acetate solution. The product was purified by recrystallization from ethyl acetate, yield 45 mg., m. p. 206–208° on the hot stage microscope. 3,5-Dibromo-4-aminobenzoylglutamic acid is a white solid soluble in organic solvents and having a typical ultraviolet absorption spectrum, Fig. 2B. For analysis the compound was dried at 100° in high vacuum for two hours, loss 0.83%.

Anal. Calcd. for $C_{12}H_{12}O_5N_2Br_2$: C, 33.98; H, 2.89; N, 6.61; Br, 37.69. Found: C, 34.34, 34.34; H, 2.98, 3.02; N, 7.17, 6.95; Br, 37.44.

Preparation of 3,5-Dichloro-4-aminobenzoylglutamic Acid.—4-Aminobenzoyl-*l*(+)-glutamic acid[8] (300 mg.) was dissolved in 107 cc. of water and 20 cc. of concentrated hydrochloric acid and heated in a water-bath to 80° with a stream of nitrogen passing through the solution. A solution of 6 cc. of *M*/8 sodium chlorate was added dropwise in fifteen minutes, kept at 80° for one hour and then cooled and extracted once with 50 cc. of ethyl acetate. Evaporation of the ethyl acetate gave a dark red oil containing some white solid. It was stirred and cooled with 3 cc. of ethyl acetate and the solid was separated. It was recrystallized from ethyl acetate six times and obtained as white feathery needles, yield 56 mg., 19%. This compound does not melt sharply but softens at about 165° and melts at 177–179° in a capillary tube. On the hot stage microscope it decomposes at 200° to give 3,5-dichloro-4-aminobenzoic acid as does the compound from the vitamin. It gives no depression when mixed with the product from oxidation of vitamin Bc.

Anal. Calcd. for $C_{12}H_{12}O_5N_2Cl_2$: C, 43.00; H, 3.61; N, 8.36; Cl, 21.16. Found: C, 43.16; H, 3.71; N, 8.59; Cl, 20.80.

The ultraviolet absorption curves are identical with those of the compound from the vitamin (Fig. 2A). It shows a low negative rotation $[\alpha]^{27}D$ −3° which could not be determined too accurately.

Summary

Vitamin Bc (pteroylglutamic acid) has been split by oxidation into two parts, a pterine which was found to have the formula $C_7H_5O_3N_5$ and a non-pterine fragment $C_{12}H_{12}O_5N_2Cl_2$. The analytical results on the vitamin itself indicated a molecular formula of $C_{19}H_{19}O_6N_7$ or $C_{21}H_{20}O_6N_8$. The formulas of the oxidation fragments eliminated the latter.

The pterine part yielded guanidine on oxidation.

The non-pterine part on heating decomposed into *dl*-pyrrolidone-carboxylic acid and a compound $C_7H_5O_2NCl_2$ identical with 3,5-dichloro-4-aminobenzoic acid.

The non-pterine part is identical with 3,5-dichloro-4-aminobenzoylglutamic acid.

DETROIT, MICHIGAN RECEIVED[10] FEBRUARY 7, 1947

(10) Original manuscript received July 22, 1946.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND CO.]

Analgesics. II.[1] The Grignard Reaction with Schiff Bases[2]

BY ROBERT BRUCE MOFFETT AND WILLARD M. HOEHN

It is well-known that Grignard reagents will add to aldimines or Schiff bases to give amines in which the hydrocarbon residue of the Grignard reagent is attached to the carbon atom. This reaction, however, has seldom been used as a preparative method. In our work a series of substituted 1,2-diphenylethylamines was desired for testing as analgesics. To prepare these we used the reaction of benzylmagnesium chloride with Schiff bases prepared from substituted benzaldehydes and primary amines.

$$ArCHO + RNH_2 \longrightarrow$$

$$ArCH{=}NR \xrightarrow{C_6H_5CH_2MgCl} ArCH(NHR){-}CH_2{-}C_6H_5$$

The Schiff bases (Table I) were made by allowing the aldehyde and primary amine to react in benzene and then refluxing the benzene with a trap to remove the water. They were usually purified by distillation, followed by recrystallization in cases where they were solids.

