crystallized from water to give 3.8 g. (81%) of buff needles, m.p. 142–144°.

Anal. Calcd. for $C_{10}H_7ClN_2O$: N, 13.58. Found: N, 13.40.

With phosphorus oxychloride this compound gives 2,5-dichloro-3-phenylpyrazine (m.p. 57–58°), as does its isomer in J.

Acknowledgments.—We are grateful to the Ortho Research Foundation for permitting all experimental work to be done in its laboratories, and to Mr. Joseph Grodsky for the microanalyses.

RARITAN, NEW JERSEY

[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

Hexamethylene-1,6-bis-*t*-amines in Which Part of the Six Carbon Chain is also Part of a Six-membered Ring

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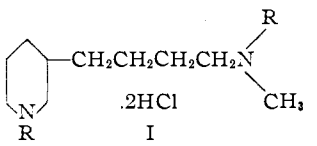
A series of hexamethylene-1,6-bis-*t*-amine hydrochlorides in which part of the six-carbon chain is part of a six-membered ring has been prepared. These compounds were tested as hypotensives and ganglionic blocking agents and some were as effective orally as hexamethonium chloride in anesthetized cats.

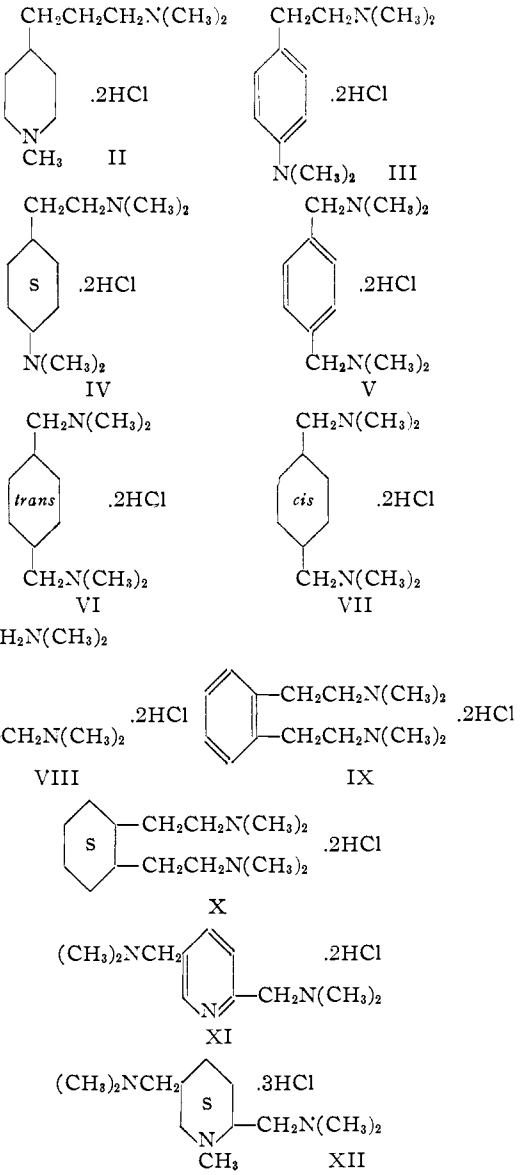
Norton and Phillips[1,2] reported that compounds of the structure I possess potent ganglionic blocking activity. It is apparent that this is a hexamethylenediamine in which part of the six-carbon chain is also part of a six-membered ring. It was decided to prepare a series of analogous compounds in which various parts of the six-carbon chain are also part of a six-membered ring. The preparation of this series of compounds constitutes the subject matter of this communication.



I

In the compounds that were prepared (II–XII) the six-membered ring was variously benzene, cyclohexane, pyridine and piperidine.

Compound II was prepared by two separate routes: (1) 1-Methyl-4-(γ-chloropropyl)-piperidine has been prepared by Ruddy and Bishop[3] by thionyl chloride treatment of 1-methyl-4-(γ-hydroxypropyl)-piperidine, which was made[4] by catalytic reduction of 4-(γ-hydroxypropyl)-pyridine followed by methylation by heating with a mixture of formic acid and formaldehyde. The intermediate 1-methyl-4-(γ-hydroxypropyl)-piperidine has now been prepared by an alternate procedure. 4-(γ-Hydroxypropyl)-pyridine was converted to its methobromide quaternary, and hydrogenated in ethanol over platinum to give the desired methylpiperidylpropanol. 1-Methyl-4-(γ-chloropropyl)-piperidine hydrochloride on treatment with an excess of dimethylamine in benzene gave a moderate yield of II which was somewhat difficult to purify. (2) 4-(γ-Hydroxypropyl)-pyridine[5] was oxidized with acidic potassium permanganate, by the procedure previously described for oxidizing 2-(γ-hy-



