(2 cc.), at room temperature. After standing at room temperature for twenty hours, the reaction mixture was poured into ether and the ether extract was washed successively with dilute hydrochloric acid, 0.5 *N* aqueous potassium hydroxide and water. The ether was removed by distillation leaving a white solid containing free palmitic acid. Palmitic acid was removed by adsorbing the crude ester from petroleum ether (15 cc.) on a column of Doucil[9] (9″ × 12 mm.). The column was washed with petroleum ether (75 cc.) and filtrate and washings were evaporated leaving a residue (0.302 g.) which was crystallized from ethyl alcohol (6 cc.) at 5°. The antioxidant palmitate formed lath-like, white crystals (0.18 g.), m. p. 40.5–41.5°, which were identified as α-tocopherol palmitate.

Anal. Calcd. for $C_{45}H_{80}O_3$: C, 80.76; H, 12.06. Found: C, 80.81; H, 11.91.

Summary

A natural antioxidant has been isolated from Mangona shark liver oil and identified as natural α-tocopherol. Evidence was obtained indicating that α-tocopherol is the major antioxidant present in this fish liver oil.

This finding is of interest since it indicates that the tocopherols may act as natural antioxidants in fish liver oils as well as in vegetable oils.

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[9] Doucil (American Doucil Company, 121 South 3d Street, Philadelphia, Pa.) is a sodium aluminum silicate.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Reactions of Organometallic Compounds with Alkyl Halides. I. The Action of Sodium Ethyl on (−)2-Bromoöctane

BY NORMAN G. BRINK,[1] JOHN F. LANE AND EVERETT S. WALLIS

Previous studies[2] in this Laboratory have shown that the Wurtz reaction of an optically active alkyl bromide with sodium leads to a completely optically inactive product. Thus, when (+)2-bromobutane is treated with sodium at room temperature, the resulting 3,4-dimethylhexane shows no detectable optical activity. This result would be consistent with a formulation[3] of the Wurtz synthesis involving initial formation of free radicals

$$Na + RX \longrightarrow R^{\cdot} + NaX \qquad (1)$$

followed by their combination to give the expected coupling product

$$2R^{\cdot} \longrightarrow R\text{–}R \qquad (2)$$

or by their disproportionation to alkane and alkene by-products

$$2R^{\cdot} \longrightarrow RH + \text{olefin.} \qquad (3)$$

Secondary alkyl radicals would be expected to show extreme optical instability, since they possess numerous planar resonance states comparable in energy to the normal state. In this they resemble the corresponding carbonium ions more closely than the corresponding carbanions, the planar resonance states of which are considerably higher in energy than the normal state.[4]

More recently,[5] sodium alkyls have been shown to act on alkyl halides in a manner typical of the salts of very weak acids, either to effect substitution of the carbanion for halogen

$$(Na^+)R_1^- + R_2X \longrightarrow (Na^+)X^- + R_1 - R_2 \qquad (4)$$

or by their strongly basic action to remove the elements of hydrogen halide with the formation of an olefin

$$(Na^+)R_1^- + R\text{—}CH_2\text{—}CH_2X \longrightarrow R_1H + R\text{—}CH\text{=}CH_2 + (Na^+)X^- \qquad (5)$$

In addition, when X is bromine or iodine, metal-halogen interchange[5b]

$$NaR_1 + R_2X \longrightarrow NaR_2 + R_1X \qquad (6)$$

can occur. It has been further suggested[5b] that the initial stage of the Wurtz synthesis may involve direct formation of a sodium alkyl

$$2Na + RX \longrightarrow NaR + NaX \qquad (7)$$

and that subsequent stages of the reaction involve the action of the sodium alkyl on additional alkyl halide according to equations (4) and (5). If this be granted, the observed products of the Wurtz synthesis may be accounted for without recourse to the concept of free radicals as critical reaction intermediates.

In order to account for the complete optical inactivity observed in the formation of 3,4-dimethylhexane from (+)2-bromobutane and sodium, however, such an interpretation must be ampli-

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[1] Sayre Fellow in Applied Chemistry, 1942–1943.

[2] Wallis and Adams, THIS JOURNAL, **55**, 3838 (1933).

[3] *Cf.* Hückel, Kraemer and Thiele, *J. prakt. Chem.*, **142**, 207 (1935); Bachmann and Clark, THIS JOURNAL, **49**, 2089 (1927); Richards, *Trans. Faraday Soc.*, **36**, 956 (1940).

[4] Baughan, Evans and Polanyi, *Trans. Faraday Soc.*, **37**, 377 (1941).

