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SYNTHESIS AND THERMAL REACTIONS OF N-(2,3-EPOXYPROPYL)DIPHENYLAMINE

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The synthesis of N-(2,3-epoxypropyl)diphenylamine is reported. It was found that thermal opening of the oxirane ring of N-(2,3-epoxypropyl)diphenylamine occurred both at the secondary and the tertiary carbon atoms but the basic reaction product is 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline.

Keywords: 3-hydroxymethyl-1-phenylindoline, 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline, N-(2,3-epoxypropyl)diphenylamine, cyclization.

Heating diphenylamine **1** with epichlorohydrin (EPCH) under pressure [1] or with the addition of sodium iodide at high temperatures [2] gives 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline (**2**). In study [3] compound **2** was obtained by heating diphenylamine **1** with excess EPCH at atmospheric pressure without a catalyst. The same authors showed that formation of compound **2** occurs *via* N-(2-hydroxy-3-chloropropyl)diphenylamine [4]. We have found [5] that the tetrahydroquinoline **2** can also be prepared from the epoxypropyl derivative of diphenylamine, i.e. N-(2,3-epoxypropyl)diphenylamine (**3**) which cyclizes upon heating with opening of the oxirane ring at the secondary carbon atom in compound **2**. The aim of this work is the synthesis of compound **3** and a study of it cyclization processes.

Compound **3** is prepared by heating diphenylamine **1** with EPCH at 60-63ºC for 50 h in the presence of glacial acetic acid with subsequent work up of the intermediate N-(2-hydroxy-3-chloropropyl)diphenylamine with sodium hydroxide [4]. The drawback of this method is the long reaction time. The method we propose for preparing compound **3** from diphenylamine **1** with EPCH in the presence of alkali differs in that the reaction is carried out at room temperature in the presence of a 13 fold excess of KOH (with respect to the starting amine) in order to shorten this time. Hence the synthesis of compound **3** can be carried out in a single step and the reaction time is shortened to 7 h.

Many experiments have shown that the optimum temperature for the cyclization of compound **3** to heterocycle **2** is 220-225ºC. Under these conditions the yield of compound **2** reaches 53%. At lower temperatures the formation of compound **2** is very slow.

A study of the thermal reactions of compound **3** has shown that the 1,3-di(diphenylamino)-2-propanol (**4**) and 3-hydroxymethyl-1-phenylindoline (**5**) are formed in addition to compound **2**. With increase in the cyclization temperature to 245-250ºC the amount of compound **5** increases but in this case the basic cyclization reaction product is compound **2**. Column chromatography of the reaction mass gave compounds **4** and **5** and also the 1-phenyl-1,2,3,4-tetrahydroquinoline (**6**) and N-(2,3-dihydroxypropyl)diphenylamine (**7**). Formation of

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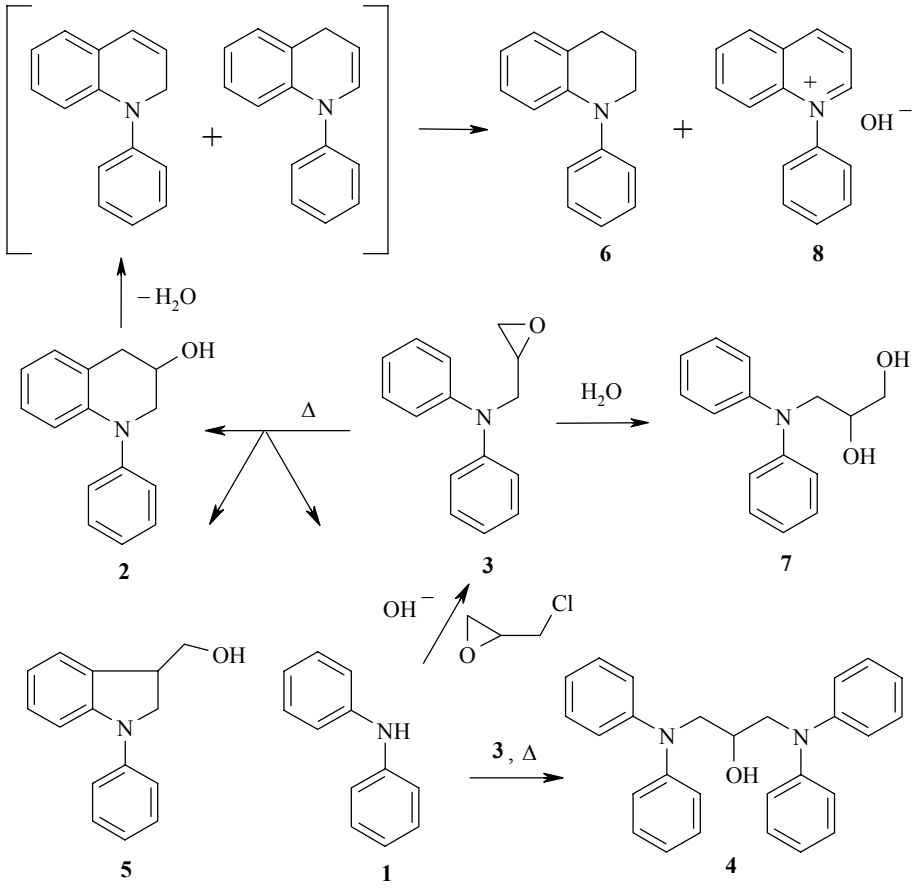
compound **5** (an indoline derivative) upon heating compound **3** is evidently because the oxirane ring opens at the bond between tertiary carbon atom and oxygen atom. We have recorded the mass, IR, and ^{1}H NMR spectra of compound **5** in order to confirm its structure.