A solution of the Schiff base was added to an excess of benzylmagnesium chloride and the addition complex was decomposed with ice and hydrochloric acid. In many cases the hydrochloride of the desired amine was relatively insoluble in the aqueous solution and could be separated in crystalline form. In several cases the hydrochloride was an oil which could be crystallized from non-aqueous solvents after thorough drying. In cases where the hydrochloride remained in the aqueous solution it was necessary to separate the ether layer, make the aqueous solution basic and extract the free amine with ether from the suspension of magnesium hydroxide. In these cases the amine was usually distilled and converted to the hydrochloride in a non-aqueous solvent by hydrogen chloride gas.

Preliminary pharmacological testing in this Laboratory by Mr. Benjamin Vaughan, Jr., by the method of Ercoli and Lewis[3] indicates that of these compounds, the hydrochlorides of the following amines have weak analgesic activity as compared to morphine.

N-Methyl-1,2-diphenylethylamine
N-Methyl-1-(*m*-hydroxyphenyl)-2-phenylethylamine
N-Methyl-1-(*p*-hydroxyphenyl)-2-phenylethylamine
N-Methyl-1-(*m*-ethoxyphenyl)-2-phenylethylamine
N-Benzyl-1-(*p*-hydroxyphenyl)-2-phenylethylamine

Experimental

The Schiff bases which have not previously been reported are listed with their physical constants in Table I. These were prepared by two general methods. Method

(1) The first paper of this series is: Goodson, Weigand and Splitter, THIS JOURNAL, **68**, 2174 (1946).

(2) Presented before the Division of Organic Chemistry at the Chicago meeting of the American Chemical Society, September, 1946.

(3) Ercoli and Lewis, *J. Pharmacol.*, **84**, 301–317 (1945).

TABLE I

SCHIFF BASES: $ArCHO + RNH_2 \longrightarrow ArCH{=}NR$

Benzaldehyde	Amine	Method	Yield, %	B. p. °C.	B. p. Mm.	M. p., °C.	$n^{25}D$	d^{25}_4	Molecular formula	Nitrogen, % Calcd.	Nitrogen, % Found
m-Hydroxy	Methyl	B	74[a]	...	...	150–153[a]	....	....	C_8H_9NO	10.36	10.44[b]
m-Methoxy	Methyl	A	83.6	128	26	.....	1.5549	1.0356	$C_9H_{11}NO$	9.39	9.41[b]
m-Ethoxy	Methyl	A	96	122	12	.....	1.5450	1.0117	$C_{10}H_{13}NO$	8.58	[c]
p-Dimethylamino	Methyl	A	91	95	0.15	54–58[d]	....	....	$C_{10}H_{14}N_2$	17.28	17.17[b]
3-Methoxy-4-hydroxy	Methyl	B	83.5[e]	...	...	131–134.5[f]	....	....	$C_9H_{11}NO_2$	8.48	8.66[b]
2-Hydroxy-3-methoxy	Methyl	A	96	97	0.09	75–78[g]	....	....	$C_9H_{11}NO_2$	8.48	8.39[h]
3,4-Dimethoxy	Methyl	A	97	145	11	55–57[i]	1.5750[j]	....	$C_{10}H_{13}NO_2$	7.82	7.85[b]
2,3-Dimethoxy	Methyl	A	95	132	12	37.5[k]	....	....	$C_{10}H_{13}NO_2$	7.82	7.63[b]
p-Methoxy	Ethyl	A[l]	96.6	80	0.72	.....	1.5524	1.5530	$C_{10}H_{13}NO$	8.58	8.48[h]
p-Methoxy	Allyl	A	90.5	95	.6	.....	1.5630	1.0138	$C_{18}H_{13}NO$	8.00	7.95[h]

