TABLE I

ALKYLATION OF BENZENE WITH 1,1-DICHLORO-3,3-DIMETHYLBUTANE

Expt.	Method	Reactants, moles		Catalyst		Ave.	Chief products	
		C_6H_6	$C_6H_{12}Cl_2$[a]	Kind	g.	temp., °C.	Formula	Yield, %
1	A	4.15	0.55	$AlCl_3$	8	3	$Me_3CCH_2CH_2Ph$	26
							$Me_3CCH_2CHPh_2$	19
2	A	4.15	.55	$AlCl_3$	20	3	$Me_3CCH_2CH_2Ph$	28
							$Me_2CCH_2CHPh_2$	20
3	A	4.15[b]	.55	$AlCl_3$	20	3	$Me_3CCH_2CH_2Ph$	60
							$Me_3CCH_2CHPh_2$	6
							MeC_5H_8Ph	48[c]
4	R	1.53	.19	$AlCl_3 \cdot MeOH$[d]	10	84	$Me_3CCH_2CH_2Ph$	6
							$Me_3CCH_2CHPh_2$	20
5	A	4.15	.55	$ZrCl_4$	5	27[e]	$Me_3CCH_2CH_2Ph$	5[f]
							$Me_3CCH_2CHPh_2$	20

[a] 1,1-Dichloro-3,3-dimethylbutane, b.p. 148° (6 mm.), prepared by the condensation of *t*-butyl chloride with vinyl chloride. [b] Also 1.8 moles methylcyclopentane. [c] Calculated on the basis of eq. 8. [d] L. Schmerling, THIS JOURNAL, 68, 280 (1946). [e] Stirring continued for ten hours after the addition of the dichlorohexane. [f] Presence of other monoalkylbenzene (not 2-phenyl-3,3-dimethylbutane, 2-phenyl-2,3-dimethylbutane, 2-phenyl-2-methylpentane, 3-phenyl-2-methylpentane, or 3-phenylhexane) was indicated by the infrared spectrum of the fraction boiling at 57–70° at 4 mm., chiefly 61–67° at 4 mm. (206–212° at 760 mm.).

Anal.[10] Calcd. for $C_{16}H_{29}N_2O_2$: N, 10.14. Found: N, 10.41.

A mixture of this diacetamido derivative with that[2] (m.p. 235°) of 2-phenyl-3,3-dimethylbutane melted at 205–210°.

1,1-Diphenyl-3,3-dimethylbutane.—The fraction boiling at 148–151° at 5 mm. (314–318° at 760 mm.) crystallized on standing; m.p. 33°.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.69; H, 9.31. Found: C, 90.85; H, 9.68.

Nitration of a pentane solution of the diphenylhexane with a 2:1 by volume mixture of sulfuric and nitric acids yield a dinitro compound; nacreous flakes (from ethanol), m.p. 156°.

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.84; H, 6.14. Found: C, 65.84; H, 5.98.

A mixture of 0.5 g. of the diphenylhexane and a solution of 3.5 g. of chromium trioxide in 5 cc. of concentrated sulfuric acid, 15 cc. of acetic acid and 15 cc. of water was heated under reflux for three hours. The cooled product was extracted with pentane and the extract was washed, dried and distilled. The residue was taken up in 5 cc. of ethanol and the solution was used for the preparation of crystalline derivatives: 2,4-dinitrophenylhydrazone, m.p. and "mixed m.p." with the 2,4-dinitrophenylhydrazone of benzophenone, 234–235°; semicarbazone, m.p. and "mixed m.p." with the semicarbazone of benzophenone, 46–47°.

(*x*-Methylcyclopentyl)-benzene.—The material boiled mainly at 149–153° at 87 mm. (226–231° at 760 mm.); $n^{20}D$ 1.5170.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.93; H, 10.07. Found: C, 90.02; H, 10.21.

The infrared spectrum of this material indicated that no significant amount of (1-methylcyclopentyl)-benzene[11] was present.

