action mixture in a 25-plate semimicro column. If the residue be taken as di-*s*-butylbenzene, the yield was 24% of di-*s*-butylbenzene. No toluene could be detected.

A mixture of 0.975 mole of ethyl ether and 0.196 mole of benzene was saturated with boron trifluoride. After 10 days at 25° the hydrocarbon portion was isolated by washing with water and then phosphoric acid. Its infrared absorption spectrum as measured on the Beckman IR2T spectrograph differed negligibly from benzene. Less than 1.5% of ethylbenzene could have been present.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

The Alkylation of Aromatic Hydrocarbons by Optically Active Secondary Butyl Methyl Ether in the Presence of Boron Trifluoride

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Alkylation of benzene by optically active *s*-butyl methyl ether with boron trifluoride yields *s*-butylbenzene of inverted configuration and optical purity of a little greater than 1%. The drastic racemization occurs during the alkylation step and is not, in significant degree, due to racemization of ether before reaction or of product after formation. The racemization may be connected with isomerization of the carbonium ion since 2-methoxypentane gives a mixture of 2- and 3-phenylpentane of near the equilibrium composition.

When benzene is alkylated by optically active *s*-butyl alcohol, *s*-butylbenzene of low rotation, opposite in sign to that of the starting alcohol, is reported to result.[1,2] Of the various alkylating agents, the rotation was largest, 0.007 of the optically pure product, for boron trifluoride and hydrogen fluoride.

The existence of finite, if low, rotations is of interest in the theory of carbonium ion reactions. Interpretation of the reported rotations[1,2] is made difficult by three considerations: (1) absence of rotation due to optically active impurities was not rigorously demonstrated, (2) absence of racemization of *s*-butylbenzene subsequent to its formation was not demonstrated, (3) absence of racemization of the alcohol previous to reaction was not demonstrated and, indeed, some racemization previous to reaction is known to occur with some of the alkylating agents studied.[3]

Study of the alkylation of benzene by optically active *s*-butyl methyl ether with boron trifluoride was undertaken to clarify these details. The ether was chosen because it is much less likely to undergo racemization before reaction[4] owing to the absence of ways in which a racemic or racemizable intermediate can be reconverted to the ether; boron trifluoride because it gave as high rotations as any of the alkylating agents.[1,2]

The alkylation gives *s*-butylbenzene of inverted configuration[5] and of an optical purity of 1.1 to 1.4% (Table I). The stereochemistry thus resembles that reported for *s*-butyl alcohol but the optical purity is roughly twice as great.

That the rotation was due to optically active *s*-butylbenzene was shown by careful purification of the product and by the identity of the rotatory dispersion of the product and that of optically pure *s*-butylbenzene.

The absence of racemization of the ether before reaction was shown by interrupting an alkylation and isolating unreacted ether. Its rotation was

TABLE I

ALKYLATION WITH OPTICALLY ACTIVE *s*-BUTYL METHYL ETHER

Technique	Aromatic hydrocarbon, moles	Ether, mole	BF_3, mole	Additive (mole)	Corrected rotation[a] monoalkylate, deg.
	Benzene				
(2)	0.272[b]	0.0360	0.0371	HSO_3Cl (0.0003)	0.30 (1.3%)
(2)	.272[b]	.0360	0.0371	H_2SO_4 (0.0015)	.26 (1.1%)
(2)	.340	.0423	Sat.[c]	H_2SO_4 (0.0008)	.33 (1.4%)
	Mesitylene				
(1)	0.18	.0415	Sat.	None	.36
	p-Xylene				
(1)	0.22	.0415	Sat.	None	.71
	Toluene				
(1)	0.24	.0415	Sat.	None	.57
(1)	.076[b]	.0166	0.0166	H_2SO_4[d]	.85[g]
(1)	.076[b]	.0166	.0166	H_2SO_4[d]	.82
(1)	076[b]	.0166	.0166	H_2O[d]	.55
(1)	.076[b]	.0166	.0166	CH_3OH[d]	.88
(1)	.076[b]	.0166	.0166	None	.85
(2)	.24[e]	.0415	.044	H_2SO_4[d]	.69
(2)	.12[f]	.021	.022	H_2O[f]	.46
(2)	.26[f]	.021	.022	H_2O[f]	.46
(1)	.12[b]	.021	Sat.	None	.80
(1)	.12[b]	.021	Sat.	CH_3OH	No reacn.[h]
(2)	.24	.0415	Sat.	H_2SO_4 (0.001)	0.48

