

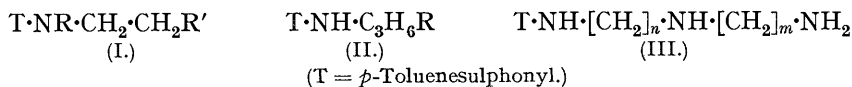
304. *Polyamines. Part III. The Preparation of Unsymmetrical Amines of the Types $\text{NHR}\cdot\text{C}_2\text{H}_4\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$ and $\text{NH}_2\cdot\text{C}_2\text{H}_4\cdot\text{NH}\cdot\text{C}_3\text{H}_6\cdot\text{NH}_2$, and the Action of Ammonia on Di-*p*-toluenesulphonylbis-(β -chloroethyl)ethylenediamine.*

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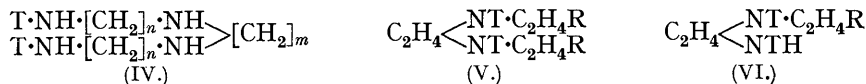
Unsymmetrical amines of the types mentioned above are of obvious interest for the preparation of co-ordination compounds with metals. The toluenesulphonamides of three of these have been prepared: $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{N}(\text{CH}_2\text{Ph})\cdot\text{C}_2\text{H}_4\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$, $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{NEt}\cdot\text{C}_2\text{H}_4\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$, $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{NH}\cdot\text{C}_3\text{H}_6\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$, and in some cases the corresponding tetramines have been prepared. By the action of ethylene oxide on di-*p*-toluenesulphonylethylenediamine, di-*p*-toluenesulphonyl-*NN'*-bis-(β -hydroxyethyl)ethylenediamine was prepared, and from it the corresponding chloro-compound by the action of thionyl chloride. This chloro-compound when treated with ammonia gave the di-*p*-toluenesulphonyl derivatives of *NN'*-bis-(β -aminoethyl)ethylenediamine and of a new cyclic polyamine.

BASES of the type $\text{NHR}\cdot\text{C}_2\text{H}_4\cdot\text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$ should form co-ordination compounds of obvious stereochemical interest. We have prepared the *p*-toluenesulphonyl derivatives (I; $\text{R} = \text{CH}_2\text{Ph}$ or Et , $\text{R}' = \text{NH}\cdot\text{C}_2\text{H}_4\cdot\text{NH}_2$) of two of these by the action of ethylenediamine upon the corresponding chloro-compounds (I; $\text{R} = \text{CH}_2\text{Ph}$ or Et , $\text{R}' = \text{Cl}$), which were prepared from the hydroxy-compounds (I; $\text{R}' = \text{OH}$) by the action of thionyl chloride. The chloro-compounds reacted much more slowly with ethylenediamine than

did *p*-toluenesulphon- β -chloroethylamide (Peacock, J., 1936, 1518). The compound (I; R = CH₃, R' = OH) has been prepared by Slotta and Behnisch (*J. pr. Chem.*, 1932,

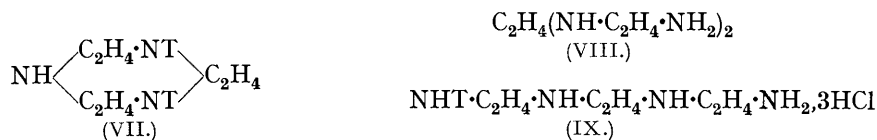


135, 225), and the corresponding bromo-compound (I; R = CH₃, R' = Br) by Marckwald and Frobenius (*Ber.*, 1901, 34, 3544). The compound (I; R = CH₂Ph, R' = OH) was heated with aluminium chloride but no tetrahydroisoquinoline could be isolated from the tarry reaction product.



When *p*-toluenesulphon- β -chloroethylamide (Slotta and Behnisch, *loc. cit.*; Peacock and Dutta, J., 1934, 1303) was heated with trimethylenediamine, two hydrochlorides were obtained; one was the *dihydrochloride* of (IV; $n = 2$, $m = 3$), and the other appeared to be the *trihydrochloride* of the base (III; $n = 2$, $m = 3$); there seems no strong reason why this base should form a trihydrochloride, but this behaviour is not unprecedented, for the benzoyl derivative of $\beta\beta'$ -dibromodiethylamine forms salts with acids (Peacock and Dutta, *loc. cit.*). *p*-Toluenesulphon- γ -hydroxypropylamide (II; R = OH) was prepared in the usual way, and the crude compound converted into the *chloro*-compound (II; R = Cl). This, when heated with ethylenediamine, gave the *hydrochlorides* of the bases (III and IV; $n = 3$, $m = 2$). The free base corresponding with the latter has been prepared by van Alphen (*Rec. trav. chim.*, 1937, 56, 343).

