Co-Reduction with Alkali Metals. II. Conjugated Dienes and Carbonyl Compounds

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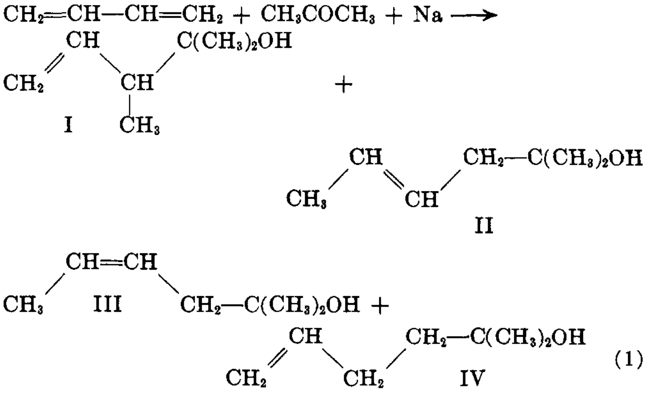
1,3-Butadiene and isoprene react with ketones, esters, and aldehydes in the presence of sodium in ethereal solvents. Butadiene and acetone yield a mixture of 1:1 adducts which are identified as 2,3-dimethylpenten-4-ol-2 (I), *cis*- and *trans*-2-methylhexen-4-ol-2 (II and III), and 2-methylhexen-5-ol-2 (IV). In addition, small amounts of 2:1 adducts incorporating two acetone and one butadiene units and 1:2 adducts are formed. The anionic polymerization is not a significant side reaction. The same mixture of adducts is obtained in diethyl ether and tetrahydrofuran. The absence of dimeric butadiene adducts in tetrahydrofuran contrasts with the condensations using styrene. The difference is examined in terms of the effect of solvent on the formation of dimer dianion from the radical-anion of butadiene and styrene. The nucleophilic properties of the radical-anion of butadiene is discussed by employing a simple theoretical model. The condensation of isoprene with acetone produces in good yield a mixture of octenols by 1,2-, 1,4-, and 4,1-addition to isoprene. A mixture of heptenones and octenones are obtained from the co-reduction of methyl propionate with butadiene and isoprene, respectively. Acetaldehyde and acrolein react sluggishly with butadiene and sodium. Simple alkenes are not co-reduced with acetone by sodium.

In the previous paper[1] the co-reduction of styrene and acetone with sodium to form hydroxylic 1:1, 2:1, 1:2, and 2:2 adducts of acetone and styrene was discussed. These adducts were characterized as phenyl methylbutanols, dimethylphenylhexanediol, diphenylheptanol, and diphenyldecanediols. The reductive condensation to form monomeric or dimeric styrene products was markedly influenced by solvent. The reaction was interpreted to proceed *via* styrene radical-anion and dimer dianion intermediates. In this report we have extended the study of co-reductions with sodium to other conjugated dienes such as butadiene and isoprene with aldehydes or esters as the carbonyl components.

Results

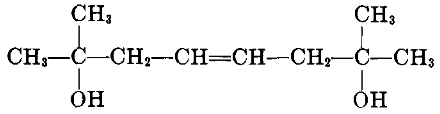
Butadiene and acetone react readily with sodium in tetrahydrofuran at −5° to 0° to produce a mixture of 1:1 acetone–butadiene adducts in 64% yield, in addition to a 2:1 adduct of two acetone and one butadiene units in 16% yield and a 1:2 adduct in 3% yield. Less than 3% undistillable polymeric material was formed. The mixture of 1:1 adducts was examined by distillation, gas–liquid chromatography and ozonolysis. Four component heptenols were identified and characterized: 2,3-dimethylpenten-4-ol-2 (I) (45%), *trans*-2-methylhexen-4-ol-2 (II) (24%), *cis*-2-methylhexen-4-ol-2 (III) (18%), and 2-methylhexen-5-ol-2 (IV) (13%). These heptenols were compared with authentic samples.



(1)

2,3-Dimethylpenten-4-ol-2 (I) was obtained by the procedure of Roberts and Young[3] which employs "crotyl" magnesium bromide and acetone. In addition to ozonolysis to formaldehyde,[3] we also identified the keto alcohol as the 2,4-dinitrophenylhydrazone of 2,3-dimethylcrotonaldehyde, a product of acid-catalyzed dehydration. The mixture of *cis*- and *trans*-2-methylhexen-4-ol-2 (II and III) was synthesized from 1-lithiopropene-1 and isobutylene oxide. It was hydrogenated to 2-methylhexanol-2 and ozonized to a mixture of acetaldehyde and a keto alcohol which was identified as the 2,4-dinitrophenylhydrazone of senecialdehyde, a product of facile dehydration catalyzed by acid. 2-Methylhexen-5-ol-2 (IV) was synthesized from allylacetone and methylmagnesium bromide. It was hydrogenated to 2-methylhexanol-2 and ozonized to yield formaldehyde.

The 2:1 adduct comprised of two acetone and one butadiene units was obtained as a crystalline solid. On the basis of its infrared spectrum (10.25 and 112 μ), its structure was assigned as the 1,4-adduct, 2,7-dimethyloctene-4-diol-2,7 (V).



$$CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_2-CH=CH-CH_2-\underset{OH}{\overset{CH_3}{C}}-CH_3$$

V

The same mixture of 1:1 and 2:1 acetone–butadiene adducts was formed in the *same* relative yields in diethyl ether solvent, but less polymeric material was found. This contrasts strongly with the co-reduction of styrene and acetone with sodium, in which the product composition was markedly influenced by solvent. In either solvent the amounts of butadiene polymers formed were much smaller than the polystyrene residues obtained in tetrahydrofuran.

