[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Condensed Polynuclear Hydrocarbons by the Cyclodehydration of Aromatic Alcohols. I. Indanes

BY MARSTON T. BOGERT AND DAVID DAVIDSON[1]

Introduction

Alkyl derivatives of indane (I) have been prepared by the reduction of derivatives of indene (II),[2] 1-indanol (III),[3] 1-indanone (IV),[4] and 1,3-indanedione (V),[5] and also by the Friedel–Crafts reaction on a monophenylated alkyl chloride, *e. g.*, 1-phenyl-3-chlorobutane.[6]


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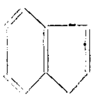
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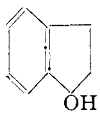
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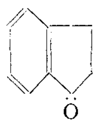
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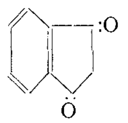
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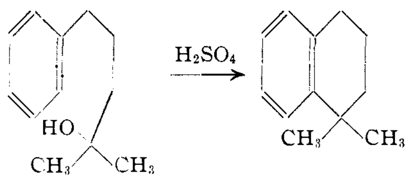
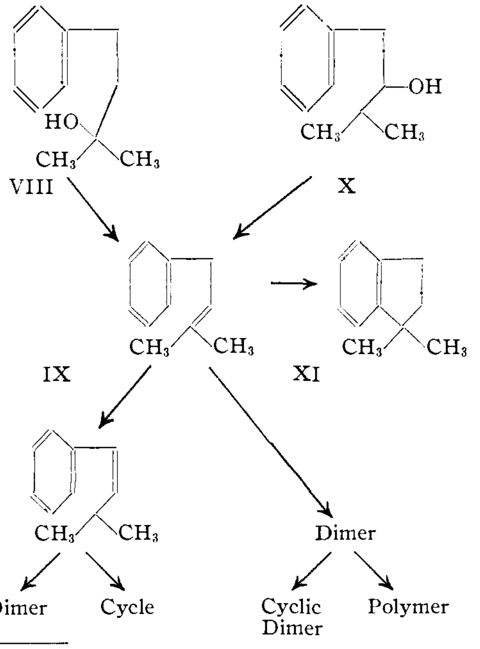
While some attention has been given to the formation of indanes by the cyclization of phenylated alcohols (or of the phenylated olefins derivable from these alcohols), it has been limited to highly phenylated indanes[7] and to the condensed cyclic derivatives of indane (hexahydrofluorenes) assumed by Wallach to be formed by the cyclodehydration of 1-benzylcyclohexanol-2 derivatives by means of phosphorus pentoxide.[8] Since the results reported in the present paper make it appear possible that Wallach misinterpreted his dehydration reactions, his work is now being reviewed in this Laboratory by Mr. David Perlman, whose findings will appear in a subsequent paper. The observation that the dimethylphenpropylcarbinol (VI) is converted by means of strong sulfuric acid into dimethyltetralin (VII)[9] led us to attempt the analogous reaction with dimethylphenethyl carbinol (VIII). The ease with which the synthesis of so complex a structure as 1,1-dimethylindane (XI) is thus accomplished made this reaction an attractive one for further investigation. The present paper, therefore, is devoted to a study of the mechanism as well as of the applicability of this reaction in the preparation of alkylated indanes. As has been indicated above, studies are now in progress dealing with the use of cyclodehydrations in the study of hydrogenated naphthalenes,[9] fluorenes, phenanthrenes,[10] and other condensed polynuclear hydrocarbons.



VI VII

The Mechanism of Cyclodehydration.—The first mechanism which suggests itself for the formation of indanes from γ-phenylpropyl alcohols by the action of sulfuric acid is *direct cyclodehydration; i. e.*, the elimination of the alcoholic hydroxyl and an ortho nuclear hydrogen atom as water. This type of reaction probably occurs in some cases, one of which will be discussed later. More generally, however, the alcohol probably undergoes dehydration to one or more olefins, IX, for example, which may



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[1] Research Assistant.