(1) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953).
(2) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(3) A. W. Ruddy and H. W. Bishop, *ibid.*, **74**, 1919 (1952).
(4) R. R. Burtner and J. M. Brown, *ibid.*, **69**, 630 (1947).
(5) Reilly Tar and Chemical Corporation.

droxypropyl)-pyridine,[6] to give a good yield of β-(4-pyridyl)-propionic acid (XIII).[7,8] XIII was converted to the corresponding dimethylamide XIV by bubbling dimethylamine through molten XIII. XIV-methobromide was prepared by treating XIV with an acetone solution of methyl bromide; reduction of XIV methobromide in water over platinum gave 1-methyl-4-(β-dimethylcarbamidoethyl)-piperidine hydrobromide (XV) in good yield. From XV the free base was liberated and treated in ether with lithium aluminum hydride, giving a base which was converted with hydrogen chloride to very pure II.

III was prepared by treating *p*-nitrophenylacetic acid with thionyl chloride followed by dimethylamine, to obtain N,N-dimethyl-*p*-nitrophenylacetamide (XVI).[9] XVI by hydrogenation in ethanol over platinum at room temperature gave *p*-aminophenylacetyldimethylamine (XVII), a nicely crystalline material. It may be noted here that N,N-dimethyl β-(*m*-nitrophenyl)-propionamide on similar reduction gave a material that could not be crystallized nor otherwise purified. XVII was subjected to a reductive methylation reaction described by Pearson and Bruton[10] to give a good yield of N,N,N′,N′-tetramethyl-*p*-aminophenylacetamide (XVIII) which on reduction with lithium aluminum hydride in ether gave a nearly quantitative yield of distilled N,N,N′,N′-tetramethyl-*p*-(β-aminoethyl)-aniline; treatment of this base with HCl gave III.[11]

IV was prepared by hydrogenation of III in acetic acid over platinum at room temperature. While IV might exist in more than one stereoisomeric form, this cyclohexane compound seemed to be homogeneous.

The free base of V is a known compound[12] and its quaternaries have also been reported,[12,13] although its dihydrochloride has not been described.

VI and VII were prepared by identical series of reactions starting with *trans*- and *cis*-cyclohexanedicarboxylic acids, respectively. Dimethyl terephthalate was hydrogenated and the hydrogenation products hydrolyzed and separated by the technique of Guha and Hazra[14] into the *cis* and *trans* isomers of cyclohexanedicarboxylic acid, which were converted to the bis-dimethylamides *via* their acid chlorides, a type of reaction previously shown not to involve any inversion.[15] The bis-dimethylamides were treated with lithium aluminum hydride to give the *trans*- and *cis*-1,4-bis-(dimethylaminomethyl)-cyclohexanes, which on treatment with HCl gave VI and VII, respectively.

VIII was prepared by a similar sequence of reactions starting from homoisophthalic acid, which was prepared by the procedures of Reinglass[16] and of Komppa and Hirn.[17]

IX and X were similarly prepared from *o*-phenylenediacetic acid, prepared by the procedure of Baeyer and Pape.[18]

XI and XII were prepared starting from pyridine-2,5-dicarboxylic acid (isocinchomeronic acid). This acid was converted to the corresponding bis-dimethylamide XIX *via* the diacid chloride; XIX on reduction with lithium aluminum hydride gave a very poor yield of 2,5-bis-(dimethylaminomethyl)-pyridine, which gave XI with HCl. XIX when treated with methyl bromide in acetone gave a good yield of XIX-methobromide, which on hydrogenation in ethanol over platinum yielded 1-methyl-2,5-bis-(dimethylcarbamido)-piperidine (XX). XX, when reduced with lithium aluminum hydride, gave 1-methyl-2,5-bis-(dimethylaminomethyl)-piperidine, which with HCl gave XII.

