benzoate was heated at 175° for four hours. As heating progressed the mixture turned semi-solid due to the precipitation of 2-(*n*-amyl)-piperidine hydrochloride. When the reaction was complete the mixture was cooled, ether added, and the solid filtered off. Dry hydrogen chloride was passed into the filtrate and the precipitated hydrochloride recrystallized from isopropyl alcohol.

In cases where the reaction was incomplete, it was necessary to evaporate the ether filtrate from the original reaction mixture and distil off the unreacted piperidine before adding the hydrogen chloride; otherwise a practically inseparable mixture of the piperidine hydrochloride and the hydrochloride of the benzoate was obtained.

Method D. Reaction of a Piperidinoalkyl Halide with a Sodium Alkoxide: γ-(2-Methylpiperidino)-propyl Butyl Ether Hydrochloride.—To a solution of 3.8 g. of sodium in 100 ml. of *n*-butyl alcohol heated to refluxing was added 25 g. of γ-(2-methylpiperidino)-propyl chloride over a period of thirty-five minutes. The mixture then was refluxed for an additional six hours. After the mixture had been cooled and the sodium chloride filtered off, the filtrate was distilled. The distillate (18 g.), which boiled at 130° (9 mm.), was dissolved in dry ether and precipitated as the hydrochloride by the addition of hydrogen chloride. The resulting hydrochloride was recrystallized from an isopropanol–ether mixture.

Method E: Reaction of an Alcohol with an Isocyanate: γ-(2-Methylpiperidino)-propyl Phenylcarbamate Hydrochloride.—To 20 g. of γ-(2-methylpiperidino)-propyl alcohol was added 15 g. of phenyl isocyanate. An immediate reaction took place. The resulting product was dissolved in 150 ml. of benzene, and hydrogen chloride gas passed into the solution. The resulting solid was filtered off and recrystallized from a mixture of ethyl and isopropyl alcohols.

Summary

The physical and pharmacological properties of eighty-nine structural variations of γ-(2-methylpiperidino)-propyl benzoate hydrochloride (Metycaine) are reported. A number of the compounds are potent local anesthetics.

The relationships of the structures of these compounds to their anesthetic actions and toxicities are pointed out and discussed.

Numerous new compounds, intermediates in the preparation of these piperidine derivatives, are listed.

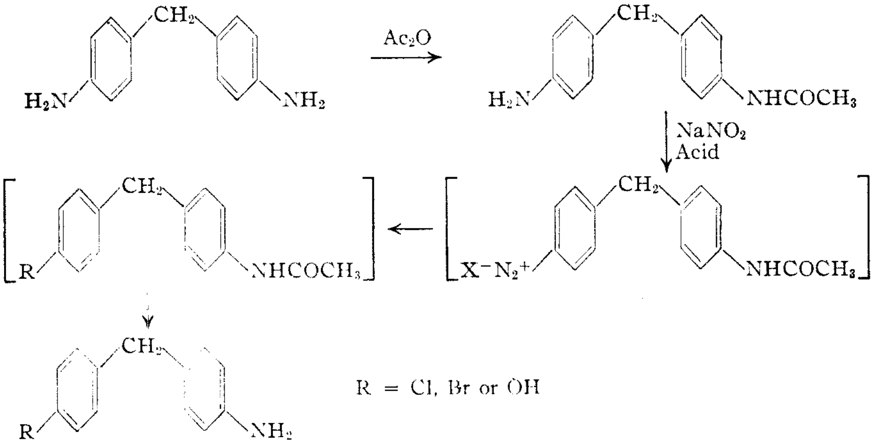
Madison, Wisconsin Received August 19, 1946

[Contribution from the Chemistry Laboratory of Indiana University]

Substituted 4-Aminodiphenylmethanes[1]

By C. E. Kaslow and R. D. Stayner[2,3]

A method has been developed for the preparation of substituted 4-aminodiphenylmethanes from 4,4′-diaminodiphenylmethane. The reaction is illustrated by the equations,



The first step in the synthesis involves the monoacetylation of 4,4′-diaminodiphenylmethane with acetic anhydride in dilute alcoholic hydrochloric acid solution in 35–43% yields. Considerable unchanged 4,4′-diaminodiphenylmethane may be recovered from the acetylation reaction but increasing the amount of acetic anhydride serves only to increase the amount of diacetylated amine and to decrease the percentage yield of monoacetyl derivative.

The diazotization of the 4-acetamido-4′-aminodiphenylmethane proceeded smoothly and replacement of the diazonium group by chlorine and bromine atoms as well as by the hydroxy group proceeded satisfactorily. It was found more satisfactory to prepare the 4-acetamido-4′-methoxydiphenylmethane by alkylation of the 4′-hydroxy compound than by direct replacement of the diazonium group by the methoxy group. Better yields were obtained if no attempt was made to isolate the intermediate acetamido compound after replacement of the diazonium group had been carried out.