[5] (a) Whitmore and Zook, THIS JOURNAL, **64**, 1783 (1942); (b) Morton, Davidson and Hakan, *ibid.*, **64**, 2242 (1942).

fied by one (or more) of the following hypotheses: (a) the sodium *s*-butyl initially formed is incapable of optical activity and the metal–halogen exchange reaction is reversible and sufficiently rapid to effect complete racemization of the halide before substitution by (4) has proceeded to an appreciable extent. (b) The hydrocarbon initially formed is optically active but is racemized by the metalating action of the sodium alkyl present, which attacks the tertiary hydrogens of the optically active centers to give an optically unstable carbanion

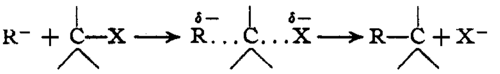
$$s\text{-}C_4H_9^- + HC(CH_3)(C_2H_5)(s\text{-}C_4H_9) \rightleftarrows C_4H_{10} + [C(CH_3)(C_2H_5)(s\text{-}C_4H_9)]^- \quad (8)$$

(c) The sodium *s*-butyl initially formed is racemic, and the subsequent substitution (4) proceeds by way of a preliminary ionization (entailing racemization) of the optically active halide; *i. e.*, the substitution is of the extreme S_N1 type[6]

$$RX \longrightarrow R^+ + X^- \text{ (slow)} \quad (9)$$

$$(X^-) + R^+ + R^-(Na^+) \longrightarrow R{-}R + (Na^+ X^-) \text{ (fast)} \quad (10)$$

(d) The sodium *s*-butyl preserves the initial (d) configuration of the halide and reaction (4) proceeds by the alternative substitution mechanism S_N2[6]



$$R^- + C{-}X \longrightarrow \overset{\delta-}{R}\ldots C\ldots \overset{\delta-}{X} \longrightarrow R{-}C + X^- \quad (11)$$

which involves complete Walden inversion on the carbon atom at which the substitution takes place and hence the exclusive formation of *meso*-3,4-dimethylhexane. (e) The substitution (4) proceeds by a process of the type (11), involving Walden inversion, but the *s*-butyl carbanions arising from sodium *s*-butyl are very easily racemized. Further, it is presumed that the *d*-form of the carbanion reacts with *d*(+)-*s*-butyl bromide much more rapidly than does the *l* form. Again *meso*-3,4-dimethylhexane will be the product formed

$$d\text{-}s\text{-}C_4H_9^- \rightleftarrows l\text{-}s\text{-}C_4H_9^- \quad (12)$$

$$d\text{-}s\text{-}C_4H_9^- + d\text{-}s\text{-}C_4H_9Br \xrightarrow{\text{(Inversion)}} meso\text{-}(s\text{-}C_4H_9)_2 \quad (13)$$

$$l\text{-}s\text{-}C_4H_9^- + d\text{-}s\text{-}C_4H_9Br \xrightarrow{\text{(Inversion)}} l\text{-}(s\text{-}C_4H_9)_2 \quad (14)$$

$$k_{13} >> k_{14}$$

There remains, of course, the possibility that in this instance, at least, the Wurtz synthesis proceeds primarily by way of free radicals (equations 1, 2, 3). In this event results of quite different stereochemical nature might be expected, were a previously prepared sodium alkyl allowed to act on an optically active alkyl halide. For this reason, and also in the hope of obtaining data which might serve to reduce the number of possible explanations of the detailed mechanism of the action of sodium on (+)2-bromobutane, we have investigated the action of sodium ethyl on a comparable halide, (−)2-bromoöctane. Since the results of this study provide a basis for the immediate exclusion of the first two hypotheses enumerated in the preceding paragraph, and since they are of importance in estimating the suitability of the last three, we present them in detail at this point before proceeding with the discussion.

Sodium ethyl was prepared from mercury diethyl and sodium according to Whitmore and Zook.[5a] (−)2-Bromoöctane, $[\alpha]^{20}{}_D$ −30.7°, was then added to the metal alkyl under pentane at −10°. After the initial reaction had subsided, the mixture was stirred for five hours, during which time it was allowed to reach the temperature of the room. Stirring was continued for twelve hours, at the end of which time 88.5% of the alkyl bromide had reacted. The unreacted 2-bromoöctane still present caused immediate precipitation of silver bromide when test samples of pentane or ether solutions of the products were treated with alcoholic silver nitrate. That it was still optically active was evidenced by the high negative rotations of solutions of the product at this stage of the operations. The mixture, having been freed from mercury diethyl by the action of gaseous hydrogen chloride at 0°, was fractionated through a seven-plate column until products boiling below 150° had been removed. These consisted mainly of octane and octylene in approximately equal amounts. The residue was digested with alcoholic silver nitrate, taken up in pentane and washed many times with cold concentrated sulfuric acid. Fractionation then gave (−)3-methylnonane, $[\alpha]^{20}{}_{6563}$ −0.20°; $[\alpha]^{20}{}_{5893}$ −0.25°; $[\alpha]^{20}{}_{5463}$ −0.32°; $[\alpha]^{25}{}_D$ −0.23°; $[M]^{25}{}_D$ −0.34° (homogeneous, 2-dm. tube); b. p. 166.8°–167.1° (769 mm.),[7] and a small amount of optically inactive 7,8-dimethyltetradecane. The yield of pure (−)3-methylnonane from the reaction of (−)2-bromoöctane with sodium ethyl was 25% (based on reacted alkyl bromide). The approximate molar ratio of the products octylene, octane,

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[6] Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[7] Calingaert and H. Soroos, THIS JOURNAL, **58**, 635 (1936), report 167.8° (760 mm.); Levene and Taylor, *J. Biol. Chem.*, **54**, 351 (1922), report 165–166.5° (751 mm.).

