher yields. Here again, the *m*-nitro-group markedly reduced the yield. Catalytic hydrogenation of the methylallyl compounds gave the corresponding *N*-isobutyl compounds in good yield.

Direct synthesis of *N*-2-hydroxyethyltoluene-*p*-sulphonanilide (II; X = ·CH₂·CH₂·, R = H) failed under a variety of conditions, but the nitro-derivative (II; X = ·CH₂·CH₂·, R = NO₂) was finally obtained by heating the sulphonanilide with ethylene chlorohydrin in alcoholic potassium hydroxide for six hours at 135°.

The lower reactivity of ethylene chlorohydrin and iodohydrin, compared with ethylene dibromide, towards attack by the sulphonanilide anion ($\ominus\text{NR}_2$) is possibly caused by intramolecular hydrogen bonding, giving rise to a 5-membered ring (V). Zumwalt and Badger (*J. Amer. Chem. Soc.*, 1940, **62**, 305) concluded, from an infra-red study of ethylene chlorohydrin, that such a ring was present, even in the vapour state. This has been confirmed by Bastiansen (*Acta Chem. Scand.*, 1949, **3**, 415) who used the electron-diffraction technique. The existence of a stable ring structure is not compatible with the reorganized configuration required, during bimolecular reaction, by an intermediate transition complex. Such a transition complex would be (VI) for



ethylene dibromide, which reacts by a bimolecular mechanism in similar nucleophilic reactions. For "cyclic" ethylene chlorohydrin, however, the transition complex could only be formed by disruption of the ring. Our experiments seem to indicate that conditions less drastic than a sealed tube at 135° do not sufficiently bring this about. In this connection, it is of interest that ethylene chlorohydrin was much less reactive than ethanol in forming a semiacetal with *lævo*-menthyl benzoylformate (Glazer and Turner, *J.*, 1949, S 169), again possibly owing to the inactivation of the chlorohydrin by internal ring formation.

EXPERIMENTAL.

Toluene-*p*-sulphonanilide and toluene-*p*-sulphon-*m*-nitroanilide were prepared in quantitative yield by condensing the amine with one equivalent of toluene-*p*-sulphonyl chloride in pyridine.

N-Benzyltoluene-*p*-sulphon-*m*-nitroanilide.—(a) A solution of toluene-*p*-sulphon-*m*-nitroanilide (5.7 g., 1 mol.) in dry ethanol (50 c.c.) was added to ethanolic sodium ethoxide [from sodium (0.5 g., 1.1 atoms) and ethanol (50 c.c.)], and freshly distilled benzyl chloride (3.0 g., 1.2 mols.) added. The whole was boiled under reflux for 6 hours, ethanol (50 c.c.) distilled off, and the residue poured into 5% aqueous sodium hydroxide (300 c.c.). When the mixture was shaken, a colourless, granular precipitate of *N*-benzyltoluene-*p*-sulphon-*m*-nitroanilide separated, having m. p. 120–121° (Found: C, 62.8; H, 4.8; N, 7.55. $C_{20}H_{18}O_4N_2S$ requires C, 62.8; H, 4.75; N, 7.3%) (6.0 g., 80%). The m. p. was unaffected on crystallisation from alcohol. Acidification of the sodium hydroxide extract yielded 1.1 g. (19%) of unchanged toluene-*p*-sulphon-*m*-nitroanilide.

(b) Toluene-*p*-sulphonyl chloride (0.9 g., 1.1 mols.) was added to a solution of *N*-benzyl-*m*-nitroaniline (1.0 g., 1.0 mol.) in pyridine (2 c.c.). The mixture was warmed to 70°, cooled, and poured into excess of dilute hydrochloric acid. The resulting precipitate was washed with dilute acid and water. Crystallisation from ethanol gave colourless crystals, m. p. 120° (1.0 g., 60%).

NN'-*p*-Xylylenebis(toluene-*p*-sulphon-*m*-nitroanilide).—A solution of toluene-*p*-sulphon-*m*-nitroanilide (5.0 g., 1 mol.) in dry methanol (50 c.c.) was added to methanolic sodium methoxide [from sodium (0.4 g., 1.0 atom) and methanol (50 c.c.)]. A saturated solution of *p*-xylylene dibromide (4.5 g., 1 mol.) in ethanol was then added and the whole boiled under reflux for $\frac{1}{2}$ hour, during which time a pale yellow flocculent precipitate was formed. The mixture was cooled and filtered. Crystallisation from benzene gave colourless crystals of NN'-*p*-xylylenebis(toluene-*p*-sulphon-*m*-nitroanilide), m. p. 193–194° (Found: C, 60.0; H, 4.7; N, 8.5. $C_{34}H_{30}O_8N_4S_2$ requires C, 59.5; H, 4.4; N, 8.2%) (8.0 g., 68%).