[a] Recrystallized from dioxane. [b] Analysis by Marie Gilliland in this Laboratory. [c] Nitrogen analysis low even after redistillation. It may contain an impurity not easily removed by distillation. [d] Freezing point of distillate 50°. A sample was recrystallized first from petroleum solvent (b. p. 69°) then from ether. [e] Crystalline product from reaction mixture. [f] Sample recrystallized from dioxane. [g] Freezing point of distillate 74°. A sample was recrystallized twice from petroleum solvent (b. p. 69°). [h] Analysis by Micro-Tech Laboratories, Skokie, Illinois. [i] Freezing point of distillate, 41°. A sample was recrystallized from a mixture of ether and petroleum solvent (b. p. 30–40°). [j] Index of refraction on supercooled liquid. [k] Freezing point of distillate. [l] A 70% aqueous solution of ethylamine was used. The reaction mixture was saturated with potassium carbonate and the aqueous layer was separated prior to refluxing with the water separator.

TABLE II

DIPHENYLETHYLAMINE $ArCH(NH{-}R){-}CH_2{-}C_6H_5$

Ar phenyl	R	Yield, %	Hydrochloride M. p., °C.	Hydrochloride Molecular formula	Chlorine, % Calcd.	Chlorine, % Found
Phenyl	Methyl	95	184–186	$C_{15}H_{17}N{\cdot}HCl$	14.31	14.35
o-Hydroxy	Methyl[a]	72[b]	185–189	$C_{15}H_{17}NO{\cdot}HCl$	13.44	13.24
m-Hydroxy	Methyl	30[c,d]	201–202	$C_{15}H_{17}NO{\cdot}HCl$	13.44	13.49
p-Hydroxy	Methyl[e]	12.7[f]	220–224[f]	$C_{15}H_{17}NO{\cdot}HCl$	13.44	13.36
o-Methoxy	Methyl[e]	78[g]	123–125	$C_{16}H_{19}NO{\cdot}HCl$	12.76	12.60
m-Methoxy	Methyl	78.3[h]	159–162	$C_{16}H_{19}NO{\cdot}HCl$	12.76	12.91
m-Ethoxy	Methyl	73.5[i]	171–175	$C_{17}H_{21}NO{\cdot}HCl$	12.15[j]	12.06[j]
p-Dimethylamino	Methyl	75[k]	182–185	$C_{17}H_{22}N_2{\cdot}HCl$	21.67	21.67
3,4-Methylenedioxy	Methyl[l]	66[i]	239–242	$C_{16}H_{17}NO_2{\cdot}HCl$	12.16	12.25
3-Methoxy-4-hydroxy	Methyl	38[c,m]	227–230[m]	$C_{16}H_{19}NO_2{\cdot}HCl$	12.07	11.95
2-Hydroxy-3-methoxy	Methyl	52.5[b]	176–179	$C_{16}H_{19}NO_2{\cdot}HCl$	12.07	12.42
3,4-Dimethoxy	Methyl	52.4[n]	154–156	$C_{17}H_{21}NO_2{\cdot}HCl$	11.52	11.56
2,3-Dimethoxy	Methyl	79[i]	104–125[o]	$C_{17}H_{21}NO_2{\cdot}HCl$	11.52	11.35
p-Methoxy	Ethyl	78.5[i]	194–196	$C_{17}H_{21}NO{\cdot}HCl$	12.15	12.04
Phenyl	Allyl[p]	78[i]	206–207.5	$C_{17}H_{19}N{\cdot}HCl$	12.98	13.06
p-Methoxy	Allyl	86[i]	177–180	$C_{18}H_{21}NO{\cdot}HCl$	11.67	11.57
p-Methoxy	β-Ethanol[q]	79.2[r]	154–155.5	$C_{17}H_{21}NO_2{\cdot}HCl$	11.52	11.59
Phenyl	Benzyl[s]	53[i]	245–249	$C_{21}H_{21}N{\cdot}HCl$	10.95	10.90
p-Hydroxy	Benzyl[s]	52[c,i]	185–187	$C_{21}H_{21}NO{\cdot}HCl$	10.43	10.51
Phenyl	Cyclohexyl[t]	40[i]	268–275	$C_{20}H_{25}N{\cdot}HCl$	11.26	11.10

