TABLE I

N-ALKYLETHYLENEDIAMINES, $RHNCH_2CH_2NH_2$

				Dihydrochloride					Dipicrate				
					% Carbon		% Hydrogen			% Carbon		% Hydrogen	
R	M. p., °C.	Yield, %	Formula	M. p., °C.	Calcd.	Found	Calcd.	Found	M. p., °C.	Calcd.	Found	Calcd.	Found
Allyl	(*a*)	28	$C_5H_{12}N_2$	173–175	34.62	34.22	8.10	8.09	149–150	36.56	36.50	3.23	3.40
n-Octyl[b]	29–31	84	$C_{10}H_{24}N_2$	208–210	49.00	48.91	10.61	10.45	131–132	41.90	41.70	4.76	4.35
n-Decyl	36–37	83	$C_{12}H_{28}N_2$	220–222	52.75	52.65	10.99	10.77	144–145	43.76	43.70	5.16	5.15
n-Dodecyl[b]	36–38	98	$C_{14}H_{32}N_2$	222–224	55.81	55.45	11.29	11.47	141–142	45.48	45.60	5.54	5.69
n-Tetradecyl	42–43	91	$C_{16}H_{36}N_2$	198–199	58.36	58.77	11.55	11.40	117–119	47.05	47.23	5.88	6.12
n-Hexadecyl	55–57	94	$C_{18}H_{40}N_2$	204–206	60.50	61.00	11.76	11.37	130–131	48.52	49.00	6.20	6.00
n-Octadecyl[c]	64–65	92	$C_{20}H_{44}N_2$	194–196	62.34	62.20	11,95	12.18	124–126	49.87	49.36	6.49	6.92

[a] B. p. 156–158°. [b] Dipicrate yellow-green. [c] Base insoluble in ligroin, soluble in dioxane. Calcd. for $C_{20}H_{44}N_2$: C, 76.92; H, 14.10. Found: C, 76.91; H, 14.00.

surface tension and form stable foams. Like the parent compound, these substituted ethylenediamines form complex metal salts with the transition elements.

The dihydrochlorides, crystallized from alcohol, give white or colorless prisms, sparingly soluble in water, slightly soluble in cold alcohol, and insoluble in dilute hydrochloric acid and in organic solvents. They melt at a relatively high temperature with decomposition.

The dipicrates crystallized from alcohol give yellow or yellow-green prisms.

The physical and analytical data relative to these bases and their dihydrochlorides and dipicrates are collected in the table.

Summary

The even-numbered straight chain alkylethylenediamines from C_8 to C_{18} have been prepared by direct alkylation of ethylenediamine and have been characterized. They are waxy, low-melting solids which combine with two equivalents of mineral acid to form neutral salts whose solutions have low surface tension and show promise as detergents.

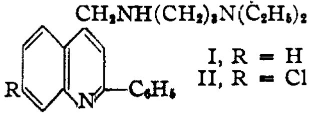
NEW YORK 17, N. Y. RECEIVED JUNE 22, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Synthesis of Some 2-Phenyllepidylamines[1]

BY D. S. TARBELL, J. F. BUNNETT, R. B. CARLIN AND V. P. WYSTRACH

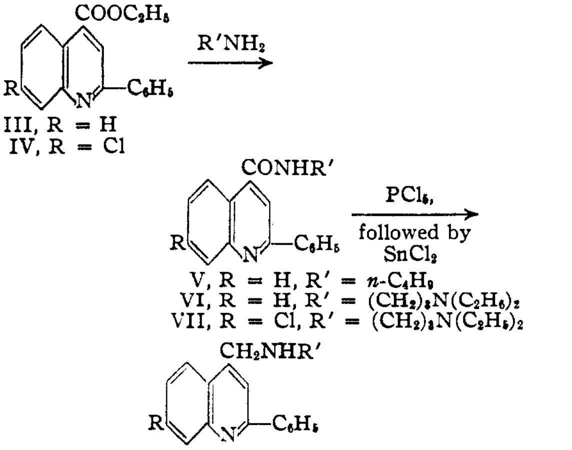
This paper reports the synthesis and properties of some 2-phenyllepidine derivatives containing 3-diethylaminopropylamino side chains on the methyl group, of the type shown.