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[10] Microanalyses byMr. C. W. Beazley, Micro-Tech Laboratories, Skokie, Illinois.

[11] H. Pines and J. D. LaZerte, unpublished results.

RIVERSIDE, ILLINOIS

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

The Synthesis of 5-Dimethylamino-4,4-diphenyl-2-pentanol

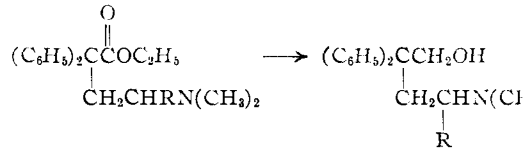
BY NELSON R. EASTON[1] AND VELMER B. FISH

RECEIVED SEPTEMBER 20, 1954

The synthesis of 5-dimethylamino-4,4-diphenyl-2-pentanol is described starting with 3,3-diphenyl-5-methyl-2-tetrahydrofuranoneimine. The formation of some derivatives and their reactions are reported.

The reduction of both methadone and isomethadone has been studied extensively.[2–5] The carbinols from these reductions either in the form of their acetoxy derivatives or the alcohols themselves generally exhibit considerable analgetic activity.

The reduction of esters of the general structure I to the amino carbinols (II) has also been reported.[4] Since compounds of this general structure usually show some analgetic activity the influence of interchanging the functional groups on the type and degree of analgetic activity should promise an interesting addition to the general study of analgesia. One of the compounds that has been prepared and found to have slight activity is 4-dimethylamino-2,2-diphenyl-1-pentanol (II, R = CH_3).[4] Interchanging the amino and hydroxy



$$\underset{\textstyle CH_2CHRN(CH_3)_2}{(C_6H_5)_2C}\overset{O}{\overset{\|}{C}}OC_2H_5 \longrightarrow \underset{\textstyle CH_2\underset{R}{CH}N(CH_3)_2}{(C_6H_5)_2C}CH_2OH$$

I II

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[1] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Indiana.

[2] (a) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948); (b) A. Pohland, F. J. Marshall and T. P. Carney, THIS JOURNAL, **71**, 460 (1949).

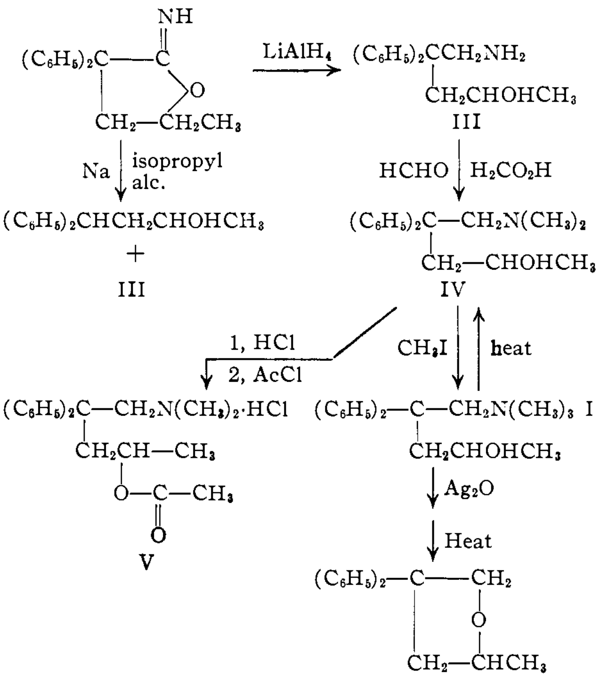
[3] E. L. May and N. B. Eddy, *J. Org. Chem.*, **17**, 1210 (1952).

[4] M. E. Speeter, W. M. Byrd, L. C. Cheney and S. B. Binkley, THIS JOURNAL, **71**, 57 (1949).