By the action of ethylenechlorohydrin or of ethylene oxide on di-*p*-toluenesulphonyl-ethylenediamine, the substances (V and VI; R = OH) were obtained, which were respectively insoluble and soluble in sodium hydroxide. The former, NN'-*di-p*-toluenesulphonyl-NN'-*bis*-(β -hydroxyethyl)ethylenediamine, was obtained in the pure state, only one form being isolated; if the three valencies of nitrogen are not in one plane, two forms



should be capable of existence, *meso*- and *dl*-; the same remarks also apply to compounds (V; R = Cl) and (V; R = NH₂). The hydroxy-compounds corresponding with (V) and (VI) were converted in the usual way into the *chloro*-compounds. When (V; R = Cl) was heated with aqueous ammonia, the *dihydrochloride* of (V; R = NH₂) was obtained, and the *monohydrochloride* of a base which was almost certainly (VII). Similar cyclic bases have been obtained by van Alphen (*loc. cit.*). The amino-compound (V; R = NH₂) on hydrolysis gave the tetrahydrochloride of NN'-*bis*-(β -aminoethyl)ethylenediamine (VIII) (Hofmann, *Proc. Roy. Soc.*, 1862, 11, 413; Peacock, J., 1936, 1518; van Alphen, *Rec. trav. chim.*, 1936, 55, 412).

p-Toluenesulphon- β -chloroethylamide, when heated with an alcoholic solution of $\beta\beta'$ -diaminodiethylamine, gave a *trihydrochloride*, probably that of *p*-toluenesulphonyl-NN'-*bis*-(β -aminoethyl)ethylenediamine (IX).

EXPERIMENTAL.

The Action of Ethylenediamine on p-Toluenesulphonbenzyl- β -chloroethylamide (I; R = CH₂Ph, R' = Cl).—The substance (I; R = CH₂Ph, R' = Cl), prepared from the hydroxy-compound (Peacock and Dutta, *loc. cit.*) by the action of thionyl chloride and pyridine, crystallised from methyl alcohol; m. p. 69° (Found: Cl, 11.1. C₁₆H₁₈O₂NSCl requires Cl, 11.0%). When this compound was boiled under reflux with an ethyl-alcoholic solution of ethylenediamine for 10 hours no reaction took place; but when the compound (12.8 g.), ethylenediamine (2.4 g.), and amyl alcohol (50 c.c.) were heated under reflux in an oil-bath at 140—145° for 12 hours,

ethylenediamine dihydrochloride was precipitated. This was filtered off, the amyl alcohol distilled off, the residue extracted with boiling dilute hydrochloric acid, and the extracts evaporated to dryness; the product (5.6 g.), a mixture of the dihydrochlorides of ethylenediamine and of the base (I; $R = CH_2Ph$, $R' = NH \cdot C_2H_4 \cdot NH_2$), was purified by extraction with alcohol, in which the former salt was practically insoluble. The latter *dihydrochloride* crystallised from absolute alcohol, m. p. 149—150° (Found: Cl, 16.6. $C_{18}H_{25}O_2N_3S_2 \cdot 2HCl$ requires Cl, 16.9%). The oily residue, insoluble in dilute hydrochloric acid, was extracted with glacial acetic acid; two products were isolated, m. p. 114° and 140°. The second product, crystallised from a mixture of methyl alcohol, water, and hydrochloric acid, had m. p. 141—142°, and appeared to be the *hydrochloride* of *NN'*-bis-(β -*p*-toluenesulphonbenzylamidoethyl)ethylenediamine (Found: Cl, 5.0, 5.16. $C_{34}H_{42}O_4N_4S_2 \cdot HCl$ requires Cl, 5.3%).

Ethylenediamine and p-Toluenesulphon-(β -chloroethyl)ethylamide (I; $R = Et$, $R' = Cl$).—By the action of either ethylene chlorohydrin or ethylene oxide on the sodium derivative of *p*-toluenesulphonethylamide, the compound (I; $R = Et$, $R' = OH$) was obtained. The yields were poor, about 40%, and the compound could not be obtained crystalline. When it (36 g.) was treated with thionyl chloride (26 g.) and pyridine (11.9 g.) in carbon tetrachloride (50 c.c.) at 7°, heated slowly to 85°, and the product worked up in the usual way, it afforded the *compound* (I; $R = Et$, $R' = Cl$) (21 g.), which, crystallised from ether-light petroleum, had m. p. 67° (Found: Cl, 13.2. $C_{11}H_{16}O_2NSCl$ requires Cl, 13.6%). This chloro-compound did not react with ethylenediamine in ethyl-alcoholic solution, but in amyl-alcoholic solution in an oil-bath at 140—150°, it afforded a viscous product. When worked up in the usual way, this did not give a crystalline hydrochloride, but when heated with *p*-toluenesulphonyl chloride, it gave the *tri-p-toluenesulphonyl* derivative of *N*- β -aminoethyl-*N'*-ethylethylenediamine (cf. I; $R = Et$, $R' = NH \cdot C_2H_4 \cdot NH_2$), m. p. 203° (Found: S, 15.7. $C_{27}H_{35}O_6N_3S_3$ requires S, 16.2%), from glacial acetic acid.