3-methylnonane, and 7,8-dimethyltetradecane was 9:12:16:1, respectively.

In order to establish whether a sodium alkyl could attack the tertiary hydrogen of optically active hydrocarbons such as (−)3-methylnonane, a 10% solution of this hydrocarbon in pentane was stirred for eighteen hours at room temperature with an excess of sodium ethyl. The hydrocarbon was recovered from this treatment with no appreciable loss of optical activity.

Since the presence of the sodium amalgam (about 10% sodium by weight) arising from the preparation of sodium ethyl from mercury diethyl and sodium might conceivably have had some effect on the alkyl halide, we investigated the action of such an amalgam on (+)2-bromoöctane, $[\alpha]^{20}_D$ +32.0°, in pentane solution for eighteen hours at the temperature of the room. The alkyl bromide was quantitatively recovered from this treatment with unchanged optical rotation.

An analysis of the results of this study leads to the following conclusions. First, from the value $[M]^{25}_D$ ±12.5°[8] for the maximal rotation of 3-methylnonane, and the value $[\alpha]^{20}_D$ ±33.8°[9] for the maximal rotation of 2-bromoöctane, it follows that if no racemization had occurred during the reaction, the product isolated by us should have had a molecular rotation $[M]^{25}_D$ −11.3°. Evidently racemization to the extent of 97% has occurred in the formation of 3-methylnonane. Moreover, it is complete in the formation of 7,8-dimethyltetradecane. The presence of the latter hydrocarbon, as well as that of octane, among the reaction products is apparently to be connected with the presence of sodium *s*-octyl arising from a metal-halogen exchange reaction of type (6). Its complete optical inactivity strongly suggests that there exists a real parallel between the method of its formation here and the formation of the corresponding hydrocarbon, 3,4-dimethylhexane from (+)2-bromobutane and sodium.[2] The cause of the racemization in both cases may very well be the same.

Second, the presence of unreacted (−)2-bromooctane among the products obtained in the present investigation precludes the possibility that a halide of this type is rapidly racemized by an exchange reaction of type (6). Furthermore, we have shown that a sodium alkyl does not attack the tertiary hydrogen of an optically active hydrocarbon of the type $R_1R_2R_3CH$, where R_1, R_2 and R_3 are alkyl groups. Therefore an interpretation of the reaction of sodium with (+)2-bromobutane, which presumes reaction (7) as the initial stage, followed by reactions of types (4), (5) and (6) may not be supplemented by the first or second of the hypotheses enumerated above to explain the optical inactivity of the product.

Now of the three remaining hypotheses, which are concerned with the detailed mechanism of the substitution process (4), we can reject the first. This requires that (4) proceed by the mechanism S_N1, involving preliminary ionization of the C–Hal bond with a sufficient time lag between the ionization and the subsequent combination of the resulting carbonium ion, and the entering (racemic) carbanion to permit complete racemization of the former. Secondary paraffin halides, however, undergo such preliminary ionization only in media possessing a relatively high dielectric constant as well as a high capacity for solvating ions. Moreover, even under conditions most favorable to such a process, racemization occurs to an extent of no more than 70%.[6,9,10] In the present investigation, complete optical inactivity resulted only in the reaction which involved the replacement of bromine by *s*-octyl. The replacement of bromine by ethyl in the same system led to an optically active product. An interpretation of these results which required that they both proceed through an initial stage involving the same carbonium ion would, however, also require that the stereochemical results of the two reactions be the same, *i. e.*, both products should have been optically active or both inactive. Since this was not the case, such an interpretation must be discarded.

It is much more likely that these replacements will occur by a mechanism of the type S_N2[6] (equation 11). Such a mechanism is favored by the low dielectric constant and solvating capacity of the medium, as well as by the high basicity of the entering anions. On this basis the important substitution reactions for the system sodium ethyl, (−)2-bromoöctane may be written

$$C_2H_5^- + s\text{-}C_8H_{17}Br \longrightarrow CH_3(C_2H_5)CHC_6H_{13} + Br^- \quad (15)$$

$$s\text{-}C_8H_{17}^- + C_2H_5Br \longrightarrow CH_3(C_2H_5)CHC_6H_{13} + Br^- \quad (16)$$

$$s\text{-}C_8H_{17}^- + s\text{-}C_8H_{17}Br \longrightarrow C_{16}H_{34} + Br^- \quad (17)$$

together with the corresponding elimination reactions

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[8] Levene and Rothen, *J. Org. Chem.*, 1, 85 (1936).

