UDC 547.831+547.551.2+542.95

INVESTIGATION OF THE PRODUCTS OF REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

II. N-(γ-Chloro-β-Hydroxypropyl)Diphenylamine and Its Reaction Products*

S. I. Kutkevichus and N. N. Vorozhtsov Jr.

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 4, pp. 549-553, 1963

Epichlorohydrin reacts with diphenylamine in the presence of acetic acid to give N-(γ-chloro-β-hydroxypropyl)diphenylamine, cyclized to N-phenyl-1, 2, 3, 4-tetrahydro-3-hydroxyquinoline; a study is also made of its conversion to N-(γ-diphenylamine-β-hydroxypropyl)pyridinium chloride, N-(γ-amino-β-hydroxypropyl)diphenylamine, (γ-diphenylamino-β-hydroxybutyronitrile, and N-(β, γ-epoxypropyl)diphenylamine, the latter on treatment with hydrogen chloride giving back the starting N-(γ-chloro-β-hydroxypropyldiphenylamine. It is shown that when γ-diphenylamino-β-hydroxybutyronitrile is heated in alkali, the products are the salt of γ-diphenylamino-β-hydroxybutyric acid and diphenylamine, i.e. a nitrogen-carbon bond is broken.

The literature states that N-phenyl-1, 2, 3, 4-tetrahydro-3-hydroxyquinoline II is obtained by heating diphenylamine with epichlorohydrin under pressure [1], or in the presence of sodium iodide under ordinary pressure [2], or by prolonged heating of diphenylamine with excess epichlorohydrin [3]. Apparently it is formed via N-(γ-chloro-β-hydroxypropyl)diphenylamine (I). It was of interest to isolate I, to carry out the cyclization, and to investigate other reactions confirming its structure.

Epichlorohydrin does not react with diphenylamine at room temperature, nor at a much higher temperature, 100° Hence, an attempt was made to react epichlorohydrin with diphenylamine in the presence of calcined soda, to prepare N-(β, γ-epoxypropyl)diphenylamine (III), which with hydrogen chloride gives I. This succeeded, but the yield of III did not exceed 14.2%. It was also shown that when diphenylamine is heated with epichlorohydrin and acetic acid, the main product is I, isolated in a crystalline state by chromatographing the reaction products on alumina. Further study showed that the reaction in the presence of acetic acid proceeds even at room temperature, and is complete after 40-50 hr.

Heating of I converts it into II. This shows that formation of II on heating epichlorohydrin with diphenylamine proceeds via I.

It should be mentioned that a pyridine ring is not formed when N-(γ-chloro-β-hydroxypropyl)-1-aminoanthraquinone is heated [4].

Boiling an ether solution of I with anhydrous alkali gives III, converted by hydrogen chloride into the starting compound I, but converted by aqueous alcoholic ammonia into N-(γ-amino-β-hydroxypropyl)diphenylamine, IV, identical with that obtained by heating N-(γ-phthalimido-β-hydroxypropyl)diphenylamine (V) with hydrobromic acid. The structure of I is also shown by conversion to N (γ-diphenylamino-β-hydroxypropyl)pyridinium chloride (VI) and to γ-diphenylamino-β-hydroxybutyronitrile (VII), which is converted by alkaline H_2O_2 to γ-diphenylamino-β-hydroxybutyramide (VIII). Heating VIII with hydrochloric acid or a solution of caustic soda gives γ-diphenylamino-β-hydroxybutyric acid IX, while when VII was heated with a solution of alkali, not only was IX isolated from the reaction products, but also diphenylamine. Since practically no diphenylamine could be isolated when VIII was subjected to alkaline hydrolysis, it must be concluded that the nitrogen-carbon bond is broken mainly in VII, and that this also determines the formation of the diphenylamine.