Reaction of Isoprene and Acetone with Sodium.—Isoprene underwent a reaction with acetone in the presence of sodium in a manner analogous to butadiene: There was formed in 81% yield a mixture of 1:1 adducts which were distillable into two fractions (b.p. 70–73° (40 mm.) and b.p. 78–81° (40 mm.)). Each fraction and intermediate fractions all had the same elemental, hydroxyl, and bromine number analyses. In addition they all formed phenyl carbamate derivatives which

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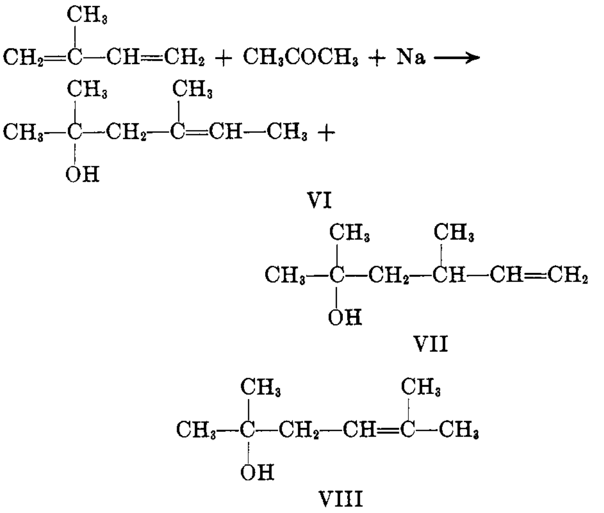
(1) Part I, J. K. Kochi, *J. Org. Chem.*, **28**, 1960 (1963).

(2) Department of Chemistry, Case Institute of Technology, Cleveland 6, Ohio.

(3) J. D. Roberts and W. G. Young, *J. Am. Chem. Soc.*, **67**, 148 (1944).

were not obtained pure (by melting point), but whose analyses corresponded to the isomeric octenols. The lower boiling fraction (70–73°) appeared homogeneous on g.l.c. while the higher boiling fraction (78–81°) showed two distinct components. Neither was pure since ozonolysis of the various distillation cuts produced acetone, acetaldehyde, and formaldehyde, in varying proportions.

These results indicated that in addition to 1,4 (VI) and 1,2 (VII) addition, 4,1 (VIII) addition was a significant route.

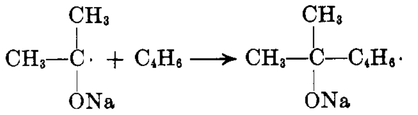


$$CH_2{=}\overset{CH_3}{C}{-}CH{=}CH_2 + CH_3COCH_3 + Na \longrightarrow \underset{\text{VI}}{CH_3{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}\overset{CH_3}{C}{=}CH{-}CH_3} + \underset{\text{VII}}{CH_3{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}\overset{CH_3}{CH}{-}CH{=}CH_2} \quad (2)$$

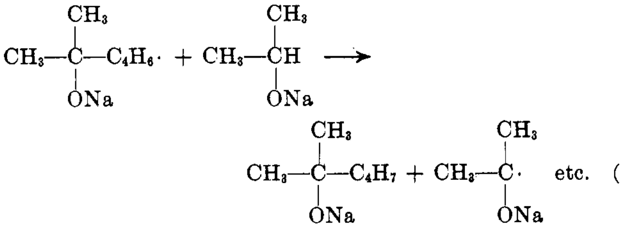
$$\underset{\text{VIII}}{CH_3{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}CH{=}\overset{CH_3}{C}{-}CH_3}$$

In addition to the 1:1 adducts of acetone and isoprene there was formed a mixture of 2:1 adducts (10%), 1:2 adducts (3%), and polyisoprene telomers, none of which were resolved. The formation of polymeric residues was a more important process with isoprene than it was with butadiene.

The addition of isopropyl alcohol served to lower the yield of reduction adducts presumably by reacting directly with sodium. Sodium isopropoxide did not enhance the yields of adducts and thus obviated the possibility of a radical chain reaction.

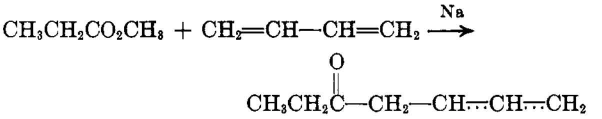


$$CH_3{-}\overset{CH_3}{\underset{ONa}{C}}\cdot + C_4H_6 \longrightarrow CH_3{-}\overset{CH_3}{\underset{ONa}{C}}{-}C_4H_6\cdot \quad (3)$$



$$CH_3{-}\overset{CH_3}{\underset{ONa}{C}}{-}C_4H_6\cdot + CH_3{-}\overset{CH_3}{\underset{ONa}{CH}} \longrightarrow CH_3{-}\overset{CH_3}{\underset{ONa}{C}}{-}C_4H_7 + CH_3{-}\overset{CH_3}{\underset{ONa}{C}}\cdot \quad \text{etc.} \quad (4)$$

Reactions of Esters and Dienes with Sodium.—Methyl propionate reacted readily with sodium in tetrahydrofuran solvent to produce propionoin in 40% yield. Both methyl propionate and ethyl acetate reacted with sodium in the presence of butadiene and isoprene at a reduced rate compared to acetone. Methyl propionate and butadiene reacted with sodium in tetrahydrofuran to produce a mixture of heptenones (27%), which was not separated, in addition to higher boiling unidentified products.



$$CH_3CH_2CO_2CH_3 + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{Na} CH_3CH_2\overset{O}{\overset{\|}{C}}{-}CH_2{-}CH{\overset{\cdot\cdot}{=}}CH{\overset{\cdot\cdot}{=}}CH_2 \quad (5)$$

Methyl propionate and isoprene reacted with sodium in tetrahydrofuran to form a mixture of unsaturated ketones similar to those formed from butadiene in approximately 20% yield. The reaction of methyl propionate and styrene with sodium in diethyl ether was slow compared to the reaction with acetone. Neither condensation products nor polymeric styrene were obtained, and reduction of the reactants to simple monomeric products was the only reaction observed. Although these reactions of esters and dienes with sodium in tetrahydrofuran were carried out at 15–25°, the polymerizations of butadiene or isoprene were not significant side reactions.

