

ium-carbinol iodides were relatively inactive in doses of 1 mg., but acetylation increased their activity considerably. This is analogous to the increase in activity obtained on acetylation of choline.¹⁵ Compound V was the most active ester, being about one-tenth as active as acetylcholine when administered in a dose of 0.01 mg. Compound IV was about one-thirtieth as active as acetylcholine, and VI produced only a slight fall in doses of 0.01 mg. Since IV is the analog of acetylcholine, while V is analogous to the less active acetyl- γ -homocholine, it was surprising to observe that V was more active than IV. The relative inactivity of VI as compared to V as a result of the introduction of a methyl group was also unexpected. It seems necessary, therefore, to consider the effect of the ring carbon atoms as substituents on the physiological moiety in interpreting the observed physiological data.

Since Hunt has shown arecoline to be one-

(15) Hunt and Taveau, *Hyg. Lab. Bull.*, No. 73, 68 (1911).

fiftieth to one-hundredth as active as acetylcholine,¹⁶ the beta ester is evidently distinctly more active than arecoline in its effect upon blood pressure. This is in line with the evidence that the choline ester type is more active than the betaine ester type. A more detailed report of the pharmacological data will be published elsewhere.

The authors wish to acknowledge the help of Dr. Daniel Green, who collaborated in the physiological experiments.

Summary

The preparation of α -piperidylcarbinol and a group of quaternary piperidinium salts of α -piperidylcarbinol, β -piperidylcarbinol and β -piperidylmethylcarbinol, analogous to simple choline esters is described. Their pharmacological activity is discussed briefly.

(16) Hunt and Renshaw, *J. Pharmacol.*, **29**, 17 (1926).

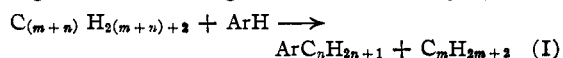
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Reaction of Paraffins with Hexahydroaromatic Hydrocarbons in the Presence of Aluminum Halides¹

BY HERMAN PINES, ARISTID V. GROSSE AND V. N. IPATIEFF

It has been shown previously that aromatic hydrocarbons are destructively alkylated by paraffins in the presence of metal halide (aluminum chloride, zirconium chloride) or phosphoric acid catalysts²⁻⁴; the reaction proceeded according to the following scheme (Ar = aryl group)



A similar reaction has now been observed to take place when hexahydroaromatic hydrocarbons such as cyclohexane or methylcyclohexane are reacted with paraffins in the presence of aluminum bromide or chloride. It was found that the destructive alkylation of naphthenes proceeds readily with 2,2,3- and 2,2,4-trimethylpentane and 3,4-dimethylhexane, whereas *n*-octane and 2,2,3-trimethylbutane do not destructively al-

kylate cyclohexane under similar conditions. The destructive alkylation of cyclohexane and methylcyclohexane by paraffins was made at temperatures ranging from 50 to 80°; the use of higher temperatures was not desirable since at such temperatures the naphthenes themselves decompose, and this phenomenon would complicate the study of the reaction products. The main reaction proceeds analogously to the equation written above, with the substitution of the hexahydroaromatic for the aromatic hydrocarbon. For example, the reaction of 2,2,4-trimethylpentane and cyclohexane yields *i*-butane and methylated cyclohexanes, the latter being formed by isomerization⁵ of *t*-butylcyclohexane.

The structure of the alkylated cyclohexanes was determined by converting them to the corresponding aromatic hydrocarbons by dehydrogenation over platinized aluminum oxide. The aromatic hydrocarbons were identified through the bromo or nitro derivatives. It was found that the al-

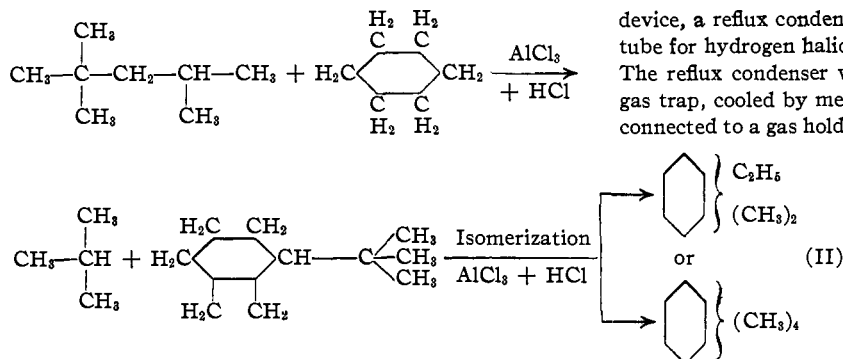
(1) Presented at the meeting of the Division of Organic Chemistry of the American Chemical Society at Rochester, N. Y., September 6-10, 1937.