[2] V. Braun, Arkeszewski and Köhler, *Ber.*, **51**, 291 (1918); Courtot, *Ann. chim.*, [9] **5**, 84 (1916).

[3] Kishner, *J. Russ. Phys.-Chem. Soc.*, **46**, 1420 (1915).

[4] Clemmensen, *Ber.*, **47**, 682 (1914); Moureu, Dufraisse and Gagnon, *Compt. rend.*, **189**, 217 (1929).

[5] Freund and Fleischer, *Ann.*, **411**, 27 (1916); **414**, 18 (1917); **422**, 231 (1921).

[6] V. Braun and Neumann, *Ber.*, **50**, 55 (1917).

[7] Schlenk and Bergmann, *Ann.*, **463**, 51 (1928); **479**, 65 (1930); Bergmann and Weiss, *ibid.*, **480**, 49 (1930); *Ber.*, **63**, 1173 (1930); **64**, 1485 (1931); compare Schoepfle and Ryan, THIS JOURNAL, **52**, 4021 (1930); Bergmann, Taubadel and Weiss, *Ber.*, **64**, 1493 (1931).

[8] Wallach, *ibid.*, **29**, 2962 (1896); *Ann.*, **305**, 264 (1899).

[9] Bogert, *Science*, **76**, 475 (1932); **77**, 197 (1933).

[10] Bogert, *ibid.*, **77**, 289 (1933).

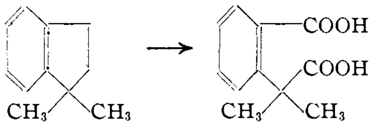
then react in three ways: (1) rearrangement, due to the shift of the double bond, (2) cyclization, by the migration of an ortho nuclear hydrogen to the double bond with simultaneous ring closure (intramolecular addition of benzene to a double bond), (3) dimerization.[11] Both the rearranged olefin and the unsaturated dimer may subsequently undergo dimerization or cyclization on their own accounts. In the case of dimethylphenethylcarbinol (VIII) there appears to be some evidence that the olefin is an intermediate in cyclodehydration. Thus by progressively reducing the strength of the sulfuric acid employed, a point is reached where the product obtained is largely olefin, indicating that with stronger acid the olefin is probably intermediate. By resorting to 85% phosphoric acid it is possible to demonstrate that olefin is formed from the alcohol immediately, while the cycle appears subsequently and only slowly. Thus, when 10 cc. of dimethylphenethylcarbinol was refluxed with 20 cc. of 85% phosphoric acid and the product isolated as described in the experimental part, the following yields of hydrocarbons were obtained.

TABLE I

Time of heating	1 min.	4 hrs.	16 hrs.
Yield, %	91	91	86
% olefin (Br titr.)	96	25	7
% cycle (by diff.)	4	75	93

Furthermore, the isolated olefin[12] undergoes cyclization when treated with strong sulfuric acid. Finally, the cycle produced by the dehydration of the alcohol (or the cyclization of the olefin) is always accompanied by non-volatile material (probably the polymerized olefin) which makes it appear likely that the cycle and the polymer have a common progenitor (the olefin). This mechanism is confirmed by the production of 1,1-dimethylindane (XI) by the dehydration of benzylisopropylcarbinol (X), which result obviously requires the assumption of the intermediate olefin (IX) for its explanation. Incidentally, in this latter case it is interesting to note that the olefin formation appears to occur in that one of the two alternative ways (in which it might normally occur) in which the double bond is found further removed from the benzene ring. This is contrary to Klages' rule.[13]

Demonstration of the Structure of the Dehydration Products.—The structures of the products obtained by dehydrating an aralkyl alcohol are readily determinable as illustrated by the case of dimethylphenethylcarbinol (VIII). In this case, the olefin (IX) which may be obtained by Hibbert's catalytic method[14] or by the action of sirupy phosphoric acid readily adds one mole of bromine at 0° yielding a dibromide of m. p. 66°.[12] It is quickly oxidized by aqueous permanganate, rendering an abundant yield of benzoic acid. The indane (XI), on the other hand, does not decolorize bromine at 0° at once (although substitution takes place slowly), and with permanganate the hydrocarbon is oxidized *without loss of carbon* to the *dibasic* acid, α,α-dimethylhomophthalic acid[15] (XII).



