[Contribution from the Chemical Laboratories of New York University,
Washington Square College]

STUDIES IN DIARYLDIAMINOALKANEDIOLS

JOSEPH B. NIEDERL and DEVINENI SUBBA RAO[1]

Received July 8, 1948

In continuation of previous investigations in the field of adrenaline-like compounds (1), it was thought desirable to commence on a program of synthesizing diaryldiaminoalkanediols. In the present paper the first attempts in this field are given, involving the preparation of diphenylethylamine types and diadrenaline types.

The preparation of both types of these compounds involved the following simple reaction scheme:

$$\mathrm{ArCOCH_2}\boxed{\mathrm{X + H}}\mathrm{NH(CH_2)_nNH}\boxed{\mathrm{H + X}}\mathrm{CH_2COAr} \xrightarrow[\mathrm{EtOH}]{\mathrm{K_2CO_3}}$$

$$\mathrm{ArCOCH_2NH(CH_2)_nNHCH_2COAr} \xrightarrow[\mathrm{Pd}]{\text{reduction}}$$

$$\mathrm{ArCHOHCH_2NH(CH_2)_nNHCH_2CHOHAr}$$

$$\mathrm{Ar} = \mathrm{C_6H_5}\text{—}, \mathrm{(HO)_2C_6H_3}\text{—}. \quad n = 2, 3 \text{ or } 5. \quad \mathrm{X} = \mathrm{Cl} \text{ or } \mathrm{Br}$$

According to the above, unsubstituted phenacyl bromide was treated with half-molar equivalent quantities of a diamine (ethylene-, trimethylene- and pentamethylene-), to yield the corresponding N,N′-diphenacyldiamines, which were then reduced to the corresponding secondary amino alcohols. In the diadrenaline series, instead of the unsubstituted phenacyl bromide, the 3,4-dihydroxyphenacyl chloride was used, which was prepared by rearranging catechol chloroacetate (2), in the conventional manner (3).

EXPERIMENTAL

Aminations. N,N′-Diphenacylethylenediamine dihydrochloride. To phenacyl bromide 6.6 g. (0.033 mole) dissolved in 20 cc. of absolute alcohol, 2.0 g. (0.033 mole) of anhydrous ethylenediamine was added drop by drop while shaking the flask in an ice-bath. After the addition was complete, the flask was shaken for five more minutes and allowed to stand for one more hour. In the mean time the dihydrobromide of the excess ethylenediamine precipitated out. This was filtered and the precipitate was washed twice with 5-cc. portions of absolute alcohol. Dry hydrochloric acid gas was passed into the filtrate for five minutes, when the solution became bluish green, and to this solution 30 cc. of anhydrous ether was added to precipitate the amine as a hydrochloride salt. After keeping this in the refrigerator overnight, it was filtered on a Jena crucible and the precipitate was washed four times with 5-cc. portions of absolute alcohol. The white residue was washed with 5 cc. of cold distilled water to remove any last traces of ethylenediamine hydrochloride present. The final product was then recrystallized from dilute alcohol.

When the reactants were refluxed for one hour on a water-bath, a pale yellow residue, insoluble in both alcohol and water, remained on the filter paper after washing off the

---

[1] Abstracted from the thesis presented by D. Subba Rao to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October 1948.

ethylenediamine hydrobromide precipitate obtained from the original reaction mixture. This substance was purified by dissolving in 5 cc. of alcohol containing 2 cc. of concentrated hydrochloric acid and reprecipitating by making it just alkaline with ammonium hydroxide. It was found by analysis to be N, N, N′, N′-tetraphenacylethylenediamine.