[9] Hughes, Ingold and Masterman, *J. Chem. Soc.*, 1196 (1937).

[10] Hughes, *Trans. Faraday Soc.*, 34, 202 (1938).

$$C_2H_5^- + s\text{-}C_8H_{17}Br \longrightarrow C_2H_6 + C_8H_{16} + Br^- \quad (18)$$

$$s\text{-}C_8H_{17}^- + C_2H_5Br \longrightarrow C_8H_{18} + C_2H_4 + Br^- \quad (19)$$

$$s\text{-}C_8H_{17}^- + s\text{-}C_8H_{17}Br \longrightarrow C_8H_{18} + C_8H_{16} + Br^- \quad (20)$$

Whether these reactions occur in the solution or at the juncture of the solution with the ionic crystal lattice of the sodium alkyl cannot yet be decided, since without a knowledge of the energies, or more properly the free energies of activation of these reactions, no lower limit can be set for the concentration of carbanion necessary to effect rapid substitution and elimination in solution.

If the additional assumption is made (hypothesis (d) above) that the sodium *s*-alkyl formed either by process (7) or by process (6) retains the initial configuration of the halide from which it is produced, then a replacement reaction such as (17) which involves Walden inversion will produce a *meso* hydrocarbon (equation 11 above). Since, under this assumption, (15) and (16) will now lead to enantiomorphic modifications of 3-methylnonane, the extensive racemization of this hydrocarbon is to be interpreted as arising from nearly equal contributions of the two processes. We are inclined, however, to reject this interpretation, since it is improbable that a sodium alkyl formed from an optically active alkyl halide by (6) or (7) will be optically active or that it could furnish optically stable carbanions for a replacement reaction of the type (17). No attempt to prepare an optically active Grignard reagent by the action of magnesium on an optically active alkyl halide has ever succeeded[11]; neither is it possible to obtain optically active amines of the type R_1R_2NH which are iso-electronic with the carbanions $R_1R_2CH^-$ involved here.

This difficulty is satisfactorily avoided, however, when the hypothesis (e) above is adopted rather than (d). Again the substitution reaction (17) leads to *meso*-7,8-dimethyltetradecane, since the conditions

$$d\text{-}s\text{-}C_8H_{17}^- \rightleftarrows l\text{-}s\text{-}C_8H_{17}^- \text{ (rapid)} \quad (21)$$

$$l\text{-}s\text{-}C_8H_{17}^- + l(-)\text{-}s\text{-}C_8H_{17}Br \longrightarrow meso\text{-}(s\text{-}C_8H_{17}^-)_2 \quad (22)$$

$$d\text{-}s\text{-}C_8H_{17}^- + l(-)\text{-}s\text{-}C_8H_{17}Br \longrightarrow d\text{-}(\text{s-}C_8H_{17}^-)_2 \quad (23)$$

$$k_{22} >> k_{23}$$

are presumed to obtain. Now process (15) leads to (−)3-methylnonane while process (16) leads to *r*-3-methylnonane. From the extent of racemization of this hydrocarbon, it is to be concluded on the basis of this formulation that (16) proceeds about thirty-two times as fast as (15). Actually with ethyl bromide the specific rates of substitution of other anions for bromine by the mechanism S_N2 are found to be much larger than those of corresponding substitutions involving secondary alkyl bromides.[12] Moreover, previous investigations[6,13] on the relative amounts of elimination and substitution in the reactions of basic anions with ethyl and *s*-alkyl halides indicate that the reaction of $C_2H_5^-$ with *s*-octyl bromide should favor elimination over substitution by a factor of about three or four, while the reaction of *s*-$C_8H_{17}^-$ with ethyl bromide will greatly favor substitution over elimination. The total production of gases would then be small, since the contributions of (18) and (19) would be small fractions of the main reaction (16). In the reaction of sodium ethyl with *n*-hexyl chloride studied by Whitmore and Zook,[5a] on the other hand, a consideration of the previous investigations[6,13] on the elimination and substitution reactions of other basic anions on higher *n*-alkyl halides would lead to the prediction that about equal amounts of the gas ethane (elimination) and of *n*-octane (substitution) would be formed. This was indeed the case (here the metal-halogen exchange did not play a significant part, so that the principal reaction was that of $C_2H_5^-$ with *n*-hexyl chloride).