(2) Grosse and Ipatieff, *THIS JOURNAL*, **57**, 2415 (1935).

(3) Grosse, Mavity and Ipatieff, *J. Org. Chem.*, **3**, 137, 448 (1938).

(4) Ipatieff, Komarewsky and Pines, *THIS JOURNAL*, **58**, 918 (1936). Ipatieff, "Catalytic Reaction under High Pressures and Temperatures," The Macmillan Co., New York, N. Y., 1936.

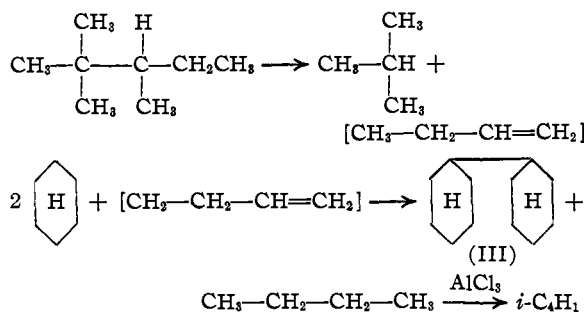
(5) V. Grignard and Stratford, *Compt. rend.*, **178**, 2149; *Bull. soc. chim.*, [4] **85**, 931 (1924).



kylated cyclohexane consisted of a mixture of different polymethyl- or methylethylcyclohexanes. The position of the alkyl groups in the cyclohexane ring was not established, but all indications pointed to the presence of dimethylethyl- and tetramethylcyclohexanes.

The gaseous hydrocarbons were composed mainly of isobutane. Even in the case where 3,4-dimethylhexane was used as an alkylating agent isobutane was obtained and not the expected *n*-butane.

Besides the main reaction described above, *side reactions* take place as, for instance, hydrogenation and isomerization into isobutane of the butene formed from the scission of 2,2,3-trimethylpentane.



In this reaction the cyclohexane acts as a donor and the olefins as an acceptor of hydrogen. This intermolecular hydrogenation-dehydrogenation accounts for the formation of isobutane in larger amounts than could be accounted for if the reaction proceeded only according to equation II (experiments 4 and 7). The fact that cyclohexane acts sometimes as a hydrogen-supplying agent has been reported⁶ previously.

Experimental Part

Apparatus and Procedure.—The apparatus consisted of a 250-cc. flask provided with a mercury-sealed stirring

device, a reflux condenser, a dropping funnel and an inlet tube for hydrogen halide sealed to the bottom of the flask. The reflux condenser was attached to a 50-cc. calibrated gas trap, cooled by means of dry ice-acetone mixture and connected to a gas holder. The flask was heated by means of a water-bath.

of a water-bath.

The naphthene and aluminum halides were placed in the reaction flask, heated to 65° and stirred; dry hydrogen halide gas was passed in with a speed of about 500 cc. per hour, while the paraffins were added dropwise.

After all the paraffins were added

the content of the flask was stirred and heated for an additional one-quarter to one-half hour. The condensable gases formed were collected in the gas trap, cooled at -78°, while the non-condensable gases were passed into the gas holder. The rate of formation of gases was recorded every few minutes.

After the reaction was completed, the content of the flask consisted of two layers: the upper, hydrocarbon, and the lower, aluminum halide layer. The lower layer was decomposed with water, washed with 15% sodium hydroxide solution, followed by water washing. An oily layer was obtained, the weight of which amounted to only a few grams.

The upper or hydrocarbon layer was washed, dried and distilled through a high precision column.

The main fractions obtained from the distillation were converted to the corresponding aromatic hydrocarbons and identified.

The gaseous products were submitted to a fractional distillation on a low temperature Podbielniak apparatus.⁷

Analytical Procedure.—The yields in the following procedures were usually between 60 and 80%.