Ethylenediamine and p-Toluenesulphon- γ -chloropropylamide (II; $R = Cl$).—*p*-Toluenesulphonamide (85.5 g.) was converted into the dry sodium salt, mixed with trimethylene chlorohydrin (42.3 g.), and heated, in a flask fitted with a mercury seal, in an oil-bath at 160—170° for 13 hours. The product was extracted with ethyl alcohol, filtered from sodium chloride, and sodium (1.15 g.) added to the solution, which was then evaporated to dryness. Trimethylene chlorohydrin (4.2 g.) was added, and the mixture heated at 160—170° for 5 hours. The product was worked up in the usual way, the crude *p*-toluenesulphon- γ -hydroxypropylamide (II; $R = OH$) being obtained as a viscous liquid. It was converted directly into the chloro-compound by treatment with thionyl chloride (119 g.) and pyridine (39.5 g.). The crude *p-toluenesulphon- γ -chloropropylamide* was freed from oily impurities by pressing on a porous plate, and then crystallised from benzene-light petroleum; yield 28 g., m. p. 53° (Found: Cl, 14.5. $C_{10}H_{14}O_2NSCl$ requires Cl, 14.34%). This compound (22 g.) was mixed with ethylenediamine (6 g.) and ethyl alcohol (50 c.c.) and boiled under reflux for 12 hours. The product was worked up in the usual way and gave the *dihydrochlorides* of (a) *N*-(γ -*p*-toluenesulphonamidopropyl)-ethylenediamine (III; $n = 3$, $m = 2$) (8.5 g.) and (b) *NN'*-bis-(γ -*p*-toluenesulphonamidopropyl)-ethylenediamine (IV; $n = 3$, $m = 2$) (5 g.). The former was readily soluble in water, and crystallised from ethyl alcohol, m. p. 202° (Found: Cl, 20.3. $C_{12}H_{21}O_2N_3S_2 \cdot 2HCl$ requires Cl, 20.6%); the latter was very sparingly soluble in cold water, slightly soluble in hot water (Found: Cl, 12.34. $C_{22}H_{34}O_4N_4S_2 \cdot 2HCl$ requires Cl, 12.6%).

The Action of Trimethylenediamine on p-Toluenesulphon- β -chloroethylamide.—The sulphonamide (36 g.), trimethylenediamine (11.5 g.), and ethyl alcohol (50 c.c.) were boiled under reflux for 8 hours. The product, worked up in the usual way, gave a hydrochloride, m. p. 205°, readily soluble in water and hot alcohol, which appeared to be the *trihydrochloride* of (III; $n = 2$, $m = 3$) (Found: Cl, 27.3, 28.9, 28.8. $C_{12}H_{21}O_2N_3S_3 \cdot 3HCl$ requires Cl, 27.9%). The *dihydrochloride* of *NN'*-bis-(β -*p*-toluenesulphonamidoeethyl)trimethylenediamine (IV; $n = 2$, $m = 3$) was very sparingly soluble in cold water; m. p. 215° (Found: Cl, 12.7. $C_{21}H_{32}O_4N_4S_2 \cdot 2HCl$ requires Cl, 13.1%).

NN'-*Di-p-toluenesulphonyl-NN'*-bis-(β -hydroxyethyl)ethylenediamine (V; $R = OH$).—*Di-p-toluenesulphonyl*ethylenediamine (184 g.) was added to a solution of sodium (2.3 g.) in ethyl alcohol (200 c.c.) and benzene (200 c.c.), and ethylene oxide (112 g.) added. The mixture was heated in an autoclave for 10 hours at 100—110°. The solvent was distilled off, and the residue extracted with 10% sodium hydroxide. The insoluble residue, crystallised from aqueous alcohol, afforded the *compound* (V; $R = OH$), m. p. 144° (97 g.) (Found: S, 14.0, 14.4; N, 6.38. $C_{20}H_{28}O_6N_2S_2$ requires S, 14.0; N, 6.14%). [The alkali-soluble product was used later (see p. 1471).] The use of ethylene chlorohydrin instead of the oxide gave lower yields.

The compound (V; R = OH) (228 g.) was mixed with pyridine (79 g.) and carbon tetrachloride (350 c.c.), and thionyl chloride (148 g.) added to the cooled mixture (5—10°). Next day, the temperature was slowly raised to 90° to complete the reaction, and the product worked up in the usual way (crude yield, 215 g.). NN'-Di-p-toluenesulphonyl-NN'-bis-(β-chloroethyl)-ethylenediamine (V; R = Cl) crystallised from benzene-light petroleum; m. p. 145° (Found: Cl, 14.0. C₂₀H₂₆O₄N₂Cl₂S₂ requires Cl, 14.4%).

