Summary

Bromine in acetic acid reacts instantly with phenyl tetraacetyl-β-D-selenoglucoside to give an orange precipitate. From the filtrate of this orange precipitate α-D-glucose pentaacetate is recoverable in fair yield. The precipitate, which is probably a salt of the composition $C_6H_5SeBr_2^+Br^-$, reverts to diphenyl diselenide on treatment with water.

Bromine in carbon tetrachloride reacts with phenyl tetraacetyl-β-D-selenoglucoside to give the orange precipitate and acetobromoglucose.

A similarity in mechanisms of these reactions and the analogous cleavage of phenyl tetraacetyl-β-D-thioglucoside with bromine is pointed out.

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Diphenylethylamines. I. The Preparation of Tertiary Amines by the Grignard Reaction[1,2]

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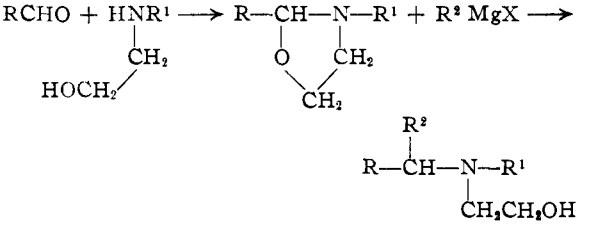
During the course of our work, it became desirable to synthesize a series of 1,2-diphenylethylamines possessing a tertiary nitrogen atom. It was hoped that these compounds would produce tumor necrosis and they were, therefore, to be screened for this activity. Our first approach to this problem was through the alkylation of primary and secondary amines by the usual methods. Some amines reacted well; N-ethyl-1,2-diphenylethylamine, for example, gave a 70% yield of tertiary amine on reaction with ethyl bromide at 120–140°. Others were troublesome as witnessed by the 10% yield of tertiary amine isolated from the reaction mixture of piperidine and 1,2-diphenylethyl bromide. Stilbene was the major product in the latter reaction.

Grignard reagents (RMgX) are known[4] to react in one of three ways with α-amino nitriles $ArCH(CN)NR_2$, as follows: (A) replacement of the cyano group, yielding $ArCHRNR'_2$; (B) addition to the cyano group to form $RCOCHArNR'_2$; (C) removal of cyano groups from two moles of the nitriles giving rise to the coupled product, $[ArCH(NR'_2)-]_2$.

The type (C) coupling reaction has not been observed in this work. Both of the other two types of reactions (A and B) have been observed but, in each of the fourteen examples described here, one type of reaction (either A or B) predominated. In the examples where the α-aminophenylacetonitrile was prepared from piperidine, alkyl-substituted piperidines, or aliphatic secondary amines, it will be noted that good yields of replacement products (A) were obtained. In the examples where the amines were morpholine or dihydroxalkylamines, the reaction proceeded primarily by addition to the nitrile group (B) to give the benzyl α-aminobenzyl ketone derivatives. An examination of the yields in Table II clearly shows that the reaction of benzylmagnesium chloride with α-aminophenylacetonitriles is a convenient preparative method for tertiary amines belonging to the diphenylethylamine class.

Since the reaction of the α-dihydroxyalkylphenylacetonitrile with benzylmagnesium chloride was found to give primarily the benzyl α-aminobenzyl ketone derivatives, another synthetic route to the N,N-dihydroxyalkyl-1,2-diphenylethylamines was sought. In 1945, Murray Senkus[5] reported the preparation of 3-substituted 2-alkyloxazolidines and their reaction with Grignard reagents.



By the reaction of aromatic aldehydes and hydroxyalkylalkylamines or dihydroxyalkylamines, we have prepared a series of 3-substituted 2-aryloxazolidines (Table III) and treated each of them with benzylmagnesium chloride (Table IV). The aldehyde amine condensations and Grignard reactions proceeded rapidly and in good yields; for example, in the case of 2-phenyl-3-(2-hydroxyethyl)oxazolidine which was obtained in 91% yield from benzaldehyde and diethanolamine, the yield of purified N,N-di-2-hydroxyethyl-1,2-diphenylethylamine was 97%. This product was shown to be identical with the material obtained in 34% yield from the reaction of 1,2-diphenylethyl bromide and diethanolamine. In this particular series of compounds (Table

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(2) Presented before the Division of Organic Chemistry, Atlantic City, N. J., September 19, 1949.