Benzalacetone and butadiene reacted with sodium in tetrahydrofuran very slowly to form a viscous amorphous products(s) which was not characterized. After approximately 10% of the reaction was completed, acrolein underwent an undesirable base-catalyzed polymerization to a product similar to disacryl. Mesityl oxide reacted readily with sodium in the presence of butadiene in tetrahydrofuran to form in reasonable yield a product of dimeric reduction of mesityl oxide. Acetaldehyde reacted easily with sodium in the presence of butadiene but after the reaction was approximately 10% complete, the surface of the sodium appeared deactivated. If the reaction was run in the presence of acetic acid, the sodium was consumed readily, largely by its reaction with acetic acid. There was formed in low yields mixtures of alcoholic products which were 1:1 and 1:2 adducts of acetaldehyde and butadiene. If acetic anhydride was used to replace the acetic acid, the yields of adducts were slightly better. There was formed in low yields a mixture of acetates which were not identified.

Reaction of Acetone and Alkenes with Sodium.—When the reduction of acetone with sodium was carried out in the presence of either hexene-1 or 2-methylpentene-1 in tetrahydrofuran, the primary reduction product was isopropyl alcohol. In addition there was formed a variety of base-catalyzed condensation products of acetone which included mesityl oxide, isophorone, and an unidentified crystalline ketone (the same as that obtained from acetone and styrene). There was no indication that either hexene-1 or 2-methylpentene-1 reacted with acetone.

Discussion

The reactions of conjugated dienes such as butadiene and isoprene with acetone and sodium are distinguished from the related condensations which involve styrene in that the ether solvents have a leveling effect with the former olefins. Thus, reactions in diethyl ether and tetrahydrofuran solvents are indistinguishable in coreductions involving butadiene, whereas diethyl ether favors monomeric styrene condensation products and tetrahydrofuran is conducive to the formation of dimeric styrene products.[1] We attribute this difference to the dimer dianion equilibrium involving the radical-anion from each olefin. With styrene radical-anion IX, the equilibrium equation 7 is presumed to be more facile and sensitive to solvent (*vide infra*) than it is with butadiene radical-anion XI (equation 7).

$$\underset{\text{IX}}{\mathrm{2NaPhCH{\doteq}CH_2}} \rightleftharpoons \underset{\text{X}}{\mathrm{[Ph\ddot{C}H{-}CH_2CH_2{-}\ddot{C}HPh]Na_2}} \quad (6)$$

$$\underset{\text{XI}}{\mathrm{2NaCH_2{=}CH{-}CH{\doteq}CH_2}} \rightleftharpoons \underset{\text{XII}}{\mathrm{[\ddot{C}H_2{-}CH{=}CH{-}CH_2CH_2CH{=}CH{-}\ddot{C}H_2]Na_2}} \quad (7)$$

It is difficult to assess quantitatively the magnitude of free energy changes involved in each of the dimerization equilibria 6 and 7. If these changes are reflected mainly in the energy of the anions (*i.e.*, neglecting the sodium counterions, solvation effects, coulombic repulsions, entropy changes, etc.), it is possible to make some attempts to calculate by the use of the simple Hückel molecular orbital method[4] the differences involved in the dimerization reactions 6 and 7. The lowest unoccupied molecular orbital in butadiene is 1.24 β higher in energy than that of the highest filled orbital, and it is 1.32 β higher in styrene. This indicates that the "electron affinity" of butadiene is 0.08 β greater than styrene. Benzyl and allyl carbanions can be used as models for the dimer dianions of styrene X and butadiene XII. The calculated difference in energy between benzyl carbanion and toluene is $2\alpha + 0.72\beta$, while that between allyl carbanion and propylene is $2\alpha + 0.83\beta$. The difference, 0.09 β, measures the amount by which allyl carbanion is more stable than its conjugate acid *relative* to benzyl carbanion and its conjugate acid.[5] The amount that butadiene radical-anion is more stable than styrene radical-anion is vitiated by almost the same amount as the allyl carbanion is stable relative to benzyl carbanion. Therefore, the driving force for dimer dianion formation from the radical-anion on the basis of these crude calculations appears to be the same for butadiene and styrene. If the differences in driving force are real, then it must be attributed to factors other than simple energy considerations, such as solvation, coulombic repulsion, etc.[7]

The alternate route for the formation of dimeric styrene products is *via* the dimer anion-radical intermediate XIII formed from the addition of styrene radical-anion to styrene.[1]

$$\mathrm{NaPhCH{\doteq}CH_2 + PhCH{=}CH_2} \longrightarrow \underset{\text{XIII}}{\mathrm{[Ph\ddot{C}H{-}CH_2CH_2{-}\dot{C}HPh]Na}} \quad (8)$$

This was followed by electron transfer.

$$\text{XIII} + \mathrm{Na} \longrightarrow \underset{\text{X}}{\mathrm{[Ph\ddot{C}H{-}CH_2CH_2{-}\ddot{C}H{-}Ph]Na_2}} \quad (9)$$

If such were the case there is no *a priori* reason for a similar process not to be obtained with butadiene radical-anion, since the latter also readily undergoes anionic polymerization[8] (10 and 11).

$$\mathrm{NaCH_2{=}CH{-}CH{\doteq}CH_2 + C_4H_6} \longrightarrow \underset{\text{XIV}}{\mathrm{[\dot{C}H_2{-}CH{=}CH{-}CH_2CH_2{-}CH{=}CH{-}\ddot{C}H_2]Na}} \quad (10)$$

$$\text{XIV} + \mathrm{Na} \longrightarrow \underset{\text{XII}}{\mathrm{[\ddot{C}H_2{-}CH{=}CH{-}CH_2CH_2{-}CH{=}CH{-}\ddot{C}H_2]Na_2}} \quad (11)$$

The ineffectiveness of a change in solvent from diethyl ether to tetrahydrofuran to effect the formation of significant quantities of dimeric butadiene adducts of acetone militates against such a mechanism.