XI XII

This oxidation product definitely establishes the indane nucleus. The structures of the other cyclic hydrocarbons described in this paper are suggested by analogy and were confirmed by bromine and oxidation tests.

Relative Ease of Dehydration of the Aralkyl Alcohols.—Since the dehydration of an alcohol involves the removal of the alcoholic hydroxyl from its carbon atom together with a hydrogen atom on an adjacent carbon atom, and since the reactivity (removability) of both the hydroxyl group and of the hydrogen involved depends on their character (primary, secondary or tertiary), it is to be expected that marked differences will be observed in the ease of dehydration of various alcohols. This is easily confirmed by the casual observation of the behavior of several alcohols when treated with one to two volumes of 90% sulfuric acid in the cold. Phenethylcarbinol dissolves instantly, the solution remaining clear for a long period. Methylphenethylcarbinol dissolves *slowly* to a clear solution which immediately clouds due to the separation of an oil. Dimethylphenethylcarbinol does not dissolve at all but is instantly dehydrated and/or cyclized to a hydrocarbon which separates as a clear upper layer. Benzylisopropylcarbinol is also cyclodehydrated without dissolving completely in 90%

(11) For the mode of dimerization of unsaturated compounds refer to Davidson and Johnson, THIS JOURNAL, **47**, 563 (1925), and to Bergmann and Taubadel, *Ber.*, **65**, 463 (1932).

(12) Klages, *ibid.*, **37**, 2314 (1904).

(13) Klages, Ref. 12, p. 2301.

(14) Hibbert, THIS JOURNAL, **37**, 1748 (1915).

(15) Gabriel, *Ber.*, **20**, 1198 (1887).

sulfuric acid. It thus appears, provisionally, at least, that the character of the alcoholic group is the principal factor in determining the ease of dehydration of an aralkyl alcohol by sulfuric acid, but that among alcohols of a given class, the relative rates of dehydration are then determined by the character of the hydrogen atoms available for elimination.

TABLE II

No.	Ref.	Alcohol	Synthesis used in this paper	B. p. of alcohol, °C.	Final product	B. p. of product, °C.	Yield, %
1	16	$C_6H_5CH_2CH_2CH_2OH$	Commercial product		Polymer only[b]	180–190 (15 mm.)	40
2	12	$C_6H_5CH_2CH_2CHOHCH_3$	$CH_3MgI + C_6H_5CH_2CH_2CHO$[a] and $C_6H_5CH_2CH_2MgBr + CH_3CHO$[a]	129–130 (17 mm.)	Polymer only		
3	12	$C_6H_5CH_2CH_2C(CH_3)_2OH$	$C_6H_5CH_2CH_2MgBr + CH_3COCH_3$[a]	123 (15 mm.)	1,1-dimethylindane	191	65
4	17	$C_6H_5CH_2CHOHCH(CH_3)_2$	$C_6H_5CH_2MgCl + (CH_3)_2CHCHO$	118–122 (15 mm.)	1,1-dimethylindane[c]	191	55
5	18	$C_6H_5CH_2C(CH_3)(OH)CH_2CH_3$	$C_6H_5CH_2MgCl + CH_3COCH_2CH_3$[a]	113–115 (14½ mm.)	Polymer only		
6	19	$C_6H_5CH_2CH(CH_3)CHOHCH_3$	$C_6H_5CH{:}C(CH_3)COCH_3$[23] + Na + EtOH[a]	135–136 (21 mm.)	Polymer only		
7	19	$C_6H_5CH_2C(CH_3)(OH)CH(CH_3)_2$	$C_6H_5CH_2MgCl + CH_3COCH(CH_3)_2$[a]	122–124 (18 mm.)	1,1,2-trimethylindane	208	90
8	19	$C_6H_5C(CH_3)_2CH_2CH_2OH$	$C_6H_5C(CH_3)_2CH_2COOEt$ + Na + EtOH[a]	137–138 (16 mm.)	1,1-dimethylindane[c]		15
9	20	$C_6H_5C(CH_3)_2CH_2CHOHCH_3$	$C_6H_5C(CH_3)_2CH_2COCH_3$ + Na + EtOH	206–208	1,1,3-trimethylindane		35
10	19	$C_6H_5C(CH_3)_2CH_2C(CH_3)_2OH$	$CH_3MgI + C_6H_5C(CH_3)_2CH_2COCH_3$[a]	133 (17 mm.)	1,1,3,3-tetramethylindane	206–209	85
11	21	$C_6H_5CH_2CH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2CH_2MgBr + CH_2O$		1,2,3,4-tetrahydronaphthalene[d]	200–205	55
11a	22	$C_6H_5CH_2CH_2CH{=}CH_2$	$C_6H_5CH_2MgCl + CH_2{=}CHCH_2Br$		Polymer only		