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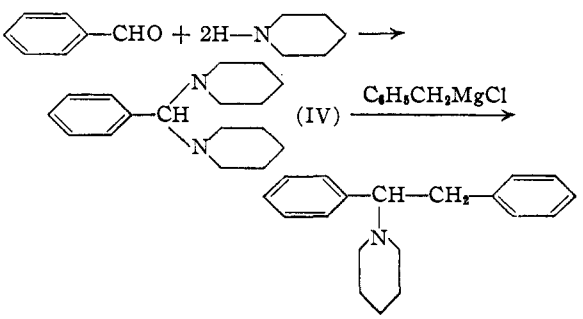
(4) Migrdichian, "The Chemistry of Organic Cyanogen Compounds," A. C. S. Monograph, No. 105, Reinhold Publishing Corp., New York, N. Y., 1947, p. 253.

(5) Senkus, THIS JOURNAL, 67, 1515 (1945).

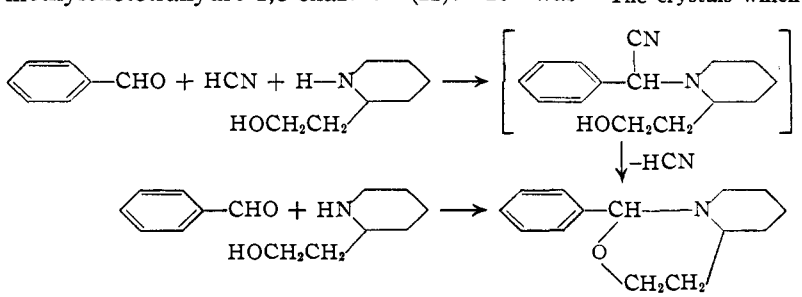
IV) difficulty was encountered in crystallizing some of the hydrochlorides of the amines produced. It was therefore necessary to prepare other salts for the characterization of these products.

It has now been demonstrated that N,N'-benzaldipiperidine reacts with benzylmagnesium chloride in boiling ether. The product, N-(1,2-diphenylethyl)-piperidine (isolated as its hydrochloride) was obtained in 18.5% yield and was identical with that described in Table II. It

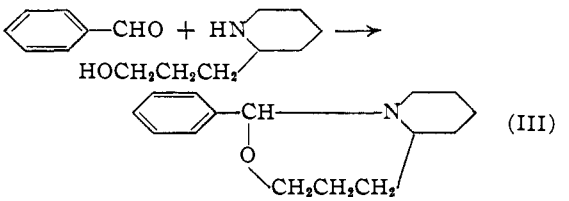


may be seen from structural formula (IV) that the dipiperidine derivative resembles the more common acetal structure and that this reaction effects the substitution of one of the piperidyl groups by the benzyl radical. Similarly the reaction of N,N'-benzaldi-4-methylpiperidine with benzylmagnesium chloride (first prepared in ether) was carried out in boiling benzene and a 14.5% yield of the corresponding N-(1,2-diphenylethyl)-4-methylpiperidine was obtained. This compound has also been prepared from the amino nitrile (Table II).

The reaction of 2-(2-hydroxyethyl)-piperidine, benzaldehyde and hydrogen cyanide proceeded smoothly and probably gave the expected product α-(2-hydroxyethyl-1-piperidyl)-phenylacetonitrile (II). However, on attempted purification of this crude oily product by vacuum distillation, hydrogen cyanide was eliminated and the distillate was shown by analysis to be 2-phenyl-3,4-tetramethylenetetrahydro-1,3-oxazine (II). It was



then found that this compound II could be prepared directly from the aldehyde and amine without going through the nitrile merely by mixing the two and removing the water formed in the reaction by azeotropic distillation with benzene. In a similar manner, benzaldehyde and 2-(2-hydroxypropyl)-piperidine condensed with the elimination of water to give a seven-membered heterocyclic ring compound, 2-phenyl-3,4-tetramethylenehexahydro-1,3-oxazepine (III). Com-



pounds II and III each reacted smoothly with benzylmagnesium chloride to give 1-(1,2-diphenylethyl)-2-(β-hydroxethyl)-piperidine and 1-(1,2-diphenylethyl)-2-(γ-hydroxypropyl)-piperidine, respectively.