Although some (III, VI, VIII, IX, XI and XII) of these compounds were essentially devoid of effect upon blood pressure or ganglionic blockade in anesthetized cats, others (II, IV and V) appeared to have an activity by the oral route, comparable to that of Methium®.[19]

Experimental[20]

Compound II. 1-Methyl-4-(γ-hydroxypropyl)-pyridinium Bromide.—4-(γ-Hydroxypropyl)-pyridine (137 g., 1.0 mole) was dissolved in 1200 ml. of an acetone solution of methyl bromide (125 g., 1.3 moles). After a few minutes the solution became cloudy and an oil started settling out. This mixture was allowed to stand overnight at 30° after which the oil had all crystallized. Recrystallization from ethanol–acetone gave 199 g. (85% of yield) of material melting at 78–80°.

Anal. Calcd. for $C_9H_{14}BrNO$: C, 46.56; H, 6.08. Found: C, 46.40; H, 5.93.

1-Methyl-4-(γ-hydroxypropyl)-piperidine Hydrobromide.—1-Methyl-4-(γ-hydroxypropyl)-pyridinium bromide (174 g., 0.75 mole) was dissolved in 700 ml. of ethanol and shaken with hydrogen over Adams platinum catalyst at 60° and 800 p.s.i. The theoretical amount of hydrogen was taken up quickly and the cooled suspension was filtered and evaporated to dryness under vacuum on the steam-bath leaving a crystalline residue which after recrystallization from 600 ml. of ethanol:acetone (1:3) weighed 150 g. (84% yield) and melted at 117–118°.

Anal. Calcd. for $C_9H_{20}BrNO$: C, 45.38; H, 8.46. Found: C, 45.59; H, 8.49.

1-Methyl-4-(γ-dimethylaminopropyl)-piperidine Dihydrochloride (II).—1-Methyl-4-(γ-chloropropyl)-piperidine hydrochloride[3] (17 g., 0.08 mole) was dissolved in 60 ml. of an ethanol solution containing dimethylamine (18 g., 0.40 mole); this solution was placed in a pressure bottle which was kept in an oven at 82° for 1.5 hours. The cooled solution was evaporated to dryness under vacuum on the steam-bath leaving a crystalline residue which after several recrystallizations from ethanol–acetone (1:2) melted at 245–246° dec. and weighed 6.0 g. (29% yield).

Anal. Calcd. for $C_{11}H_{26}Cl_2N_2$: N, 10.89. Found: N, 10.22.

(6) F. H. McMillan and J. A. King, This Journal, **73**, 3165 (1951). This oxidation was first carried out on the present compound by A. W. Ruddy and G. Conrad of these laboratories.

(7) J. R. Stevens and R. H. Beutel, *ibid.*, **65**, 449 (1943).

(8) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

(9) H. J. Taverne, *Rec. trav. chim.*, **16**, 38 (1897).

(10) D. E. Pearson and J. D. Bruton, This Journal, **73**, 864 (1951).

(11) Quaternary salts of this compound have been reported to have ganglionic blocking activity by M. Borovička, Z. Šedivý, J. O. Jilek and M. Protiva, *Coll. Czech. Chem. Communs.*, **20**, 437 (1955), and by R. Wien and D. F. J. Mason, *Brit. J. Pharmacol.*, **8**, 306 (1953).

(12) R. Fusco, S. Chiavarelli, G. Palazzo and D. Bovet, *Gazz. chim. ital.*, **78**, 951 (1948).

(13) A. P. Phillips, This Journal, **77**, 1693 (1955).

(14) P. C. Guha and G. D. Hazra, *J. Ind. Inst. Sci.*, **22A**, 263 (1939); *C. A.*, **34**, 2822 (1940).

(15) R. Malachowski, J. J. Wasowska and S. Jozkiewicz, *Ber.*, **71**, 759 (1938).

(16) P. Reinglass, *ibid.*, **24**, 2416 (1891).

(17) G. Komppa and T. Hirn, *ibid.*, **36**, 3610 (1903).

(18) A. Baeyer and C. Pape, *ibid.*, **17**, 447 (1884).

(19) Methium® is Warner-Chilcott Laboratories brand of hexamethonium chloride.

(20) Boiling points and melting points are uncorrected. Microanalyses were carried out by Miss Lorelinde Einstein.