[5] N. B. Eddy, E. L. May and E. Mosettig, *J. Org. Chem.*, **17**, 321 (1952).

groups of the compound would give 5-dimethylamino-4,4-diphenyl-2-pentanol (IV). A study of the activity of this compound IV compared to its isomer reported above should provide an interesting correlation of activity in relation to spacial arrangement.

The ready availability of 5-methyl-3,3-diphenyl-2-furanoneimine[6,7] suggested the synthetic procedure in the accompanying diagram.



The reduction of the imidolactone with sodium in isopropyl alcohol gave a small yield of the desired aminocarbinol (III). The major product was a non-basic compound, 4,4-diphenyl-2-butanol. This is not an unexpected product since the hydroxynitrile which would be the linear isomer of the imidolactone would be expected to cleave the nitrile group under these conditions, as this procedure has been used to prepare 2-dimethylamino-4,4-diphenylbutane from 2,2-diphenyl-4-dimethylaminopentanenitrile[8] and similar compounds.[9] Also, it has been reported[5] that the reduction of methadone with sodium and isopropyl alcohol causes a cleavage of the propionyl group to the extent of approximately 5%.

The reduction of the imidolactone with lithium aluminum hydride proceeded smoothly and in good yield. In addition to the expected product a second material was isolated in small quantity, which from the analyses apparently is 3,3-diphenyl-4-amino-1-butanol. This material is evidently obtained from the appropriate imidolactone which is present in this starting material because of the presence of small amounts of ethylene oxide in the propylene oxide used.[10] The methylation with formic acid and formaldehyde gave II in good yield. The best method of acetylation of IV was found to take place by heating the hydrochloride of IV with acetyl chloride.

It has been reported[11,12] that ketones of the methadone type give ethylidenetetrafurans on the pyrolysis of their methiodides and that the carbinols from these ketones give tetrahydrofurans under the same conditions.[13] Pyrolysis of the dimethylamino alcohol (IV) under these conditions was made. In contrast with the related compounds, the pyrolysis of the methiodide of IV gave no appreciable quantity of neutral material but did split off methyl iodide to give the parent compound IV which was isolated as the hydrochloride. The decomposition of the quaternary hydroxide, as would be expected, gave a good yield of 3,3-diphenyl-5-methyltetrahydrofuran, a compound which has been previously prepared[14] by the cyclization of 2,2-diphenyl-1,4-pentanediol.

Neither compound IV as the hydrochloride nor compound V showed any analgetic activity at a dosage level of 25 mg./kg.

Experimental

Reduction of 3,3-Diphenyl-5-methyl-2-furanoneimine. a. With Lithium Aluminum Hydride.—To a slurry of 8 g. of lithium aluminum hydride in 300 ml. of ether there was added slowly a solution of 45 g. of 3,3-diphenyl-5-methyl-2-furanoneimine in 300 ml. of dry benzene. The mixture was refluxed for seven hours, and the resulting mixture was neutralized carefully with water until a granular precipitate appeared. The mixture was filtered, and the precipitate was washed with ether and benzene. The filtrate was washed with a 20% solution of sodium hydroxide, dried over sodium carbonate and concentrated at reduced pressure. Trituration of the remaining oil with petroleum ether gave 32.5 g. of product melting at 83.5–85°. After recrystallization from a mixture of methylcyclohexane and petroleum ether, the 5-amino-4,4-diphenyl-2-pentanol melted at 85–86.5°.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 79.75; H, 8.32.

Hydrochloride m.p. 135–137° (103–105°).

Anal. Calcd. for $C_{17}H_{22}ONCl$: Cl, 12.15. Found: Cl, 12.02.

The mother liquor was evaporated under reduced pressure, the residue was taken up in isopropyl ether, and alcoholic hydrogen chloride was added. An oil precipitated which was separated by decantation. Trituration of the oil with ethyl acetate gave a solid melting at 204–206°. After recrystallization from a mixture of ethanol and ethyl acetate, it melted at 210–211°.