Experimental

α-Aminophenylacetonitriles (Table I).—A secondary amine (0.50 mole) was neutralized as exactly as possible with concd. hydrochloric acid. The aromatic aldehyde (0.50 mole) was added and the resulting mixture was stirred during the dropwise addition of an aqueous solution of potassium cyanide (0.55 mole). When the addition was complete the mixture was stirred and heated on a steam-bath for one to two hours. If the resulting nitrile did not crystallize on cooling the reaction mixture, the product was separated and distilled.

1,2-Diphenylethylamines and Benzyl α-Aminobenzyl Ketones (Table II).—Benzylmagnesium chloride (0.5 to 1.5 moles; the larger quantity was added if the nitrile had active hydrogen atoms) was prepared from benzyl chloride, magnesium and ether in the usual manner. To this was added 0.25 mole of the amino nitrile (selected from Table I) dissolved in anhydrous ether. After a three-hour reflux period the reaction mixture was decomposed by pouring onto ice and 100 to 300 ml. of concd. hydrochloric acid (Hood!). The resulting amine hydrochloride, if crystalline, was filtered and purified; otherwise the aqueous phase was treated with enough sodium hydroxide solution to liberate the amine and to precipitate only a part of the magnesium as its hydroxide. The amine was extracted with ether, dried and precipitated as its hydrochloride with gaseous hydrogen chloride.

N-Ethyl-1,2-diphenylethylamine Hydrochloride.[6]—To a solution of benzylmagnesium chloride (prepared from 25.3 g. of magnesium, 138.2 g. of benzyl chloride and 450 ml. of anhydrous ether) was added 73 g. of N-ethylbenzalamine. After refluxing for three hours the mixture was poured into ice and 250 ml. of concentrated hydrochloric acid. The crystals which separated were filtered, washed with ether and dried; yield, 154 g., m. p. 215–234°. Crystallization from 95% alcohol gave 110 g., m. p. 240–241°.

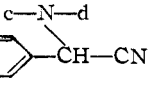
Anal. Calcd. for $C_{16}H_{19}N\cdot HCl$: Cl, 13.55. Found: Cl, 13.60.

N,N-Diethyl-1,2-diphenylethylamine Hydrochloride.—The preferred method of synthesis utilizes the Grignard reaction (Table II), but it was first prepared in the following manner: ten grams of N-ethyl-1,2-diphenylethylamine was mixed with 12 g. of ethyl bromide and heated in a sealed tube at 120–140° for three hours. The resulting clear resin was warmed with dilute aqueous hydrochloric acid; 0.5 g. of stilbene m. p. 123–125°

(6) The preparation of this compound by the Leuckart reaction has already been described, L. H. Goodson, C. J. W. Wiegand and J. S. Splitter, THIS JOURNAL, 68, 2174 (1946).