N-2-Bromoethyltoluenesulphonanilide.—A solution of toluene-*p*-sulphonanilide (5.0 g., 1 mol.) in dry ethanol (50 c.c.) was added to ethanolic sodium ethoxide [from sodium (0.5 g., 1.1 atoms) and ethanol (50 c.c.)]. Freshly distilled ethylene dibromide (3.8 g., 1 mol.) was added and the whole boiled under reflux for 3 hours. Some ethanol (50 c.c.) was distilled off and the remaining solution poured into 5% aqueous sodium hydroxide (300 c.c.). A colourless granular precipitate of *N*-2-bromoethyltoluene-*p*-sulphonanilide, m. p. 89–90° (1.1 g., 15%), was slowly deposited. Crystallisation from ethanol gave colourless crystals, m. p. 89–90° (Found: Br, 21.9. $C_{15}H_{16}O_2NBrS$ requires Br, 22.6%). Unchanged toluene-*p*-sulphonanilide (4.1 g., 82%) was recovered by acidifying the sodium hydroxide extract.

N-2-Bromoethyltoluenesulphon-*m*-nitroanilide, similarly prepared (reflux for 11 hours; yield 13%), crystallised from alcohol-acetone as colourless crystals, m. p. 117.5° (Found: Br, 19.4. $C_{15}H_{15}O_4N_2BrS$ requires Br, 20.0%).

N-2-Methylallyltoluene-*p*-sulphonanilide, prepared from the sodium salt of toluene-*p*-sulphonanilide and freshly distilled 2-methylallyl chloride in dry ethanol under reflux for 3 hours, was obtained as colourless crystals, m. p. 110–111° (from ethanol) (80%) (Found: C, 68.0; H, 6.6; N, 4.5. $C_{17}H_{19}O_2NS$ requires C, 67.7; H, 6.4; N, 4.7%). The corresponding *m*-nitroanilide (prep.: $7\frac{1}{2}$ hours under reflux) was deposited from ethanol as colourless crystals, m. p. 109–109.5° (48%) (Found: N, 7.9. $C_{17}H_{18}O_4N_2S$ requires N, 8.1%).

Hydrogenations.—Reduction of the foregoing nitro-compound (5.7 g.) in acetic acid (90 c.c.) with platinum dioxide as catalyst gave *N*-isobutyltoluene-*p*-sulphon-*m*-nitroanilide as lemon-yellow crystals (from ethanol), m. p. 125° (4.5 g., 79%) (Found: C, 59.0; H, 6.0; N, 7.8. $C_{17}H_{20}O_4N_2S$ requires C, 58.6; H, 5.8; N, 8.0%). The reduction was stopped after 40 minutes to prevent reduction of the nitro-group.

Similar hydrogenation of *N*-2-methylallyltoluene-*p*-sulphonanilide gave *N*-isobutyltoluene-*p*-sulphonanilide (Hickinbottom, *J.*, 1930, 992), m. p. 122–123° (93%).

N-2-Hydroxyethyltoluene-*p*-sulphon-*m*-nitroanilide.—Toluene-*p*-sulphon-*m*-nitroanilide (4.75 g., 1 mol.), ethylene chlorohydrin (3.0 g., 2.3 mols.), potassium hydroxide (2.5 g.), and ethanol (10 c.c.) were heated (135°) in a sealed tube for 6 hours. The product was poured into excess of dilute alkali; gummy brown crystals separated and were purified by two precipitations with water from acetone-alcohol solution. *N*-2-Hydroxyethyltoluene-*p*-sulphon-*m*-nitroanilide separated as orange crystals, m. p. 65–66° (~100%) (Found: C, 53.0; H, 4.9; N, 8.1. $C_{15}H_{16}O_5N_2S$ requires C, 53.6; H, 4.8; N, 8.3%).

When the sodium salt of the sulphonanilide was heated under reflux with ethylene chlorohydrin (or iodohydrin) in anhydrous ethanol, alcoholic sodium hydroxide, or toluene (in the last case the presence of copper-bronze catalyst had no effect), or when the sulphonanilide was heated under reflux with ethylene chlorohydrin in pyridine, the original sulphonanilide was recovered quantitatively.

Analyses for C, H, and N are by Drs. Weiler and Strauss, Oxford.

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