I, R = H
II, R = Cl

One method of synthesis for this type of compound was developed by Work[2]; in attempting to prepare 4-quinolinealdehyde by the Sonn–Müller method from the corresponding anilide, he obtained N-phenyllepidylamine in good yield, instead of the expected aldehyde. This reaction was applied by him to the synthesis of some dialkylaminoalkyllepidylamines.[2a]

We have found that, by careful control of the experimental conditions, the reaction can be applied to the synthesis of 2-phenyllepidylamines, such as I and II. The steps involved are indicated below; the product formed by the action of phosphorus pentachloride on the amide is probably the amidodichloride,[2] and this intermediate is very sensitive to heat, so that operations must be carried out at temperatures below 80°.



III, R = H
IV, R = Cl

V, R = H, R' = *n*-C_4H_9
VI, R = H, R' = $(CH_2)_3N(C_2H_5)_2$
VII, R = Cl, R' = $(CH_2)_3N(C_2H_5)_2$

I, R = H, R' = $(CH_2)_3N(C_2H_5)_2$
II, R = Cl, R' = $(CH_2)_3N(C_2H_5)_2$
VIII, R = H, R' = *n*-C_4H_9

An attempt to apply this method to the synthesis of the 6-methoxy analog of I was unsuccessful; no pure product except starting material could be isolated from the treatment of the amide with phosphorus pentachloride and stannous chloride.

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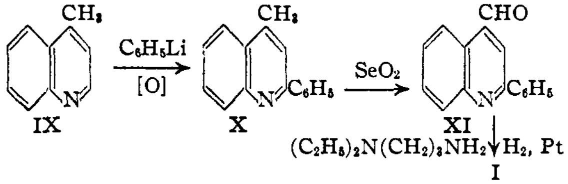
[1] The work described in this article was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

[2] Work, *J. Chem. Soc.*, 429 (1942).

[2a] The preparation of secondary amines by reduction of the chloroimides with hydrogen and palladium has been described by Tishler, Wendler, Ladenburg and Wellman, THIS JOURNAL, **66**, 1328 (1944), and Bergel, Cohen and Haworth, *J. Chem. Soc.*, 165 (1945).

Presumably there was some chlorination of the methoxylated ring.

An alternative method of synthesis for this series, which seemed to offer some advantages for some substituted lepidylamines, was also investigated using compound I as a model. 2-Phenyllepidine, which can be made by condensing acetophenone with *o*-aminoacetophenone,[3] was prepared by the action of phenyllithium on lepidine; the methyl group was oxidized to the aldehyde by selenium dioxide, yielding 2-phenyl-4-quinolinealdehyde, XI, which was then condensed with the appropriate diamine in the presence of hydrogen and platinum, to yield I.



The lepidine was conveniently obtained by reduction of 2-chlorolepidine with hydrogen and Raney nickel in alcoholic alkali.

The compounds I, II and VIII were obtained as solid disulfate salts. Those of I and II were characterized by titration curves which showed a break corresponding to the removal of two of the four replaceable hydrogens, and another break corresponding to the removal of the third. No break was observed, however, for removal of the fourth hydrogen.

Experimental[4]

Ethyl 2-phenylcinchoninate[5] (III) was prepared from cinchophen, absolute alcohol and sulfuric acid, and purified by vacuum distillation.

Ethyl 2-phenyl-7-chlorocinchoninate (IV) was prepared by the same method. The crude ester was precipitated by neutralization as a solid, which, after recrystallization from ethanol, gave needles, m. p. 88.5°, in 72% yield. Further recrystallization from the same solvent yielded long white needles, m. p. 89–89.5°.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.34; H, 4.53. Found: C, 69.41; H, 4.36.

