removed by filtration, mixed thoroughly with 700–800 ml. of boiling water, filtered again, the solid washed with 300 ml. of one per cent. sodium bicarbonate solution and finally with two 300-ml. portions of boiling water. The solid was dried at 100–110°. The yield was 45.8 g. (91.5%); m. p. 395–400° (dec.). No solvent was found which could be used to recrystallize the substance.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: N, 8.48. Found: N, 8.33.

6,6′-Methylenebis-2-chlorolepidine.—A mixture of 40 g. (0.12 mole) of 6,6′-methylenebis-4-methylcarbostyril 60 g. (0.3 mole) of phosphorus pentachloride and 200 ml. of phosphoryl trichloride was heated in a 500-ml. round-bottomed flask in an oil-bath at 120° for five hours. At the end of this time most of the phosphoryl trichloride was removed by distillation and the contents of the flask poured onto 1 kg. of ice. Sodium hydroxide was added until no further precipitation occurred, then the crude 6,6′-methylenebis-2-chlorolepidine removed by filtration and crystallized from two liters of boiling ethyl alcohol. The yield was 17 g. (38.6%); m. p. 184–185°.

Anal. Calcd. for $C_{21}H_{16}Cl_2N_2$: N, 7.63. Found: N, 7.76.

6,6′-Methylenebis-2-methoxylepidine.—Twenty-four grams (0.065 mole) of 6,6′-methylenebis-2-chlorolepidine was added to a solution of 36 g. (1.55 mole) of sodium in 360 ml. of absolute methyl alcohol and the mixture was refluxed for five hours. After 250 ml. of methyl alcohol had been removed by distillation, the residue was diluted with 400 ml. of water, the solid removed by filtration and crystallized from 500 ml. of 70% ethyl alcohol. The yield was 14.5 g. (62.2%); m. p. 124–125°.

Anal. Calcd. for $C_{23}H_{22}O_2N_2$: N, 7.82. Found: N, 7.89.

The other bis-2-alkoxy derivatives were prepared in a similar manner using the appropriate alcohol; the results are summarized in Table I.

6,6′-Methylenebis-2-piperidinolepidine.—Twenty-one grams (0.057 mole) of 6,6′-methylenebis-2-chlorolepidine in 50 ml. of piperidine was refluxed in an oil-bath for forty-eight hours. After the excess piperidine was removed by distillation, the residue was extracted with 100 ml. of 2 *N* hydrochloric acid, the solution treated with Norite, filtered and dilute sodium hydroxide added to precipitate the amino compound. The solid was removed by filtration and crystallized twice from 500 ml. of 80% ethyl alcohol. The yield was 15.5 g. (58.5%); m. p. 142–143°.

Anal. Calcd. for $C_{31}H_{36}N_4$: N, 12.07. Found: N, 12.3.

The bis-morpholino derivative was prepared in an analogous manner.

6,6′-Methylenebis-2-morpholinolepidine, m. p. 126–128°, gave a yield of 57%.

Anal. Calcd. for $C_{29}H_{32}N_4O_2$: N, 11.96. Found: N, 11.78.

TABLE I

6,6′-METHYLENEBIS-2-ALKOXYLEPIDINE

Alkoxy group	M. p., °C.	Yield, %	Empirical formula	N analyses, % Calcd.	Found
C_2H_5O—	162–163	59	$C_{25}H_{26}N_2O_2$	7.28	7.40
n-C_3H_7O—	133–135	45	$C_{27}H_{30}N_2O_2$	6.76	6.50
n-C_4H_9O—	83–85	52	$C_{29}H_{34}N_2O_2$	6.34	6.67

Summary

6,6′-Methylenebis-4-methylcarbostyril has been prepared from 4,4′-methylenebisacetoacetanilide and the former substance has been converted to 6,6′-methylenebis-2-chlorolepidine.

The corresponding 6,6′-methylenebis-2-methoxy, 2-*n*-propoxy, 2-*n*-butoxy, 2-piperidino and 2-morpholino-lepidines have been synthesized from 6,6′-methylenebis-2-chlorolepidine.

