129 g. (0.44 mole) of 2-bromo-1,4-bis-(trifluoromethyl)-benzene and 44.5 g. (0.12 mole) of 2,5-dibromo-1,4-bis-(trifluoromethyl)-benzene representing conversions of 44 and 12%, and yields of 67 and 18%, respectively. In other experiments, it was found that at a reaction temperature of 100° bromination occurred very slowly. At temperatures above 125°, however, the conversion to the dibromide increased with a corresponding decrease in the conversion to the monobromide.

The technique described above for the bromination of 1,4-bis-(trifluoromethyl)-benzene was used in the bromination of 1,3-bis-(trifluoromethyl)-benzene, 1,2-bis-(trifluoromethyl)-benzene, 2-chloro-1,4-bis-(trifluoromethyl)-benzene, 2-chloro-1,3-bis-(trifluoromethyl)-benzene, 4-chloro-1,3-bis-(trifluoromethyl)-benzene and 1,2-dichloro-3,4-bis-(trifluoromethyl)-benzene.

Summary

A procedure for the bromination of trifluoromethyl and bis-(trifluoromethyl) derivatives of benzene and chlorobenzene is described which comprises the simultaneous use of bromine and chlorine in the presence of the halogen carrier, antimony(V) chloride. Physical properties of the new compounds are reported.

LAFAYETTE, INDIANA RECEIVED NOVEMBER 12, 1949

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

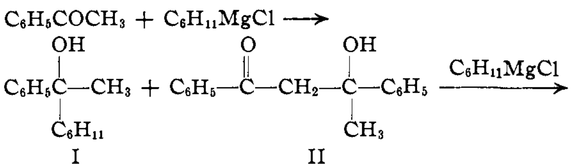
The Dehydration of Cyclohexylmethylphenylcarbinol and Related Tertiary Alcohols[1]

BY JAMES ENGLISH, JR., CHARLES A. RUSSELL AND F. V. BRUTCHER, JR.

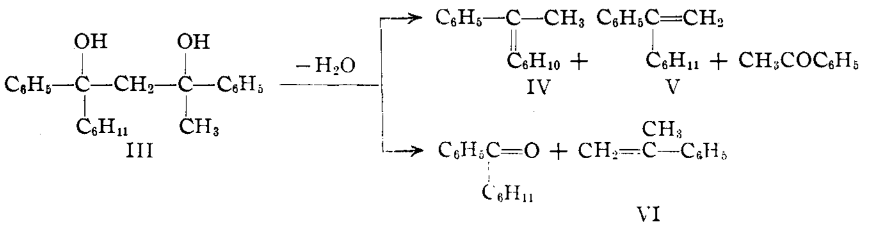
Cyclohexylmethylphenylcarbinol has been prepared by Venus-Danilova and Bol'shukhin[2] and by Sabatier and Mailhe.[3] The former reported the product of the reaction between acetophenone and cyclohexylmagnesium halide as a liquid while the latter reported a liquid having a "stereoisomeric" solid form melting at 100–111°.

When this synthesis was repeated, the product was found to be a mixture of a liquid alcohol and a solid product, m. p. 119.5°, presumably the compound of Sabatier and Mailhe.

Dehydration with potassium bisulfate or anhydrous oxalic acid of either the crude reaction product or the crystalline substance gave a poor yield of a mixture of 1-cyclohexylid*in*ethylbenzene (IV) and α-cyclohexylstyrene (V) together with about 30% of cyclohexyl phenyl ketone. Ozonolysis of the hydrocarbon mixture showed that it was composed of approximately 90% α-cyclohexylstyrene and 10% 1-cyclohexylid*in*ethylbenzene.