[a] These syntheses reported for the first time in this paper.

[b] Practically completely polymerized by H_3PO_4 at 230–240°.

[c] Product identified by oxidation.

[d] Product converted to naphthalene by sulfur.

Owing to the oxidizing and sulfonating action of hot sulfuric acid, temperatures much above room temperature could not be employed to force the dehydration of sluggish alcohols such as phenethylcarbinol, for example. In this case, as well as in other cases in which it was feared that the conditions necessary for the dehydration of the alcohol might be too drastic for the cyclization of the intermediate olefin, recourse was had to the use of phosphoric acid at 230–240°.

Relation between the Constitution of the Probable Intermediate Olefins and their Cyclizability.—It was soon found that of the alcohols which might theoretically undergo cyclodehydration to indanes, only a few actually yielded significant quantities of the bi-cyclic hydrocarbons. The experimental results which are summarized in Table II are susceptible of the following interpretation.

TABLE III

ANALYSES

		Carbon, %		Hydrogen, %	
		Calcd.	Found	Calcd.	Found
Alcohol No.	6	80.4	80.6	9.8	9.9
	7	80.8	80.4	10.2	10.6
	8	80.4	79.7	9.8	10.4
	10	81.2	81.1	10.5	10.9
Indane No.	3	90.3	90.4	9.7	10.0
	7	89.9	89.7	10.1	10.4
	9	89.9	89.4	10.1	11.1
	10	89.6	89.6	10.4	10.8

(1) Aralkyl alcohols which bear an hydroxyl group on the carbon atom in the three position with respect to the phenyl group are incapable of undergoing *direct* cyclodehydration (ring closure by elimination of alcoholic hydroxyl and nuclear hydrogen). Apparently the steric relationships are such that normal dehydration to olefins takes precedence over cyclodehydration to indanes.

(2) Accepting the intermediate olefin mechanism, it follows that with sufficiently vigorous treatment to ensure the consumption of the olefin, the final products must be cycles or polymers or a mixture of the two, depending on the relative rates of the competing reactions, which

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(16) Ramart-Lucas and Amagat, *Compt. rend.*, **188**, 638 (1929); *Bull. soc. chim.*, **51**, 108 (1932).

(17) Levi, *ibid.*, [4] **33**, 1664 (1923).

(18) Tiffeneau and Lévy, *ibid.*, **33**, 759 (1923).

(19) This paper.

(20) Hoffman, THIS JOURNAL, **51**, 2542 (1929).

(21) V. Braun, *Ber.*, **44**, 2871 (1911); and Ramart-Lucas and Amagat, *Bull. soc. chim.*, **51**, 108 (1932).