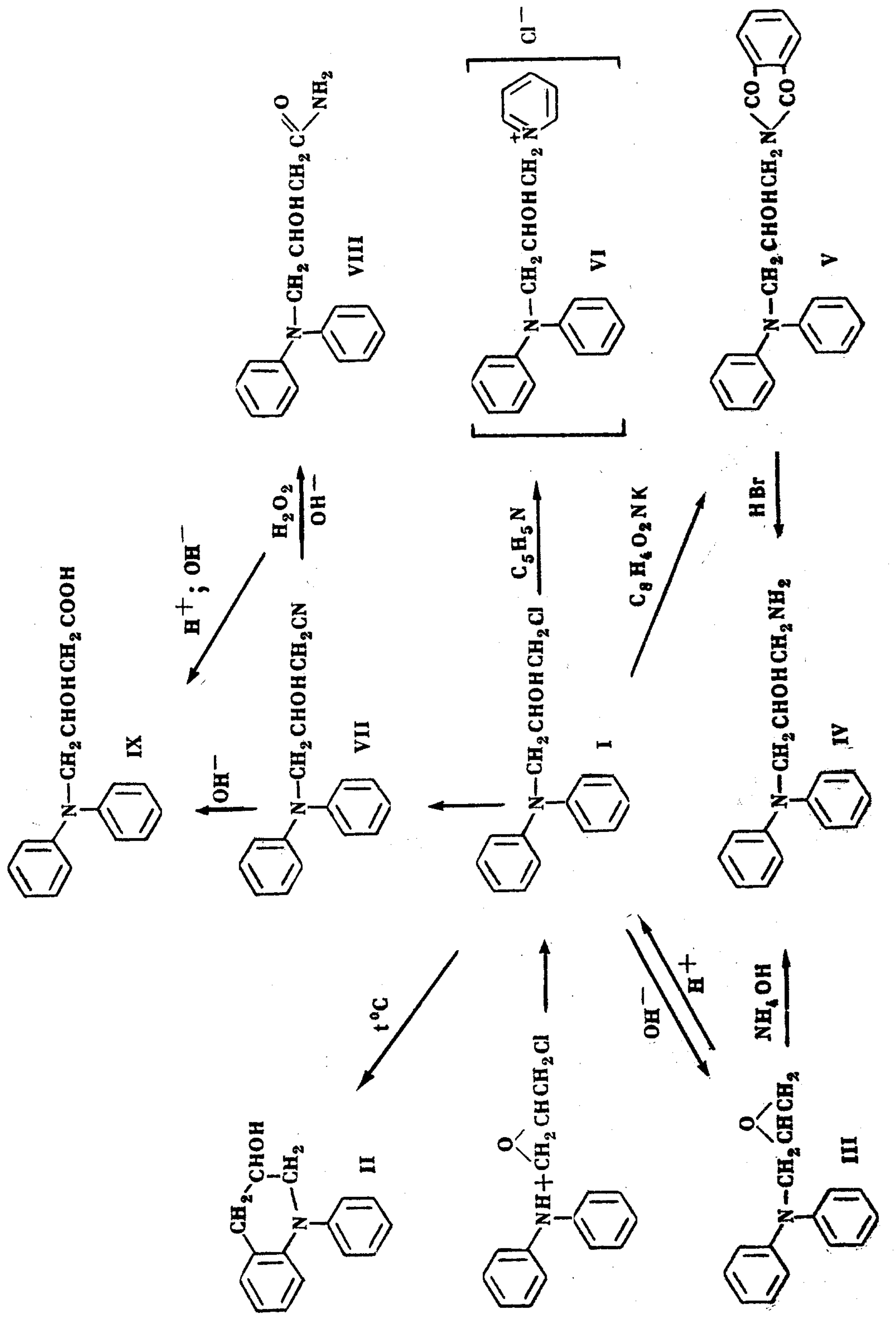
Experimental

N-(γ-chloro-β-hydroxypropyl)diphenylamine (I).

a) 135.2 g (0.8 mole) diphenylamine, 148.0 g (1.6 mole) epichlorohydrin, and 48.0 g 98% acetic acid were heated together at 60-62° for 48 hr. (At room temperature reaction was complete after 45-50 days). The reaction products were shaken with water (600 ml), and then extracted with ether (1200 ml), after which the ether solution was washed with water until no longer acid, treated with active carbon, and dried over sodium sulfate. After distilling off the ether, the residue was dried on a vacuum (0.5-1.0 mm) at 80-85° for 40 min. Mass 207.3 g. The transparent immobile mass was chromatographed. The solution (0.3 g material in 45 ml benzene) was run on to an alumina column, and eluted, first with benzene (120 ml), and then with ether, to give 0.21 g I, mp 43.5-44° (from petrol ether). Found: N 5.5, 5.3; Cl 13.4, 13.2%. Calculated for $C_{15}H_{16}ClNO$: N 5.4; Cl 13.5%.

---

*For Part I see [3].