Dehydrogenation.—The hydrocarbons to be dehydrogenated were passed with a liquid space velocity of 0.2 per hour over 35 g. of aluminum oxide containing 7% of platinum; this catalyst was obtained by impregnating alumina with the required amount of chloroplatinic acid solution, drying and reducing in a slow stream of hydrogen at 150 to 240°. The dehydrogenation was accomplished at 240°; the gas evolved was collected in a gas holder, measured and analyzed. The liquid product obtained by this reaction was fractionally distilled.

Bromination.—To 1 cc. of the dehydrogenated product was added slowly at room temperature 5 cc. of bromine containing 1% of iodine. At the beginning a copious evolution of hydrogen bromide takes place. The product was allowed to stand overnight, the excess bromine was distilled off and the brominated product was crystallized from ethanol.

Nitration.—One cc. of dehydrogenated product was treated with 10 cc. of nitrating mixture consisting of 1 part of 72% nitric acid and 3 parts of 96% sulfuric acid. The product was heated to a boil, cooled and poured over ice. The solid nitro compound was crystallized from ethanol.

Oxidation.—One cc. of dehydrogenated product was mixed with 15 cc. of 72% nitric acid and 25 cc. of water. It was sealed in a 60-cc. heavy-walled glass tube and placed

(6) Ipatieff and Pines, *THIS JOURNAL*, **59**, 56 (1937).

(7) W. Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **5**, 172 (1933).

TABLE I

Expt.	Reagents used			Cyclohexane, g.	AlCl ₃ , g.	Gases formed				Content of the flask	
	Paraffin Kind	G.	Conditions of reaction Temp., °C.			Time, hours	Amount, g.	% iso-butane	Pentanes and hexanes, %	Hydrocarbon layer, g.	Catalyst layer, g.
1	<i>n</i> -Octane	28.5	65-78	63.0	20	3	0
2	3,4-Dimethylhexane	28.5	78	63.0	20	3	8.0	87.9	12.1	72.4	27.6
3	2,2,4-Trimethylpentane	28.5	50-60	63.0	20	3	14.5	97.6	2.4	66.7	26.0
4	2,2,3-Trimethylpentane	21.2	60-75	48.2	15	3	17.0	92.3	7.7	48.7	17.6
5	2,2,3-Trimethylbutane	20.5	75	52.0	20	3	0	62.3	29.0
6	2,2,4-Trimethylpentane	28.5	50	73.5 ^b	12.9 ^c	3	17.5	98.3 ^a	6.7	83.1	17.9
7	2,2,4-Trimethylpentane	28.5	50	73.4 ^b	19.8	3	20.3	96.9	3.6	66.2	34.0

^a The gas contained 88.1% *i*-C₄H₁₀ and 5.2% *n*-C₄H₁₀ used.

^b Methylcyclohexane was used. ^c Aluminum bromide was used.

in an Ipatieff bomb; the latter was charged with 40 atmospheres of nitrogen, in order to counterbalance the high pressure developed within the reaction tube. The bomb was heated at 135° for two hours. The bomb was cooled, nitrogen pressure was released and the reaction tube cooled to -20° and opened. The crystalline product was filtered and washed. The neutralization equivalent was determined and the acid was converted to its methyl ester in the usual way.

Experimental Data

The conditions of the experiments and the results obtained are summarized in Table I.

Experiment 1 (*n*-Octane and Cyclohexane).—Alkylation did not take place.

Experiment 2^s (3,4-Dimethylhexane and Cyclohexane).—The following is the result of distillation: (1) 72-81°, 58.3%, *n*²⁰_D 1.4218; (2) 81-114°, 11.6%; (3) 114-125°, 9.4%, *n*²⁰_D 1.3984; (4) 125-153°, 4.6%; (5) 153-168°, 10.5%; (6) 168-182, 2.5%.

Fraction 1, b. p. 72-81°, consists of a mixture composed mainly of unreacted cyclohexane with some methylcyclopentane.

Fraction 3, b. p. 114-125°, consists of isomeric octanes. *Anal.* Calcd. for C₈H₁₈: C, 84.10; H, 15.90. Found: C, 84.01; H, 15.79.