Attempts at nitration of 4-acetamido-4′-methoxydiphenylmethane gave only tars from which no identifiable substance could be isolated. Nitration of 4-acetamido-4′-aminodiphenylmethane gave a 53% yield of *p*-nitroacetanilide as well as some unidentified high melting material which was insoluble in all of the ordinary solvents.

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(1) Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, September 12, 1946.

(2) Abstracted from a thesis submitted to the faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(3) Present address: California Research Corporation, Richmond California.

Experimental

4-Acetamido-4′-aminodiphenylmethane.—To a solution of 70 ml. of concentrated hydrochloric acid in 2200 ml. of water at 35° was added 198 g. (1 mole) of 4,4′-diaminodiphenylmethane in 500 ml. of hot 98% ethyl alcohol. The solution was stirred vigorously with an efficient wire stirrer and 99 g. (0.97 mole) of acetic anhydride added dropwise into the apex of the swirling cone produced by the stirrer. The reaction mixture was seeded with one-tenth gram of 4,4′-diacetamidodiphenylmethane to aid in crystallization of the latter substance which is formed as a by-product. After the addition of the acetic anhydride was complete, 500 ml. of hot water (80°) was added and the diacetyl derivative removed by filtration on a Buchner funnel. The solid was mixed thoroughly with a solution of 80 ml. of 95% ethyl alcohol in 500 ml. of water, filtered again and allowed to dry. The combined mother liquor and filtrate was warmed to 35° and a hot (70–75°) solution of 280 g. of hydrated sodium acetate in 350 ml. of water was added in one portion. The mixture was stirred thoroughly and cooled in an ice-and-water-bath for two hours. The precipitated 4-acetamido-4′-aminodiphenylmethane was isolated by filtration, washed twice with a cold solution of 70 ml. of 95% ethyl alcohol in 430 ml. of water and dried at 55–60°. The yield of the substance was 100 g. (42.5%); m. p. 129–131°. The purity of the 4-acetamido-4′-aminodiphenylmethane is high enough that it may be used in subsequent reactions without further purification. The substance may be recrystallized from such solvents as 95% ethyl alcohol, 80% ethyl alcohol, benzene and xylene, as white platelets, m. p. 135.5–136°.[4]

Anal. Calcd. for $C_{15}H_{16}N_2O$: N, 11.67. Found: N, 11.90.

The unchanged diamine may be recovered by addition of alkali to the filtrate from removal of the crude 4-acetamido-4′-aminodiphenylmethane. The 4,4′-diacetamidodiphenylmethane which was obtained as a byproduct may be hydrolyzed in hot 40% sulfuric acid solution to recover a further quantity of the diamine.

4-Amino-4′-hydroxydiphenylmethane.—Ninety-six grams (0.4 mole) of powdered 4-acetamido-4′-aminodiphenylmethane was placed in a 5-liter three-necked flask, enough ice water added to make a thin paste and 250 ml. of concentrated sulfuric acid added in 25-ml. portions. The mixture was kept cold and enough ice water (800 ml.) added from time to time to keep the solid in suspension. The flask and its contents were placed in a salt–ice-bath and a solution of 34 g. of sodium nitrite in 80 ml. of water was added dropwise over a period of one hour while the suspension was stirred and maintained at 5°. The stirring was continued until all of the solid was in solution, then 12 g. of urea in 25 ml. of water was added and the solution stirred for ten minutes. The diazonium salt solution was added over a period of thirty minutes to 100 ml. of boiling 50% sulfuric acid solution and the solution allowed to continue to reflux for three hours. The cold solution was extracted with 250 ml. of ether, the acid solution was kept cold while it was made strongly alkaline with 40% sodium hydroxide so as to dissolve the aminophenol, the alkaline solution extracted with ether and then glacial acetic acid was added until a *p*H 6 was attained in order to precipitate the 4-amino-4′-hydroxydiphenylmethane. The buff-colored granular solid was removed by filtration, washed with two 250-ml. portions of water and dried at 60°. The yield was 64.7 g. (81%); m. p. 144–146°. The substance was recrystallized three times from a mixture of equal volumes of benzene and 95% ethyl alcohol to give colorless platelets, m. p. 151–151.5°.[5]

Anal. Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 7.01.

The molecular weight of the substance was determined ebulliometrically in benzene according to the method described by Shriner.[6]

Anal. Calcd. for $C_{13}H_{13}NO$: mol. wt., 199. Found: mol. wt., 192.