[a] Schiff base reported by Dennstedt and Zimmermann, *Ber.*, 21, 1553 (1888). [b] On decomposing the Grignard reaction mixture, the hydrochloride remained as an oil insoluble in both the water and ether layers. The oil was separated as completely as possible and dried in a vacuum desiccator which caused it to crystallize. A small additional yield was obtained by extracting the aqueous solution with *n*-butanol, washing the butanol solution with saturated salt solution, and removing the butanol *in vacuo*. The residue was combined with the first yield and recrystallized from absolute ethanol and absolute ether. [c] The Schiff base was dissolved in dioxane for addition to the benzylmagnesium chloride solution. [d] On decomposition of the Grignard reaction mixture, part of the amine hydrochloride separated in crystalline form. A further yield of crude hydrochloride was obtained by concentrating the aqueous solution *in vacuo* and cooling. The combined yield was recrystallized from methanol. [e] Schiff base reported by Cromwell and Hoeksema, THIS JOURNAL, 67, 1658 (1945). [f] On decomposing the Grignard reaction mixture the amine hydrochloride remained in solution. The aqueous layer was removed, washed with ether, and made basic by adding an excess of solid sodium carbonate. The mixture was extracted twice with *n*-butanol and then with ether and the combined extracts were dried over sodium sulfate. The solvent was distilled *in vacuo* and the residue was taken up in methanol, treated with decolorizing charcoal and concentrated. Some 4-hydroxystilbene separated (m. p. 186–187°) which was discarded. The filtrate was saturated with hydrogen chloride gas and then diluted with ether to turbidity. After standing, the solution was washed with ether and distilled *in vacuo* to a small volume. On cooling crystals formed and were collected and recrystallized from a mixture

of methanol and ether, m. p. 170–173°. On continued heating at the melting point, the sample crystallized and re-melted at 220–224°. [g] The crude amine was distilled giving nearly colorless liquid, b. p. 104° (0.14 mm.), $n^{25}D$ 1.5648, d^{25}_4 1.0465. The hydrochloride was recrystallized from dry acetone. [h] On decomposing the Grignard reaction mixture the hydrochloride of the amine separated as an oil which soon crystallized and was recrystallized from methanol plus ether. [i] On decomposing this Grignard reaction mixture, the hydrochloride separated in crystalline form; this was recrystallized from methanol. [j] Calcd. N, 4.80 Found: N, 4.87. [k] By treating an ether solution of the crude amine with aqueous sodium bisulfite a white crystalline precipitate was obtained. This was collected and dried, m. p. 163–165° (dec.). This complex was dissolved in dilute hydrochloric acid, made strongly basic with sodium hydroxide and the amine was extracted out with ether. The solution was dried over sodium sulfate and the ether was removed leaving an oil which crystallized, m. p. 70–73°. A sample was recrystallized from petroleum solvent (b. p. 30–40°) giving white crystals, m. p. 71–73°. The yield is based on free amine. The hydrochloride was recrystallized from absolute ethanol. [l] Schiff base reported by Andree, *Ber.*, **35**, 420 (1902). [m] The reaction mixture became very thick and finally set to a solid. The lumps were broken up and decomposed by ice and hydrochloric acid. On standing a crystalline precipitate of the amine hydrochloride separated and was collected, washed with ether, dried, and recrystallized from methanol giving white crystals m. p. 178–189.5°. On continued heating of the melting point sample, it resolidified and melted again at 227-230°. The aqueous filtrate was made basic with sodium hydroxide and extracted with ether. Removal of the ether gave a crystalline residue which after recrystallization from methanol gave 4.5 g. of nearly white amine, m. p. 132–134°. A sample was converted to the hydrochloride and gave the same melting point as the above. [n] The free amine was obtained as a nearly colorless oil which was not distilled but was converted to the hydrochloride in ether by passing in hydrogen chloride gas. This was crystallized from a mixture of methanol and ether. [o] The crystals from methanol at 80–95° and contained solvent of crystallization. A sample dried *in vacuo* at 100° for five hours melted at 104–125°. [p] Schiff base reported by Bergmann and Miekeley, *Ber.*, **57B**, 662 (1924). [q] The reaction product of ethanolamine and anisaldehyde is reported by Meltsner, Walsman and Kremer, THIS JOURNAL, 62, 3494 (1940), to have an oxazolidine structure. [r] The yield is based on the distilled free amine, b. p. 160° (0.013 mm.), $n^{25}D$ 1.5727, d^{25}_4 1.0982. The hydrochloride was precipitated as a gummy solid from ether by hydrogen chloride gas and was crystallized from absolute ethanol. [s] Schiff base reported by Mason and Winder, *J. Chem. Soc.*, 65, 191 (1894). [t] Schiff base reported by West, *J. Soc. Chem. Ind.*, 61, 158 (1942).

