[CONTRIBUTION FROM ABBOTT LABORATORIES]

2,2-Diphenyl-1,3-propanediamines and N-Substituted Derivatives

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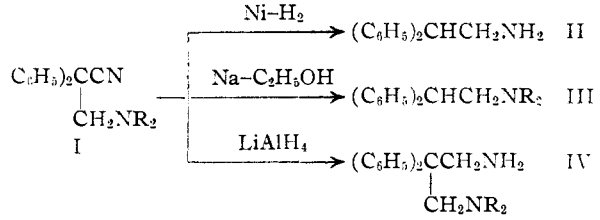
RECEIVED AUGUST 7, 1952

Whereas both catalytic hydrogenation and sodium in alcohol reduction of α,α-diphenyl-β-*t*-aminopropionitriles gave cleavage products, reduction by excess lithium aluminum hydride produced the desired 2,2-diphenyl-1,3-propanediamines. The preparation, for pharmacologic study, of a number of methylated and acylated derivatives of these diamines was carried out.

An accompanying paper[1] describes the preparation of six α,α-diphenyl-β-*t*-aminopropionitriles (I) by the Mannich reaction of diphenylacetonitrile. The present work is concerned with the reduction of the nitrile group in these Mannich products to produce the corresponding diamines IV convertible, in turn, to N-alkylated and N-acylated derivatives of potential pharmacologic interest.

Preliminary attempts to reduce the nitrile group led to abnormal cleavage products. Hydrogenation of the nitrile I (R = CH_3) with Raney nickel in the presence of methanolic ammonia produced β,β-diphenylethylamine (II) in a 75% yield; but when reduced with sodium in alcohol, the two nitriles I (R = CH_3 and C_2H_5) underwent cleavage at a different point to give the amines III (R = CH_3 and C_2H_5) in 65 and 57% yields, respectively.



Elimination of the nitrile group under similar conditions has been noted elsewhere.[2]

Likewise, initial experiments using lithium aluminum hydride as the reducing agent were discouraging. With half a mole of reducing agent per mole of nitrile I (R = CH_3), the proportions indicated by preliminary quantitative work[3] to be most appropriate, there resulted a complex mixture from which no pure product could be isolated. A similar mixture was obtained with a 1:1 molar ratio of lithium aluminum hydride to nitrile, the proportions which Amundsen and Nelson[4] found optimal for the reduction of several simple nitriles; but when two moles of reducing agent were employed for each mole of nitrile I (R = CH_3), the diamine IV (R = CH_3) was isolated in an 86.5% yield. Although the diethylaminonitrile I (R = C_2H_5) was not successfully reduced to the diamine IV (R = C_2H_5), the pyrrolidino and piperidino nitriles I were readily converted to the corresponding diamines IV under these conditions. Consistent with these observations, Nace and Smith[5] found that best yields were obtained in the lithium aluminum hydride reduction of cyclohexanone cyanohydrin when a 2:1 ratio of reducing agent to reactant was employed. It appears, however, that the number of molecules of lithium aluminum hydride per molecule of nitrile necessary to form the intermediate complex varies with the type of compound; and for preparative purposes, large excesses of hydride can be used to good advantage in the reduction of nitriles. Indeed, very similar characteristics of the reaction of Grignard reagents with nitriles have been recognized for many years.[6]

A number of derivatives of the three propanediamines IV (-NR_2 = $N(CH_3)_2$, pyrrolidino and piperidino) were prepared. Methylation of IV (R = CH_3) gave the symmetrical N-tetramethyl-2,2-diphenyl-1,3-propanediamine, from which both the monomethiodide and dimethiodide could be prepared. Many amides, carbamates and ureides were obtained from the three diamines IV by reactions involving the primary amino group. These compounds are listed in Table I. Attempts to convert the acetyl derivative, $(C_6H_5)_2CCH_2NHCOCH_3$, to the corresponding dihydroisoquinoline by a Bischler–Napieralski[7] reaction, using either phosphorus pentoxide or polyphosphoric acid as condensing agent, were fruitless.