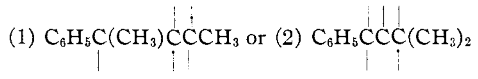
(22) André, *ibid.*, [4] **9**, 193 (1911).

(23) Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932).

in turn will depend on the character of the double bond. The receptivity (saturability) of the double bond appears to increase with the number of methyl groups attached to the doubly bound carbon atoms. On the other hand, the polymerizability of the double bond seems to increase with the number of hydrogen atoms remaining attached to the doubly bound carbon atoms. Doubtless the question of directed addition to the double bond is also a factor.[24] At any rate, when sufficiently vigorous conditions are employed to ensure the practically complete conversion of intermediate olefins, only those monophenylated alcohols which can give rise to 3-phenyl-1-propenes containing *two methyl groups in the 1-position* yield cycles, the others being converted to non-volatile (with steam) polymers.[25]

(3) In those cases in which the polymer was the final product some volatile material could be isolated by moderating the conditions of the reaction. In every case of this sort the volatile oil obtained was proved to be mainly olefinic by its odor, its unsaturation, and its oxidation to benzoic acid. The presence of a trace of cycle was indicated, however, for the oxidation mother liquors from which benzoic acid had separated gave perceptible tests for phthalic acid when treated with phenol.[26] Thus, it is seen that the behavior of the alcohols studied really differs merely in degree and not in kind, except from a practical point of view.

The Influence of a Gem-Dimethyl Group on the Formation of Indanes.—Because of the general effect of a *gem*-dimethyl group on ring formation,[27] it was of interest to study the alcohols numbered 8, 9 and 10 in Table II, which bear such a group. The results obtained with $C_6H_5C(CH_3)_2CH_2CH_2OH$, however, indicate that owing to the presence of a quaternary carbon atom in these alcohols, their dehydration may not proceed normally, but may occur with molecular rearrangements. Thus, with the alcohol just mentioned, dehydration with phosphoric acid yielded a mixture of hydrocarbons which, on oxidation, gave both benzoic acid and α,α-dimethylhomophthalic acid. Treatment of the mixtures of hydrocarbons with 85% sulfuric acid gave a hydrocarbon which, on oxidation, yielded only dimethylhomophthalic acid. Direct cyclodehydration would have yielded 1,1-dimethylindane which is oxidized to dimethylhomophthalic acid, while normal dehydration would have produced $C_6H_5C(CH_3)_2CH{=}CH_2$ which would be oxidized to dimethylphenylacetic acid. The presence of benzoic acid indicates a rearrangement during dehydration with the formation of olefins containing either of the skeletons:


(1) $C_6H_5C(CH_3)CCCH_3$ or (2) $C_6H_5CCC(CH_3)_2$

While these facts render the interpretation of the behavior of the first two alcohols in this series difficult, the high yield of cycle in the third case, $C_6H_5C(CH_3)_2CH_2C(CH_3)_2OH$, indicates definitely that a *gem*-dimethyl group aids ring closure. (In this case the migration of the phenyl group to the opposite end of the chain would result in a carbon skeleton identical with the original while the migration of a methyl group would result in a skeleton incapable of cyclization, which latter apparently did not occur.)

A Case of Direct Cyclodehydration.—In a preceding section it was postulated that the steric relationships between the alcoholic hydroxyl group and the *ortho* nuclear hydrogen atoms in 3-phenyl-1-propanol were unfavorable for ring closure. It was, therefore, of interest to compare the behavior of 4-phenyl-1-butanol when subjected to dehydration. In this case direct cyclodehydration did occur, since a fair yield of tetrahydronaphthalene was obtained and attempts to cyclize 4-phenyl-1-butene (which would be formed if normal dehydration occurred) were unsuccessful, owing to polymerization or other side reactions.[28]

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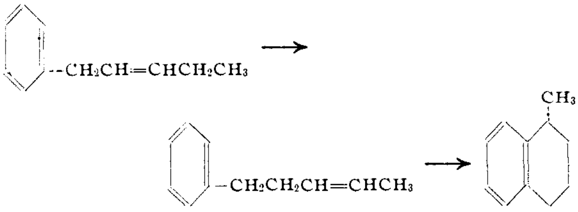
(24) Kharasch, McNab and Mayo, THIS JOURNAL, **55**, 2468, 2521, 2531 (1933).