[a] In the first three runs, optical purity is also listed. The rotations are corrected to optically pure ether. [b] A batch of hydrocarbon, ether and BF_3 was prepared, and split into two or more parts for treatment with different additives. [c] Purified BF_3. [d] One small drop. [e] Reaction period was two days at −10°. [f] Two small drops. [g] Centrifuged during reaction period. [h] No turbidity appeared, no *s*-butyltoluene could be isolated by distillation. [i] A batch was split between two tubes and inoculated with water. Extra toluene was added to one tube.

(1) C. C. Price and M. Lund, THIS JOURNAL, **62**, 3105 (1940).

(2) R. L. Burwell, Jr., and S. Archer, *ibid.*, **64**, 1032 (1942).

(3) R. L. Burwell, Jr., *ibid.*, **64**, 1025 (1942).

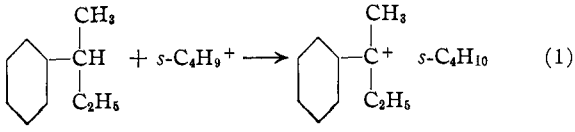
(4) R. L. Burwell, Jr., L. M. Elkin and L. G. Maury, *ibid.*, **73**, 2428 (1951).

(5) J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935), reported that (+)*s*-butyl *p*-toluenesulfonate reacts with phenylmagnesium bromide to give (−)*s*-butylbenzene. (+)*s*-Butyl *p*-toluenesulfonate is configurationally related to (+)*s*-butyl alcohol. By analogy with the work of R. L. Letsinger (THIS JOURNAL, **70**, 406 (1948)) on the condensation of organosodium compounds with optically active 2-bromoalkanes, the reaction of Kenyon, *et al.*, probably involves inversion. Thus, *s*-butyl alcohol and *s*-butylbenzene of like sign are probably configurationally related. That assumption will be made in this paper.

substantially that of the original reactant (last paragraph in the Experimental section).

Only a minor amount of racemization of *s*-butylbenzene can occur subsequent to its formation. This was shown by an experiment in which inactive ether was employed and a small quantity of (−)-*s*-butylbenzene was added before reaction. The rotation of the isolated *s*-butylbenzene indicated that little racemization of the *s*-butylbenzene originally added had occurred.

It had been suspected that racemization of the alkylate might occur by a chain reaction initiated thus



(1)

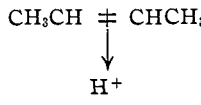
Further reaction of the carbonium ion on the right of equation (1) with *s*-butylbenzene could lead to extensive racemization similar to that of (+)3-methylheptane by chlorosulfonic acid.[6] However, under the conditions studied here, the rate of addition of $s\text{-}C_4H_9^+$ to benzene must be fast compared to the rate of its reaction in (1). This is analogous to the finding[7] that the rate of addition of $s\text{-}C_3H_7^+$ to benzene is many times faster than the reaction

$$C_3H_7^+ + HC(CH_3)_3 \longrightarrow C_3H_8 + {}^+C(CH_3)_3 \quad (2)$$

The alkylation reaction presumably proceeds as a carbonium ion reaction.[8] The large racemization, of the order of 99%, is entirely or largely confined to the alkylation step itself. This step cannot, then, in general, involve a concerted displacement with inversion[9] to any substantial degree.