Frank and Foster[9a] have shown that such dimeric butadiene products can be formed under special conditions in a manner not dissimilar to the formation of dimeric styrene adducts. There are certain indications that the dimer dianions X or XII are not readily dissociated.[9,10] And it is not necessary to postulate reactions 6 and 7 as reversible (*vide supra*), *provided* solvents affect the *rates* of the dimerizations.[11] The critical role played by solvent in the formation of octadiene dianion XII from butadiene and diphenyl butane dianion X from styrene has been demonstrated.[9]

The composition of the mixture of 1:1 adducts of acetone and butadiene which are the only significant products from sodium, shows interesting distribution of isomers. The intermediate which directly leads to reaction with acetone is the butadiene radical-anion. The calculated spin densities at positions 1 and 2 of this species are shown in Fig. 1. These densities correspond to the nucleophilic center being mainly on the terminal positions which react with acetone by addition to form the alkoxide-radical XV in preference to the alkoxide-radical XVI, formed by reaction at the internal positions.

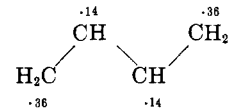
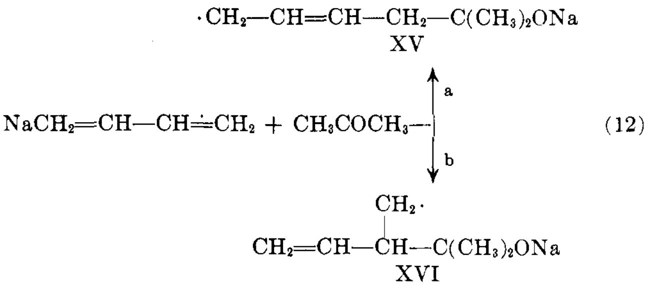


Fig. 1.—Spin densities in the butadiene radical-anion.



$$\mathrm{NaCH_2{=}CH{-}CH{\doteq}CH_2 + CH_3COCH_3} \begin{cases} \xrightarrow{a} \underset{\text{XV}}{\mathrm{\cdot CH_2{-}CH{=}CH{-}CH_2{-}C(CH_3)_2ONa}} \\ \xrightarrow{b} \underset{\text{XVI}}{\mathrm{CH_2{=}CH{-}\overset{\displaystyle CH_2\cdot}{\overset{|}{C}H}{-}C(CH_3)_2ONa}} \end{cases} \quad (12)$$

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[4] A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961.

[5] If a value of 50 kcal./mole is used for β, this difference amounts to 4.5 kcal. Experimentally, these values should be reflected in pK_a values, but these are not readily available. However, since both benzyl and allyl radicals are odd alternant hydrocarbons, the addition or subtraction of an electron to the 0th molecular orbital involves no change in the relative differences in energy. Therefore, the difference in energies of the benzyl and allyl moieties as carbanions, free radicals, or carbonium ions are the same. The readily accessible bond dissociation energies[6] are in agreement with these calculated values. For example, the bond dissociation energies of $\mathrm{PhCH_2{-}CH_3}$ and $\mathrm{CH_2{=}CHCH_2{-}CH_3}$ are 63 ± 1.5 and 61.5 kcal./mole, respectively (difference = ~2 kcal./mole), and $\mathrm{PhCH_2{-}I}$ and $\mathrm{CH_2{=}CHCH_2{-}I}$ are ~39 and 36 ± 1 kcal./mole, respectively (difference = ~3 kcal./mole).

[6] T. L. Cottrell, "The Strengths of Chemical Bonds," Butterworths Scientific Publications, London, 1954, pp. 201, 213.

[7] (a) N. D. Scott, J. F. Walker, and V. L. Hansley, *J. Am. Chem. Soc.*, **58**, 2442 (1936); (b) D. E. Paul, D. Lipkin, and S. I. Weissman, *ibid.*, **78**, 116 (1956); (c) J. L. Down, *et al.*, *Proc. Chem. Soc.*, 209 (1957); (d) M. Szwarc, *Makromol. Chem.*, **35**, 133 (1960).

[8] (a) K. Ziegler, *Angew. Chem.*, **49**, 499 (1936); *Ann.*, **567**, 72 (1950), (b) F. W. Stavely, *et al.*, *Ind. Eng. Chem.*, **48**, 778 (1956); (c) M. Sittig, "Sodium," Reinhold Publishing Corp., New York, N. Y., 1956, p. 313 ff.

[9] (a) C. E. Frank and W. E. Foster, *J. Org. Chem.*, **26**, 303 (1961); (b) C. E. Frank, J. R. Lecbrick, L. F. Moormeir, J. A. Scheben, and O. Homberg, *ibid.*, **26**, 307 (1961).

[10] M. Szwarc and R. Asami, *J. Am. Chem. Soc.*, **84**, 2269 (1962).

[11] This statement is also applicable to our earlier discussion[1] of the formation of styrene dimer dianion.