N-(*n*-Butyl)-2-phenylcinchoninamide (V).—A mixture of ethyl 2-phenylcinchoninate (22 g.) and 11 g. of freshly distilled *n*-butylamine was refluxed for twenty-four hours, and poured into 300 cc. of cold water. The yellow oil which separated quickly solidified and, after filtration, was recrystallized from a mixture of 180 cc. of methanol and 50 cc. of water. On cooling the solution, 15.5 g. of white crystals, m. p. 129.5–130.5°, was obtained and washed with cold 78% methanol; only 0.2 g. of additional product of the same purity was obtained by concentrating the mother liquor, the total yield being 65%. One more recrystallization by the same method raised the m. p. to 130–131°.

Anal.[6] Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62. Found: C, 79.24; H, 6.77.

N-(3-Diethylaminopropyl)-2-phenylcinchoninamide (VI).—A mixture of 77 g. of ethyl 2-phenylcinchoninate and 44 g. of 3-diethylaminopropylamine was heated on a steam-bath for twenty hours, then the flask was fitted with a distilling head and heated in an oil-bath at 140–150° for about three hours; during this time, 5 cc. of distillate was collected. The residue was poured into 2 liters of ice and water with stirring; the sticky mass which formed solidified on standing overnight. The crude amide was extracted with several 600–800 cc. portions of hot petroleum ether (b. p. 60–70°), and each saturated portion of solvent after treatment with Norite and filtration, yielded when cooled to 0° about 6 g. of purified amide as white cottony needles. The m. p. of the crops increased from 80–81.5° for the first to 84.5–85.5° for the last; total yield 49.8 g. (50%). The m. p. could not be raised by further crystallization. The compound turns yellow on prolonged exposure to light.

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53. Found: C, 76.35; H, 7.53.

N-(3-Diethylaminopropyl)-2-phenyl-7-chlorocinchoninamide (VII).—Ethyl 2-phenyl-7-chlorocinchoninate (88.5 g.) and 41.5 g. of 3-diethylaminopropylamine were heated together at 130–140° for twenty-four hours in a distilling apparatus in a stream of dry nitrogen; 14.5 cc. of distillate was collected. The crude partially solid amide obtained by pouring the reaction mixture into cold water was recrystallized from 310 cc. of ethanol, then dissolved in 420 cc. of ethanol and the solution cooled to room temperature. The amide, 62.1 g. (55%), m. p. 126–127.5°, separated as white needles. Concentration of the mother liquors yielded 6.2 g. of ester, and additional amounts of mixed amide and ester. Recrystallization of the amide from petroleum ether yielded fine white needles, m. p. 128.5–129.5°.

Anal. Calcd. for $C_{23}H_{26}ClN_3O$: C, 69.77; H, 6.62. Found: C, 69.91; H, 6.46.

N-(3-Diethylaminopropyl)-2-phenyl-6-methoxycinchoninamide.—A mixture of 83 g. of ethyl 2-phenyl-6-methoxycinchoninate[7] and 40 g. of diethylaminopropylamine was heated in a stream of nitrogen for twelve hours. The reaction mixture was worked up as described above for the chloro compound, and the amide (54 g., 50%) was recrystallized from 50% ethanol, m. p. 114–115°.

Anal. Calcd. for $C_{24}H_{29}N_3O_2$: C, 73.60; H, 7.46. Found: C, 73.40; H, 7.23.