4-Acetamido-4′-hydroxydiphenylmethane.—A solution of 50 g. (0.25 mole) of 4-amino-4′-hydroxydiphenylmethane in 300 ml. of warm methanol was decolorized with Norite, cooled to room temperature and treated with 25 g. (0.41 mole) of acetic anhydride in one portion. After standing for five minutes the solution was heated to boiling, diluted with 200 ml. of water and placed in an ice box. The white crystalline solid was removed by filtration, washed with 50 ml. of 50% ethyl alcohol and dried at 60°. The yield was 49 g. (82%); m. p. 161–161.5°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.95.

A 6.5-g. portion of slightly lower melting material was obtained when the mother liquor was concentrated to 250 ml. and allowed to cool.

4-Amino-4′-methoxydiphenylmethane.—To a cold solution of 16.8 g. (0.42 mole) of sodium hydroxide in one liter of water contained in a three-liter three-necked flask equipped with an efficient stirrer was added 96.4 g. (0.40 mole) of 4-acetamido-4′-hydroxydiphenylmethane in one portion. As soon as the solid was dissolved in the stirred solution, the temperature was adjusted to 20° and 52.8 ml. (0.42 mole) of dimethyl sulfate was added at a rate of two drops per second while the temperature was maintained at 20–22°. After the addition of the dimethyl sulfate was complete, the cooling bath was removed, and the stirring was continued for one hour. The solid was collected on a Buchner funnel, washed twice with water and hydrolyzed by refluxing the substance with one liter of 40% sulfuric acid solution for five hours. The cold acid solution was neutralized with 40% sodium hydroxide, the solid removed by filtration, washed three times with water and dried at 60°. The yield of light brown solid was 70 g. (82%); m. p. 84–85°. The substance could be obtained colorless only by vacuum distillation; b. p. 190–192° (6 mm.), m. p. 85–86°. The substance may be recrystallized from a ligroin (b. p. 75–80°)-benzene solution (3:1).

Anal. Calcd. for $C_{14}H_{15}NO$: N, 6.60. Found: N, 6.47.

4-Acetamido-4′-methoxydiphenylmethane.—This substance was prepared from 24.1 g. (0.1 mole) of 4-acetamido-4-hydroxydiphenylmethane exactly as described in the first part of the preceding experiment. The yield of dry crude 4-acetamido-4′-methoxydiphenylmethane was 25.3 g. (99%); m. p. 98–100°. Colorless platelets of the substance were obtained by three recrystallizations of the substance from 75–80% ethyl alcohol; m. p. 110–110.5°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: N, 5.49. Found: N, 5.52.

4-Amino-4′-bromodiphenylmethane.—One hundred and twenty grams (0.5 mole) of 4-acetamido-4′-aminodiphenylmethane was added in one portion to 200 ml. of cold 48% hydrobromic acid contained in a one-liter three-necked flask equipped with a stirrer, thermometer and a dropping funnel. The stirred mixture was diluted with 250 ml. of water, the solution cooled to 0° by a salt–ice-bath and the substance diazotized by the dropwise addition of a solution of 35 g. of sodium nitrite in 100 ml. of water while the temperature was maintained at 0–5°. After the addition of the sodium nitrite solution was completed, 1 g. of urea was added and the diazonium salt solution allowed to run slowly into one liter of cuprous bromide solution at 70°. (The cuprous bromide was prepared from 145 g. of copper sulfate, 75 g. of sodium bromide, 35 g. of sodium bisulfite and 20 g. of sodium hydroxide.) The solution was warmed to 65–70°, then cooled and the light tan colored solid collected on a Buchner funnel and washed twice with cold water. The solid was extracted by boiling with 900 ml. of 95% ethyl alcohol, filtered and the residue

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(4) Brode and Piper, THIS JOURNAL, **63**, 1502 (1941), reported a melting point of 121–122°.

(5) Bently and Catlow, *C. A.*, **33**, P6879 (1939), have reported the substance but no melting point was given.

(6) Shriner, "Quantitative Analysis of Organic Compounds," 3d ed., Edwards Bros., Inc., Ann Arbor, Michigan, p. 63.

extracted with 200 ml. of boiling alcohol. The combined filtrates were diluted with 2 liters of cold water, filtered, the solid washed with water. The crude 4-acetamido-4′-bromodiphenylmethane (m. p. 155–158°) was refluxed for four hours with 1 liter of 40% sulfuric acid solution then cooled and neutralized with 40% sodium hydroxide solution. The oil was extracted with two 400-ml. portions of ether, the extract dried with anhydrous magnesium sulfate, and after the ether was removed the residue was distilled under reduced pressure. The yield was 84.5 g. (64.5%); b. p. 194–195° (6 mm.), m. p. 50–51°.

Anal. Calcd. for $C_{13}H_{12}BrN$: N, 5.35. Found: N, 5.33.