Fraction 4, b. p. 153-168°, was identified as 1,3-dimethyl-5-ethylcyclohexane. Oxidation of the dehydrogenated product with dilute nitric acid yields trimesic acid which was identified as trimethyl trimesate, m. p. 141°. It showed no depression in melting point with an authentic sample. The bromo derivative of the dehydrogenated product corresponds to 2,4,6-tribromo-1,3,5-dimethyl-ethylbenzene, m. p. 89°. *Anal.* Calcd. for C₁₀H₁₁Br₃: Br, 64.70. Found: Br, 64.40.

Experiment 3 (2,2,4-Trimethylpentane and Cyclohexane).—The following is a summary of the distillation data of the washed and dried hydrocarbon layer: (1) 76-80°, 63.2%, *n*²⁰_D 1.4280; (2) 148-156°, 10.5%, *n*²⁰_D 1.4313; (3) 156-168°, 18.2%, *n*²⁰_D 1.4370; (4) above 168°, 6.4%.

Fraction 1, b. p. 76-80°, consists of a mixture composed of unreacted cyclohexane and of methylcyclopentane.

Fraction 2, b. p. 148-156°, identified as 1,3,5-trimethylcyclohexane. The nitro derivative of the dehydrogenated product corresponds to 2,4,6-trinitromesitylene, m. p.

(8) A repetition of experiment 2 gave quantitatively the same results.

227°. The mixed melting point with a known sample showed no depression.

Fraction 3, b. p. 156-168°, identified as 1,2,3,5-tetramethylcyclohexane. *Anal.* Calcd. for C₁₀H₂₀: C, 85.63; H, 14.37; mol. wt., 140. Found: C, 85.32; H, 14.38; mol. wt., 134. The nitro derivative of the dehydrogenated product corresponds to 4,6-dinitro-1,2,3,5-tetramethylbenzene, m. p. 178°. *Anal.* Calcd. for C₁₀H₁₂N₂O₄: N, 12.50. Found: N, 12.36.

Experiment 4 (2,2,3-Trimethylpentane and Cyclohexane).—Distillation of the hydrocarbon layer: (1) 73-90°, 55.0%, *n*²⁰_D 1.4215; (2) 90-145°, 6.3%; (3) 145-165°, 16.3%, *n*²⁰_D 1.4335; (4) 165-212°, 13.5%; (5) above 212°, 8.9%.

Fraction 1, b. p. 73-90°, is composed of a mixture consisting of unreacted cyclohexane and of about 20% of methylcyclopentane.

Fraction 2, b. p. 145-165°, consists of alkylated cyclohexane; 60% of the product undergoes dehydrogenation to aromatic hydrocarbons which results in the increase of index of refraction from *n*²⁰_D 1.4335 to 1.4552.

Fraction 5a, b. p. 217-222°, obtained from Fraction 5 on redistillation. It was stable to nitrating mixture. It consists probably of dicyclohexyl or of its isomers such as dimethylcyclopentyl. *Anal.* Calcd. for C₁₂H₂₂: C, 86.75; H, 13.25. Found: C, 86.22; H, 13.50.

Experiment 5 (2,2,3-Trimethylbutane and Cyclohexane).—The hydrocarbon layer distilled from 75 to 82°. Apparently no alkylation has taken place.

Experiment 6 (2,2,4-Trimethylpentane, Methylcyclohexane and Aluminum Bromide).—The hydrocarbon layer distilled within the following range: (1) 98-105°, 69%; *n*²⁰_D 1.4200; (2) 105-145°, 14%; (3) 145-179°, 3%; (4) 179-194°, 8%. All fractions were stable toward nitrating mixture.

Fraction 1, b. p. 98-105°, consists mainly of unreacted methylcyclohexane.

Fraction 4, b. p. 179-194°. This fraction consists of alkylated cyclohexane, since on dehydrogenation aromatic hydrocarbons are obtained boiling from 180 to 206° with an index of refraction of 1.4899. Calcd. for C₁₁H₂₂: C, 85.63; H, 14.37; mol. wt., 154. Found: C, 85.32; H, 14.32; mol. wt., 143, *d*²⁰₄ 0.8026, *n*²⁰_D 1.4433.