TABLE I

DIAMINES

Cmpd.	B.P., °C.	Mm.	Yield., %	Empirical Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
III	72–75	0.05	94	$C_{12}H_{20}N_2$	74.95	10.48	14.57	74.86	10.35	14.52
VI	62	.03[a]	57	$C_{12}H_{26}N_2$			14.13			14.03
VII	58	.05	..	$C_{12}H_{26}N_2$			14.13			14.02
VIII	68	.05	59	$C_{13}H_{22}N_2$	75.67	10.75	13.58	75.59	10.88	13.49
IX	85	.05	68	$C_{14}H_{24}N_2$	76.31	10.98	12.72	76.29	10.51	12.53
XI	84	.07	10	$C_{11}H_{19}N_3$	68.35	9.91	21.74	68.30	9.90	21.31
XII	60	.05	35	$C_{12}H_{27}N_3$	67.55	12.76	19.69	67.67	12.77	19.55

[a] M.p. 35°

TABLE II

DIAMINE DIHYDROCHLORIDES

Cmpd.	m.p., °C. dec.	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
II	254–255	20	$C_{11}H_{26}Cl_2N_2$	51.35	10.19	10.89[a]	51.21	9.98	10.61[a]
III	227–228	85	$C_{12}H_{22}Cl_2N_2$	54.34	8.36	26.74	54.46	8.54	26.70
IV	280	68	$C_{12}H_{28}Cl_2N_2$	53.13	10.40	26.14	53.05	10.38	26.20
V	295	82	$C_{12}H_{22}Cl_2N_2$	54.34	8.36	26.74	54.47	8.33	26.80
VI	309–310	37	$C_{12}H_{28}Cl_2N_2$	53.13	10.40	26.14	53.11	10.46	25.64
VII	290	..	$C_{12}H_{28}Cl_2N_2$	53.13	10.40	26.14	53.48	10.28	26.35
VIII	253–255	50	$C_{13}H_{24}Cl_2N_2$	55.91	8.66	25.40	56.06	8.75	25.47
IX	233	81	$C_{14}H_{26}Cl_2N_2$	57.33	8.94	24.18	57.39	8.96	24.16
X	240–242	55	$C_{14}H_{32}Cl_2N_2$	56.17	10.78	23.69	56.07	10.52	22.96
XI	265	36	$C_{11}H_{21}Cl_2N_3$	49.62	7.95	26.64	49.78	8.05	26.68
XII[b]	266	66	$C_{12}H_{30}Cl_3N_3$	44.65	9.37	32.96	44.49	9.34	32.93

[a] Nitrogen analysis. [b] Trihydrochloride.

β-(4-Pyridyl)-propionic Acid (XIII).—4-(γ-Hydroxypropyl)-pyridine (137 g., 1.0 mole) was dissolved in 1600 ml. of water containing sulfuric acid (65 g., 0.67 mole). Potassium permanganate (211 g., 1.33 moles) was added slowly to this solution with stirring at such a rate that the temperature remained at about 50°; when the addition was complete and the exothermic reaction was over the mixture was warmed to 80° and the precipitated MnO_2 was removed by filtration. The filtrate was concentrated to 500 ml. and chilled giving crystals melting at 205–216° which after recrystallization from water weighed 92 g. (61% yield) and melted at 221–224°. The reported m.p.[8] for this acid is 220°.

N,N-Dimethyl-β-(4-pyridyl)-propionamide (XIV).—β-(4-Pyridyl)-propionic acid (75.5 g., 0.50 mole) was dissolved in somewhat more than 0.5 mole of 25% aqueous dimethylamine solution; this solution was heated in a metal-bath until most of the water had evaporated and then dimethylamine was bubbled slowly through the acid solution while the metal-bath was maintained at 210° for 14 hours. The cooled mixture was triturated with benzene (200 ml.) and filtered yielding some unchanged acid; the filtrate was evaporated under vacuum on the steam-bath and the residue was distilled through a short column giving 35 g. (39% yield) of material, boiling at 143.5–145° (0.35 mm.).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.46; H, 7.97; N, 15.72.

N,N-Dimethyl-β-(4-pyridyl)-propionamide Methobromide.—Compound XIV (21.5 g., 0.177 mole) was dissolved in 80 ml. of an acetone solution of methyl bromide (24 g., 0.25 mole) in a pressure bottle; within a few minutes the solution temperature rose to 40° and it was allowed to stand for several hours while the crystalline methobromide formed. The crystals were recrystallized by suspending them in 100 ml. of boiling acetone and adding ethanol until all was dissolved. There was recovered 22 g. (46% yield) of material melting at 113.5–115.5°.