4-Acetamido-4′-bromodiphenylmethane.—This substance was prepared from 2.6 g. (0.01 mole) of 4-amino-4′-bromodiphenylmethane according to the directions for 4-acetamido-4′-hydroxydiphenylmethane. The yield was 2.3 g. (75%); m. p. 170–173°. The substance was recrystallized from 95% ethyl alcohol as white needles; m. p. 173–173.5°.

Anal. Calcd. for $C_{15}H_{14}BrNO$: N, 4.60. Found: N, 4.61.

4-Amino-4′-chlorodiphenylmethane.—One hundred and twenty grams (0.5 mole) of 4-acetamido-4′-aminodiphenylmethane was dissolved in 400 ml. of cold concentrated hydrochloric acid, 480 ml. of water added and the stirred solution was treated dropwise at 0–3° with a solution of 35 g. of sodium nitrite in 100 ml. of water. After the diazotization was completed, 1 g. of urea was added and the cold solution was added over a period of thirty minutes to one liter of a vigorously stirred solution of cuprous chloride at 70°. (The cuprous chloride solution was prepared from 145 g. of blue vitriol, 120 g. of sodium chloride, 31 g. of sodium bisulfite and 20 g. of sodium hydroxide.) After the addition was complete, the solution was heated to 65–70°, cooled, extracted with ether and isolated in the same manner described for the corresponding bromo compound. The substance was distilled under reduced pressure; b. p. 185–187° (6 mm.), m. p. 73–74°. The yield was 79.5 g. (73%).

Anal. Calcd. for $C_{13}H_{12}ClN$: N, 6.44. Found: N, 6.56.

The substance is a very strong skin irritant, causing a skin eruption very similar to that produced by poison ivy.

4-Acetamido-4′-chlorodiphenylmethane.—This substance was prepared according to the method described for the corresponding 4′-hydroxy compound in 77% yield; m. p. 165.5–166°. The substance may be recrystallized from ethyl alcohol.

Anal. Calcd. for $C_{15}H_{14}ClNO$: N, 5.38. Found: N, 5.54.

4-Amino-4′-methoxybenzophenone.—A solution of 10.2 g. (0.04 mole) of 4-acetamido-4′-methoxydiphenylmethane in 50 ml. of glacial acetic acid containing 1 ml. of water and 4 g. of chromic anhydride was heated on a steam bath for one hour. The solution was diluted with 400 ml. of water, the solid removed by filtration, washed and hydrolyzed by boiling with 50 ml. of 40% sulfuric acid solution. The amino compound was precipitated by the addition of 40% sodium hydroxide solution, the solid collected on a Buchner funnel, washed and dried at 60–65°. The yield was 8 g. (88%); m. p. 102–106°. The substance was purified by recrystallization from 70–75% ethyl alcohol; m. p. 119–120°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: N, 6.17. Found: N, 6.30.

Nitration of 4-Acetamido-4′-aminodiphenylmethane.—Sixty grams (0.25 mole) of the substance was dissolved in 250 ml. of cold concentrated sulfuric acid, the solution stirred mechanically and cooled to 0° then 11.5 ml. (0.275 mole) of fuming nitric acid added while the temperature was maintained at 0 to −5°. The temperature was held at this value for fifteen to twenty minutes after the addition was complete, then the acid solution was poured onto 1 kg. of ice shavings, the solid removed by filtration and washed free of acid. The solid was extracted with two 500-ml. portions of 95% alcohol, the extract concentrated and allowed to cool. The yield of white crystalline material was 24.1 g. (53.5%), m. p. 212–213°. A mixture of the substance with an authentic sample of *p*-nitroacetanilide show no depression in melting point.

The alcohol insoluble residue could not be crystallized from any of the common solvents. The residue weighed 13.3 g.; m. p. 185–195°. Neutralization of the acid filtrate from the diluted nitration mixture gave only tar from which no crystalline substance could be isolated.

Summary

1. A satisfactory method for the preparation of 4-acetamido-4′-aminodiphenylmethane from 4,4′-diaminodiphenylmethane has been described.

2. The preparation of 4′-bromo-, 4′-chloro- and 4′-hydroxy-4-aminodiphenylmethane by diazotization of 4-acetamido-4′-aminodiphenylmethane and replacement of the diazonium group has been described as well as the preparation of the 4′-methoxy compound by methylation and hydrolysis of 4-acetamido-4′-hydroxydiphenylmethane. The acetyl derivatives of the above amino compounds were also prepared.

3. Only tars were produced by nitration of 4-acetamido-4′-methoxydiphenylmethane while a 53% yield of *p*-nitroacetanilide was obtained by nitration of 4-acetamido-4′-aminodiphenylmethane.

BLOOMINGTON, INDIANA

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