$$C_6H_5COCH_3 + C_6H_{11}MgCl \longrightarrow \underset{\text{I}}{C_6H_5C(OH)(CH_3)C_6H_{11}} + \underset{\text{II}}{C_6H_5\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_2\text{—}C(OH)(CH_3)\text{—}C_6H_5} \xrightarrow{C_6H_{11}MgCl}$$



$$\underset{\text{III}}{C_6H_5\text{—}C(OH)(C_6H_{11})\text{—}CH_2\text{—}C(OH)(CH_3)\text{—}C_6H_5} \xrightarrow{-H_2O} \begin{cases} \underset{\text{IV}}{C_6H_5\text{—}\underset{C_6H_{10}}{\underset{\|}{C}}\text{—}CH_3} + \underset{\text{V}}{C_6H_5\underset{C_6H_{11}}{\underset{|}{C}}{=}CH_2} + CH_3COC_6H_5 \\ C_6H_5\underset{C_6H_{11}}{\underset{|}{C}}{=}O + \underset{\text{VI}}{CH_2{=}\overset{CH_3}{\overset{|}{C}}\text{—}C_6H_5} \end{cases}$$

When cyclohexylmethylphenylcarbinol was prepared from cyclohexyl phenyl ketone and methylmagnesium iodide the product was a homogeneous liquid which, on dehydration, yielded only the mixture of hydrocarbons (IV and V). No evidence for the presence of cyclohexyl phenyl ketone could be obtained. This result, coupled with the absence of any methane, which might have been expected from a thermal cracking of cyclohexylmethylphenylcarbinol[4] or any one-carbon oxidation products from possible oxidation[5] of α-cyclohexylstyrene led to the suspicion that the crystalline product of Sabatier and Mailhe was not cyclohexylmethylphenylcarbinol.

The analysis and molecular weight of this crystalline substance were found to agree best with the formula $C_{22}H_{28}O_2$. Its dehydration products on careful fractionation were found to include some α-methylstyrene and a trace of acetophenone as well as cyclohexyl phenyl ketone and the hydrocarbon mixture (IV and V) mentioned above. It appears that this substance is in fact 1,3-diphenyl-1-cyclohexyl-1,3-butanediol (III) and that it was produced as a result of the condensation of acetophenone with itself followed by reaction with cyclohexylmagnesium chloride as shown in the equations.

Although Grignard reagents are known[6,7] to lead to condensation reactions, we are not aware of a previous reaction in which the condensation product in turn has been shown to react with the Grignard reagent. The cleavage of II as shown might be predicted by analogy with the work of Grignard[8]

---

[1] This paper is taken in part from the thesis presented by Charles A. Russell to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Venus-Danilova and Bol'shukhin, *J. Gen. Chem.* (USSR), **12**, 73 (1942).

[3] Sabatier and Mailhe, *Ann. chim. phys.*, [8] **10**, 538 (1907).

[4] Grignard and Escourrou, *Compt. rend.*, **176**, 1860 (1923); **182**, 299 (1926).

[5] Tiffeneau, *Ann. chim. phys.*, [8] **10**, 539 (1907).

[6] Shine and Turner, *Nature*, **158**, 170 (1946).

[7] V. Grignard, *Bull. soc. chim.*, [4] **39**, 1285; Tuot, *Compt. rend.*, **206**, 1019 (1938).

[8] Grignard and Chambret, *Compt. rend.*, **182**, 299 (1926).

TABLE I

			Products of dehydration of crude carbinols	
	Starting materials	% olefin	Ketone obtained	% ketone
1	$C_6H_5COCH_3 + C_6H_{11}MgCl$	35	$C_6H_5COC_6H_{11} + CH_3COC_6H_5$	31
2	$C_6H_5COC_6H_{11} + CH_3MgI$	73		0
3	p-$CH_3OC_6H_4COCH_3 + C_6H_{11}MgCl$	35	p-$CH_3OC_6H_4COC_6H_{11}$	20
4	p-$CH_3C_6H_4COCH_3 + C_6H_{11}MgCl$	25	p-$CH_3C_6H_4COC_6H_{11}$	16
5	$C_6H_5COCH_3 + i$-C_3H_7MgBr	70	$C_6H_5COCH(CH_3)_2$	8
6	$C_6H_5COCH_3 + n$-C_4H_9MgBr	66	$C_6H_5COC_4H_9$	2
7	$C_6H_5COC_2H_5 + C_6H_{11}MgCl$	75	$C_6H_5COC_6H_{11}$	7

on the pyrolysis of some tertiary alcohols and of Barbot[9] on the dehydration of some 1,3-diols.

2-Phenyl-1-benzoyl-2-propanol (II) was prepared by the method of Grignard and Cologne[10] and found to react readily with cyclohexylmagnesium chloride to yield III.