Comparing the IR spectra of compound **2** and **5** shows that both spectra show a broad, strong absorption band at 3280 and 3300 cm^{-1} respectively, typical of hydroxyl group stretching vibrations. The vibration associated with the C–OH group appears at 1065 and 1040 cm^{-1} respectively. In the first case the band is more characteristic of a secondary and in the second a primary alcohol [6]. The mass spectrum of compound **5** shows a rather low intensity (36%) molecular ion peak [M$^+$ 225] together with a more stable fragment of even mass [M-31]$^+$ which can be formed by simple fission of a single bond from the molecular ion with odd mass [7]. In addition disruption of the aromaticity of the pyrrole part of the indole molecule infers that the initial loss of the substituent as a whole occurs from position 3 [8]. According to this the substance separated is compound **5** and this structure is also confirmed by ^{1}H NMR spectroscopy.

The formation of compound **4** by heating **3** can evidently be represented as the result of desalkylation of the latter, forming diphenylamine **1** which reacts with the starting compound **3**. The production of compounds **6** and **7** can be rationalized as a dehydration of the cyclization product **2** to give 1-phenyl-1,2- (or 1,4-) dihydroxyquinoline which then disproportionates to **6** and the 1-phenylquinolinium base **8** as shown in [9]. However, we were unable to separate and identify compound **8**. The water formed in the process of dehydration of compound **2** takes part in a reaction with the epoxypropyl derivative **3** to form **7** which proved identical to that obtained by treating compound **3** with diluted trifluoroacetic acid in dioxane.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Tesla BS-487C spectrometer (80 MHz) with HMDS (δ 0.05 ppm) as internal standard. IR spectra were taken on an IR-20 spectrometer for KBr tablets. Mass spectra were recorded on a Hitachi M-80A instrument with direct sample introduction into the ion chamber and a voltage of 80 eV. Monitoring of the course of the reactions was carried out by TLC on Silufol UV-254 plates which were revealed with a UV lamp with 254 filter or by iodine vapor. Chemapol L40/100 was used for the column chromatography.

N-(2,3-Epoxypropyl)diphenylamine (3). A mixture of diphenylamine (50.7 g, 0.3 mol), EPCH (277.5, 3.0 mol), and powdered anhydrous potassium carbonate (58.5 g, 0.45 mol) was stirred for 20-30 min and powdered potassium hydroxide (198 g, 3.0 mol) was added at such a rate that the reaction temperature did not exceed 30ºC. The reaction was carried out for 7 h (TLC, ether–petroleum ether, 1:1) and then treated with cold water and extracted with ether. After removal of ether and excess EPCH the residue was distilled *in vacuo* in a nitrogen stream. The fraction with bp 158-159ºC was collected at 1-2 mm Hg (bp 161-163ºC at 2.5 mm Hg [4]) to give compound **3** (61.8 g, 91.5%).

1,3-Di(diphenylamino)-2-propanol (4). A mixture of compound **1** (12.7 g, 0.075 mol) and compound **3** (11.3 g, 0.05 mol) was heated at 150-155ºC to the disappearance of the starting materials (4 days, TLC, acetone-hexane, 1:4) to give compound **4** (9.9 g, 50%); mp 92-93ºC (hexane). IR spectrum, ν, cm^{-1}: 3540 (OH); 3065, 3090 (arom. CH); 2925 with sh. at 2935, 2875 (aliph. CH); 1595 (C=C); 1500 with sh. at 1460 (C=C, aliph. CH); 750 with sh at 745, 700 (CH, monosubstitued benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.5-6.5 (20H, m, Ar); 4.40-4.35 (5H, m, NCH_2CHCH_2N); 1.12 (1H, m, OH). Found, %: C 82.02; H 6.52; H 7.23. $C_{27}H_{26}N_2O$. Calculated, %: C 82.20; H 6.64; N 7.10.