TABLE I

DIPHENYLETHYLAMINE COMPOUNDS

NAME	FORMULA	M.P.; °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N, N′-Diphenacylethylenediamine:				
Free amine	$C_{18}H_{20}N_2O_2$	105–109 (darkens)	9.47	9.18
Dihydrochloride	$C_{18}H_{22}Cl_2N_2O_2$	258–259	7.59	7.45
Disulfate	$C_{18}H_{24}N_2O_{10}S_2$	252–253	5.70	5.52
N-Benzoyl(mono)deriv.	$C_{24}H_{24}N_2O_3$	233–234	7.10	7.29
N, N′-Di(phenylethanol)ethylenediamine:				
Dihydrochloride	$C_{18}H_{26}Cl_2N_2O_2$	290–292d	7.50	7.24
N, N′-Diphenacyltrimethylenediamine:				
Free amine	$C_{19}H_{22}N_2O_2$	120–122	9.03	8.72
Dihydrochloride	$C_{19}H_{24}Cl_2N_2O_2$	250–251	7.31	7.20
Disulfate	$C_{19}H_{26}N_2O_{10}S_2$	204–205	5.52	5.51
N, N′-Di(phenylethanol)trimethylenediamine:				
Dihydrochloride	$C_{19}H_{28}Cl_2N_2O_2$	237–238	7.23	7.45
N, N′-Diphenacylpentamethylenediamine:				
Free amine	$C_{21}H_{26}N_2O_2$	115–117	8.38	8.02
Dihydrochloride	$C_{21}H_{28}Cl_2N_2O_2$	253–254	6.81	6.70
Disulfate	$C_{21}H_{30}N_2O_{10}S_2$	222–223	5.24	5.47
N, N′-Di(phenylethanol)pentamethylenediamine:				
Free amine	$C_{21}H_{30}N_2O_2$	103–104	8.18	7.92
Dihydrochloride	$C_{21}H_{32}Cl_2N_2O_2$	240–241	6.74	7.02

TABLE II

TETRAPHENYLETHYLAMINE COMPOUNDS

NAME	FORMULA	M.P.; °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N, N, N′, N′-Tetraphenacylethylenediamine:				
Free amine	$C_{34}H_{32}N_2O_4$	196–198	5.26	5.47
Dihydrochloride	$C_{34}H_{34}Cl_2N_2O_4$	131–133d	4.66	4.77
Picrate(mono)	$C_{40}H_{35}N_5O_{11}$	168–169	10.27	9.90
N, N, N′, N′-Tetra(phenylethanol)ethylenediamine:				
Free amine	$C_{34}H_{40}N_2O_4$	165–169d	5.18	4.97
Dihydrochloride	$C_{34}H_{42}Cl_2N_2O_4$	124–126d	4.56	4.48

N, N′-Diphenacyl tri- and penta- methylenediamine dihydrochlorides. To phenacyl bromide 7.8 g. (0.04 mole), dissolved in 20 cc. of absolute alcohol, 4.0 g. of potassium carbonate (anhydrous) and 1.6 g. (0.02 mole) of trimethylenediamine (4) [2.0 g. (0.02 mole) in case of pentamethylenediamine] were added and refluxed on a water-bath for two hours. After keeping the reaction mixture at room temperature overnight, it was filtered and the precipitate was washed twice with 5-cc. portions of absolute alcohol, and with 5-cc. portions of cold distilled water to remove the excess potassium carbonate and potassium bromide. The residue along with the filter paper, was treated with 20 cc. of hot alcohol containing 2 cc. of concentrated hydrochloric acid and filtered while hot. On cooling, glistening plates were obtained. More of these hydrochloride crystals were obtained by passing dry hydrochloric acid gas into the alcoholic filtrate from the original reaction mixture for five minutes and keeping it overnight with the addition of 30 cc. of anhydrous ether.

Free amines. The alcoholic-ether filtrates, after filtering off the hydrochloride salts, were allowed to evaporate to dryness at room temperature. The residues thus obtained were then treated with 50 cc. of hot water (80°) and filtered. The cooled filtrates were made alkaline to litmus with ammonium hydroxide and were filtered after cooling in an ice-bath for one hour. The free amines thus obtained were purified by reprecipitating two more times after dissolving in 50 cc. of hot hydrochloric acid and neutralizing with ammonium hydroxide. Total yields: ethylenediamine, 22%; trimethylenediamine, 31%; pentamethylenediamine, 29%.