The assumption upon which this interpretation rests, namely, that reaction (22) is a much more rapid process than (23) remains unproved, of course, until the diastereomeric 7,8-dimethyltetradecanes can be synthesized in the pure state and their properties compared with those of the product obtained by this method. It might be expected, however, that the energy of the transition state (and hence the energy of activation) of the process (22) would be considerably lower than that for (23), since the distances between the larger alkyl groups, which tend to repel one another, will be larger in the former than in the latter transition state.[14] Similar considerations would apply to the processes (13) and (14). The 3,4-dimethylhexane obtained by Wallis and

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(11) Pickard and Kenyon, *J. Chem. Soc.*, **99**, 65 (1911); Schwarz and Johnson, THIS JOURNAL, **53**, 1063 (1931); Porter, *ibid.*, **57**, 1436 (1935).

(12) Hughes, Ingold and their co-workers find for ethyl bromide with sodium hydroxide (alcohol solution) $10^5\ k_{S_N2} = 171$; for *i*-propyl bromide under identical conditions $10^5\ k_{S_N2} = 4.75$ (ref. 6, p. 612).

(13) Hughes and Ingold, *Trans. Faraday Soc.*, **34**, 657 (1941); see especially pp. 677–680.

(14) This was pointed out to us by Dr. R. E. Powell, of this Laboratory.

Adams,[2] therefore, may well have been the *meso* form.[15]

It is to be noted that if the foregoing formulation is correct, the formation of (–)3-methylnonane from (–)2-bromoöctane by reaction (15) must have involved the Walden inversion. Apparently inversion of configuration has occurred, since (–)2-bromoöctane is configurationally identical with (–)octanol-2, which in turn has been shown by Levene[8] very probably to possess the same configuration as (+)3-methylnonane.

Finally, it is of interest to consider an alternative interpretation, which is consistent with known facts. The calculations of Baughan, Evans and Polanyi[4] have shown that for sodium methyl there exists a barrier of about 25 kcal. between the normal ionic state, $Na^+CH_3^-$, and the state of homopolar dissociation into sodium atoms and methyl radicals, $Na^{\cdot}\ldots CH_3^{\cdot}$. For any other sodium alkyl this barrier will be lowered by an amount, $R - R^-$, where R is the resonance energy of the alkyl radical and R^- that of the corresponding carbanion. The latter will be quite small for carbanions such as ethyl, *i*-propyl, *s*-butyl, etc., since the energies of the resonance states lie considerably above those of the normal state. The resonance energy R of an ethyl radical is about 7 kcal.; however, that of a secondary alkyl radical is about 12 kcal. It would thus appear that while for a primary sodium alkyl a rather high barrier exists for dissociation into sodium atoms and free radicals, for a secondary sodium alkyl it will be rather low (∼13 kcal.). A secondary sodium alkyl may well be in equilibrium with a free radical concentration sufficient to effect appreciable formation of coupling and disproportionation products (equations 2 and 3 above). If this is more rapid than the alternative substitution and elimination reactions of the corresponding carbanion with the alkyl halide the reaction scheme for the action of sodium on (+)2-bromobutane becomes

$$
\begin{array}{rcl}
2Na + s\text{-}C_4H_9Br & \longrightarrow & s\text{-}C_4H_9Na + NaBr \\
s\text{-}C_4H_9Na & \rightleftarrows & Na + s\text{-}C_4H_9^{\cdot} \\
2\text{-}s\text{-}C_4H_9^{\cdot} & \longrightarrow & (s\text{-}C_4H_9)_2 \\
 & \searrow & C_4H_8 + C_4H_{10}
\end{array}
$$

Since the concentration of ethyl radicals will be very small, and since the reaction of anions with ethyl halides is a rapid process, equations (15), (16), (18) and (19) above require no modification. The reaction scheme for the present investigation then becomes

$$
\begin{array}{lll}
C_2H_5^- + (-)s\text{-}C_8H_{17}Br & \nearrow (-)C_2H_5CH(CH_3)(C_6H_{13}) + Br^- & (15) \\
 & \searrow C_2H_6 + C_8H_{16} + Br^- & (18) \\
(r)s\text{-}C_8H_{17}^- + C_2H_5Br & \nearrow r\text{-}C_2H_5CH(CH_3)(C_6H_{13}) + Br^- & (16) \\
 & \searrow C_8H_{18} + C_2H_4 + Br^- & (19) \\
2s\text{-}C_8H_{17}Na \rightleftarrows (2Na + 2s\text{-}C_8H_{17}\cdot) & \nearrow C_{16}H_{34} & \\
 & \searrow C_8H_{18} + C_8H_{16} & (24)
\end{array}
$$

Again the formation of 3-methylnonane by (16) is much more rapid than by (15), and (15) leads to a Walden inversion. The 7,8-dimethyltetradecane produced by (24) would be optically inactive for reasons cited at the beginning of this paper, although now it might be supposed to consist of comparable amounts of *meso* and *dl* forms.