N-(2,3-Dihydroxypropyl)diphenylamine (7). Compound **3** (5.6 g, 0.025 mol) was dissolved in dioxane (25 ml) and 0.12 ml of a solution of trifluroacetic acid in water (0.8 g CF_3COOH in 100 ml water) was added at 105ºC over 5 min. The mixture was refluxed to the absence of starting material (TLC, acetone-hexane, 1:4). The mixture was then cooled and diluted with water (200 ml). The water was decanted and compound **7** (4.9 g) was obtained as an oily substance crystallizing on standing. Yield 80.7%; mp 95.5-96.5ºC (from a mixture of toluene and hexane, 1:1). IR spectrum, ν, cm^{-1}: 3500-3100 (br, OH); 3070, 3045 (arom. CH); 2960, 2940, 2900, 2880 (aliph. CH); 1595 (C=C); 1500 with sh. at 1455, 1470 (C=C, aliph. CH); 1065 with sh. at 1040 (primary and secondary OH); 750 with sh. at 780, 735, 700 (CH, monosubstituted benzene). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 7.62-6.75 (10H, m, Ar); 4.15-3.00 (7H, $CH_2CH(OH)CH_2OH$). Found, %: C 73.99; H 6.87; N 5.64. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76.

Cyclization of N-(2,3-epoxypropyl)diphenylamine (3). A. Compound **3** (11.3 g, 0.05 mol) was heated at 220-225ºC in a nitrogen atmosphere for 30 h. The reaction product was chromatographed eluting with acetone-hexane (1:4) to give compound **2** (6.0 g, 53.1%); mp 77-78ºC and compound **4** (1.5 g, 7.6%); mp 92-93ºC. Compound **5** was also observed by chromatography in addition to **2** and **4**. The spectroscopic data for compound **2** has been published in [5].

B. Compound **3** (45 g, 0.2 mol) was heated at 245-250ºC for 8 h. The reaction product was separated analogously to method A to give compound **4** (2.4 g) with mp 92.2-93ºC (mixed sample with compound **4** prepared as above did not give a melting point depression) as well as compound **6** [2.1 g, yield 5%, bp 142-145ºC, 2-3 mm Hg; bp 142.5-145, 2-3 mm Hg, [3]), compound **7** [1.7 g, yield 3.5%, mp 95.5-96.5ºC], and a mixture of compounds **2** and **5** (20 g) which was dissolved in ethanol. Cooling to 0-2ºC gave crystals which were filtered off and crystallized three times from ethanol to give compound **2** (16.2 g, 36.6%) with mp 79-80.5ºC. After evaporation of the mother liquor the residue was purified by column chromatography eluting with acetone–ether–hexane (1:1:3) to give compound **2** (5.5%) and compound **5** plus an admixture of compound **2** (0.8 g) which was separated by repeated column chromatography. Yield of compound **5** was 0.5 g;

mp 81-83ºC (from ethanol). IR spectrum, ν, cm^{-1}: 3300 (br, OH); 3050 with sh. at 3025 (arom. CH); 2920-2880 (aliph. CH); 1590 (C=C); 1040 (C–OH); 748 with sh. at 765, 752, 700 (CH mono and *o*-disubstituted benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.38-6.71 (9H, m, Ar); 4.15-3.76 (4H, m, CH_2OH, N–CH_2); 3.56 (1H, m, CH); 1.6 (1H, m, OH). Mass spectrum, *m/z* (I_{rel}, %): 225 $[M]^+$ (24), 194 $[M\text{-}CH_2OH]^+$ (100). Found, %: C 79.81; H 6.62; N 5.98. $C_{15}H_{15}NO$. Calculated, %: C 79.97; H 6.71; N 6.22.

C. Compound **3** (22.5 g, 0.1 mol) was heated at 260-265ºC in a nitrogen atmosphere for 2.5 h. The reaction product was separated as indicated above to give compound **2** (6.2 g, 27.5%), compound **6** (2 g, 8.9%), compound **7** (2.5 g, 12%), compound **5** (1.1 g, 0.5%), and compound **4** (2 g, 5%).

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