

was left at 25° for an hour, poured into ice water, and neutralized with barium carbonate. There was no unchanged (I). The barium salt, precipitated from 7 ml. of aqueous solution by addition of alcohol, weighed 1.5 g. For analysis, a sample was dried at 140° for three hours.

Anal. Calcd. for $C_6H_5NO_7S_3Ba$: Ba, 31.49. Found: Ba, 31.20.

Reaction with Diazotized Benzidine.—To the filtered diazo solution made (as above) from 0.35 g. of benzidine hydrochloride was added a solution of 0.6 g. of the barium salt in 5 ml. of water. An orange precipitate appeared after a couple of minutes; yield, 0.3 g. The color of this salt is intensified by mineral acids but becomes nearly colorless in alkaline solution.

Anal. Calcd. for $C_{13}H_{13}N_5O_7S_3$: S, 18.93. Found: S, 18.60.

Diazotization.—In view of the inability of 2-thiophenamine to undergo diazotization, the following experiment strikingly demonstrates the fact that a sulfonated 2-thiophenamine does diazotize. A few drops of 60% fuming sulfuric acid were added to 50 mg. of 2-thiophenaminium chlorostannate, $(C_4H_5SNH_3)_2SnCl_6$. Fumes were evolved. After dilution with ice and water the mixture was treated with a few drops of sodium nitrite solution, then with alkaline 2-naphthol. An intense red dye formed. As a matter of fact, a red color appeared before addition of the naphthol, caused, no doubt, by coupling of the diazotized portion on some of the unreacted thiophene nuclei.

Acknowledgment.—The analyses for nitrogen reported in this paper were micro-Dumas determinations performed by Margaret M. Ledyard, Winifred Brandt, and T. S. Ma.

Summary

Syntheses of several halogen, azo and organic mercury derivatives of aceto-2-thiophenamide are described.

Aceto-2-thiophenamide couples readily in the 5-position with diazo compounds, even in acid solution. The halogen derivatives of this amide also couple not only when the 5-position is unsubstituted but also when a 5-halogen substituent is present, the latter requiring neutral or alkaline conditions. In reactions of the latter type the halogen is ejected, but halogen atoms on positions 3,4 are not disturbed.

Fuming nitric acid causes replacement of a 5-azo group or a 3-halogen substituent by nitro.

Sulfonic derivatives of aceto-2-thiophenamide are described. The diazotizability of a sulfonated 2-thiophenamine is demonstrated.

EVANSTON, ILLINOIS

RECEIVED DECEMBER 2, 1946

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Diquinolylmethanes

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Very few diquinolylmethanes have been recorded in the literature. Schuller³ prepared 5,5'-methylenebis-8-hydroxyquinoline by treatment of 8-hydroxyquinoline with formaldehyde in concentrated sulfuric acid 6,6'-methylenebisquinoline⁴ was obtained by a Skraup reaction on 4,4'-diaminodiphenylmethane. Borsche and Meyer⁵ synthesized 6,6'-methylenebis-2-methylquinoline by the action of alcoholic alkali and acetone on 5,5'-diisatylmethane and decarboxylation of the 6,6'-methylenebis-2-methylcinchoninic acid which was obtained from the reaction. The corresponding 2-phenyl derivative was prepared in a similar manner. Monti and Verona⁶ have reported a methylenebis-6-hydroxyquinoline.

The present paper reports on the synthesis of several 6,6'-methylenebislepiline derivatives from corresponding 6,6'-methylenebisacetacetanilides through the carbostyrils and chlorolepiline derivatives. The latter have also been converted to 2-alkyl ethers and two cyclic tertiary amino derivatives.

(1) The Wm. S. Merrell Company Research Fellow, 1944.

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(3) Schuller, *J. prakt. Chem.*, [2] **88**, 180 (1913).

(4) Borsche and Kienitz, *Ber.*, **43**, 2334 (1910).

(5) Borsche and Meyer, *ibid.*, **54**, 2841 (1921).

(6) Monti and Verona, *Gazz. chim. ital.*, **62**, 878 (1932).

Experimental⁷

4,4'-Methylenebisacetacetanilide.—A stirred solution of 59.4 g. (0.3 mole) of 4,4'-diaminodiphenylmethane in 400 ml. of warm acetone contained in a three-necked flask was treated dropwise with 54.6 g. (0.65 mole) of diketene. The rate of addition was regulated so as to cause the acetone to reflux rapidly. The 4,4'-methylenebisacetacetanilide did not start to precipitate until most of the diketene has been added. The stirred reaction mixture was heated on a steam-bath for an additional hour. The solid was removed by filtration, washed with three 100-ml. portions of acetone and dried at 80–85°. The yield was 86.2 g. (78.5%); m. p. 167.5–168.5°. Recrystallization of 4 g. of the substance from 135 ml. of a boiling solution of absolute ethyl alcohol-acetone (3:1) gave 3.7 g. of white granular solid, m. p. 168.5–169°. The melting point could not be raised further.

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: N, 7.65. Found: N, 7.60.

An additional 16.5 g. was obtained by concentration of the combined mother liquor and filtrate; m. p. 161–164°. One recrystallization of the low melting material raised the m. p. to 166–168°; yield 11.3 g.

6,6'-Methylenebis-4-methylcarbostyril.—To 90 ml. of concentrated sulfuric acid at 70–75° was added 54.9 g. (0.15 mole) of 4,4'-methylenebisacetacetanilide in 2–3 g. portions. The temperature was not allowed to go above 95°. After all of the substance had been added, the reaction mixture was heated in a boiling water-bath for fifteen minutes, then cooled until much solid had separated and water was added cautiously, and cooled from time to time, until 300–350 ml. had been added. The solid was

(7) All melting points are corrected.

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-methylcarbostyryl 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 $C_{23}H_{20}O_2N_2$: 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

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

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.

Summary

6,6'-Methylenebis-4-methylcarbostyryl 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 Campbell³ has made use of this same method for

the preparation of some lepidylamines derived from 6-chloro and 7-chlorolepidines.

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 prerduced 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.

(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).