An interesting conclusion to be drawn from this analysis is that a sodium *s*-alkyl should show a considerable tendency to decompose into sodium, di-*s*-alkyl, alkane and alkene, even at comparatively low temperatures. We hope to conduct a study of the properties of such metal alkyls in the near future. We also contemplate a study of the action of a sodium alkyl on an optically active *s*-alkyl chloride. This should reduce the metal–halogen exchange to a minimum, so that the principal reactions would be the substitution and elimination reactions corresponding to (12) and (15). While considerable olefin formation would be anticipated, the substitution product should show little if any racemization.

Experimental Part

Materials.—(+)2-Bromoöctane, $[\alpha]^{20}D$ +32.4° (homogeneous), b. p. 81–82° (19 mm.), was prepared in 90% yield according to the method of Shriner and Young[16] from (–)octanol-2, $[\alpha]^{20}D$ –8.95° (homogeneous), b. p. 85° (20 mm.), obtained from the resolution of *dl*-octanol-2 (Eastman Kodak Co., White Label) according to Kenyon.[17] In like manner (–)2-bromoöctane, $[\alpha]^{20}D$ –30.7° (homogeneous) b. p. 78–79° (16 mm.), was prepared from (+)

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(15) We wish to emphasize at this point that the argument here presented applies only to the action of sodium *s*-alkyls on *s*-alkyl halides and not, for example, to the action of sodium (or of the corresponding sodium alkaryl) on optically active alkaryl halides. Indeed, in reactions of the latter type the mutual attraction of the aryl groups would be expected considerably to lower the activation energy for the formation of the optically active hydrocarbon, (Alk)(Ar)CHCH-(Alk)(Ar). In agreement with this interpretation, Ott (*Ber.*, **61**, 2124 (1928)) has observed the formation of (–)2,3-diphenylbutane from the action of sodium on (+)α-phenethyl chloride. Wallis and Adams (ref. 2), on the other hand, obtained an optically inactive product from the action of sodium on an optically active alkaryl bromide. The difference in these results is due in all probability to the extreme susceptibility of the bromide to racemization by a halogen–metal exchange reaction (equation 8).

(16) Shriner and Young, THIS JOURNAL, **54**, 1680 (1932).

(17) Kenyon, "Organic Syntheses," Coll. Vol. I, p. 410.

octanol-2, $[\alpha]^{20}_D$ +9.06° (homogeneous), b. p. 85° (20 mm.). Mercury diethyl, b. p. 159–161°, was prepared from ethylmagnesium bromide and mercuric chloride by the method of Gilman and Brown.[18] The *n*-pentane used in these experiments was a product of the Phillips Petroleum Co.; it contained about 8% isopentane and was free of unsaturates. A sample in a 4-dm. tube showed no optical activity.

Action of Sodium Ethyl on (–)2-Bromoöctane.—Sodium ethyl was prepared by the action of 14.3 g. of sodium on 76.7 g. of mercury diethyl according to the method of Whitmore and Zook.[5a] The reaction was carried out in a two-liter, three-necked flask fitted with thermometer, dropping funnel, reflux condenser, and a mercury-sealed stirrer. Gases were led out via the condenser, passed through an acetone–dry-ice cold trap, and collected over saturated sodium chloride solution. The air in the apparatus was replaced by purified nitrogen.

The rapidly stirred mixture of sodium ethyl, sodium amalgam, and mercury diethyl in 200 cc. of pentane was cooled to –10° by means of an alcohol–dry-ice-bath, and over a period of about two hours 82.9 g. (0.43 mole) of (–)2-bromoöctane was added. During this period and for a short time thereafter, it was necessary to maintain the temperature of the bath at about –18° in order to hold the temperature of the material in the reaction flask at –12 to –8°. After an additional ninety minutes it was apparent that no more heat was being evolved at –10°, and the temperature was slowly raised to 0°. Since the temperature of the reaction mixture showed no tendency to rise above that of the bath, the mixture was gradually brought to room temperature, and stirring continued overnight. Less than half a liter of gas was evolved.

To the reaction mixture was cautiously added 300 cc. of water, and after an hour of stirring the two layers were separated. The aqueous layer was filtered to remove the partially decomposed amalgam and diluted to one liter. Five-ml. aliquot portions were analyzed for bromide by the Volhard method; two samples required, respectively, 19.00 and 19.10 ml. of 0.100 *N* silver nitrate, the average corresponding to 0.380 mole of bromide in the aqueous layer. To 5-ml. aliquots of the aqueous material were added 10-ml. portions of 0.104 *N* hydrochloric acid, and these solutions were back-titrated with 0.2922 *N* sodium hydroxide. Two samples required, respectively, 1.28 and 1.30 ml. of the alkali, corresponding to 3.04 g. of sodium in the aqueous layer. The partially decomposed amalgam was hydrolyzed by addition of 50 ml. of 1.055 *N* sulfuric acid and the solution diluted to 500 ml. Two 25-ml. aliquot portions required, respectively, 4.13 and 4.07 ml. of 0.2922 *N* alkali, indicating 0.66 g. of undecomposed sodium in the amalgam. The yield of sodium ethyl, based on 3.7 g. of unreacted sodium, was 24 g. (78%).