BLOOMINGTON, INDIANA RECEIVED DECEMBER 24, 1946

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Cinchoninaldehyde and Aliphatic Amines—Preparation of Some Lepidylamines

BY ARTHUR P. PHILLIPS

A number of lepidylamines have been prepared by earlier workers[1a,b] and were found to possess valuable pharmacological properties. The previous compounds were made from 4-aminomethylquinoline derivatives obtained by reduction of the corresponding 4-cyanoquinolines. Our study of the reactivity of and possible uses for cinchoninaldehyde has been applied to the preparation of several lepidylamines, as this aldehyde seems to offer a simpler route to these substances.

Starting with cinchoninaldehyde and primary aliphatic amines, the initially formed azomethines were reduced to the secondary amines by the general method, described by Campbell,[2] for the preparation of secondary amines. More recently Campbell[3] has made use of this same method for the preparation of some lepidylamines derived from 6-chloro and 7-chlorolepidines.

(1) (a) Wojahn, *Arch. Pharm.*, **274**, 83 (1936); (b) Schöhöfer, "Medicine and Its Chemical Aspects," Vol. III, published by Bayer, Leverkusen, Germany, 1938, p. 62.

(2) Campbell, Sommers and Campbell, THIS JOURNAL, **66**, 82 (1944).

(3) Campbell, Sommers, Kerwin and Campbell, *ibid.*, **68**, 1851 (1946).

Experimental

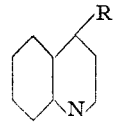
A. Preparation of Azomethines.—Cinchoninaldehyde (0.1 mole) and the appropriate primary amine (0.12 mole) were mixed in 20 volumes of benzene and allowed to stand five hours at room temperature. The mixture was separated from any water layer which may have settled out and was then evaporated on the steam-bath to remove all benzene. The residue usually was reduced immediately to the secondary amine without further purification.

B. Preparation of Secondary Amines.—The azomethine (0.05 mole) was dissolved in 50 cc. of absolute ethanol and was reduced by shaking with prereduced platinum oxide and hydrogen at about 2 atmospheres overpressure. The hydrogen uptake was usually complete within forty-five minutes. After removal of the platinum by filtration, alcoholic hydrogen chloride was added (either 1 equivalent or a large excess, depending upon whether the mono- or polyhydrochloride was desired) and the corresponding hydrochloride was precipitated by the addition of ether.

The yields of the secondary amines obtained were, in general, poor (usually between 50–60%). So far no effort has been made to determine the reason for the low yields. Further investigation could undoubtedly lead to considerable improvement in that direction.

TABLE I

ALIPHATIC AMINO COMPOUNDS FROM CINCHONINALDEHYDE



R	M. p., °C.	Cryst. solvent	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
—CH_2—N(—CH_2CH_3)(—$CH_2CH_2COOCH_3$)·2HCl	223–225	MeOH–acetone	50	55.62	55.25	6.43	6.34
—CH_2—N(—CH_2CH_3)(—$CONH_2$)	143–144	EtOAc–hexane	45	68.12	68.28	6.60	6.75
—CH_2—NH—$CH_2CH_2CH_3$·HCl	162–163	EtOH–Et_2O	60	65.93	65.89	7.24	7.57
—CH_2—N(—$CH_2CH_2CH_3$)(—$CONH_2$)	169–170	EtOAc–hexane	55	69.14	69.13	7.05	7.46
—CH_2—NH—$CH_2CH_2CH_2CH_3$·HCl	147–148	EtOH–Et_2O	54	67.01	66.86	7.64	7.56
—CH_2—NH—$CH_2C_6H_5$·2HCl·$2H_2O$	205–210	EtOH–Et_2O	70	57.11	57.40	6.22	6.01
—CH_2—N(—$CH_2C_6H_5$)(—$CONH_2$)	209–210	EtOAc–hexane	75	74.19	73.96	5.89	5.71
—CH_2—N(—$CH_2C_6H_5$)(—$CONHC_6H_5$)	153–154	Benzene–hexane	100	78.44	78.20	5.77	5.77
—CH=N—$CH_2CH_2C_6H_3$—3,4—$(OCH_3)_2$	84–85	Hexane	85	74.96	74.72	6.30	5.93
—CH_2—NH—$CH_2CH_2C_6H_3$—3,4—$(OCH_3)_2$·HCl	175–176	EtOH–acetone	50–60	66.91	66.92	6.46	6.61
—CH_2—N(—$CONH_2$)—CH_2CH_2—N(—$CONH_2$)—CH_2—	250–251	EtOH	70–75	67.26	67.10	5.65	5.73