The extent of racemization is much greater than in other reactions believed to involve carbonium ion intermediates, even tertiary carbonium ion intermediates.[10] A kinetically free carbonium ion intermediate should, of course, lead to a completely racemic product. The small observed rotation found in the alkylation reaction could result from a carbonium ion of relatively long life, shielded by the counteranion and thus configurationally stabilized to some extent.[11]

The carbonium ion could perhaps be formulated as a π-complex between 2-butene and a proton[12]



The form derived from *cis*-2-butene is optically inactive but that derived from *trans*-2-butene exists in two enantiomeric forms. Slight favoring of one form could lead to the observed rotation.

Alkylation of benzene by 2-methoxypentane yields a monoalkylate composed of 75% 2-phenylpentane and 25% 3-phenylpentane. This is in the vicinity of the equilibrium mixture as judged from the observed ratios of these two materials obtained in alkylating benzene with 2- and 3-pentanol by aluminum chloride or hydrogen fluoride.[13] Such isomerization must occur if a π-complex is a "stable" intermediate. One could test whether the proton transfer is intramolecular by suitable experiments with isotopic hydrogen. In any case, the isomerization shows that if a *s*-butylcarbonium ion is an intermediate the following isomerization must occur and be involved in the racemization

$$CH_3\overset{+}{C}HCH_2CH_3 \rightleftharpoons CH_3CH_2\overset{+}{C}HCH_3 \quad (3)$$

Since alkylbenzenes alkylate somewhat preferentially to benzene,[14] less racemization might be expected to occur than with benzene. Accordingly, as shown in Table I, alkylation of toluene, *p*-xylene and mesitylene was investigated. Rotations of the monoalkylate were somewhat larger than with benzene, but in the absence of the rotations of the optically pure compounds, there is no reason to believe that very much higher optical purities resulted in these cases. The results with toluene are complicated by the presence of three isomers, *o*-, *m*- and *p*-*s*-butyltoluene. Infrared analysis of one of the products of alkylating toluene in comparison with authentic samples of the three butyltoluenes demonstrated the presence of 37, 21 and 42% of each constituent, respectively. These results correspond closely with those reported for the alkylation of toluene by *i*-propyl chloride and hydrogen fluoride.[15]

Since rotations of the *s*-butyltoluenes were two to three times those of the corresponding benzene derivatives, a number of experiments with toluene were run to study the effect of process variables upon the rotation of the product. As shown in Table I, all rotations agreed to within a factor of two and no definite effect of such variables was detected. The experiments included: change in proportion of toluene, variation in promoter,[8] reaction at −10°, centrifuging during reaction period to minimize interface effects during the period of turbidity,[8] and the use of purified[8] rather than tank boron trifluoride. Apparently, no considerable variation in the life of the carbonium ion was occasioned by these variations.

Acknowledgment.—We are indebted to Dr. Donald Cram for a sample of high optical purity *s*-butylbenzene and to Dr. Herman Pines for the sample of *p*-*s*-butyltoluene. One of us, L. M. E., was the holder of a du Pont fellowship.

Experimental

All rotations are homogeneous and, unless otherwise indicated, corrected to 1 dm. *s*-Butyl methyl ether[4] whose optical purity was 35–70% was employed. In computing optical purity, the rotation of optically pure ether[4] was taken as 17.4° and that of *s*-butylbenzene[16] as 23.6°. The

(6) G. S. Gordon III and R. L. Burwell, Jr., THIS JOURNAL, **71**, 2355 (1949).

(7) F. E. Condon and M. P. Matuszak, *ibid.*, **70**, 2539 (1948).

(8) R. L. Burwell, Jr., L. D. Elkin and A. D. Shields, *ibid.*, **74**, 4567 (1952).

(9) C. G. Swain, *ibid.*, **70**, 1119 (1948).

(10) E. D. Hughes and C. K. Ingold, *Nature*, **166**, 679 (1950).