A few of the compounds in Table I showed strong but brief analgesic action, and nearly all exhibited local anesthetic activity.

Acknowledgments.—Thanks are due to Mr. E. F. Shelberg of the Abbott Microanalytical Laboratory for the elementary analyses. The authors acknowledge the technical assistance of Mr. M. Freifelder in carrying out the catalytic hydrogenation and the autoclave reactions.

Experimental

Catalytic Hydrogenation of I (R = CH_3). Formation of β,β-Diphenylethylamine (II).—Sixty-eight grams of the nitrile I (R = CH_3) was dissolved in methanol (300 cc.) and treated with liquid ammonia (30 g.). The solution was hydrogenated in the presence of 9 g. of commercial Raney nickel at 120° and 1500 pounds pressure for one hour. Filtration and distillation of the methanol gave an oil which solidified slowly; trituration with cold pentane gave 40 g. (75%) of a solid, m.p. 42–47°; hydrochloride, needles from isopropyl alcohol, m.p. 256–257°.

Anal. Calcd. for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; N, 5.99. Found: C, 72.24; H, 6.78; N, 5.98.

Mixed with an authentic sample of β,β-diphenylethylamine (prepared by hydrogenation of diphenylacetonitrile) it produced no depression of melting point.

(1) H. E. Zaugg, B. W. Horrom and M. R. Vernsten, THIS JOURNAL, **75**, 288 (1953).

(2) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, N. Y., 1947, p. 167.

(3) H. E. Zaugg and B. W. Horrom, *Anal. Chem.*, **20**, 1026 (1948).

(4) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

(5) H. R. Nace and B. B. Smith, *ibid.*, **74**, 1861 (1952).

(6) R. L. Shriner and T. A. Turner, *ibid.*, **52**, 1267 (1930).

(7) W. M. Whaley and T. R. Govindachari in Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.