C. Preparation of the Ureas.—The secondary amine in the presence of at least 2 equivalents of dilute hydrochloric acid was treated with 1.5–2.0 equivalents of potassium cyanate and the mixture was heated for two hours on the steam-bath. The product ordinarily precipitated from the aqueous solution either as a solid or viscous oil which solidified on cooling and scratching. The solution was brought to *p*H 5–6, and after cooling the urea was collected by filtration.

D. Preparation of the Phenyl Urea.—The secondary amine base in benzene solution was treated with a slight excess of phenyl isocyanate, and was heated one hour on the steam-bath. The product was precipitated by the addition of hexane and cooling.

E. Preparation of N-Ethyl-N-(β-carbomethoxyethyl)-ω-lepidylamine.—The secondary amine base (ethyllepidylamine) was combined with 4 equivalents of methyl acrylate in an equal volume of benzene and the mixture was refluxed for ten hours. After cooling an excess of methanolic hydrogen chloride was added and the dihydrochloride was precipitated with ether.

Acknowledgment.—Thanks are due to Mr. Samuel W. Blackman for the microanalytical results reported here.

Summary

A series of lepidylamine derivatives has been obtained by catalytic hydrogenation of the Schiff base-like products formed from cinchoninaldehyde and some primary aliphatic amines.

TUCKAHOE 7, NEW YORK RECEIVED JANUARY 10, 1947

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Barbituric Acids and Related Compounds Containing Alicyclicalkyl Groups[1]

BY WILLIAM BRAKER, EDWARD J. PRIBYL AND W. A. LOTT

The observation that cyclopropylcarbinol and cyclobutylcarbinol had anesthetic activity when administered rectally suggested that these alicyclicalkyl residues might confer desirable pharmacological properties if introduced into compounds containing an auxapharm group, such as ureides, carbamates, barbituric acids or thiobarbituric acids.

The literature records only a very few barbituric acids containing alicyclicalkyl groups attached to the 5-carbon atom.[2,3,4] Apparently no such compounds containing cyclopropyl or cyclobutylalkyl groups are recorded.

A number of compounds containing the alicyclicalkyl radical have been prepared in which the size of the alicyclicalkyl group was varied to determine any differences in pharmacological properties.

The alicyclic carbinols utilized in this investigation were prepared by known literature methods. Thus, cyclopentylcarbinol and cyclohexylcarbinol were prepared by the action of gaseous formaldehyde on the Grignard compound of the corresponding cycloalkyl halide according to the method described for cyclohexylcarbinol.[5] Cyclopropylcarbinol and cyclobutylcarbinol were prepared by the method of Demjanow.[6] β-(Δ²-Cyclopentenyl)-ethanol was obtained from cyclopentadiene by the method of Noller and Adams.[7] Ethylcyclopropylcarbinol was prepared according to the method of Bruylants[8] in a 60% yield by reduction

(1) Presented before the Division of Medicinal Chemistry, 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April, 1946.

(2) Keach, THIS JOURNAL, **55**, 2977 (1933).

(3) Katsnelson and Brodski, *Compt. rend. acad. sci., U. R. S. S.*, **17**, 477 (1937); *C. A.*, **32**, 2912 (1938); Merkulov, *Bull. med. exptl., U. R. S. S.*, **6**, 64 (1938); *C. A.*, **33**, 2922 (1939).

(4) Blicke and Zienty, THIS JOURNAL, **63**, 2991 (1941).

(5) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 182.

(6) Demjanow, *Ber.*, **40**, 4960 (1907).

(7) Noller and Adams, THIS JOURNAL, **48**, 2446 (1926).

(8) Bruylants, *Rec. trav. chim.*, **28**, 187 (1909).