Formation of terminal adducts II, III, and IV in larger yield (55%) than the sole secondary product I is consistent with this formulation. On the other hand, if acetone ketyl were the intermediate which added to butadiene, only terminally substituted products from the alkoxide-radical intermediate XV are expected.

The reduction by electron transfer of alkoxide-radical XV yields an alkoxide-anion XVII which can suffer protonation at three positions to yield the isomeric heptenols II, III, and IV, or addition to acetone to form decenediol V.

$$CH_2\underset{\cdot}{-}CH{=}CH{-}CH_2{-}C(CH_3)_2ONa + Na \longrightarrow \underset{\text{XVII}}{[:CH_2{-}CH{=}CH{-}CH_2{-}C(CH_3)_2O:]Na_2} \quad (13)$$

$$\text{XVII} + CH_3COCH_3 \begin{cases} \xrightarrow{a} \text{II} \\ \xrightarrow{b} \text{III} + CH_3COCH_2Na \\ \xrightarrow{c} \text{IV} \end{cases} \quad (14),$$

$$\text{XVII} + CH_3COCH_3 \longrightarrow \text{V} \quad (15)$$

The position of protonation of the allylic carbanion XVII is not easy to predict. The simple butenyl Grignard reagent reacts with acetone and other carbonyl electrophiles[3] and ethylene oxide[12] exclusively at the secondary position. The position it is neutralized to yield butene is dependent on the acid, and is not specific to the 3-position, although butene-1 is usually the predominant product.[13] However, the cinnamyl carbanionic moiety reacts with electrophiles at either the primary or secondary position depending on the electrophile and the metal gegenion.[14,15]

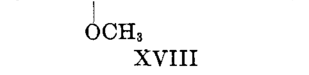
The alkoxide-anion XVII exists in two geometric forms. The formation of approximately equal amounts of *cis*- and *trans*-2-methylhexen-4-ol-2 reflects their relative populations. Statistically, it is expected that protonation at the internal position of XVII to form 2-methylhexen-5-ol-2 (IV) would be favored by a factor of two over either *cis*- or *trans*-2-methylhexen-4-ol-2 (II or III). However, the negative charge on the alkoxide oxygen may repel the negative charge to the terminal position of the allylic system and favor the formation of II or III. The low yield of IV relative to II and III is in accord with such a formulation.

An alternative path involving protonation first of the butadiene radical-anion followed by reduction and condensation with acetone is a possibility which cannot be discounted. The formation of a butadiene dianion, which results from two electron transfers, as an intermediate is disfavored on energetic grounds. The dianion of such a simple structure[7b] would not be expected to produce the heptenols observed in such yields.

The chemistry of isoprene is related to that of butadiene and its reaction with acetone and sodium resembles that of the latter. Whereas free radical additions to isoprene occur predominantly at the 1-position,[16] such adducts are not the sole products of co-reduction. Significant amounts of additions at the 4-position occur, and it is further evidence that the co-reduction reactions are not proceeding *via* an addition of the acetone ketyl intermediate. Although anionic polymerization is quite a facile process with isoprene, little dimeric isoprene condensation products were observed in the reaction with acetone and sodium.

The reaction of esters with conjugated dienes to produce unsaturated ketones is analogous to reactions with acetone. It probably involves the addition of the radical-ion to the ester to form a hemiketal intermediate XVIII which suffers electron transfer, protonation, and hydrolysis.

$$CH_2{=}CH{-}CH{\dot{=}}CH_2 + CH_3CH_2CO_2CH_3 \longrightarrow$$

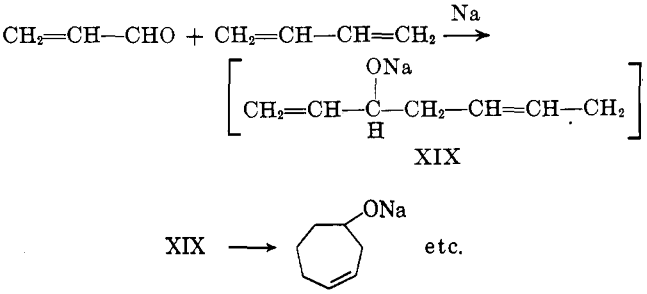


$$CH_3CH_2{-}\overset{\overset{\textstyle O:}{|}}{\underset{\underset{\textstyle OCH_3}{|}}{C}}{-}CH_2{-}CH{=}CH\underset{\cdot}{-}CH_2 \quad (16)$$

XVIII

The unreactivity of styrene radical-anion in this reaction is probably due to the slowness of the addition step such as 12. In this respect the anion-radicals of styrene and butadiene show lower nucleophilic reactivity than conventional organo-sodium derivatives.

The possibility of carrying out co-reductive cyclizations with α,β-conjugated carbonyl compounds and butadiene was investigated.



However, we found no indications that such reactions were successful.

Experimental

Materials.—1,3-Butadiene: Matheson Co., C.P. grade, bulb distilled *in vacuo* after drying over calcium chloride. Isoprene: Phillips Petroleum Co., polymerization grade, redistilled. 2-Methylbutene-1 and hexene-1: Phillips Petroleum Co., pure grade. Methyl propionate, benzalacetone: Eastman Kodak, White Label. Mesityl oxide, acrolein: Shell Chemical Co. 1-Bromopropene-1: Matheson Coleman and Bell. Material was carefully redistilled through a 40-plate Oldershaw column. Other materials were the same as those used in the previous report.[1]