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 172.

(12) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p. 213.

(13) H. Pines, W. D. Huntsman and V. N. Ipatieff, THIS JOURNAL, **73**, 4343, 4483 (1951).

(14) F. E. Condon, *ibid.*, **70**, 2265 (1948).

(15) J. H. Simons and H. Hart, *ibid.*, **69**, 979 (1947). See also, F. E. Condon, *ibid.*, **71**, 3544 (1949).

(16) P. W. B. Harrison, J. Kenyon and J. R. Shepherd, *J. Chem. Soc.*, 658 (1926).

rotation of the isolated monoalkylate was always opposite in sign to that of the ether.

Reaction mixtures were prepared with or without exclusion of atmospheric moisture, techniques (2) and (1) of Techniques (ref. 8). After reaction, the monoalkylate was isolated from the washed hydrocarbon layer by distillation in a micro distilling column of several theoretical plates. Results are presented in Table I.

The first two samples of *s*-butylbenzene listed in Table I were combined and distilled in a Piros–Glover, rotating-band, fractionating column. Four successive fifths were collected, $n^{25}D$ 1.48694, 1.48730, 1.48727, 1.48732 and $\alpha^{30}D$ (2 dm.) −0.393°, −0.400°, −0.396° and −0.395°. The rotatory dispersion of a combined sample was measured on a Bellingham and Stanley polarimeter with spectroscopic eyepiece. The relative rotations, with that of the 5461 Å. line taken as 1.00, were: 5893 Å., 0.86, 0.82; 5790 Å., 0.91, 0.87; 5461 Å., 1.00, 1.00; 4358 Å., 1.82, 1.82. The results of this research are given first, those of Harrison, Kenyon and Shepherd,[16] second. They agree to within the experimental error. These data support the ascription of the rotation of the alkylate to *s*-butylbenzene.

A mixture of benzene (0.326 mole), 2-methoxypentane (0.0477 mole), boron trifluoride (0.0474 mole) and water (2 drops) was allowed to stand several days. The phenylpentane fraction was analyzed by infrared spectrophotometry by measurement at 8.85, 10.17 and 12.03 microns. The analysis, 25% 3-phenylpentane, was confirmed by comparing the transmission curve of the fraction from 6 to 15 microns with that of a synthetic mixture containing 74.3% 2-phenylpentane and 25.7% 3-phenylpentane. The curves were indistinguishable.

A mixture of the following composition was prepared: (−)*s*-butylbenzene ($\alpha^{25}D$ −21.64°), 0.00189 mole; benzene, 0.254 mole; *dl*-*s*-butyl methyl ether, 0.0359 mole; boron trifluoride, 0.0362 mole; and sulfuric acid, 0.0008 mole. A 66% yield of *s*-butylbenzene resulted. During the distillation two fractions were collected for both of which $n^{25}D$ 1.4871 and $\alpha^{25}D$ −1.30°. If 0.00189 mole of the (−)*s*-butylbenzene had been diluted with inactive material to the resultant 0.0238 mole *s*-butylbenzene, a rotation of −1.71° would result. However, since the (−)*s*-butylbenzene, being present initially, would have been preferentially converted to di-*s*-butylbenzene, the racemization which occurred is probably less than the 24% racemization which results from the indicated computation.

The following mixture was prepared: toluene, 0.24 mole; (−)*s*-butyl methyl ether ($\alpha^{25}D$ −5.70°), 0.0415; boron trifluoride to near saturation; sulfuric acid, 0.001. After one hour at 25°, 1.0 cc. of lower layer had formed. This with 9 cc. of the upper layer was withdrawn and allowed to react to completion. The remaining 20 cc. was run into ice-water. From the first fraction, *s*-butyltoluene, $\alpha^{25}D$ +0.15°, was recovered. From the second fraction, *s*-butyltoluene, $\alpha^{25}D$ +0.16°, and *s*-butyl methyl ether, $\alpha^{25}D$ −5.45°, were recovered. Thus, negligible racemization of the ether occurs prior to reaction.