A similar cleavage reaction was observed also in the dehydration of a number of other crude tertiary carbinols as shown in Table I.

Pure samples of dicyclohexylmethylcarbinol, diphenylmethylcarbinol and dimethylcarbinol, on the other hand, were found to yield no ketones on dehydration. It is believed that in those cases in which ketones were produced formation of 1,3-diols occurred in the same manner as postulated above. In none of these experiments except (1) of Table I could crystalline diols be isolated.

Experimental[11]

The Reaction of Cyclohexylmagnesium Chloride with Acetophenone.—A solution of 60 g. (0.5 mole) of dry acetophenone in 100 ml. of dry ether was added with stirring and cooling to 210 ml. of ether solution containing 92 g. (0.65 mole) of cyclohexylmagnesium chloride.[12] The mixture was then refluxed for two hours, cooled and poured into saturated ammonium chloride solution and the product extracted with ether. The ether extract was washed with water and sodium bicarbonate and, after removal of the ether, the residue was steam distilled until all unchanged acetophenone, cyclohexane, and other steam volatile impurities had been removed. There remained 67 g. of crude sirupy reaction product. A small amount of petroleum ether was added and after vigorous stirring the product solidified partially, was filtered, and the solid recrystallized from either petroleum ether or 80% alcohol. In this way 16 g. of pure 1,3-diphenyl-1-cyclohexyl-1,3-butanediol, m. p. 119.5°, was obtained.

A slightly higher yield (24%) of crystalline product could be obtained by dropping the Grignard reagent (0.9 mole) into a stirred ether solution of acetophenone (0.7 mole) and working the reaction up as before.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.5; H, 8.65; active hydrogen (Zerewitinoff), 0.62; mol. wt., 324. Found: C, 81.8; H, 8.43; active hydrogen, 0.65, 0.66; molecular wt. (ethyl acetate), 336.

1,3-Diphenyl-1-cyclohexyl-1,3-butanediol.—An excess of cyclohexylmagnesium chloride was added gradually to an ether solution of 1 g. of 2-phenyl-1-benzoyl-2-propanol[9] with stirring at room temperature. As soon as the addition was complete, the mixture was decomposed by pouring into saturated ammonium chloride solution and the product extracted with ether. After removal of the solvent the residue crystallized and after recrystallization from petroleum ether (b. p. 30–60°) melted at 119–120° and gave no depression when mixed with 1,3-diphenyl-1-cyclohexyl-1,3-butanediol prepared as described above.

Cyclohexylmethylphenylcarbinol.—Methylmagnesium iodide (0.25 mole) in anhydrous ether was added slowly to a solution of 40 g. (0.21 mole) of cyclohexylphenyl ketone[13] in 160 ml. of anhydrous ether. After stirring at room temperature for twenty minutes, the mixture was decomposed with saturated ammonium chloride solution and the product isolated by extraction with ether and distillation. Pure cyclohexylmethylphenylcarbinol boiled without decomposition at 96–97° (0.3 mm.) $n^{20}D$ 1.5408. No crystalline compounds could be obtained from this reaction.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.4; H, 9.81; mol. wt., 204. Found: C, 82.6, H, 10.2; mol. wt. (ethyl acetate), 203.

Synthesis of Carbinols.—The other products reported in Table I were prepared in the same manner as described for cyclohexylmethylphenylcarbinol. Compounds 3, 4 and 7 could not be distilled and were dehydrated in crude form after removal of all ketonic material by steam distillation. Compounds 5 and 6 were distilled once before dehydration.

Dehydration Procedure.—The carbinol to be dehydrated was mixed with an equal weight of anhydrous potassium bisulfate and heated in a nitrogen atmosphere in a bath held at 135–145° for eight hours. The flask was equipped with a reflux condenser and suitable traps to catch any volatile products (CO_2, etc.). In no case was any evidence obtained for the evolution of carbon dioxide, formic acid, formaldehyde, or non-condensable gases. At the end of this time the mixture was dissolved in water and the reaction products extracted with ether, dried, and distilled.