The organic layer was dried over magnesium sulfate and most of the pentane removed through a Vigreux column at 36°. At this point the material had a volume of 100 cc., and an observed rotation α^{20}_D –1.09° (2-dm. tube). One-fourth of the material was removed and a number of experiments were performed to determine suitable conditions for the separation and purification of the products. The remaining three-fourths was then treated as follows.

Ether was added and the solution saturated with hydrogen chloride gas at 0°, preliminary experiments having shown this method of decomposing mercury diethyl to be essentially quantitative. The precipitate of ethyl mercuric chloride was filtered off, most of the ether removed from the filtrate through a Vigreux column, and cold pentane was added; an additional precipitate of ethylmercuric chloride was removed. The total recovered ethylmercuric chloride (from both portions of the material) was 20 g.

After the bulk of the pentane had been removed, the solution was fractionated through a seven-plate column and 12.2 g. of material boiling between 115 and 125° was obtained. This was analyzed for unsaturation by the method of Uhrig and Levin.[19] Samples weighing 0.173 and 0.188 g. required, respectively, 5.25 and 5.50 ml. of a 0.130 *N* solution of bromine in acetic acid. From these data it may be concluded that this fraction consisted of 5.4 g. of octene and 6.8 g. of octane.

Between the temperatures 125 and 150° only an insignificant amount of material was collected. At this point the fractionation was discontinued and the residual liquid in the boiler was taken up in dilute ethyl alcohol. To the solution was added 18 g. of silver nitrate and the mixture was refluxed for one-half hour. The precipitated silver bromide was then removed by filtration, the filtrate poured into 300 cc. of water, and extracted several times with pentane. About 250 cc. of pentane was used in all. The pentane solution was washed twenty times with cold concentrated sulfuric acid, five times with a saturated solution of magnesium sulfate, and dried over magnesium sulfate and potassium carbonate. Most of the pentane was removed through a Vigreux column. At this point the concentrated solution gave a negative Beilstein test, and a small portion remained clear on boiling with alcoholic silver nitrate solution. In order to show positively that this method removed all the alkyl bromide, a test mixture of *dl*-3-methylnonane containing 7% (–)2-bromoöctane was subjected to identical treatment; the product was without activity in a 1-dm. semi-micro tube.

All of the pentane was removed and fractionation continued through the seven-plate column. Fractions: 1–2, b. p. 50–159°, 0.9 g.; 3–4, b. p. 161–164°, 1.2 g.; 5, b. p. 164.5–165°, 9.2 g. (755 mm.). Redistillation of the last fraction using an accurately calibrated thermometer gave the true boiling point 166.8–167.1° (769 mm.); d^{20}_4 0.7355; d^{25}_4 0.7347.

Rotation. (l = 2, homogeneous). α^{20}_{6563} –0.30°; $[\alpha]^{20}_{6563}$ –0.20°. α^{20}_{5893} –0.37°; $[\alpha]^{20}_{5893}$ –0.25°. α^{20}_{5463} –0.47°; $[\alpha]^{20}_{5468}$ –0.32°. α^{25}_D –0.34°; $[\alpha]^{25}_D$ –0.23°; $[M]^{25}_D$ –0.34°.

Anal. Calcd. for $C_{10}H_{22}$: C, 84.41; H, 15.59. Found: C, 84.38; H, 15.59; Br, less than 0.1.[20]

The high-boiling residue from the fractionation was taken up in ether, decolorized, and the ether removed. The liquid showed no rotation in a 1-dm. semi-micro tube. It was distilled at atmospheric pressure: 1 g., b. p. 275°, was obtained. The distillate was optically inactive (1-dm. semi-micro tube). A semi-micro cryoscopic determination

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[18] Gilman and Brown, THIS JOURNAL, **52**, 3314 (1930).

[19] Uhrig and Levin, *Ind. Eng. Chem., Anal. Ed.*, **13**, 90 (1941).

[20] Test performed by Dr. D. F. Hayman, Analyst, Merck and Co., Inc., Rahway, N. J.

of the molecular weight gave a value of 234; calcd. for $C_{16}H_{34}$, 226.

Anal. Calcd. for $C_{16}H_{34}$: C, 84.86; H, 15.14. Found: C, 85.36; H, 14.85.