TABLE I

DERIVATIVES OF 2,2-DIPHENYL-1,3-PROPANEDIAMINES $(C_6H_5)_2CCH_2NHCOR'$ with CH_2NR_2

R'	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
		$-NR_2 = N(CH_3)_2$				
H	113–114	$C_{18}H_{22}N_2O$[a]	76.56	76.86	7.86	7.85
CH_3	97–98	$C_{19}H_{24}N_2O$	76.99	76.96	8.16	8.00
CH_3CH_2	80–81	$C_{20}H_{26}N_2O$	77.38	77.67	8.44	8.28
$CH_3CH_2CH_2$	69–71	$C_{21}H_{28}N_2O$	77.73	77.98	8.70	8.69
$C_6H_5CH_2$	86–88	$C_{25}H_{28}N_2O$	80.60	80.82	7.58	7.44
C_6H_5[b]	95–96	$C_{24}H_{26}N_2O$	80.41	80.71	7.31	7.20
o-Cl-C_6H_5	249–250[c] dec.	$C_{24}H_{26}Cl_2N_2O$	67.13	67.61	6.10	6.29
m-Cl-C_6H_5	211–212[c] dec.	$C_{24}H_{26}Cl_2N_2O$	67.13	66.61	6.10	6.04
p-Cl-C_6H_5	160–163[c]	$C_{24}H_{26}Cl_2N_2O$	67.13	66.01	6.10	6.36
OC_2H_5	216–217[c] dec.	$C_{20}H_{27}ClN_2O_2$	66.19	66.45	7.50	7.37
NH_2	175–177	$C_{18}H_{23}N_3O$[d]	72.69	72.42	7.79	7.60
		$-NR_2$ = pyrrolidino				
H	112–113	$C_{20}H_{24}N_2O$	77.88	78.12	7.84	7.89
CH_3	86.5–87.5	$C_{21}H_{26}N_2O$	78.22	78.45	8.13	8.31
CH_3CH_2	94–96	$C_{22}H_{28}N_2O$	78.53	79.27	8.39	8.41
$CH_3CH_2CH_2$	79–80	$C_{23}N_{30}N_2O$	78.81	78.90	8.63	8.45
$C_6H_5CH_2$	88–90	$C_{27}H_{30}N_2O$	81.37	81.55	7.59	7.93
C_6H_5	152–153	$C_{26}H_{28}N_2O$	81.21	81.39	7.34	7.22
OCH_3	215–216[c] dec.	$C_{21}H_{27}ClN_2O_2$	67.27	67.02	7.26	6.98
OC_2H_5	209–210[c] dec.	$C_{22}H_{29}ClN_2O_2$	67.94	67.85	7.52	7.38
NH_2	151–152	$C_{20}H_{25}N_3O$	74.27	74.50	7.79	7.67
		$-NR_2$ = piperidino				
H	96–97	$C_{21}H_{26}N_2O$	78.22	78.33	8.13	7.98
CH_3	119–120	$C_{22}H_{28}N_2O$[e]	78.53	78.65	8.39	8.12
CH_3CH_2	89–90.5	$C_{23}H_{30}N_2O$	78.81	78.98	8.63	8.58
$CH_3CH_2CH_2$	72–74	$C_{24}H_{32}N_2O$	79.07	79.47	8.85	8.77
$C_6H_5CH_2$	80–81	$C_{28}H_{32}N_2O$	81.51	81.67	7.82	8.08
C_6H_5	133–134	$C_{27}H_{30}N_2O$	81.37	81.60	7.59	7.47
OCH_3	227–228[c] dec.	$C_{22}H_{29}ClN_2O_2$	67.94	67.91	7.52	7.42
OC_2H_5	197–198[c] dec.	$C_{23}H_{31}ClN_2O_2$	68.55	68.79	7.76	7.59
NH_2	161–163	$C_{21}H_{27}N_3O$	74.74	74.57	8.07	8.13

[a] Calcd.: N, 9.92. Found: N, 10.08. [b] Hydrochloride, m.p. 228–229° (dec.). *Anal.* Calcd. for $C_{24}H_{27}ClN_2O$: N, 7.10. Found: N, 7.28. [c] Hydrochloride. [d] Calcd.: N, 14.14. Found: N, 14.13. [e] Calcd.: N, 8.32. Found: N, 8.26.

Reduction of I (R = CH_3) with Sodium and Ethanol. Formation of III (R = CH_3).—To 5 g. of the nitrile I (R = CH_3) dissolved in 90 cc. of absolute ethanol was added 6.5 g. of sodium. The mixture was refluxed for 30 minutes and the alcohol was removed by distillation *in vacuo*. The residue was poured into excess cold dilute hydrochloric acid, extracted with ether and made alkaline with 20% sodium hydroxide. The precipitated oil was taken up in ether, washed and dried. The crude base obtained after evaporation of the ether was distilled. There was obtained 2.9 g. (65%) of a colorless oil, b.p. 114–118° (0.5 mm.), $n^{25}D$ 1.6000.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.57; H, 8.66; N, 6.13.

The corresponding hydrochloride was obtained in the form of colorless leaflets from acetone, m.p.[8] 198–199.5°.

Anal. Calcd. for $C_{16}H_{20}ClN$: C, 73.41; H, 7.70; N, 5.35; Cl, 13.54. Found: C, 73.45; H, 7.61; N, 5.10; Cl, 13.58 (titration).

N,N-Diethyl-β,β-diphenylethylamine (III, R = C_2H_5).—From 5 g. of the nitrile I (R = C_2H_5) treated in the same way as was I (R = CH_3), there was obtained 2.6 g. (57%) of III (R = C_2H_5), b.p. 121–122° (0.4 mm.), $n^{25}D$ 1.5499; hydrochloride, colorless platelets from acetone, m.p. 155–156°.