Dehydration of 1,3-Diphenyl-1-cyclohexyl-1,3-butanediol.—Thirty grams of crystalline 1,3-diphenyl-1-cyclohexyl-1,3-butanediol was dehydrated by this procedure and the product chilled in a Dry Ice-bath after removal of all solvent. Crude cyclohexyl phenyl ketone crystallized out, was filtered, washed with cold petroleum ether (b. p. 30–60°) and recrystallized from this same solvent. A total of 10.4 g. (60%) of pure cyclohexylphenyl ketone m. p. 55–56° was isolated. This substance was identified by comparison with an authentic sample[13] and conversion to its oxime m. p. 162° and 2,4-dinitrophenylhydrazone m. p. 199–200°. There was no depression in melting points of mixtures of the ketone or its derivatives with authentic samples. A similar yield of ketone, b. p. 110° (3 mm.), could be obtained by direct distillation of the reaction mixture.

The mother liquors from the crystallization of the cyclohexyl phenyl ketone were fractionated in vacuum through a 20-plate column. The following fractions of distillate were obtained: 1, b. p. 41–43° (6 mm.) 2.7 g.; 2, b. p. 60–70 (7 mm.) 0.8 g.; 3, b. p. 99–101 (3 mm.) 2.7 g.; 4, residue. Fraction 1 was re-distilled over sodium, b. p. 165° (760 mm.) and found to be α-methylstyrene,[14] $n^{17}D$ 1.5381.

Anal. Calcd. for C_9H_{10}: C, 91.5; H, 8.47. Found: C, 91.5; H, 8.68.

Permanganate oxidation of 2 g. of this fraction gave 0.6 g. of acetophenone, identified as its 2,4-dinitrophenylhydrazone, m. p. 248°, together with a smaller amount of benzoic acid. Fraction 2 was identified as acetophenone by conversion to its 2,4-dinitrophenylhydrazone. Frac-

---

[9] Barbot, *Bull. soc. chim.*, [5] **2**, 1438 (1935).

[10] Grignard and Cologne, *Compt. rend.*, **194**, 929 (1932).

[11] All boiling and melting points are corrected.

[12] Gilman, THIS JOURNAL, **53**, 1945 (1931).

[13] Meyer and Scharvin, *Ber.*, **30**, 1942 (1897).

[14] Sabetay, *Bull. soc. chim.*, [4] **47**, 614 (1930).

tion 3, $n^{22}D$ 1.5404, was analyzed and found to be a hydrocarbon mixture (IV and V).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.3; H, 9.68. Found: C, 90.2; H, 9.79.

Ozonolysis of 1.76 g. (0.008 mole) of this fraction according to the method of Whitmore and Church[15] gave 0.001 mole of formaldehyde, 0.0039 mole of acetophenone 3,4-dinitrophenylhydrazone and 0.004 mole of cyclohexyl phenyl ketone 2,4-dinitrophenylhydrazone. The yield of fraction 3 varied from 7–20% of theory, depending, apparently, on the conditions of distillation. The residue 4 which appeared to be polymerized hydrocarbon material increased with the decreased yields of fraction 3.

Cyclohexyl *p*-Anisyl Ketone.[16]—This substance, b. p. 125–135° (2 mm.), m. p. 58–59° (re-crystallized from ligroin) was isolated by distillation from the dehydration of crude cyclohexyl-*p*-anisylmethylcarbinol. The 2,4-dinitrophenylhydrazone prepared in the usual way melted at 115.5–116°.

Cyclohexyl *p*-tolyl ketone was isolated from the dehydration product of cyclohexyl-*p*-tolylmethylcarbinol by distillation (b. p. 105–110° at 2 mm.) and recrystallization, m. p. 64–65°. This substance does not appear to have been reported previously.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.1; H, 8.90. Found: C, 83.0; H, 8.71.

The 2,4-dinitrophenylhydrazone melted at 166.5°.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.9; H, 5.79; N, 14.6. Found: C, 63.2; H, 6.01; N, 14.1.

Isobutyrophenone was isolated from the dehydration products of 10 g. isopropylphenylmethylcarbinol in the form of its 2,4-dinitrophenylhydrazone. There was obtained 1.6 g., m. p. 162°,[17] after recrystallization from alcohol.