Anal. Calcd. for $C_{16}H_{20}NOCl$: C, 69.17; H, 7.27; Cl, 12.76. Found: C, 69.40; H, 7.05; Cl, 12.78.

b. With Sodium in Isopropyl Alcohol.—A solution of 10 g. (0.04 mole) of 3,3-diphenyl-5-methyl-2-furanoneimine in 100 ml. of isopropyl alcohol was heated to reflux with 7 g. of sodium metal. More sodium was added at intervals in order to maintain an excess of the unreacted metal. A total of 15 g. was required over a period of two hours. The mixture was allowed to cool, and 50% aqueous alcohol was added carefully to decompose the unreacted sodium; 200 ml. of water was then added, and the layers separated. The aqueous layer was extracted with diethyl ether. The

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(11) N. R. Easton, S. J. Nelson, V. B. Fish and P. N. Craig, *ibid.*, **75**, 3751 (1953).

(12) N. R. Easton and V. B. Fish, *ibid.*, **76**, 2836 (1954).

(13) S. J. Nelson, V. B. Fish and N. R. Easton, *ibid.*, **77**, 1908 (1955)

(14) N. R. Easton, C. A. Lukach, V. B. Fish and P. N. Craig, *ibid.*, **75**, 3751 (1953).

organic layer was added to the ether solution, and the mixture was extracted twice with dilute hydrochloric acid. On neutralization of the acid layer with sodium hydroxide, an oil was obtained which was converted to the hydrochloride. This material amounted to 3.5 g.; m.p. 103–105°. The base which was obtained from this hydrochloride melted at 84–86°, and a mixture with the compound obtained by the action of lithium aluminum hydride on 3,3-diphenyl-5-methyl-2-furanoneimine showed no depression in m.p. The ether solution was concentrated, and the residue was distilled under reduced pressure. The fraction obtained at 153–158° and 3 mm. amounted to 4.0 g. The oil crystallized and was recrystallized several times from petroleum ether (b.p. 90–100°); m.p. 64.5–66°.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.80; H, 7.97.

5-Dimethylamino-4,4-diphenyl-2-pentanol Hydrochloride.—A mixture of 16.7 g. of 5-amino-4,4-diphenyl-2-pentanol, 50 ml. of formalin and 50 ml. of formic acid was refluxed for seven hours. The solution was poured into an equal volume of water, the mixture was extracted with ether, and the organic layer was dried over sodium carbonate. The addition of alcoholic hydrogen chloride produced an oil that crystallized on standing. The yield of hydrochloride melting at 199–201° was 16.2 g. An analytical sample was recrystallized from ethanol–isopropyl ether solution; m.p. 200–202°.

Anal. Calcd. for $C_{19}H_{26}NOCl$: C, 71.34; H, 8.19; Cl, 11.08. Found: C, 71.40; H, 8.11; Cl, 11.10.

1-Dimethylamino-2,2-diphenyl-4-acetoxypentane.—A mixture of 4 g. of 5-dimethylamino-4,4-diphenyl-2-pentanol hydrochloride and 20 ml. of acetyl chloride was heated gently; the solid gradually dissolved and a clear solution resulted. The solution was then refluxed for a half hour. (After 10 minutes of refluxing a solid started to precipitate.) Isopropyl ether was added and the solid was collected. The yield was 4 g.; m.p. 200–202°. The melting point did not change on recrystallization from ethanol–isopropyl ether. A mixture of this compound with the hydrochloride of 5-dimethylamino-4,4-diphenyl-2-pentanol had a melting point of 182–187°.

Anal. Calcd. for $C_{21}H_{28}NO_2Cl$: Cl, 9.80. Found: Cl, 9.65.

Decomposition of Methiodide of II.—The methiodide was prepared in the usual manner and melted at 229–230°.

Anal. Calcd. for $C_{20}H_{28}NOI$: C, 56.47; H, 6.65. Found: C, 57.17; H, 6.83.