Anal. Calcd. for $C_{18}H_{24}ClN$: C, 74.60; H, 8.31; N, 4.84. Found: C, 74.80; H, 8.17; N, 4.69.

(8) E. Eidebenz, German Patent 725,844 (1942), reported 202° as the melting point for this compound.

Reduction of I (R = CH_3) with Lithium Aluminum Hydride. Preparation of IV (R = CH_3).—To a mixture of 25.8 g. (0.68 mole) of lithium aluminum hydride and 600 cc. of dry ether in an atmosphere of dry nitrogen was added with stirring a solution of 85 g. (0.34 mole) of the nitrile I (R = CH_3) in 400 cc. of dry ether. The temperature was kept below 5° by means of an ice-bath during the addition which required 1.5 hours. After stirring for an additional hour and a half at ice-bath temperature, the reaction mixture was poured with stirring into ice-water kept under a nitrogen atmosphere. The whole mixture was then passed by suction through a filter medium (Filtercel). The filtrate and filter cake were washed well with ether which, after separation, was extracted with excess dilute hydrochloric acid. This acid extract was then rendered alkaline with excess 20% sodium hydroxide and the resulting oil was taken up in ether. After drying over anhydrous magnesium sulfate the ether was removed by distillation and the residual oil (78.5 g.) was distilled to give 74.7 g. (86.5%) of diamine IV (R = CH_3) b.p. 126–128° (0.2 mm.), $n^{24}D$ 1.5737. The product solidified slowly and completely; large cubes (from pentane), m.p. 37–39°.

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.26; H, 8.72; N, 11.02. Found: C, 80.39; H, 8.69; N, 11.08.

IV (R = CH_3) dihydrochloride, m.p. 242–244° (dec.) (from methanol–ether).

Anal. Calcd. for $C_{17}H_{24}Cl_2N_2$: N, 8.56. Found: N, 8.55.

2,2-Diphenyl-3-pyrrolidinopropylamine (IV, $-NR_2$ = pyrrolidino).—Reduction of the nitrile I ($-NR_2$ = pyrroli-

dino) according to the preceding method gave the diamine IV (NR_2 = pyrrolidino) in an 82.5% yield, m.p. 51–54°. The product was purified by recrystallization from Skellysolve B (petroleum ether, b.p. 63–68°), m.p. 54–55° (large prisms).

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63. Found: C, 81.52; H, 8.49.

2,2-Diphenyl-3-piperidinopropylamine (IV, $-NR_2$ = piperidino).—This compound was prepared from the corresponding nitrile in the above manner. The distilled product was obtained in a 71% yield in the form of a very viscous oil, $n^{28}D$ 1.577, boiling over a wide temperature range. A pure dihydrochloride could not be prepared. A monoformate was obtained, m.p. 148–149° (from methanol–ether).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29. Found: C, 74.65; H, 8.08.

The once-distilled product was used in the preparation of amine derivatives (Table I).

Attempts to prepare the ethylated diamine IV (R = C_2H_5) were unsuccessful. The reduction product distilled over a wide temperature range and isolation of pure derivatives failed.

N-Tetramethyl-2,2-diphenyl-1,3-propanediamine.—A mixture of 10.16 g. (0.04 mole) of the diamine IV (R = CH_3), 80 cc. of 90% formic acid and 3.0 g. of paraformaldehyde was refluxed for five hours after which time the formic acid was removed by distillation *in vacuo*. The residual oil was dissolved in water and reprecipitated by the addition of excess 20% sodium hydroxide. The oil was taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Filtration followed by removal of the ether and vacuum distillation of the residue gave 9.1 g. of colorless, viscous, completely methylated diamine, b.p. 110–114° (0.1 mm.), $n^{25}D$ 1.5579.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28. Found: C, 80.71; H, 9.24.

The **monomethiodide** was prepared by treatment of the base with excess methyl iodide in dry ether, m.p. 148–149° (dec.) (from methanol–ether).