TABLE I

α-AMINOPHENYLACETONITRILES

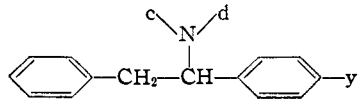


y	c	d	M. p., °C.[a]	B. p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found	Approx. yield, %
H	$-CH_3$	$-CH_3$		85–87	1.0	1.5128	$C_{10}H_{12}N_2$	17.49	17.55	75
H	$-C_2H_5$	$-C_2H_5$		78–80	0.05	1.5029	$C_{12}H_{16}N_2$	[b]		80
H		$-C_5H_{10}-$	62–64[h]				$C_{13}H_{16}N_2$	[c]		94
4-OH		$-C_5H_{10}-$	149–151[h]				$C_{13}H_{16}N_2O$	[d]		61
4-OCH_3		$-C_5H_{10}-$	76–78[h]				$C_{14}H_{18}N_2O$	[e]		60
4-CH_3		$-C_5H_{10}-$		108–110	.2	1.5299	$C_{14}H_{18}N_2$	13.07	13.12	79
4-$N(CH_3)_2$		$-C_5H_{10}-$	78–80[f]				$C_{15}H_{21}N_3$	17.27	17.16	89
4-OCH_3		$-CH(CH_3)(CH_2)_4-$	55–58[g]	134–136	.05		$C_{15}H_{20}N_2O$	11.47	11.52	49
4-CH_3		$-CH_2-CH(CH_3)-(CH_2)_3-$		103–106	.05	1.5224	$C_{15}H_{20}N_2$	12.27	12.00	71
H		$-CH(CH_3)(CH_2)_4-$		104–106	.06	1.5257	$C_{14}H_{18}N_2$	13.08	13.17	81
H		$-CH_2CH(CH_3)(CH_2)_3-$		100–103	.2	1.5237	$C_{14}H_{18}N_2$	13.08	13.07	82
H		$-(CH_2)_2CH(CH_3)(CH_2)_2-$	53–54.5	99–101	.05	1.5208	$C_{14}H_{18}N_2$	13.08	13.28	81
H		$-CH_2CH_2OCH_2CH_2-$	68–70[h]				$C_{12}H_{14}N_2O$	13.85	13.81	82
H	$-CH_2CH_2OH$	$-CH_2CH_2OH$	91–94[i]				$C_{12}H_{16}N_2O_2$	12.72	12.70	56
H	$-CH_2CHOHCH_3$	$-CH_2CHOHCH_3$	113–116[j]				$C_{14}H_{20}N_2O_2$	11.29	11.17	63

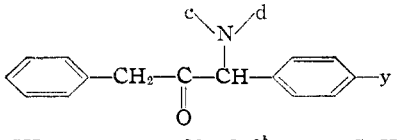
[a] Both melting points and boiling points were determined with thermometers corrected for 76-mm. immersion. [b] Klages and Margolinsky, *Ber.*, **36**, 4192 (1903). [c] Christiaen, *Bull. soc. chim. Belg.*, **33**, 483 (1924). [d] N. K. Yurashevskiĭ and N. L. Stepanova, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 141 (1946). [e] Knoevenagel, *Ber.*, **37**, 4086 (1904). [f] Crystals from alcohol–water mixture. [g] From ether–alcohol mixture. [h] Crystals from ether. [i] Crystals from toluene. [j] From 95% alcohol. [k] From methanol.

TABLE II

COMPOUNDS PREPARED BY THE ACTION OF BENZYLMAGNESIUM CHLORIDE ON THE α-AMINOPHENYLACETONITRILES LISTED IN TABLE I



y	c	d	M. p. of HCl, °C.[a]	Formula	Chlorine, % Calcd.	Found	Approx. yield, %
H	$-CH_3$	$-CH_3$	210–211[b,c]	$C_{16}H_{19}N\cdot HCl$	13.54	13.46	82
H	$-C_2H_5$	$-C_2H_5$	167–169[d]	$C_{18}H_{23}N\cdot HCl$	12.24	12.29	80
H		$-C_5H_{10}-$	207–208.5[e]	$C_{19}H_{23}N\cdot HCl$	11.75	11.60	32
4-OH		$-C_5H_{10}-$	173–175[g]	$C_{19}H_{23}NO\cdot HCl$	11.16	11.06	73[l]
4-OCH_3		$-C_5H_{10}-$	132–135[f]	$C_{20}H_{25}NO\cdot HCl$	10.68	10.53	78
4-CH_3		$-C_5H_{10}-$	152–156[g]	$C_{20}H_{25}N\cdot HCl$	11.23	11.26	41
4-$N(CH_3)_2$		$-C_5H_{10}-$	173–175 d.[h]	$C_{21}H_{28}N_2\cdot 2HCl$	18.59	18.64	44[l]
4-OCH_3		$-CH(CH_3)(CH_2)_4-$	104–108 d.[i]	$C_{21}H_{27}NO\cdot HCl$	10.27	10.11	57
4-CH_3		$-CH_2-CH(CH_3)(CH_2)_3-$	235–237[k]	$C_{21}H_{27}N\cdot HCl$	10.75	10.72	32
H		$-CH(CH_3)(CH_2)_4-$	193.5–195[g]	$C_{20}H_{25}N\cdot HCl$	11.23	11.32	79[l]
H		$-CH_2CH(CH_3)(CH_2)_3-$	226–228.5[g]	$C_{20}H_{25}N\cdot HCl$	11.23	11.26	67[l]
H		$-(CH_2)_2-CH(CH_3)-(CH_2)_2-$	230.5–231.5[g]	$C_{20}H_{25}N\cdot HCl$	11.23	11.27	71[l]