A (exemplified below by N-(*m*-methoxybenzal)-methylamine) was used when the product was a liquid or low melting solid. Method B (exemplified below by N-(*m*-hydroxybenzal)-methylamine) was used when the product was a high melting solid.

Method A. N-(*m*-Methoxybenzal)-methylamine.—To a cooled solution of 46.4 g. (0.38 mole) of *m*-methoxybenzaldehyde in 100 ml. of benzene was added a solution of 15.5 g. (0.5 mole) of anhydrous methylamine in 50 ml. of benzene. On standing the solution became warm and water separated. When the initial reaction had subsided the benzene was refluxed with a trap to separate the water. When no more water came off the solvent was removed and the residue was distilled from a Claisen flask giving 47.4 g. (93.6%) of nearly colorless liquid, b. p. 128° (26 mm.).

Method B. N-(*m*-Hydroxyphenyl)-methylamine.—To a suspension of 24.1 g. (0.2 mole) of *m*-hydroxybenzaldehyde in benzene was added a benzene solution of 9.3 g. (0.3 mole) of methylamine and after standing for some time with occasional vigorous shaking was refluxed with the trap to separate water. The solid did not all dissolve, but the character of the crystals changed as the reaction proceeded. After cooling the crystals were collected and dried and recrystallized from dioxane giving 20 g. (74%) of light brown crystals melting at 150–153°.

The diphenylethylamines and their hydrochlorides are listed in Table II. These were all prepared by the general method described below for N-methyl-1,2-diphenylethylamine and its hydrochloride. The numerous differences in procedure are listed on footnotes.

N-Methyl-1,2-diphenylethylamine and Hydrochloride.[1]—Benzylmagnesium chloride was prepared in the usual way from 19.5 g. (0.8 mole) of magnesium, 92 ml. (102 g., 0.8 mole) of benzyl chloride, and 300 ml. of dry ether. To this solution was slowly added with stirring a solution of 24.0 g. (0.202 mole) of N-benzalmethylamine[4] in 50 ml. of dry ether. After refluxing with stirring for two hours, the mixture was cooled and decomposed by pouring it slowly onto a mixture of the minimum amount of ice and 200 ml. of concentrated hydrochloric acid. The layers were separated, the aqueous layer was washed with ether and made basic with sodium hydroxide. The suspension of magnesium hydroxide was extracted repeatedly with ether (total volume about 2.5 liters) which was washed with water and dried over potassium carbonate. After removing the ether by distillation the residue was distilled from a Claisen flask giving 40.5 g. (95%) of colorless liquid, b. p. 83° (0.04 mm.), $n^{25}D$ 1.5640.

Ten grams of this amine was converted to its hydrochloride by dissolving it in 150 ml. of anhydrous ether and saturating the solution with hydrogen chloride gas. The hydrochloride separated as a white crystalline precipitate which was collected, washed with ether and dried; yield 12 g., m. p. 184–186°. This was recrystallized by dissolving it in a little methanol and adding absolute ether. The melting point remained unchanged.

(4) Zaunschirm, *Ann.*, **245**, 231 (1888).

Summary

1. The reaction of benzylmagnesium chloride on the Schiff bases from substituted benzaldehydes and primary amines has been found to be a suitable method for the preparation of 1,2-diphenylethylamines.

2. Nineteen new secondary amines have been prepared by this reaction.

3. Ten new Schiff bases were prepared as intermediates.

4. Preliminary pharmacological testing indicates that some of the amine hydrochlorides are weak analgesics.

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