A pyrolytic decomposition of 4 g. was carried out in the usual way.[9] No appreciable amount of neutral material was obtained, but a considerable quantity of a base was formed which gave a hydrochloride melting point of 196–199°. This compound gave no depression when mixed with the hydrochloride of II.

Decomposition of the Quaternary Hydrochloride of II.—A mixture of 6.5 g. of the methiodide and 3 g. of silver oxide in aqueous alcohol was stirred vigorously until no iodide ion could be detected. The mixture was filtered and washed well with water and ethanol. The solution was concentrated at reduced pressure. The residue was transferred to a Claisen flask (with a minimum amount of ethanol) and pyrolyzed over a free flame. The distillate was crystallized from aqueous methanol, m.p. 45–46° (1.1 g.). A mixed melting point with 3,3-diphenyl-5-methyltetrahydrofuran[14] showed no depression.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.75; H, 7.61.

Acknowledgment.—The authors wish to thank Mr. Carl Lukach for preparing the 3,3-diphenyl-5-methyl-2-tetrahydrofuranoneimine used in this work, and the Smith, Kline and French Laboratories for testing these compounds.

BETHLEHEM, PENNSYLVANIA

[CONTRIBUTION NO. 133 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Preparation and Properties of Substituted Benzhydryl Carbonium Ions

BY HILTON A. SMITH AND R. GENE THOMPSON

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The behavior of the following benzhydrols and symmetrical benzhydryl ethers in 100% sulfuric acid has been studied: 4,4′-dichlorobenzhydrol, 2,3,4,5,6-pentamethylbenzhydrol, 2,2′,3,3′,4,4′,5,5′,6,6′-decamethylbenzhydrol, 2,2′,3,4,4′,5,6,6′-octamethylbenzhydrol, bis-(4,4′-dimethylbenzhydryl) ether and bis-(2,3,4,4′,5,6-hexamethylbenzhydryl) ether. All the compounds gave fairly stable carbonium ions, as indicated by their *i*-factors, colors, ultraviolet and near-visible spectra, and chemical properties, all observed in 100% sulfuric acid. With the exception of 4,4′-dichlorobenzhydrol, all the compounds were shown to undergo some sulfonation in addition to carbonium ion formation.

Introduction

It has been shown that many triphenylcarbinols[1,2] and certain benzhydrols[2–4] ionize in 100% sulfuric acid to give stable carbonium ions. The ionizations are generally represented as

$$(C_6H_5)_3COH + 2H_2SO_4 \longrightarrow (C_6H_5)_3C^+ + 2HSO_4^- + H_3O^+$$

$$(C_6H_5)_2CHOH + 2H_2SO_4 \longrightarrow (C_6H_5)_2CH^+ + 2HSO_4^- + H_3O^+$$

While triphenylcarbinols are quite stable in sulfuric acid, benzhydrol is not stable and undergoes rapid polymerization and sulfonation.

The carbonium ion studies have been extended to include several substituted benzhydrols and benzhydryl ethers. In this work it was desired to find out the influence of substituents, especially methyl groups, on the formation and stabilization of benzhydryl carbonium ions.

Results

***i*-Factors.**—Table I gives the *i*-factors for the various compounds studied. Referring to the previous equations, an *i*-factor of 4.0 should be observed for the simple carbonium ion formation in the benzhydrol series. Simple carbonium ion formation from a symmetrical benzhydryl ether would be expected to give an *i*-factor of 6.0. For example

$$(C_6H_5)_2CHOCH(C_6H_5)_2 + 3H_2SO_4 \longrightarrow 2(C_6H_5)_2CH^+ + 3HSO_4^- + H_3O^+$$

According to the above equation the same benzhydryl carbonium ion would be expected from either a symmetrical ether or its corresponding benzhydrol in sulfuric acid. In confirmation of this, the spectra of pentamethylbenzhydrol and bis-(pentamethylbenzhydryl) ether were found to be identical

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