Valerophenone was isolated from the dehydration products of 15 g. of *n*-butylmethylphenylcarbinol in the form of its 2,4-dinitrophenylhydrazone. After recrystallization from acetic acid there was obtained 0.17 g., m. p. 166.[15]

Summary

Cyclohexylmethylphenylcarbinol prepared from cyclohexylmagnesium chloride and acetophenone has been found to contain 1,3-diphenyl-1-cyclohexyl-1,3-butanediol.

The anomalous behavior of cyclohexylmethylphenylcarbinol and some analogous carbinols on dehydration has been interpreted on the basis of the presence of 1,3-diols in these preparations.

NEW HAVEN, CONNECTICUT
RECEIVED SEPTEMBER 7, 1949

---

(15) Whitmore and Church, THIS JOURNAL, **54**, 3710 (1932).

(16) Hughes and Lions, *Chem. Abst.*, **33**, 589 (1939).

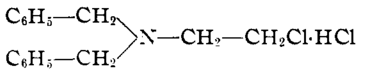
(17) Evans, *J. Chem. Soc.*, **138**, 788 (1936).

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

o-Benzylphenyl Derivatives. IV.[1] β-Chloroethylamines

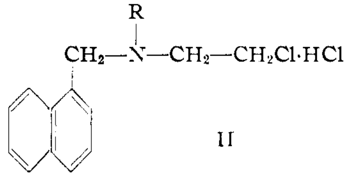
BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, LEE C. CHENEY AND S. B. BINKLEY

The discovery of Nickerson and Goodman[2a] that dibenzyl β-chloroethylamine hydrochloride (Dibenamine, I) blocks, or in higher doses, reverses the pressor effect of epinephrine has stimulated extensive research in the field of β-haloethylamines. An excellent review of sympatholytics, both of the β-haloethylamine and of other types, was presented by Nickerson at the Medicinal Chemistry Symposium of the American Chemical Society which was held at Ann Arbor, June 17–19, 1948.[2c] Published data indicate that the β-haloethylamine moiety is essential to sympatholytic activity in compounds related to Dibenamine, as increasing the distance between nitrogen and halogen or replacement of the halogen by other groups results in complete loss of activity.[2b] It has been stated that at least one benzyl-on-nitrogen group is also essential for activity in this series.

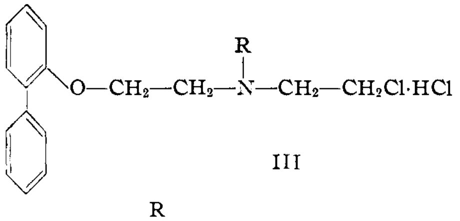


$$\left.\begin{array}{l}C_6H_5—CH_2\\C_6H_5—CH_2\end{array}\right\rangle N—CH_2—CH_2Cl\cdot HCl \qquad I$$

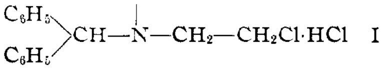
More recent work has substantiated the statement that the β-haloethylamine moiety is essential, but has shown that certain groups may replace the benzyl radical without inactivation. Several new series of sympatholytics have been disclosed: for example, the α-naphthylmethyl (II), 2-biphenoxyethyl (III) and benzohydryl series (IV).[3]



II



III



$$\left.\begin{array}{l}C_6H_5\\C_6H_5\end{array}\right\rangle CH—\overset{R}{\overset{|}{N}}—CH_2—CH_2Cl\cdot HCl \qquad IV$$

Many of the members of these series are potent epinephrine antagonists, and some possess antihistaminic properties in varying degrees. Even more recently, a series of fluorene sympatho-

---

(1) For the preceding paper in this series, see Wheatley, Cheney and Binkley, THIS JOURNAL, **71**, 3795 (1949).

(2)(a) Nickerson and Goodman, *Fed. Proc.*, **5**, 194 (1946); (b) Nickerson, Nomaguchi and Goodman, *ibid.*, **5**, 195 (1946); (c) *cf.* Nickerson, *J. Pharmacol.*, **95**, 27 (1949).

(3) (a) Achenbach and Loew, *ibid.*, **6**, 304 (1947); Rieveschl and Fleming, paper presented at the Division of Medicinal Chemistry of the A. C. S., New York Meeting, Sept. 17, 1947; (b) Hunt, *J. Pharmacol.*, **95**, 177 (1949).