Synthesis of 2,3-Dimethylpenten-4-ol-2 (I).—Butadiene (427 g.) was added to 500 ml. of benzene and chilled to 0°. Anhydrous hydrogen bromide was bubbled through the solution at 0° for 2 hr. The solution was washed with aqueous sodium bicarbonate and dried over calcium chloride. Distillation yielded 350 g. of butenyl bromide boiling at 97–104°. The butenyl bromide (300 g.) in 3 l. of diethyl ether was added slowly over 11 hr. to 160 g. of magnesium in a liter of ether. Acetone (130 g.) in 300 ml. of ether was added over an hour and the reaction worked up under near neutral conditions (ammonium sulfate). It yielded 240 g. of 2,3-dimethylpentene-4-ol-2 boiling at 133–135°; n^{25}D 1.4323–1.4332. It was contaminated with a ketonic impurity which was

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[12] L. S. Wu, R. A. Finnegon, and K. W. Greenlee, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 7Q,

[13] (a) W. G. Young, S. Winstein, and A. N. Prater, *J. Am. Chem. Soc.*, **58**, 289 (1936); (b) W. G. Young and M. Eisner, *ibid.*, **63**, 2113 (1941); (c) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Co., New York, N. Y., 1954, pp. 1145 ff.

[14] J. E. Leffler, "The Reactive Intermediates in Organic Chemistry," Interscience Publishers, Inc., New York, 1956, pp. 215–216.

[15] We are examining the effect of structure on the reactions of allylic carbanions.

[16] (a) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 3946 (1962); (b) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, *ibid.*, **84**, 3897 (1962).

readily removed by treatment with Girard P reagent (n^{25}D 1.4331).

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.4; bromine no., 130. Found: C, 73.67; H, 12.36; bromine no., 145.

Hydrogenation over Adam's catalyst in ethyl acetate yielded 2,3-dimethylpentanol-2.[17] Examination by g.l.c. showed the presence of only one component (emergence time: 10-ft. Ucon Polar/firebrick at 114°, 25.7 min.; 10-ft. DEGS/firebrick at 90°, 33 min.).

Synthesis of 2-Methylhexen-4-ol-2 (*cis* and *trans* Mixture) (II and III).—1-Bromopropene-1 (186 g.) was added to a solution of 15.6 g. of lithium in 1 l. of diethyl ether over a period of 4 hr. 1-Lithiopropene-1 then reacted with a solution of 108 g. of isobutylene oxide in 100 ml. of ether. The reaction was worked up under near neutral conditions and yielded 47 g. of 2-methylhexen-4-ol-2 boiling at 142–143°; n^{25}D 1.4365–1.4369.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.4; bromine no., 140. Found: C, 73.2; H, 12.3; bromine no., 142.

It was hydrogenated over platinum to 2-methylhexanol-2.[17] The methylhexenol was examined by g.l.c. and found to consist of two components of approximately equal amounts (emergence times: 29 and 35 min. on 10-ft. Ucon Polar at 114° and 39 and 46 min. on 10-ft. DEGS/firebrick at 90°). The early emerging component was assigned the *trans* structure and the later component the *cis* structure. The infrared spectrum was also consistent with these structures, since strong bands appeared at 965 cm.$^{-1}$ (*trans*) and 980 cm.$^{-1}$ (*cis*).

2-Methylhexen-5-ol-2 (IV) was prepared from allylacetone and methylmagnesium bromide.[17] It was separated by g.l.c. from the isomeric alcohols using a 10-ft. Ucon Polar/firebrick column at 114° (emergence time, 37.3 min.) and less efficiently with a 10-ft. DEGS/firebrick column at 90° (emergence time, 48.7 min.).

Reaction of Butadiene and Acetone with Sodium in Tetrahydrofuran.—Sodium wire (30 g.) and 350 ml. of tetrahydrofuran were cooled to −80° and 5 ml. of acetone and 300 ml. of butadiene were added. Acetone (135 ml.) was added dropwise at 10° to −5° over 1 hr. The reaction was stirred for an additional 10 min. at 0° and then poured onto a mixture of ice and water containing 80 g. of sulfuric acid. It was extracted with ether and the ethereal solution washed with saturated sodium bicarbonate and water. It yielded 55.5 g. of 1:1 adducts (b.p. 122–131°; n^{25}D 1.4313–1.4347), 18 g. of 2:1 adducts, 3.1 g. of 1:2 adducts, and 1.4 g. of nondistillable residue (b.p. >120° (2 mm.); n^{25}D 1.5014).

The same reaction conducted in diethyl ether at −5° to 0° gave essentially the same results. The reaction yielded 47 g. of 1:1 adducts, 10 g. of 2:1 adducts, 1.5 g. of 1:2 adducts, and 1 g. of nondistillable residue.

A similar reaction containing 25 ml. of isopropyl alcohol conducted at 0° in tetrahydrofuran yielded 36.5 g. of 1:1 adducts, 7.1 g. of 2:1 adducts, and 2.3 g. of nondistillable residues (b.p., >150° (2 mm.), n^{25}D 1.4976). These reactions also yielded mesityl oxide and isophorone.

Butadiene–Acetone Adducts. 1:1 Adducts.—The mixture of adducts containing one acetone and one butadiene unit (b.p. 122–131°) was carefully refractionated at 90 mm. with a 3-ft. spinning band column. The distillation pattern is as follows. Fraction, boiling range (°C.), n^{25}D, wt. (g.): 16, 77.0–77.5, 1.4398, 5.8; 17, 77.5, 1.4389, 10.8; 18, 76.8–78.0, 1.4389, 15.0; 19, 78.0–77.8, 1.4368, 15.6; 20, 77.8–80.0, 1.4348, 13.0; 21, 80.0–84.0, 1.4343, 12.0; 22, 84.0–85.0, 1.4349, 17.5; 23, 85.0–85.6, 1.4352, 9.2; 24, 85.8–86.5, 1.4352, 15.7.