(25) Unpublished work of Mr. Richard O. Roblin, Jr., in this Laboratory indicates that the presence of a higher alkyl (ethyl) group in the 1-position of 3-phenyl-1-propene may result in the formation of a *six*-membered cycle, namely, a tetralin derivative, thus



Compare also the behavior of isopropylphenethyl carbinol [Bogert, *Science*, **77**, 197 (1933)].

(26) Breithut and Apfelbaum, *Ind. Eng. Chem.*, **17**, 534 (1925).

(27) Brooks, "Non-Benzenoid Hydrocarbons," The Chemical Catalog Co., Inc., New York, 1922, p. 118.

(28) It is interesting to note that according to unpublished results of Mr. Richard O. Roblin, Jr., in this Laboratory, the next higher primary alcohol, 5-phenyl-1-pentanol, appears to undergo normal dehydration to the olefin. The bearing of the above-mentioned case of direct cyclodehydration on the mechanism of the formation of tetralins is now being considered in connection with a study of the applicability of the cyclodehydration of alcohols to the preparation of tetralins.

Experimental

Preparation of Alcohols.—The aralkyl alcohols used in this study were prepared by general methods as indicated in Table II. When employed, the Grignard reaction was carried out in the usual way. Sodium and alcohol reductions were performed according to "Organic Syntheses," **10**, 62 (1930).

Dehydration of Alcohols: Tertiary.—One volume of a tertiary alcohol was slowly dropped into 1.2 volumes of 85% sulfuric acid with efficient stirring while the internal temperature was maintained at about 10° by means of an ice-bath. The reaction appeared to be complete at once but stirring was continued for an hour at room temperature to ensure this. The reaction mixture consisting of an upper layer of hydrocarbon and a lower layer of acid was then diluted with 10–15 volumes of water and distilled. The distillate consisted of a mixture of hydrocarbon and water which was separated, the water being returned to the still. This distillation was continued until measurement indicated that only a negligible proportion of oil appeared in the distillate. The organic residue (polymer) appeared as a viscous liquid or a resinous semi-solid. The separated oil was redistilled from alkalinized water, the oil separated, dried over calcium chloride, and finally distilled at atmospheric pressures.

Secondary.—These were dehydrated as in the case of the tertiary but by using 90% sulfuric acid in place of 85%, or by using twice the volume of 85% acid and allowing the internal temperature to rise to 35–40°, or by first dehydrating the alcohols with phthalic anhydride or with phosphoric acid (as described below) and subsequently treating with one volume of 85% sulfuric acid (repeatedly if necessary to eliminate olefin). The isolation of volatile products was performed as described above.

Primary.—Fifty cc. of 85% phosphoric acid was placed in a distilling bulb (125 cc.) attached to a downward condenser and distilled until a thermometer in the liquid read 230°. Ten to forty cc. of the alcohol was then slowly admitted to the acid by means of a tube which ended in a capillary reaching to the bottom of the liquid, while the internal temperature was maintained between 230–240°. Any distillate as well as the residue was then distilled with water as described above in order to separate the volatile products. The varied behavior of the primary alcohols employed requires the following additional details.