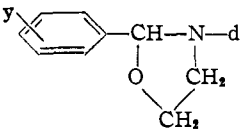


H	$-CH_2CH_2-O-CH_2CH_2-$	203–206[h]	$C_{19}H_{21}NO_2\cdot HCl$[k]	10.68	10.58	56[l]
H	$-CH_2CHOHCH_3$ $-CH_2CHOHCH_3$	193–196[j]	$C_{21}H_{27}NO_3\cdot HCl$	9.38	9.36	53[l]

[a] Unless otherwise stated the melting points were determined by heating the bath so that the temperature rose between two and three degrees per minute at the melting point. In general slower heating gave a lower melting point and a wider melting range. [b] Exhibits a double melting point. It first melts at 187°, resolidifies and remelts at 210–211°. T. S. Stevens, J. M. Cowan and J. Mackinnon, *J. Chem. Soc.*, 2568 (1931); *C. A.*, **26**, 693 (1932). [c] Crystallized from alcohol. [d] Crystallized from methyl isobutyl ketone. [e] Crystallized from water or methyl ethyl ketone. If heated rapidly it exhibits a double melting point; first it melts at 158°, solidifies and remelts at 207–208.5°. Christiaen, *Bull. soc. chim. Belg.*, **33**, 483 (1924). [f] From toluene. [g] From methyl ethyl ketone. [h] From absolute alcohol. [i] It crystallizes nicely from toluene as a solvate which appears to possess 0.75 molecule of toluene. *Anal.* Calcd. for $C_{21}H_{22}NO\cdot HCl\cdot 0.75\ CH_3C_6H_5$: Cl, 8.55. Found: Cl, 8.57. When the sample is dried over sulfuric acid in a vacuum at 76° and 0.05 mm. the toluene is lost and the material is no longer crystalline. [j] From methanol. The crystals are hygroscopic. [k] *Anal.* Calcd.: C, 68.71; H, 6.68. Found: C, 68.51; H, 6.50. [l] Only part of the reaction product was purified. The yield is based on the weight of dry crude crystalline product first obtained.

TABLE III

3-SUBSTITUTED 2-ARYLOXAZOLIDINES[a]

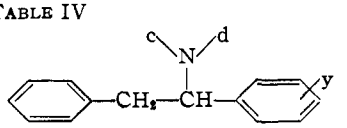


y	d	B. p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found	Approx. yield, %
H	$-C_2H_5$	73–75	0.1	1.5189	$C_{11}H_{15}NO$	7.91	7.90	98
4-CH_3	$-C_2H_5$	68–70	.03	1.5183	$C_{12}H_{17}NO$	7.32	7.29	88
H	$-CH_2CH_2OH$	130–133	.2	1.5417	$C_{11}H_{15}NO_2$	7.25	7.36	91
4-CH_3	$-CH_2CH_2OH$	123–124	.2	1.5385	$C_{12}H_{17}NO_2$	6.76	6.71	83
4-$CH(CH_3)_2$	$-CH_2CH_2OH$	128–130	.2	1.5286	$C_{14}H_{21}NO_2$	5.95	6.00	97
3,4-OCH_2O–	$-CH_2CH_2OH$	148–150	.02	1.5553	$C_{12}H_{15}NO_4$	5.91	6.00	92
H	$-CH_2CHOHCH_3$[b]	96–98	.05	1.5160	$C_{13}H_{19}NO_2$	6.33	6.25	88

[a] These compounds are all moderately viscous oils which range from a very pale straw color to colorless. [b] This compound has a methyl group at the 5-position of the oxazolidine ring.