N—$CH_2CHOHCH_2COOH$
IX
H^+; OH^-
N—$CH_2CHOHCH_2CN$
VII
OH^-
N—$CH_2CHOHCH_2C(=O)NH_2$
VIII
H_2O_2
OH^-
CH_2—CHOH
CH_2
N
II
t°C
NH + CH_2CHCH_2Cl
O
N—$CH_2CHOHCH_2Cl$
I
C_5H_5N
N—$CH_2CHOHCH_2N^+$
Cl^-
VI
$C_8H_4O_2NK$
N—$CH_2CHOHCH_2N$
CO
CO
V
HBr
N—$CH_2CHOHCH_2NH_2$
IV
OH^-
H^+
NH_4OH
N—CH_2CHCH_2
O
III

b) 22.5 g (0.1 mole) III was dissolved in methanol (125 ml), the solution saturated with hydrogen chloride, diluted with water (350 ml), the whole extracted with ether, and the ether solution washed with water until a reaction for chlorine ion was no longer obtained. I was then isolated as described in a) above, mp 43.5-44.0°. On distilling the residue in a vacuum, part passed over at 190-193° (17 g). In addition 1.5 g II was isolated from the distillate.

Epichlorohydrin does not react with diphenylamine under similar conditions when acetic acid is not present.

N-(γ-chloro-β-hydroxypropyl)diphenylamine perchlorate. 2.6 g I was shaken with 20 ml 40% perchloric acid, when it gave 3.4 g perchlorate. Recrystallization from a 1 : 3 methanol-perchloric acid mixture (substance dissolved in methanol, then diluted with HCO_4) gave colorless plates (washed with absolute alcohol), mp 136.5-137.5°. Found: Cl 19.7, 19.5%. Calculated for $C_{15}H_{17}Cl_2NO_5$: Cl 19.6%.

N-phenyl-1, 2, 3, 4-tetrahydro-3-hydroxyquinoline II. 26.2 g I was heated in a vacuum (40 mm), in a current of nitrogen, at 210-215° for 1-2 hr, then the residue distilled, and the main cut bp 187-195° (2 mm) recrystallized from methanol, to give 14.5 g (64.4%) II mp 78.5-79.0°; the literature gives [1] 79.0°.

N-(β, γ-epoxypropyl)diphenylamine III.

a) 16.9 g (0.1 mole) diphenylamine, 13.9 g (0.15 mole) epichlorohydrin, and 10.6 g (0.1 mole) calcined soda were heated at 150-160° for 18 hr. After removing the salts the mass was distilled in a vacuum, in a current of nitrogen. The cut bp 150-170° (2.5 mm) (7.1 g) was repeatedly distilled, to give a cut bp 161-163° (2.5 mm), yield 3.2 g (14.2%). Found: C 79.9, 80.1; H 6.8, 6.9; N 6.4, 6.3%. Calculated for $C_{15}H_{15}NO$: C 80.0; H 6.7; N 6.2%.

b) 50.7 g (0.3 mole) diphenylamine, 55.5 g (0.6 mole) epichlorohydrin, and 18.0 g 98% acetic acid were heated at 60-63° for 50 hr. The reaction products were shaken with water (400 ml), and extracted with ether, (850 ml). After drying over sodium sulfate, 30.0 g powdered sodium hydroxide was added to the ether solution, which was then refluxed for 2 hr. After removing the sodium chloride and excess sodium hydroxide with water, and also the ether, the residue was distilled in a vacuum, in a current of nitrogen. The main part passed over at 158-159°. Yield 57.5 g (85.0%) transparent pale-yellow viscous liquid. Found: C 79.9, 80.1; H 6.7, 6.9; N 6.2, 6.1%. Calculated for $C_{15}H_{15}NO$: C 80.0; H 6.7; N 6.2%.

N-(γ-amino-β-hydroxypropyl)diphenylamine IV.

a) 4.5 g (0.02 mole) III, 120 ml methanol, and 45 ml 25% ammonia were kept at 25-30° for 20 hr. Then 30 ml ammonia was added, and the mixture left for three days at the same temperature. After removing solvent and excess ammonia, the residue was treated with ether (25 ml), the residue then remaining recrystallized from absolute alcohol. Mass 2.1 g, colorless plates IV mp 105.5-106°. Found: N 11.8, 11.7%. Calculated for $C_{15}H_{18}N_2O$: N 11.6%.

b) 13.1 g I, 45 ml dimethylformamide, and 12.0 g potassium phthalimide were heated at 120-125° for 3 hr 30 min. The reaction products were treated with water (200 ml), and then extracted with ether (300 ml). After distilling off the ether, recrystallization from methanol gave 14.2 g N-(γ-phthalimido-β-hydroxypropyl)diphenylamine (V), pale yellow needles mp 128-128.5°. Found: N 7.5, 7.6%. Calculated for $C_{23}H_{20}N_2O_3$: N 7.5%.

7.4 g (0.02 mole) V and 100 ml hydrobromic acid (d 1.38) was heated at 140-145° for 4 hr. After separating off the phthalic acid, the filtrate was made alkaline with sodium hydroxide and cooled to 0-2°. The precipitate which separated after 6 hr was recrystallized from absolute alcohol, yield 4.2 g (87.5%), mp 105.5-106°. The picrate of IV was obtained, mp 195.5-196° (from methanol). Found: N 15.1, 14.9%. Calculated for $C_{21}H_{21}N_5O_8$: N 14.9%.