Anal. Calcd. for $C_{11}H_{17}BrN_2O$: C, 48.36; H, 6.27. Found: C, 48.42; H, 6.18.

1-Methyl-4-(β-dimethylcarbamidoethyl)-piperidine Hydrobromide (XV).—XIV-Methobromide (9.5 g., 0.035 mole) was dissolved in 100 ml. of water and Adams platinum (0.25 g.) was added; this solution was shaken with hydrogen at atmospheric pressure and room temperature until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was evaporated under vacuum on the steam-bath; the residue was recrystallized from acetone containing a few per cent. of ethanol to give 8 g. (75% yield) of material melting at 130–132°. A small sample after another recrystallization from acetone melted at 134–135°.

Anal. Calcd. for $C_{11}H_{23}BrN_2O$: C, 47.31; H, 8.30; N, 10.03. Found: C, 47.43; H, 8.45; N, 10.03.

1-Methyl-4-(γ-dimethylaminopropyl)-piperidine Dihydrochloride (II).—Compound XV (8 g., 0.029 mole) was added to 30 ml. of 30% potassium carbonate solution; the organic layer was separated and the water layer was extracted with three 30-ml. portions of benzene. The benzene extracts were combined with the original organic layer, dried over anhydrous sodium sulfate and then evaporated to dryness leaving 5.5 g. (98% yield) of oil which was taken up in 25 ml. of dry benzene.

Lithium aluminum hydride (1.9 g., 0.05 mole) was stirred with 100 ml. of absolute ether until well disintegrated and then at room temperature the benzene solution of the dimethylamide was added over a 15-minute period after which the mixture was heated at reflux for two hours. The reaction mixture was chilled in an ice-bath while ethyl acetate (8.8 g.) was slowly added followed by a saturated ammonium chloride solution (10.7 g. in 30 ml. of H_2O). The hydrolyzed solution was then stirred at ice-bath temperature while anhydrous sodium sulfate was added until the aqueous phase was solid. The organic layer was decanted and treated with a slight excess of a solution of HCl in ethanol which caused precipitation of the dihydrochloride of the diamine. After recrystallization from acetone–ethanol it melted at 254–255° dec. and weighed 1.5 g. (20% yield). A mixture of this material with the material prepared by the first method (m.p. 245–246° dec.) melted at 248–249° dec.

Compounds III and IV. N,N-Dimethyl-*p*-nitrophenylacetamide (XVI).—A mixture of *p*-nitrophenylacetic acid (181 g., 1.0 mole) and thionyl chloride (300 g.) was heated at reflux for two hours and the excess thionyl chloride was evaporated under water-pump vacuum on a steam-bath. The residue was dissolved in 200 ml. of benzene and this benzene solution was added dropwise to a solution of dimethylamine (100 g., 2.2 moles) in 500 ml. of benzene keeping the reaction temperature below 10°. When the addi-

tion was complete the mixture was heated at reflux for one hour and while still hot dimethylamine hydrochloride was removed by filtration. Chilling the filtrate gave crystalline dimethylamide which after recrystallization from benzene weighed 87.5 g. (42% yield) and melted at 88–90° (lit. m.p. 90–91°[9]).

p-**Aminophenylacetyldimethylamine (XVII).**—Compound XVI (85 g., 0.35 mole) was dissolved in 800 ml. of ethanol, 1.0 g. of platinum oxide was added and the mixture was shaken with hydrogen at 25° until the theoretical amount of hydrogen was absorbed. The platinum was removed by filtration and the solvent was evaporated under vacuum on the steam-bath leaving a crystalline residue which was recrystallized from benzene giving 58 g. (81% yield) of material melting at 98–100°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.49; H, 7.90; N, 15.78.