TABLE IV

1,2-DIPHENYLETHYLAMINES[a]



y	c	d	M. p. of salt, °C.[b]	Formula	Analyses, % Calcd.	Found	Approx. yield, %
H	$-CH_2CH_2OH$	$-C_2H_5$	115.5–118.5[c]	$C_{19}H_{23}NO\cdot HCl$	Cl, 11.60	11.78	88
4-CH_3	$-CH_2CH_2OH$	$-C_2H_5$	150–152[d]	$C_{19}H_{25}NO\cdot C_6H_3N_3O_7$	N, 10.93	10.77	76
H	$-CH_2CH_2OH$	$-CH_2CH_2OH$	166–167.5[e]	$C_{18}H_{22}NO_2\cdot HCl$	Cl. 11.02	11.04	97
4-CH_3	$-CH_2CH_2OH$	$-CH_2CH_2OH$	153.5–155.5[f]	$C_{19}H_{25}NO_2\cdot C_6H_3N_3O_7$	N, 10.60	10.46	89
4-$CH(CH_3)_2$	$-CH_2CH_2OH$	$-CH_2CH_2OH$	120–124[f]	$C_{21}H_{29}NO_2\cdot HCl$	Cl, 9.74	9.73	58
3,4-$O-CH_2O$–	$-CH_2CH_2OH$	$-CH_2CH_2OH$	142.5–143.5[g]	$C_{19}H_{23}NO_4\cdot C_6H_3N_3O_7$	N, 10.04	10.28	71
H	$-CH_2CHOHCH_3$	$-CH_2CHOHCH_3$	196–199 d.[h]	$(C_{20}H_{27}NO_2)_2\cdot H_2PtCl_6$			90

[a] These compounds were prepared by the action of benzylmagnesium chloride upon the 2-aryl-3-substituted oxazolidines listed in Table III. [b] Only three of the amine hydrochlorides could be obtained in a crystalline condition. The remaining compounds were identified by conversion to their picrates or chloroplatinates. [c] Crystallized from methyl ethyl ketone. This compound was also prepared in a yield of 13% by the reaction of 1,2-diphenylethyl bromide with ethylethanolamine. [d] Crystallized from methanol. [e] Crystallizes from methyl ethyl ketone or 95% alcohol. This compound was also prepared in 34% yield by the reaction of 1,2-diphenylethyl bromide with diethanolamine. [f] Crystallized from methyl ethyl ketone. [g] From methyl isobutyl ketone. [h] The chloroplatinate was prepared by treating an aqueous solution of the amine hydrochloride with aqueous chloroplatinic acid. The resulting oil was stirred alternately with ether and alcohol. The resulting crystalline material was extracted with boiling methyl ethyl ketone and then with boiling absolute alcohol. *Anal.* Calcd. for above formula: C, 46.33; H, 5.44. Found: C, 46.37; H, 5.44.

was filtered from the solution. The filtrate was cooled to 0° and treated with 2 g. of sodium nitrite and 100 ml. of ether. After vigorous shaking for ten minutes the ether layer was separated and replaced with fresh ether and the shaking repeated. The water layer was separated and made strongly basic with sodium hydroxide. The free base was taken into ether, dried carefully over potassium carbonate and treated with gaseous hydrogen chloride. The crude amine hydrochloride was crystallized from methyl isobutyl ketone; yield 9 g. (70%) of glistening white needles, m. p. 167–169°.

2-Phenyl-3,4-tetramethylenetetrahydro-1,3-oxazine.—In an attempt to prepare α-(2-hydroxyethyl-1-piperidyl)-phenylacetonitrile, 2-(2-hydroxyethyl)-piperidine was kept cool while it was neutralized with concentrated hydrochloric acid. Benzaldehyde (53 g.) was added and the mixture was stirred during the addition of a solution of 33.5 g. of technical potassium cyanide and then heated on a steam-bath for one hour. After cooling, the oily layer was separated, dried and distilled. A slow stream of hydrogen cyanide was given off during the distillation and the fraction, b. p. 113–115° at 0.7 mm., weighed 80 g. This was crystallized from petroleum hexane to give 65 g. of product, m. p. 56–58°.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.81.