3-Phenyl-1-propanol.—The phosphoric acid treatment alone sufficed to bring about almost complete polymerization, since only 2.5% of volatile material was obtained. This boiled at 157° and yielded benzoic acid on oxidation with permanganate. It was thus identified as 3-phenyl-1-propene. The non-volatile residue was extracted with benzene, washed free of acid and distilled *in vacuo*. About 40% of a fraction boiling at 180–190° was obtained. It did not decolorize bromine immediately and analysis indicated that it was not di-phenpropyl ether.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.4; H, 8.6. Calcd. for $C_{18}H_{22}O$: C, 85.0; H, 8.7. Found: C, 90.3; H, 9.6.

3-Phenyl-3-methyl-1-butanol.—Twenty-five grams of this alcohol yielded 13 g. of volatile oil, which, on fractionation, gave 6.3 g. of a fraction of b. p. 188–193°. This decolorized a solution of bromine in carbon tetrachloride quite readily and gave a mixture of benzoic and dimethylhomophthalic acids on oxidation with permanganate. Treatment of this fraction with 85% sulfuric acid removed the olefins and returned about half the oil as a product which on oxidation gave dimethylhomophthalic acid but no benzoic acid. The presence of phthalic acid was demonstrated in the mother liquors. (NOTE.—Dimethylhomophthalic acid does not respond to the test for phthalic acid.)

4-Phenyl-1-butanol.—This alcohol yielded 55% of an oil which boiled mainly between 197 and 207°. The fraction boiling at 200–205° yielded naphthalene, m. p. 80° (mixed m. p.) when treated with sulfur.[29]

Oxidation of Hydrocarbons.—Oxidations were carried out by refluxing (stirring!) the hydrocarbons with an aqueous solution of the calculated quantity of permanganate (30 cc. of water per gram of permanganate). Decolorization usually was complete within six hours or was then brought about with a little alcohol. The filtrate obtained by removing the precipitated manganese dioxide was concentrated to small volume and acidified with hydrochloric acid. 1,1-Dimethylindane was easily identified in this way by its conversion to α,α-dimethylhomophthalic acid which melts with decomposition at about 120°, yielding the anhydride which then melts at 81–82°.[15] A sample of this acid obtained from the hydrocarbon from dimethylphenethylcarbinol was analyzed.

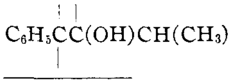
Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.8. Found: C, 63.4; H, 5.7.

Sulfonation of Indanes.—The hydrocarbons were stirred with 1–1.5 volumes of concd. sulfuric acid. The reaction was accompanied by the evolution of heat, after which the mixture was stirred at 60° until a drop gave a clear solution in water. One volume of water was then added to the cooled reaction mixture. This caused the separation of the sulfonic acid from the aqueous sulfuric acid usually as an oil which was separated and taken up in chloroform. The addition of carbon tetrachloride to the chloroform solution precipitated the sulfonic acids at once or on standing. Repeated crystallization from carbon tetrachloride or a mixture of carbon tetrachloride and chloroform gave products of constant melting point: 1,1-dimethylindanesulfonic acid, m. p. 67°; 1,1,2-trimethylindanesulfonic acid, m. p. 109°; 1,1,3,3-tetramethylindanesulfonic acid, m. p. 107–108°.

Acknowledgments.—The authors wish to express their appreciation to Messrs. Percy M. Apfelbaum and Richard O. Roblin, Jr., for providing some of the intermediates used in this work, and to Dr. Edwin A. Robinson for assistance in the literature search.

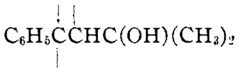
Summary

1. Monophenylated alcohols of the types



$C_6H_5CC(OH)CH(CH_3)_2$

and



$C_6H_5CCHC(OH)(CH_3)_2$

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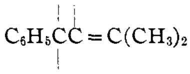
[29] Ruzicka and Rudolph, *Helv. Chim. Acta*, **10**, 915 (1927).

which on dehydration may be expected to yield olefins of the type  $C_6H_5\overset{|}{\underset{|}{C}}\overset{|}{C}=C(CH_3)_2$ are converted into indanes by 85% sulfuric acid.