N,N,N′,N′-Tetramethyl-*p*-aminophenylacetamide (XVIII).—Compound XVII (32 g., 0.18 mole) was chilled and then added to a chilled mixture of prereduced platinum (0.5 g. of platinum oxide), concentrated hydrochloric acid (15.1 ml., 0.18 mole), 40% formaldehyde solution (26.6 g., 0.18 mole) and 95% ethanol (100 ml.). This mixture was shaken with hydrogen at 25° and three atmospheres; 0.18 mole of hydrogen was taken up quite rapidly and the reaction mixture became a little warm. The catalyst was removed by filtration and the filtrate was evaporated to dryness under vacuum at the water-pump vacuum; the residue was taken up in 100 ml. of water and this solution was made strongly alkaline by adding a 50% sodium hydroxide solution after which the alkaline mixture was extracted with 100 ml. of benzene. Acetic anhydride (10 ml.) was added to the benzene extract, this solution was warmed on the steam-bath for 15 minutes, and then, after cooling, was shaken with 100 ml. of 10% sodium hydroxide solution to decompose the excess acetic anhydride. The benzene layer was separated and extracted with 125 ml. of dilute hydrochloric acid (1:4); the acidic extract was made alkaline with 50% sodium hydroxide solution and then extracted with benzene. The benzene extract was dried over anhydrous potassium carbonate and the solvent removed under vacuum on the steam-bath. The residue was distilled giving 30 g. (81% yield) of material boiling at 125–130° (0.1 mm.) which subsequently crystallized and melted at 78–79°.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.79; H, 8.71; N, 13.44.

N,N,N′,N′-Tetramethyl-*p*-(β-aminoethyl)-aniline.—To a solution of lithium aluminum hydride (1.9 g., 0.05 mole) in 100 ml. of ether there was added over a half-hour period a solution of compound XVIII (10.3 g., 0.05 mole) in 250 ml. of ether after which the mixture was heated at reflux for an additional half-hour. The cooled mixture was treated with ethyl acetate (13.2 g., 0.15 mole) and then with a saturated ammonium chloride solution (10.7 g. of ammonium chloride in 35 ml. of water). The ether layer was decanted from the sticky salts, dried over anhydrous potassium carbonate and the ether was evaporated under vacuum leaving a mobile liquid residue which was distilled giving 9.0 g. (94% yield) of material boiling at 72–75° (0.05 mm.).

N,N,N′,N′-Tetramethyl-*p*-(β-aminoethyl)-aniline Hydrochloride (III).—The free base (9.0 g., 0.047 mole) was dissolved in 100 ml. of absolute ethanol and there was added 8.5 ml. of concentrated hydrochloric acid. The hydrochloride was precipitated by adding 100 ml. of absolute ether and then recrystallized from 100 ml. of absolute ethanol giving 10.6 g. (85% yield) of material melting at 227–228° dec.

1-Dimethylamino-4-(β-dimethylaminoethyl)-cyclohexane (IV).—Compound III (16.5 g., 0.062 mole) was dissolved in 130 ml. of glacial acetic acid, platinum oxide (1.0 g.) was added and the mixture was shaken with hydrogen at 25° and atmospheric pressure. The theoretical amount of hydrogen was taken up in 48 hours and the solvent was then evaporated under water-pump vacuum on the steam-bath. The crystalline residue was recrystallized from 300 ml. of ethanol giving 11.5 g. (68% yield) of material melting at 280° dec.

N,N-Dimethyl-β-(*p*-nitrophenyl)-propionamide.—By the same procedure used to prepare N,N-dimethyl-*p*-nitrophenylacetamide (XVI), β-(*p*-nitrophenyl)-propionic acid[21] was converted to N,N-dimethyl-β-(*p*-nitrophenyl)-propionamide in 56% yield melting at 63.5–64.5° after recrystallization from benzene–petroleum ether (b.p. 60–80°) (1:1).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.35; H, 6.21; N, 12.56.

Compounds VI and VII. 1,4-*trans*-Bis-(dimethylcarbamido)-cyclohexane.—The diacid chloride of *trans*-cyclohexane-1,4-dicarboxylic acid[15] (41.8 g., 0.20 mole), dissolved in 100 ml. of dry benzene, was added slowly to a solution of dimethylamine (58 g., 1.3 moles) in 300 ml. of dry benzene at below 20° after which the mixture was warmed to boiling and filtered hot to remove dimethylamine hydrochloride. The filtrate was chilled giving crystalline diamide which after recrystallization from benzene melted at 201° and weighed 12.5 g. (28% yield).

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.76; H, 9.71; N, 12.37.

***cis*-1,4-Bis-(dimethylcarbamido)-cyclohexane.**—The diacid chloride of *cis*-cyclohexane-1,4-dicarboxylic acid[15] was converted to the bis-(dimethylamide) by the same procedure used for the *trans* isomer; 33% yield melting at 123–123.5° after recrystallization from benzene.