Experiment 7 (2,2,4-Trimethylpentane and Methylcyclohexane).—The product distilled as follows: (1) 98-110°, 55.7%, *n*²⁰_D 1.4230; (2) 150-180°, 15.3%, *n*²⁰_D 1.4357-1.4400; (3) 180-185°, 15.8%; (4) 185-225°, *n*²⁰_D 1.4559; (5) 225-255°, 10.0%. All fractions were stable to nitrating mixture, which shows the absence of olefins.

Fraction 1, b. p. 98–110°, consists mainly of unreacted methylcyclohexane.

Fraction 3, b. p. 180–185°, identified as 1,3-dimethyl-5-propylcyclohexane. *Anal.* Calcd. for $C_{11}H_{22}$: C, 85.63; H, 14.37; mol. wt., 154. Found: C, 85.36; H, 14.52. n_D^{20} 1.4422, d_4^{20} 0.8012, mol. wt., 150. The dehydrogenated product was oxidized with dilute nitric acid ($1HNO_3: 2H_2O$) at 130°. It yielded trimesic acid, identified as trimethyl trimesate, m. p. 141°. The mixed melting point with a known sample showed no depression.

Fraction 5a, b. p. 240–245°, was obtained on redistillation of fraction 5. It consists probably of dimethylcyclohexyl. *Anal.* Calcd. for $C_{14}H_{26}$: C, 86.60; H, 13.40; mol. wt. 194. Found: C, 86.44; H, 13.43; n_D^{20} 1.4672; d_4^{20} 0.8581; mol. wt., 195.

Acknowledgment.—The authors wish to express their thanks to Mr. Bruno Kvetinskas for the assistance he rendered.

Summary

The reaction analogous to the destructive alkylation of aromatics with paraffins is described with hexahydroaromatic hydrocarbons.

Paraffinic hydrocarbons with branched chains such as 2,2,3-trimethylpentane, 2,2,4-trimethylpentane, and 3,4-dimethylhexane react with cyclohexane or methylcyclohexane in the presence of aluminum halides. Isobutane is formed in each case. The alkylated hydrocarbons produced consist of polymethylcyclohexanes, methylethylcyclohexanes and dicyclic compounds. 2,2,3-Trimethylbutane and *n*-octane do not react with cyclohexane under similar conditions.

RIVERSIDE, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

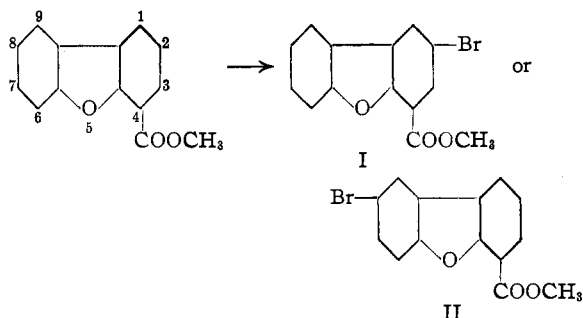
Dibenzofuran. VIII. Heteronuclear Substitution

BY HENRY GILMAN, MARIAN WESTON VAN ESS AND DAN M. HAYES

Introduction

The 4- or 4,6-substituted dibenzofurans appear at this time to be the most significant dibenzofuran types from a biological viewpoint. Among the more accessible compounds having a water-solubilizing group is 4-dibenzofurancarboxylic acid, which is readily available by metalation of dibenzofuran followed by carbonation.¹ Preliminary to the examination of the effect of additional groups, it was necessary to establish the positions of nuclear substituents.

Bromination of methyl 4-dibenzofurancarboxylate gives a bromo-ester which, subsequent to hydrolysis and decarboxylation, yields 2-bromodibenzofuran. Accordingly, the bromo-ester might be methyl 2-bromo-4-dibenzofurancarboxylate (I), formed by homonuclear substitution; or methyl



(1) Gilman and Young, *THIS JOURNAL*, **56**, 1415 (1934); **57**, 1121 (1935).

2-bromo-6-dibenzofurancarboxylate (II), formed by heteronuclear substitution.

2-Bromo-4-methyldibenzofuran was synthesized by a series of reactions resulting in ring closure, described in the Experimental Part. Unfortunately, this compound could not be oxidized to the corresponding 2-bromo-4-dibenzofurancarboxylic acid, and thus comparison with (I) was precluded.

Then (II) was synthesized by the following transformations, and the product shown to be identical with that obtained by bromination of methyl 4-dibenzofurancarboxylate.