This compound was best prepared by condensing 10.6 g. of benzaldehyde with 12.9 g. of 2-(2-hydroxyethyl)-piperdine and removing the water formed by azeotropic distillation with benzene. The benzene was removed under reduced pressure and the residue was crystallized from petroleum hexane. It was then recrystallized from acetone containing a little water; yield 10 g., m. p. 58–59°. (An additional 8 g. of slightly lower melting crystals was obtained from the mother liquors.)

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.37.

2-(2-Hydroxyethyl)-1-(1,2-diphenylethyl)-piperidine Hydrochloride.—To a solution of benzylmagnesium chloride (prepared from 24.3 g. of magnesium, 126.5 g. of benzyl chloride and 500 ml. of ether) was added 61.1 g. of 2-phenyl-3,4-tetramethylenetetrahydro-1,3-oxazine. The mixture was stirred and refluxed three hours, and poured into ice and 250 ml. of concentrated hydrochloric acid. The ether layer was discarded and the amine was liberated by the addition of sodium hydroxide solution. The amine was taken up in ether and dried; approximately half of this solution was reserved for other purposes and half converted to its hydrochloride by passing gaseous hydrogen chloride into it. The resulting oil was hygroscopic; however, it crystallized slowly (two weeks) from dioxane when treated with a seed crystal. The crude hydrochloride was recrystallized from absolute alcohol; yield, 14 g., m. p. 195–198°.

Anal. Calcd. for $C_{21}H_{27}NO\cdot HCl$: Cl, 10.25. Found: Cl, 10.15.

2-Phenyl-3,4-tetramethylenehexahydro-1,3-oxazepine.—A mixture of 21.2 g. of benzaldehyde, 28.6 g. of 2-(3-

hydroxypropyl)-piperidine, 0.1 ml. of acetic acid and 200 ml. of benzene was refluxed for three hours using a water-trap (3.4 ml. of water collected). Distillation gave 42.0 g. (91%) of product, b. p. 93° at 0.04 mm., $n^{25}D$ 1.5433.

Anal. Calcd for $C_{15}H_{21}NO$: N, 6.06. Found: N, 6.11.

2-(3-Hydroxypropyl)-1-(1,2-diphenylethyl)-piperidine Hydrochloride.—To a solution of benzylmagnesium chloride (1 mole) was added 57.8 g. of 2-phenyl-3,4-tetramethylenehexahydro-1,3-oxazepine dissolved in dry ether. After stirring and refluxing for four hours it was poured into ice and 250 ml. of concentrated hydrochloric acid. The ether layer was separated and discarded. The water layer was treated with enough sodium hydroxide solution to liberate the amine. The amine was extracted with ether and the extracts were dried over potassium carbonate. The hydrochloride was precipitated with gaseous hydrogen chloride as a hygroscopic, gummy material. After boiling with methyl ethyl ketone and cooling, it gave 29 g. of white crystals, m. p. 185–188°. Recrystallization gave 25 g. of pure product, m. p. 188–191°.

Anal. Calcd. for $C_{22}H_{29}NO\cdot HCl$: Cl, 9.85. Found: Cl, 9.82.

N-(1,2-Diphenylethyl)-piperidine Hydrochloride.—The preferred method of preparation of this compound was by the treatment of α-piperidylphenylacetonitrile with benzylmagnesium chloride (Tables I and II). Two alternatives are described below:

(a) **Alkylation.**—1,2-Diphenylethyl bromide (44 g. prepared by treating 1,2-diphenylethanol with phosphorus tribromide at 0 to 10°) was allowed to react with 30 g. of piperidine in 50 ml. of alcohol for one month at room temperature. The stilbene was removed (approx. 24 g.) and the product obtained weighed 3.8 g., m. p. 207–208.5°. This product appeared to be identical with that of Christiaen (*loc. cit.*), m. p. 120°. When Christiaen's procedure was followed, the product obtained melted low until it was vacuum-dried at 76°, after which it melted at the higher temperature and gave no mixed melting point depression (probably polymorphic forms). As noted in Table II this compound also melts at 158°.