TABLE III

DIADRENALONE AND RELATED COMPOUNDS

NAME	FORMULA	M.P., °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N,N′-Di(3,4-dihydroxyphenacyl)ethylenediamine (Diadrenalone):				
Free amine	$C_{18}H_{20}N_2O_6$	About 210 (softens)	7.78	7.92
N,N′-Di(3,4-dihydroxyphenacyl)trimethylenediamine:				
Free amine	$C_{19}H_{22}N_2O_6$	About 200 (darkens)	7.48	7.64
N,N′-Di(3,4-dihydroxyphenacyl)pentamethylenediamine:				
Free amine	$C_{21}H_{26}N_2O_6$	About 225 (softens)	6.96	6.83
Dihydrochloride	$C_{21}H_{28}Cl_2N_2O_6$	258–260	5.89	6.22

Disulfates were obtained by treating the hydrochloride salts with alcohol and concentrated sulfuric acid and heating until the solution became clear. After filtering while hot and upon cooling, the disulfate salts were precipitated out.

N,N′-Di(3,4-dihydroxyphenacyl) ethylene-, trimethylene- and pentamethylenediamines. In a three-neck flask (250 cc.), fitted with a mercury sealed stirrer, a reflux condenser, and a delivery tube, 50 cc. of alcoholic solution containing 12.5 g. (0.066 mole) of 3,4-dihydroxyphenacyl chloride was mixed with 4.0 g. (0.066 mole) of ethylenediamine (5.0 g. of trimethylenediamine and 6.8 g. of pentamethylenediamine respectively). Immediately a yellow, finely grained precipitate of the addition product separated out. While passing nitrogen through the reaction mixture and stirring it vigorously, it was heated on a water-bath for one hour and a half. To the dark brown reaction mixture, 15 cc. of concentrated hydrochloric acid was added. After cooling, it was filtered and to the filtrate ammonium hydroxide was added drop by drop until a dark brown precipitate was obtained. This was filtered and rejected as an impurity. Addition of some more ammonium hydroxide to the filtrate until it was just alkaline to litmus yielded the free amine. This was filtered, washed with water and dried *in vacuo*. Total yields: ethylenediamine, 34%; trimethylenediamine, 55%; pentamethylenediamine, 32%.

In the case of pentamethylenediamine, when the reaction mixture was filtered, 0.5 g. of reaction product remained on the filter paper. This was dissolved in 5 cc. of hot distilled water (80°), decolorized with carbon, and filtered. To the filtrate 20 cc. of concentrated hydrochloric acid was added, and the reaction mixture kept in cold water overnight, thus hastening precipitation of N,N′-di(3,4-dihydroxyphenacyl)pentamethylene dihydrochloride.

Reduction. Half a gram of keto-amine hydrochloride was dissolved in 20 cc. of hot distilled water and 0.1 g. of palladium-charcoal catalyst (5) was added. The mixture was shaken in a hydrogenator under 45 pounds pressure at room temperature for two hours. The used catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 20 cc. of hot absolute alcohol and reprecipitated by adding 20 cc. of anhydrous ether.

SUMMARY

In the course of systematic studies in the preparation of diaryldiaminoalkanediols, a series of diphenylethylamine and diadrenaline types of compounds were prepared. The new compounds were properly characterized and derivatized. The physiological properties of these new compounds are under investigation.

New York City, N. Y.

REFERENCES

(1) Niederl and Lay, *J. Am. Chem. Soc.*, **63**, 1498 (1941).
(2) Levin and Hartung, *J. Org. Chem.*, **7**, 408 (1942).
(3) Stolz, *Ber.*, **37**, 4149 (1904).
(4) Putokhin, *Chem. Abstr.*, **23**, 2938 (1929).
(5) Iwamoto and Hartung, *J. Org. Chem.*, **9**, 514 (1944).