Anal. Calcd. for $C_{20}H_{29}N_2I$: C, 56.60; H, 6.89; N, 6.60. Found: C, 56.87; H, 6.96; N, 6.60.

The **dimethiodide** was prepared by treating the base with excess methyl iodide in dry methanol, m.p. 203–204° (dec.) (from methanol).

Anal. Calcd. for $C_{21}H_{32}N_2I_2$: C, 44.53; H, 5.70. Found: C, 44.35; H, 5.50.

N-Substituted Derivatives of the Propanediamines IV.—The derivatives of the three diamines IV ($-NR_2$ = $N(CH_3)_2$, pyrrolidino and piperidino) are listed in Table I. The N-formyl derivatives were prepared by the action of ethyl formate on the diamines according to the elegant procedure of Human and Mills.[9] They were isolated as the free bases and recrystallized from Skellysolve B or Skellysolve C (petroleum ether, b.p. 88–98°).

The other acylated amines were prepared by ordinary methods involving use of the acid anhydrides or acid chlorides. Whenever the reagent was readily available, it was used in excess as a solvent, the product was isolated in the form of the free base and recrystallized from a Skellysolve. In other cases benzene was used as a solvent with the acid chloride, and if the hydrochloride of the product precipitated in filterable condition, it was isolated in that form, and recrystallized from an alcohol–ether mixture. The carbamates were all prepared in this manner, using methyl or ethyl chloroformate in solvent benzene.

The ureides were prepared by the action of potassium cyanate on the neutral aqueous solutions of the diamine hydrochlorides.[10] They were isolated as the free bases and purified by recrystallization from alcohol or alcohol–water mixtures.

(9) J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).

(10) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd Ed., Longmans, Green and Co., London, 1948, p. 298.

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A Further Study of the Course of Ring-opening of Unsymmetrical Epoxides with Nucleophilic Reagents

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RECEIVED AUGUST 11, 1952

Styrene oxide and butadiene monoxide react with cyanacetic ester to yield α-cyano-γ-phenyl-γ-butyrolactone and α-cyano-γ-vinyl-γ-butyrolactone, respectively. Fractional crystallization and fractional distillation were used to separate what were subsequently shown to be diastereoisomers in both cases. The significance of these results relating to the mechanisms of epoxide ring-opening is discussed.

A substantial literature concerning the mechanism of epoxide ring-opening has been accumulated. There have been important exceptions to the generalizations formerly used to explain the mechanics of ring-opening. We should note that the opening of saturated unsymmetrical epoxides appears to be straight-forward, that is, occurring at the primary carbon atom; but exceptions are seen to occur in cases involving unsaturated members possessing allylic resonance within the epoxide itself.

Some presently held conceptions regard the major influences to be steric factors and the allylic resonance within the epoxide. The steric factors are of two types: first, the relative "bulkiness" of the attacking anion; and, secondly, the size and configuration of the unsymmetrical epoxide. Let us consider malonic, acetoacetic and cyanacetic esters as typical nucleophilic reagents and study them in order of decreasing size of their anions.

Russell and VanderWerf,[1] in their study of the condensation of styrene oxide and butadiene monoxide with malonic ester, demonstrated that attack in both of these cases occurred solely at the primary carbon atom. The conclusion was that the phenyl group pushes electrons into the benzylic position so as to permit attack at only the primary carbon. A group in this department[2] working with 3,4-dihydronaphthalene-1,2-oxide and ethyl methylmalonate demonstrated that in this case attack occurred exclusively at the benzylic position, despite the fact that steric factors of *both* epoxide and nucleophilic reagent are greater here than was the case with styrene oxide and malonic ester. In the case of the 3,4-dihydronaphthalene-1,2-oxide con-

(1) R. R. Russell and C. A. VanderWerf, THIS JOURNAL, **69**, 11 (1947).

(2) E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, *ibid.*, **72**, 488 (1950).