N-(3-Diethylaminopropyl)-2-phenyllepidylamine (I).—A solution of 32.2 g. of N-(3-diethylaminopropyl)-2-phenylcinchoninamide (VI) and 18.8 g. of phosphorus pentachloride in 115 cc. of chloroform was refluxed for a few minutes, and then heated to 71° under reduced pressure to remove volatile materials. (In one run, the product completely decomposed with fuming and tar formation when heated at 90–100° to remove the last traces of volatile material.) The residue, a viscous amber-colored mass, was dissolved in 70 cc. of chloroform and added to a mixture prepared by passing dry hydrogen chloride into 74.7 g. of anhydrous stannous chloride[8] in 170 cc. of dry ether until there was a clear lower layer. (Some heat is evolved in mixing the chloroform solution with the ethereal stannous chloride, and cooling is necessary to prevent loss of ether at this point.) Some glass beads were added, the bottle was stoppered and shaken, then opened and, as soon as no more gas presssure was produced, the bottle was tightly stoppered and shaken vigorously for twenty hours. Then the ether solution was decanted from a yellow sludge, and the latter heated with 20% alkali on the steam-bath for three hours. The cooled solution was extracted twice with ether, and the combined extracts dried.

After evaporation of the ether, the residue was distilled at 1 mm., 16.3 g. of a viscous pale red oil, b. p. 180–235°, being collected as the crude base I. Concentrated sulfuric acid was added dropwise to a solution of this oil in 300 cc. of ether until no more of the gummy sulfate was precipi-

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[3] O. Fischer, *Ber.*, **19**, 1037 (1886).

[4] All melting points corrected; analyses by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y., unless otherwise indicated.

[5] Pfitzinger, *J. prakt. Chem.*, [2] **56**, 297 (1897).

[6] Analysis by Lois E. May, Columbia University.

[7] John and Lukas, *J. prakt. Chem.*, [2] **130**, 318 (1931).

[8] Prepared according to Williams, "Organic Syntheses," Vol. **23**, p. 64.

tated. After isolation, this was dissolved in 53 cc. of water, and acetone was added until an oil started to separate; the solution was boiled until it became clear again and finally *n*-propanol (about 800 cc.) was added, while warming the solution on the steam-bath, until there was a copious precipitate. After cooling to 0°, 17.2 g. (37%) of product, m. p. 173-175°, was obtained. It was purified by dissolving in the minimum amount of hot water and slowly adding acetone until precipitation was complete. The m. p. varied from 173.5 to 177.5° depending on rate of heating.

Anal. Calcd. for $C_{23}H_{33}N_3O_8S_2$: C, 50.81; H, 6.12; mol. wt., 544. Found: C, 50.27; H, 5.93; mol. wt. (from neut. equiv.), 552, 560.

N-(*n*-Butyl)-2-phenyllepidylamine (VIII).—This product was prepared in essentially the manner described above; the product was isolated first as the hydrochloride and then converted to the sulfate by treating the free base in ether with concentrated sulfuric acid. The sulfate was obtained pure by recrystallization from absolute alcohol, m. p. 223-224° with decomposition.

Anal. Calcd. for $C_{20}H_{26}N_2O_8S_2$: C, 49.37; H, 5.39. Found: C, 49.75; H, 5.25.

N-(3-Diethylaminopropyl)-2-phenyl-7-chlorolepidylamine (II).—This product was prepared by a similar procedure from 35 g. of the amide (VII), 19 g. of phosphorus pentachloride, 74.5 g. of stannous chloride and appropriate amounts of solvents. The solution of the undistilled crude reduction product in ether was extracted with dilute acid, the free base precipitated with alkali and collected. The white solid (this solid changed to an oil on standing; apparently a hydrate is precipitated which then gives up water to the air) so obtained was freed of unchanged amide by digesting twice with petroleum ether (b. p. 60-70°), 5.7 g. (16%) of amide remaining undissolved. The petroleum ether extracts, when cooled to 0°, deposited a small amount of white solid which was discarded, and the filtrate was treated with a solution of 13 cc. of concentrated sulfuric acid in 150 cc. of absolute ethanol. The crude sulfate (30.1 g., 59%) was recrystallized from absolute ethanol, m. p. about 172° with decomposition.

Anal. Calcd. for $C_{23}H_{32}ClN_3O_8S_2$: C, 47.78; H, 5.58; mol. wt., 578. Found: C, 47.53; H, 5.65; mol. wt. (from neut. equiv.), 590.