(b) **From Benzaldipiperidine.**[7]—To a solution of benzylmagnesium chloride (1 mole) in ether was added 64.5 g. of benzaldipiperidine. The mixture was stirred and refluxed four hours and then poured into ice and 250 ml. of concentrated hydrochloric acid. After standing overnight at +5° the mixture was filtered to give 14 g. of white crystals of N-(1,2-diphenylethyl)-piperidine hydrochloride, m. p. 207–209°, which gave no mixed melting point depression with the material prepared by the other methods.

N-(1,2-Diphenylethyl)-4-methylpiperidine Hydrochloride. (a) **From Benzaldi-γ-pipecoline.**—A mixture of 26.5 g. of benzaldehyde, 50 g. of γ-pipecoline and 250 ml. of benzene was refluxed using a water-trap for four hours (8.5 ml. of water was collected). Since this product could not be made to crystallize and since these compounds cannot be distilled by conventional means without decomposition, this impure intermediate, benzaldi-γ-pipecoline, was added directly to benzylmagnesium chloride (1 mole) in ether. The ether was replaced with benzene and the mixture was heated to 80° for two hours. It was then poured into ice and concentrated hydrochloric acid. The amine was separated from the aqueous layer and precipitated from ether solution as its hydrochloride; yield, 17.5 g. Crystallization from methyl ethyl ketone containing a few drops of water gave 10.5 g., m. p. 230.5–231.5.

Anal. Calcd. for $C_{20}H_{25}N\cdot HCl$: Cl, 11.23. Found: Cl, 11.27.

(b) **From α-(4-Methylpiperidyl)-phenylacetonitrile.**—To a solution of benzylmagnesium chloride (0.5 mole) in ether was added 53.6 g. of α-(4-methylpiperidyl)-phenylacetonitrile. The mixture was refluxed for three hours, then poured onto ice and 100 ml. of concd. hydrochloric acid; yield of crystalline product 56.5 g. Recrystallization from methyl ethyl ketone containing a little alcohol, yielded 34 g. of amine hydrochloride, m. p. 228–230°, identical with the preparation described above.

(7) Laun, *Ber.*, **17**, 678 (1884).

Summary

Diphenylethylamines having a tertiary nitrogen atom have been prepared by the addition of benzylmagnesium chloride to: (a) α-aminophenylacetonitriles, (b) 3-substituted 2-aryloxazolidines and (c) benzaldipiperidines.

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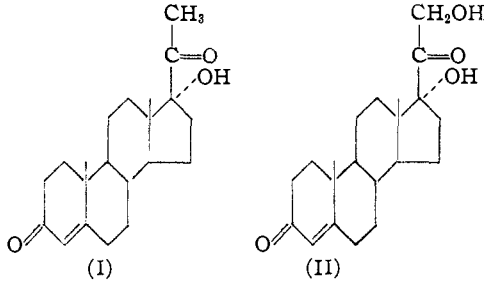
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. IX. The Selective Halogenation and Dehalogenation of Certain Steroids (Part 1)

BY PERCY L. JULIAN* AND WILLIAM J. KARPEL

The broad program, planned in this Laboratory several years ago, on the large-scale preparation of 17-hydroxysteroids, included as first objectives the preparation of what have now come to be designated 17α-hydroxyprogesterone (I) and 17-α-hydroxy-11-desoxycorticosterone (II). It appeared to us that, if the hurdles involved in the large-scale preparations of these 17α-hydroxysteroids could be successfully overcome, a significant part of the groundwork for the commercial preparation of substances like Kendall's Compound E and related cortical hormones would have been laid.

For our proposed preparation of 17α-hydroxyprogesterone (I) and related substances, we desired a clean-cut route to 17-bromopregnenolones (VII) or pregnanolones, as precursors for the corresponding 16-dehydro-derivatives (VIII).[1] No such clean-cut route is discernible in the



(I) (II)

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(1) Julian, Meyer and Ryden, THIS JOURNAL, **71**, 756 (1949).