N-(γ-diphenylamino-β-hydroxypropyl)pyridinium chloride (VI). 2.6 g (0.01 mole) I, 2.4 g (0.03 mole) pyridine, and 4 ml chlorobenzene were heated at 115-120° for 12 hr. The crystals formed were filtered off, washed with acetone, and dried at 50-60°. The substance was quite soluble in water and alcohol, but not very soluble in acetone. Recrystallized from absolute alcohol, it formed colorless needles, VI mp 174.5-175.5°, mass 2.0 g. Found: C 70.6, 70.7; H 6.3, 6.4; N 8.3, 8.4; Cl 10.4, 10.4%. Calculated for $C_{20}H_{21}ClN_2O$: C 70.5; H 6.2; N 8.2; Cl 10.4%.

γ-Diphenylamino-β-hydroxybutyronitrile (VII). 26.2 g I, 125 ml methanol, and 7.5 g potassium cyanide were heated at 60-64° for 1 hr. After removing the solvent, the residue was washed with water, and recrystallized twice from methanol, to give colorless crystals VII, yield 16.2 g (64.3%), mp 96.5-97.5°. Found: N 11.4, 11.4%. Calculated for $C_{16}H_{16}N_2O$: N 11.1%.

γ-Diphenylamino-β-hydroxybutyramide (VIII). 2.5 g (0.01 mole) VII, 25 ml methanol, 10 ml water, 0.6 g (0.01 mole) potassium hydroxide, and 15 ml 10% H_2O_2 were kept at 47-50° for 1 hr. Then the products were kept at −5° for 12 hr, and the resultant precipitate filtered off and recrystallized from alcohol, to give colorless needle-shaped crystals, mass 1.8 g, mp 126.5-127.5°. Found: N 10.6, 10.3%. Calculated for $C_{16}H_{18}N_2O_2$: N 10.4%.

γ-Diphenylamino-β-hydroxybutyric acid (IX).

a) 2.7 g (0.01 mole) VIII and 100 ml hydrochloric acid (d 1.19) were heated at 120-125° for 45 min, diluted with water (200 ml), and extracted with ether (150 ml). After removing the ether, the residue was dissolved in 2% sodium hydroxide, treated with active carbon, acidified with acetic acid, and extracted with ether. After evaporating off the ether, the residue gave colorless crystals. Yield 2.2 g (81.5%), mp 105.5-106.0° (from absolute alcohol). Found: N 5.3, 5.4%. Calculated for $C_{16}H_{17}NO_3$: N 5.2%.

b) 2.7 g (0.01 mole) VIII, 10 ml alcohol, 5 ml water, and 0.8 g (0.02 mole) sodium hydroxide were heated at 100-105° for 2 hr 30 min (evolution of ammonia showed that reaction continued.) The reaction products were kept at about −3° for 2 hr, and the crystals filtered off and dissolved in water. The aqueous solution was acidified with acetic acid, and extracted with ether (50 ml). After removing the ether colorless crystals were obtained, yield 2.3 g (85.2%), mp 105.5-106° (from absolute alcohol).

c) 18.8 g (0.075 mole) VII, 75 ml alcohol, 37.5 ml water, and 6.0 g (0.15 mole) sodium hydroxide were heated at 100-105° for 4 hr. After evaporating off the solvent the residue was dissolved in water (250 ml), and cooled to about −1°. The crystals which had separated after 6 hr were filtered off, yield 5.6 g (43.1%), mp 53.5-54.0° (from methanol), mixed mp with diphenylamine undepressed. The filtrate was acidified with 3% sulfuric acid and extracted with ether (200 ml) the ether evaporated off to give a residue from which 4.2 g (20.7%) IX was isolated, mp 105.5-106° (from absolute alcohol).

The potassium salt of IX had mp 117.5-118.5° (from absolute alcohol, sealed capillary). Found: N 4.8, 4.4%. Calculated for $C_{16}H_{16}NO_3K$: N 4.5%.

REFERENCES

1. German Patent 284291 (Fr. XII, 152)
2. W. Davies and W. Savige, J. Chem. Soc., 890, 1950.
3. N. N. Vorozhtsov Jr. and S. I. Kutkevichus, KhGS, 374, 1965.
4. A. B. Tomchin and L. S. Efros, ZhOKh, 33, 2321, 1963.

28 November 1964

Institute of Organic Chemistry, Siberian
Division AS USSR, Novosibirsk