Action of Alcoholic Ammonia on (V; R = Cl).—The chloro-compound (30 g.) was heated in an autoclave with ethyl-alcoholic ammonia (6N, 450 c.c.) for 7 hours at 100—120°. The cooled solution was filtered, and the alcohol distilled off. The crude bases were extracted with cold (A) and then with hot (B) dilute hydrochloric acid. From (B) the hydrochloride of (VII) (5.1 g.) crystallised on cooling. The mother-liquors from (B) and the solution (A) were mixed and basified, giving (V; R = NH₂) (15.9 g.). The dihydrochloride of NN'-di-p-toluenesulphonyl-NN'-bis-(β-aminoethyl)ethylenediamine (V; R = NH₂) readily crystallised from alcoholic hydrochloric acid; m. p. 243° (Found: Cl, 13.45. C₂₀H₃₀O₄N₄S₂·2HCl requires Cl, 13.47%). The free base was insoluble in water, but crystallised from aqueous alcohol; m. p. 134° (Found: S, 13.6. C₂₀H₃₀O₄N₄S₂ requires S, 14.1%). The hydrochloride of 1:4-di-p-toluenesulphonyl-1:4:7-triazacyclononane (VII) readily crystallised from hot water; m. p. 289° (Found: Cl, 7.25, 7.35. C₂₀H₂₇O₄N₃S₂·HCl requires Cl, 7.49%). The free base, crystallised from alcohol, had m. p. 218° [Found: M (Rast), 421; M (ebullioscopic in acetone), 438. C₂₀H₂₇O₄N₃S₂ requires M, 437]. A third hydrochloride was isolated but is still under examination.

The Tetrahydrochloride of NN'-Bis-(β-aminoethyl)ethylenediamine (VIII).—The compound (V; R = NH₂) was hydrolysed by heating with concentrated sulphuric acid (105 g.) and water (56 c.c.) under reflux in an oil-bath at 160—170° for 10 hours. The product was basified with concentrated sodium hydroxide, and steam-distilled from an oil-bath at 180—190°. The distillate was acidified with hydrochloric acid and evaporated to dryness. The tetrahydrochloride (25 g.) was then obtained; m. p. (from alcoholic hydrochloric acid) 265°.

Di-p-toluenesulphonyl-N-β-chloroethylethylenediamine (VI; R = Cl).—75 G. of alkali-soluble product, obtained in the preparation of (V; R = OH) (see p. 1470), were extracted with hot methyl alcohol (200 c.c.). The solution, filtered from unchanged di-p-toluenesulphonylethylenediamine, was distilled, and the viscous residue dried by distillation with benzene and converted into the chloro-compound (VI; R = Cl) by the action of thionyl chloride; the product (15 g.), crystallised from ether-light petroleum, had m. p. 111° (Found: Cl, 8.6; S, 15.1, 15.2. C₁₈H₂₃O₄N₂ClS₂ requires Cl, 8.24; S, 14.8%). When 2.1 g. of this compound were heated with a solution of sodium (0.12 g.) in alcohol (10 c.c.), it afforded the di-p-toluenesulphonyl derivative of piperazine (1.5 g.), m. p. 291° (Found: S, 16.5. Calc. for C₁₈H₂₂O₄N₂S₂: S, 16.25%) (see J., 1934, 1304); and this (3.8 g.) was also obtained (m. p. 291°) when 4.3 g. of (VI; R = Cl) were heated with ethylenediamine (1.2 g.) in alcohol (40 c.c.).

The Action of ββ'-Diaminodiethylamine on p-Toluenesulphon-β-chloroethylamide.—The trihydrochloride of the base (20.9 g.) was heated with a solution of sodium (6.9 g.) in absolute alcohol (100 c.c.), and the sodium chloride filtered off; 21 g. of the sulphonamide were added to the filtrate, and the mixture boiled under reflux for 8 hours. The solution was cooled, and the crystalline product filtered off and extracted with alcoholic hydrochloric acid; di-p-toluenesulphonylpiperazine remained, and from the filtrate the trihydrochloride of p-toluenesulphonyl-NN'-bis-(β-aminoethyl)ethylenediamine (IX) crystallised; m. p. above 360° (Found: Cl, 25.3. C₁₃H₂₄O₂N₄S₃·3HCl requires Cl, 26.0%).

We thank Mr. F. O'Donel and Mr. L. Kee Sim for help in this work, and the University of Rangoon for a grant in aid. Work on these and related compounds and the co-ordination compounds of the corresponding bases is proceeding.