The analyses for each fraction are as follows. Fraction, C, H, hydroxyl value (equiv./100 g.), bromine no. (g./100 g.): 17, 73.9, 11.5, —, —; 18, 73.1, 11.7, —, —; 19, 72.9, 11.9 (0.809, 0.827), —; 20, 73.6, 12.2 (0.853, 0.907), —; 21, 73.4, 12.4, —, —; 22, 73.5, 12.3 (0.868, 0.898), 135; 23, 13.3, 12.3, —, —; 24, 73.2, 12.3, —, —; theoretical (calcd. for heptenol, $C_7H_{14}O$), 73.6, 12.37, 0.876, 138.

The phenyl carbamate derivatives were obtained crystalline by the same procedure employed for the octenols obtained from isoprene. Fraction 24 yielded a urethane derivative melting at 60–62° and fraction 19 yielded a derivative melting at 48.5–49.5°.

Anal. Calcd. for phenylurethane of fractions 19, 22, 24 ($C_{14}H_{19}NO_2$): C, 72.0; H, 8.22; N, 6.0. Found (fraction 19): C, 72.2; H, 8.2; N, 5.8. (Fraction 22): C, 72.0; H, 8.1; N, 6.1. (Fraction 24): C, 72.1; H, 8.1; N, 5.8.

The mixtures of 1:1 adducts of acetone and butadiene were examined by g.l.c. Mesityl oxide was poorly separated from 2,3-dimethylpenten-4-ol-2 on a 10-ft. DEGS/firebrick column at 90° but was cleanly separated on a 10-ft. UCON Polar/firebrick column at 114°. The former column poorly separated *cis*-2-methylhexen-4-ol-2 from 2-methylhexen-5-ol-2 while the latter column separated them cleanly. The two columns used in conjunction enabled determination of four isomeric heptenols. The total yields of heptenols also were determined by hydrogenating an aliquot of the reaction mixture with Adam's catalyst. The heptenols, 2,3-dimethylpentanol-2 and 2-methylhexanol-2, were not separated from each other by g.l.c., but were cleanly separated from 4-methylpentanone-2 and they were analyzed by the marker technique.

The relative yields of heptenols were as follows: 2,3-dimethylpenten-4-ol-2, 44.7%; *trans*-2-methylhexen-4-ol-2, 24.4%; *cis*-2-methylhexen-4-ol-2, 17.6%; 2-methylhexen-5-ol-2, 13.4%. Virtually the same ratios of isomeric heptenols were obtained in diethyl ether and tetrahydrofuran solvents.

Thus, fractions 18 and 19 consisted mainly of 2,3-dimethylpenten-4-ol-2. Fractions 23 and 24 were mixtures of *cis*-2-methylhexen-4-ol-2 and 2-methylhexen-5-ol-2. The intermediate fractions consisted of mixtures of all four components. Further evidence was obtained from ozonolysis studies. As expected, no acetone was formed. The two lower carbonyl compounds were acetaldehyde estimated by g.l.c. and formaldehyde estimated by methone formation. The yields of these two components were as follows: fraction, formaldehyde, acetaldehyde: 19, 18%, —; 20, 4.5%, 12.5%; 23, 8.5%, 38%.

The aqueous mother liquor from the ozonation of fraction 19 was clear and homogeneous. It was treated directly with 2,4-dinitrophenylhydrazine reagent which on standing gave a heavy red precipitate. It was recrystallized twice from ethyl acetate–ethanol mixture to yield dense scarlet crystals, m.p. 195–196°. The same DNP was obtained from the urethane of fraction 19. The reported melting point of the DNP from 2,3-dimethylcrotonaldehyde was 198°[18a] and 200–201°.[18b]

The mixture melting point with an authentic sample[18a] made from the selenium dioxide oxidation of 2,3-dimethylbutene-2 was undepressed (m.p. 194–196°).

Anal. Calcd. for 2,3-dimethylcrotonaldehyde DNP ($C_{12}H_{14}N_4O_4$): C, 51.8; H, 5.08; N, 20.1. Found: C, 51.3, 51.0, 51.2[18a]; H, 5.0, 5.0, 5.0[18a]; N, 20.3, 20.1, 20.2.[18a]

The aqueous mother liquor was treated directly with semicarbazide in ethanol. Within 1 hr. a heavy precipitate of semicarbazone was formed. Recrystallization from methanol yielded platelets (m.p. 239–240°, sealed capillary). Literature value for 2,3-dimethylcrotonaldehyde semicarbazone is 234°[18a] and 239–240°.[18b] The mother liquor was acidified with sulfuric acid and stirred with ether for 36 hr. The ether solution on washing with sodium bicarbonate and water and drying with sodium sulfate, yielded a mixture of carbonylic oils (infrared bands at 5.75 μ (shoulder), 5.82, 6.00, and 6.1 μ). It reacted rapidly with semicarbazide to form the same derivative (m.p. 239–240°) obtained from the mother liquor directly.

Anal. Calcd. for 2,3-dimethylcrotonaldehyde semicarbazone ($C_7H_{13}N_3O$): C, 54.1; H, 8.45; N, 27.1. Found: C, 53.9, 54.2; H, 8.4, 8.5; N, 27.6.

Fraction 24 on ozonolysis yielded primarily acetaldehyde, and the homogeneous aqueous mother liquor on treatment with 2,4-DNP reagent yielded red crystals which on recrystallization from ethyl acetate–ethanol yielded a scarlet DNP, melting at 180.0–180.5°. The DNP of senecialdehyde (β-methylcrotonaldehyde) melted at 181.5°,[19] 181–182°, 179°.

Anal. Calcd. for senecialdehyde DNP ($C_{11}H_{12}N_4O_4$): C, 49.9; H, 4.58; N (Dumas), 21.2. Found: C, 49.3, 49.2; H, 4.5, 4.6; N, 21.2, 21.3.