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.64; H, 9.98; N, 12.35.

Compound VIII. Bis-(dimethylamide) of Homoisophthalic Acid.—A mixture of homoisophthalic acid[17] (39 g., 0.216 mole) and thionyl chloride (150 ml.) was heated at reflux for one hour. The excess thionyl chloride was evaporated under vacuum on the steam-bath and the residue was dissolved in 150 ml. of dry benzene. This benzene solution of the acid chloride was added slowly to a solution of dimethylamine (45 g., 1.0 mole) in dry benzene (300 ml.) while keeping the reaction temperature below 20°. The reaction mixture was then heated to boiling for a few minutes and after cooling dimethylamine hydrochloride was removed by filtration. The benzene solution was washed with 100 ml. of 30% potassium carbonate solution and then evaporated to dryness. The residue was distilled giving 33 g. (65% yield) of material boiling at 170–175° (0.1 mm.) which crystallized, m.p. 88–90°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.52; H, 7.60; N, 11.95.

Compounds IX and X. Bis-(dimethylamide) of *o*-Phenylenediacetic Acid.—By the same procedure used to prepare the bis-(dimethylamide) of homoisophthalic acid, *o*-phenylenediacetic acid[18] was converted to the corresponding bis-(dimethylamide) in 54% yield melting at 160.5–161° after recrystallization from benzene.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.62; H, 7.98; N, 11.22.

Compounds XI and XII. Bis-(dimethylamide) of Isocinchomeronic Acid (XIX).—A mixture of isocinchomeronic acid (100 g., 0.60 mole) of thionyl chloride (500 g.) was heated at reflux for 16 hours; a little insoluble material was removed by filtration and the excess thionyl chloride was evaporated under vacuum on the steam-bath. The residue was dissolved in 250 ml. of dry benzene and this solution was added slowly to a solution of dimethylamine (162 g., 3.6 moles) in dry benzene (700 ml.) while keeping the reaction temperature below 20°. After the addition was complete the mixture was heated at reflux for a few minutes. The hot mixture was filtered to remove dimethylamine hydrochloride and the filtrate was chilled giving crystals of the bis-(dimethylamide) which after recrystallization from benzene (500 ml.) weighed 72 g. (54% yield) and melted at 139.5–140.5°.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.59; H, 6.70; N, 18.83.

Methobromide of the Bis-(dimethylamide) of Isocinchomeronic Acid.—Compound XIX (11.1 g., 0.05 mole) was dissolved in 50 ml. of acetone containing methyl bromide (9.0 g., 0.095 mole) and the solution was put in a pressure bottle and kept in an oven at 65° for 16 hours. The crystals which formed were recrystallized from ethanol–ether giving 24 g. (76% yield) of material melting at 158–161°.

Anal. Calcd. for $C_{12}H_{18}BrN_3O_2$: C, 45.58; H, 5.74; Br^-, 25.28. Found: C, 45.69; H, 5.85; Br^-, 25.19.

1-Methyl-2,5-bis-(dimethylcarbamido)-piperidine (XX).—The methobromide of the bis-(dimethylamide) of isocinchomeronic acid (24 g., 0.076 mole) in 100 ml. of absolute

(21) S. Gabriel and H. Steudemann, *Ber.*, **15**, 842 (1882).

ethanol with 1 g. of platinum oxide was shaken with hydrogen until the theoretical amount was taken up (about 16 hours). The catalyst was removed by filtration and the filtrate was evaporated to dryness under vacuum on the steam-bath. The residue was taken up in 10 ml. of water and to this was added a solution of potassium carbonate (50 g.) in 75 ml. of water; the resulting mixture was extracted with four 75-ml. portions of benzene. The benzene extracts were dried over anhydrous potassium carbonate, the benzene was evaporated under vacuum, and the residue was distilled giving 10 g. (55% yield) of material boiling at 145–150° (0.02 mm.).

Anal. Calcd. for $C_{12}H_{23}N_3O_2$: C, 59.72; H, 9.61; N, 17.41. Found: C, 59.85; H, 9.41; N, 17.30.