Lepidine.—2-Chlorolepidine[9] (53.4 g.) was reduced with hydrogen and Raney nickel at room temperature in two portions using 17.3 g. of potassium hydroxide and 190 cc. of ethanol, and shaking overnight. The catalyst and potassium chloride were removed by filtration, the solvent removed, and the product isolated by distillation in 82% yield after washing with water and drying.

2-Phenyllepidine.[10]—To a solution of phenyllithium prepared from 6.94 g. of lithium, 78.5 g. of bromobenzene and 300 cc. of ether, was added with cooling by an ice-bath, a solution of 30 g. of lepidine in 50 cc. of ether. After the addition was complete, the ice-bath was removed, the mixture stirred for thirty minutes, and decomposed by adding 250 cc. of water. The ether layer was separated, the aqueous solution extracted with a 50-cc. portion of ether and the combined ether extracts dried. The 2-phenyllepidine was isolated as the picrate by evaporating the ether, dissolving the residue in 200 cc. of ethanol and adding a solution of 50 g. of picric acid in 250 cc. of hot ethanol. The red orange picrate was collected while the mixture was still hot, and a second crop was obtained after cooling the filtrate. The moist picrate was decomposed by boiling for thirty minutes with 10% aqueous alkali, and the alkaline solution was then extracted with ether for several hours in a continuous extractor until the ether layer was no longer colored. The 2-phenyllepidine was isolated as two crops of crude crystals from the ether, totaling 24.6 g. (54%). The methiodide, prepared by refluxing a sample with methyl iodide, melted with decomposition at 184-185°, in agreement with the literature.[11]

2-Phenyl-4-quinolinealdehyde (XI).—A solution of 2-phenyllepidine (15 g.) in 30 cc. of dioxane was added to a mixture of 7.7 g. of freshly prepared selenium dioxide,[12] 70 cc. of dioxane and 3 cc. of water at 80° with shaking, the addition taking about ten minutes. The mixture was then refluxed for seventy minutes and 100 cc. of dioxane distilled off; the remainder was poured into 250 cc. of saturated sodium bisulfite solution and allowed to stand with frequent shaking for about two hours. The bisulfite addition compound which was collected and washed thoroughly with ether weighed 20 g. It was decomposed by warming with aqueous sodium carbonate solution, and the aldehyde, which separated as an oil, crystallized on standing overnight in the ice-box. The dark solid was collected and digested with a total of about 150 cc. of petroleum ether (b. p. 60-70°); the clear yellow solution was separated from the insoluble residue and concentrated. A total of 6.7 g. (42%) of the aldehyde, m. p. 75.5-76°, was obtained.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.38; H, 4.75. Found: C, 82.51; H, 4.83.

The aldehyde, when shaken with diethylaminopropylamine in ethanol with hydrogen and platinum, yielded compound I as its disulfate, identical with the sample prepared by reduction of the amide VI.

Acknowledgment.—We are indebted to Drs. R. C. Elderfield and W. J. Gensler of Columbia University for assistance in obtaining some of the starting materials used in this work.

Summary

1. Three 2-phenyllepidylamine derivatives have been prepared by treatment of the corresponding 2-phenylcinchoninamides with phosphorus pentachloride, followed by reduction with stannous chloride in ether.

2. 2-Phenyl-4-quinolinealdehyde has been prepared by selenium dioxide oxidation of 2-phenyllepidine; it condenses with diethylaminopropylamine in the presence of hydrogen and platinum to yield the same 2-phenyllepidylamine which is obtained from the corresponding amide.

Rochester, N. Y. Received June 11, 1945

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[9] Kaslow and Lauer, "Organic Syntheses," Vol. 24, p. 28.

[10] *Cf.* Ziegler and Zeiser, *Ber.*, **63**, 1847 (1930); Gilman and Spatz, This Journal, **66**, 621 (1944).

[11] Bernthsen and Hess, *Ber.*, **18**, 34 (1885).

[12] Kaplan, This Journal, **63**, 2654 (1941).