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

3′,7′-Dihydroxy-1,2,5,6-dibenzanthracene[1]

BY LILLI SCHWENK HORNIG

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The synthesis of 3′,7′-dihydroxy-1,2,5,6-dibenzanthracene and certain of its derivatives which is here reported was undertaken to test the hypothesis that the phenol is identical with the rabbit metabolite of the carcinogenic parent hydrocarbon. The desired phenol was synthesized by application of the Pschorr reaction to the product resulting from condensation of phenylene-1,4-diacetic acid with two moles of 2-nitro-5-methoxybenzaldehyde, and proved to be not identical with the product of rabbit metabolism.

The several carcinogenic polynuclear hydrocarbons whose metabolism has been investigated invariably are detoxicated, in rats and mice, to simple phenolic derivatives bearing the hydroxyl groups in positions sterically analogous to the 4′-position of 1,2-benzanthracene.[2] The only common carcinogen containing two angular condensed benz rings, 1,2,5,6-dibenzanthracene, is converted to the symmetrical 4′,8′-dihydroxy derivative.[2a]

The existence of marked species differences in the response to carcinogens has long been recognized, and it is known that rabbits, which are relatively resistant to experimental cancer production, metabolize the hydrocarbons differently than rats and mice. Thus, the dihydroxydibenzanthracene isolated from rabbits[3] (which develop only papillomas on treatment with dibenzanthracene) is not identical with the 4′,8′-dihydroxy derivative excreted by rats and mice. On the basis of the fact that anthracene is excreted in part as a 1,2-dihydro-1,2-dihydroxy derivative[4] Cason and Fieser[2a] suggested that the rabbit metabolite of dibenzanthracene might be the 3′,7′-dihydroxy compound XI, arising from a tetraol precursor (identical with the probable rat and mouse intermediary metabolite) by elimination of water. The present work reports the synthesis of 3′,7′-dihydroxydibenzanthracene, undertaken to test this hypothesis. The synthetic phenol was in fact not identical with the rabbit metabolite, and it appears, therefore, that the species difference in the metabolism of dibenzanthracene is manifested at an earlier stage in the metabolic process and that in fact the molecule is originally attacked at positions which differ radically, in the relatively cancer-resistant rabbit, from those in the much more susceptible rat and mouse.

Since the inception of this work some years ago, the rabbit metabolite of 3,4-benzpyrene has been identified as the 10-hydroxy derivative[5] which is sterically analogous to the 2′,6′-dihydroxy derivative of dibenzanthracene.

The most promising route to the desired phenol

(1) This paper is based on a thesis presented to the Graduate Faculty of Arts and Sciences of Radcliffe College for the Degree of Doctor of Philosophy, January, 1950.

(2) (a) J. Cason and L. F. Fieser, THIS JOURNAL, **62**, 2681 (1940); (b) I. Berenblum and R. Schoental, *Cancer Research*, **3**, 145 (1943); (c) I. Berenblum, D. Crowfoot, E. R. Holiday and R. Schoental, *ibid.*, **3**, 151 (1943); (d) I. Berenblum and R. Schoental, *ibid.*, **3**, 686 (1943); (e) F. Dickens and H. Weil-Malherbe, *British Empire Cancer Campaign, Annual Reports*, **22**, 55 (1945).

(3) (a) A. A. Levi and E. Boyland, *Chemistry and Industry*, **15**, 446 (1937); (b) E. Boyland, A. A. Levi, E. H. Mawson and E. Roe, *Biochem. J.*, **35**, 184 (1941).

(4) E. Boyland and A. A. Levi, *ibid.*, **29**, 2679 (1935); **30**, 728, 1225 (1936).

(5) I. Berenblum and R. Schoental, *Cancer Research*, **6**, 699 (1946).