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Asymmetric Reductions. III. The Action of (+)-2-Methylbutylmagnesium Chloride on Substituted Benzophenones

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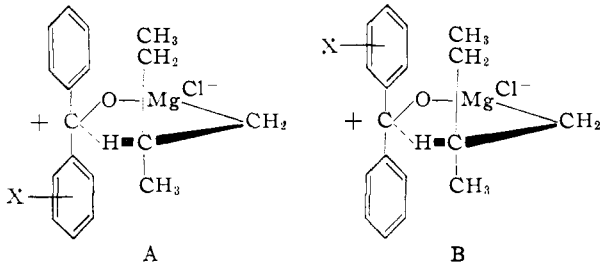
The action of the Grignard reagent prepared from (+)-2-methylbutyl chloride on *p*-chlorobenzophenone, *p*-methoxybenzophenone and *o*-chlorobenzophenone gave the corresponding benzhydrol in each case. In the cases of *p*-chlorobenzophenone and *p*-methoxybenzophenone optically inactive benzhydrols were obtained, whereas the *o*-chlorobenzhydrol was optically active. These findings are in complete agreement with the predictions made on the basis of the mechanism for Grignard reductions involving a hydrogen transfer within a six-membered ring transition state.

It has been proposed by Whitmore[1] that the reduction of carbonyl compounds by Grignard reagents proceeds *via* a six-membered ring transition state. Evidence has been obtained in support of this mechanism in the asymmetric reduction of methyl *t*-butyl ketone with (+)-2-methylbutylmagnesium chloride[2] and in the non-asymmetric reduction of this same ketone with (+)-3-methylpentylmagnesium chloride.[3] Additional evidence is now presented based on the reduction of three substituted benzophenones by (+)-2-methylbutylmagnesium chloride.

The transition state for the reduction of a substituted benzophenone by such an optically active Grignard reagent may be represented as in either A or B. If the shift of hydrogen with its accompanying electron pair takes place through the transition state represented by A, then one isomer will be



A B

formed; B leads to its enantiomorph. This mechanism would require that the presence of a substituent in the *para* position should not appreciably favor one transition state over the other, since the substituent in the *para* position of the planar benzene ring is too distant from the methyl and ethyl groups of the reducing reagent to exert any selective steric effect. In other words, the *para* substituted phenyl group should have essentially no more steric interference in this reaction than an unsubstituted phenyl, and a racemic product should be formed. But if the substituent is in the *ortho* position, then one would predict that the energy of activation of the transition state represented by A would be less than that for B since in A the substituent interferes with the methyl group, while in B it interferes with the more bulky ethyl group.[4] These predictions are made on the assumption that the factors governing this asymmetric reduction are steric and independent of the electronic nature of the substituent group.[4]

The predictions have been tested and confirmed in the reactions of *p*-chloro-, *p*-methoxy- and *o*-chlorobenzophenone with the Grignard reagent from (+)-2-methylbutyl chloride. The results and essential data are presented in Table I.

In the case of the two *p*-substituted examples there was isolated only one product in near quantitative yield which was at once crystalline and optically inactive. The reduction product of *o*-chlorobenzophenone, on the other hand, was a dextrorotatory oil. It retained its activity after two successive distillations at 2 mm. and was converted in 91% yield to a crystalline levorotatory half-phthalate. That the activity was a property of the half-phthalate of *o*-chlorobenzhydrol and not of an impurity was demonstrated conclusively by repeated recrystallization, infrared spectra and analysis. The more active material concentrated in the mother liquors, in accord with reported solubilities of the racemic and active forms.

Experimental[5]

The Action of (+)-2-Methylbutylmagnesium Chloride on *p*-Chlorobenzophenone.—The Grignard reagent was pre-

(1) F. C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, April, 1943.

(2) H. S. Mosher and E. La Combe, THIS JOURNAL, **72**, 3994 (1950).

(3) H. S. Mosher and E. La Combe, *ibid.*, **72**, 4991 (1950).

(4) It would, of course, be better to test this prediction with a 2,6-disubstituted benzophenone since this would prevent the substituted benzene ring from assuming an orientation in which the substituent could be directed away from the interfering groups. To our knowledge no 2,6-disubstituted benzhydrol has been resolved. Until such a compound has been resolved, no information beyond that already obtained from the reduction of the simple *o*-substituted benzophenone can be obtained by such an experiment. In addition a preliminary experiment with 2,6-dichlorobenzophenone has shown that this is a more complex reaction giving very little if any simple reduction product.

(5) All melting points taken on Kofler hot-stage, uncorrected.