2. The isolated intermediate olefins are cyclized to indanes under the influence of 85% sulfuric acid.

3. A case of direct cyclodehydration appears to exist in the conversion of 4-phenyl-1-butanol into tetralin by the action of hot phosphoric acid.

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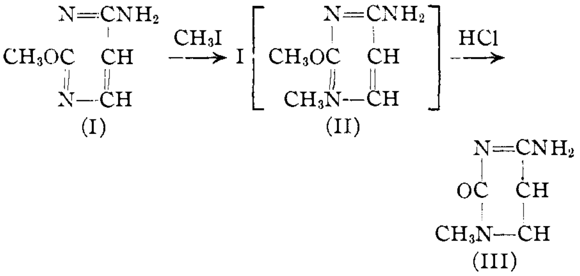
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY, AND THE FIXED NITROGEN DIVISION OF THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

The Alkylation of Pyrimidines. An Attempt to Prepare 1-Glucosidocytosine

BY GUIDO E. HILBERT

With the object of seeking a method for the synthesis of a model of cytidine, the action of methyl iodide on 4-amino-2-methoxypyrimidine (I) was investigated. This method of attack was suggested by previous work[1] in which it was shown that the action of methyl iodide on 2,4-dimethoxypyrimidine yielded 1,2-dihydro-2-keto-1-methyl-4-methoxypyrimidine which was readily converted by hydrolysis to 1-methyluracil. Subsequently,[2] this method for the synthesis of 1-alkyl uracils was extended to the synthesis of nucleosides by the substitution of acetobromoglucose for the alkyl halides in the interaction with 2,4-dimethoxypyrimidine and resulted in the formation of 1,2-dihydro-2-keto-1-tetraacetylglucosido-4-methoxypyrimidine, which on simultaneous deacetylation and dealkylation with alcoholic hydrochloric acid yielded 1-glucosidouracil. One would thus expect by analogy that 4 - amino - 2 - methoxypyrimidine would interact with methyl iodide to form 1-methylcytosine and with acetobromoglucose to form 1-tetraacetylglucosidocytosine, in which the glucose residue probably occupies the same position as ribose in cytidine.

Methyl iodide interacted with 4-amino-2-methoxypyrimidine (I) to yield a crystalline methiodide, $C_6H_{10}N_3OI$. Since there are three potential basic groupings in (I), methyl iodide could form an ammonium salt by combining with either of the cyclic nitrogen atoms in the (1) and (3) positions or with the amino group in the (4) position. Theoretically, since the grouping (—N=C(NH$_2$)—) is the ammono analog of an amide, (O=C(NH$_2$)—), interaction of the amino radical with methyl iodide would not be expected under the conditions of this experiment. There is, however, no information that allows one to predict which of the nitrogens in positions (1) and (3) would be more subject to attack. Upon treatment with hydrochloric acid the methiodide lost the elements of methyl iodide to form 1-methylcytosine (III). The structure of this was confirmed by conversion on bromination in aqueous solution to 1-methyl-5-bromouracil, the properties of which were identical with those of a specimen prepared by the bromination of 1-methyluracil. Methyl iodide therefore attacked 4-amino-2-methoxypyrimidine in the (1) position, forming 4-amino-2-methoxypyrimidine-1-methiodide (II). This is the first case in which a stable methiodide has been obtained from this type of pyrimidine and is additional evidence in favor of the mechanism postulating the intermediate formation of a methiodide in the reaction between alkyl halides and 2,4-dialkoxypyrimidines to form 1,2-dihydro-2-keto-1-alkyl-4-alkoxypyrimidines.



On heating, the methiodide (II) melted at 128° with vigorous effervescence and then resolidified to melt again over a wide range from 190–235°. Since Knorr[3] showed that 4-methoxyquinoline-1-methiodide was decomposed on heating to form

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[1] Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).

[2] Hilbert and Johnson, *ibid.*, **52**, 4489 (1930).

[3] Knorr, *Ber.*, **30**, 922 (1897).