Action of 10% Sodium Amalgam on Active 2-Bromooctane.—Five grams of (+)2-bromoöctane, $[\alpha]^{20}D$ +32.4°, in 25 cc. of pentane was stirred overnight with 3 g. of a 10% sodium amalgam. The pentane was removed and the bromide (5 g.) distilled at 83° (21 mm.), $[\alpha]^{20}D$ +32.4°. There was no high-boiling residue.

Action of Sodium Ethyl on (−)3-Methylnonane.—Sodium ethyl was prepared in the usual manner from 1.1 g. of sodium and 6.1 g. of mercury diethyl in about 40 cc. of pentane. Four cc. of (−)3-methylnonane, $[\alpha]^{20}D$ −0.25° was added, and the mixture stirred overnight at room temperature. The sodium alkyl was destroyed by addition of water, and the amalgam hydrolyzed with dilute sulfuric acid to recover 3.7 g. of mercury, corresponding to a 77% yield of sodium ethyl. The organic layer was dried and the mercury diethyl decomposed as before. The solvent was removed and the residual liquid was heated for one-half hour at 70° under a pressure of 100 mm. It then had a specific rotation $[\alpha]^{25}D$ −0.23° ($\alpha^{25}D$ −0.34°; $l = 2$; homogeneous).

The authors wish to thank Merck and Company, Inc., Rahway, New Jersey, for the analyses reported in this paper.

Summary

The action of sodium ethyl on (−)2-bromooctane, $[\alpha]^{20}D$ −30.7°, in pentane solution leads to the production of octylene, octane, 3-methylnonane, and 7,8-dimethyltetradecane in the approximate molar ratio 9:12:16:1, respectively. The 3-methylnonane (obtained in 25% yield) was optically active, $[M]^{25}D$ −0.34°; although racemization to the extent of 97% occurred during its formation. The 7,8-dimethyltetradecane was optically inactive.

These results are discussed in conjunction with the previous observation[2] that the action of sodium on (+)2-bromobutane leads to optically inactive 3,4-dimethylhexane. It is concluded that the production of an optically inactive di-*s*-alkyl hydrocarbon might in each instance have resulted from the action of a sodium *s*-alkyl on the optically active halide provided the *d* and *l* forms of the carbanion arising from the sodium alkyl were easily interconvertible and reacted at markedly different rates with the *s*-halide, such that only the production of *meso* hydrocarbon occurred.

An alternative mechanism involving free *s*-alkyl radicals as critical reaction intermediates is presented.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. VIII. Homologs of 2-Sulfanilamidothiazoline

BY ALAN H. NATHAN, JAMES H. HUNTER AND H. G. KOLLOFF

Preliminary studies on the chemotherapeutic activity and toxicity of 2-sulfanilamidothiazoline ("sulfathiazoline"), a recently prepared[1] analog of sulfathiazole, have indicated it to be equal to sulfathiazole in activity and at least as free from toxicity.[2] Considering the efficacy and relatively low toxicity reported for the 4-methyl derivative of sulfathiazole,[3] it was of interest to undertake a study of the corresponding sulfathiazoline derivative as well as its isomeric 5-methyl compound. On the basis of preliminary tests in experimental streptococcal and pneumococcal infections in white mice, these two derivatives possess a high order of activity and low toxicity; however, sufficient data have not yet been accumulated to evaluate accurately the place of these new derivatives in relation to sulfathiazole, sulfamethylthiazole and sulfathiazoline.

The requisite aminothiazolines, 2-amino-4-methylthiazoline and 2-amino-5-methylthiazoline, were prepared from 1-bromo-2-aminopropane hydrobromide and 1-amino-2-bromopropane hydrobromide, respectively, by treatment with potassium thiocyanate according to the methods given in the literature.[4,5]

Condensation of acetylsulfanilyl chloride with the aminomethylthiazolines in pyridine–acetone solution resulted in derivatives containing two acetylsulfanilyl groups per molecule of amino-

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[1] (a) Jensen and Thorsteinsson, *Dansk. Tids. Farm.*, **15**, 41 (1941); *Chem. Abs.*, **35**, 5109 (1941); (b) Sprague and Kissinger, THIS JOURNAL, **63**, 578 (1941); (c) Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941); (d) Raiziss and Clemence, *ibid.*, **63**, 3124 (1941); (e) Kolloff and Hunter, unpublished results.

[2] Kolmer, *J. Lab. Clin. Med.*, **27**, 1043 (1942).

[3] Herrel and Brown, *Proc. Staff Meet. Mayo Clin.*, **14**, 753 (1939); Long, *J. Am. Med. Assoc.*, **114**, 870 (1940); Ruegsegger and Hamburger, *Ohio State Med. J.*, **37**, 25 (1941); Ivanovics, *J. Path. Bact.*, **51**, 91 (1940).

[4] Gabriel and Ohle, *Ber.*, **50**, 813 (1917)

[5] Hirsch, *ibid.*, **23**, 965 (1890).