2:1 Adducts.—The 2:1 adduct consisting of two acetone and one butadiene unit distilled at 82–84° (1 mm.) (n^{25}D 1.4634) and melted at 68–69°. Its infrared absorption spectrum showed prominent bands at 10.25 and 11.10. It was probably the 1,4-adduct, 2,7-dimethyloctene-4-diol-2,7.

Anal. Calcd. for dimethyloctenediol ($C_{10}H_{20}O_2$): C, 69.8; H, 11.69; hydroxyl value, 1.16; bromine no., 93. Found: C,

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(17) J. K. Kochi, *J. Am. Chem. Soc.*, **85**, 1958 (1963).

(18)(a) W. Hickinbottom, *J. Chem. Soc.*, 4400 (1954); (b) E. Braude, *ibid.*, 3334 (1955).

(19) W. Hickinbottom, *ibid.*, 1380 (1955); R. Heilman and Glenat, *Bull. soc. chim. France*, 1586 (1955); M. Julia and J. Surzur, *Comp. rend.*, **238**, 2426 (1954).

69.9, 69.8; H, 11.7, 11.7; hydroxyl value, 1.11, 1.11; bromine no., 93.

Reaction of Isoprene and Acetone with Sodium in Tetrahydrofuran.—To a mixture of sodium wire (33 g.) in 400 ml. of tetrahydrofuran at −40° was added 125 ml. of isoprene. Acetone (150 ml.) was then added dropwise at such a rate to maintain the temperature at 3–5° (30 min.). The light yellow homogeneous reaction was allowed to stir at 25° for 30 min. to react all of the sodium. Sulfuric acid (30%) was added dropwise to the mixture with cooling. The mixture was then added to an ice–water slurry and extracted three times with ether. The ethereal solution was washed with saturated sodium bicarbonate and water and dried with sodium sulfate. The ethereal solution on distillation yielded 67 g. of a mixture of dimethylhexenols (b.p. 143–151°; $n^{25}\text{D}$ 1.4746–1.4754), 4 g. of trimethyldecadienols (b.p. 95–125° (2 mm.); $n^{25}\text{D}$ 1.4829) and 10.3 g. of nondistillable residue ($n^{25}\text{D}$ 1.5018–1.5035; b.p. >190° (2 mm.)). In addition, mesityl oxide (10.5 g.) and isophorone (6.7 g.) were formed from the base-catalyzed condensation of acetone.

If the reaction was carried out at 20–25° the amount of 1:1 adduct (55.9 g.) remained approximately constant. There was formed, however, 33.4 g. of a mixture of 2:1 and 1:2 adducts and 22.2 g. of polyisoprene residues.

The addition of sodium isopropoxide did not enhance the formation of addition products. For example, a reaction consisting of 26 g. of sodium in 375 ml. of tetrahydrofuran and 50 ml. of isopropyl alcohol was refluxed for 3 hr. to convert the alcohol to sodium isopropoxide. The reaction mixture was cooled to −30° and 100 ml. of isoprene added, and followed by the dropwise addition of 75 ml. of acetone. The temperature was maintained at −10° (20 min.). The mixture was stirred for an additional 15 min. at 0°. The homogeneous solution was poured into an ice-water slurry containing 60 g. of sulfuric acid and extracted with ether. The mixture yielded 15.4 g. of 1:1 adducts, 1.5 g. of a mixture of 1:2 and 2:1 adducts, and 3.8 g. of polyisoprene residues.

The addition of isopropyl alcohol decreased the amount of 1:2 and 2:1 adducts. A reaction consisting of 30 g. of sodium wire in 350 ml. of tetrahydrofuran was chilled to −40° and 25 ml. of isopropyl alcohol and 200 ml. of isoprene were added. Acetone (130 ml.) was then added dropwise (30 min.) keeping the temperature at −5° to 0°, and the reaction stirred for 30 min. at 0°. The mixture was poured onto an ice–water slurry containing 70 g. of sulfuric acid and extracted with ether. It yielded 36.1 g. of 1:1 adducts, 6.0 g. of a mixture of 2:1 and 1:2 adducts, and 4.7 g. of nondistillable residues.

Isoprene-Acetone Adducts. 1:1 **Adducts.**—The 1:1 adducts of isoprene and acetone consisted of a mixture containing, at most, four possible structural isomers: 2,4-dimethylhexen-4-ol-2, 2,4-dimethylhexen-5-ol-2, 2,5-dimethylhexen-4-ol-2, and 2,5-dimethylhexen-5-ol-2. The distillation pattern is as follows. Fraction, boiling range, $n^{25}\text{D}$, weight: 3, 67.5–69.5°, 1.443, 2.4 g.; 4, 69.5–71.0°, 1.4438, 7.3 g.; 5, 71.0–73.5°, 1.4438, 6.8 g.; 6, 73.5–75.2°, 1.4438, 7.8 g.; 7, 75.2–76.7°, 1.4444, 4.4 g.; 8, 76.7–76.8°, 1.4443, 4.6 g.; 9, 76.8–78.8, 1.4452, 7.8 g.; 10, 78.8–80.2°, 1.4442, 9.8 g.; 11, 80.2–80.5°, 1.4440, 52 g.; 12, 80.5–98.0°, 1.4440, 2.7 g.

Analyses of various fractions were also obtained. Fraction, C, H, bromine no. (g./100 g.), hydroxyl value (equiv./100 g.): 3, 77.1%, 12.2%, —, —; 4, 77.3%; 12.5%, —, —; 5, 76.4%, 12.5%, —, —; 6, 76.0%; 12.5%, —, —; 7, (75.18, 75.14), (12.53, 12.52), —, .732; 8, 75.0%, 12.5%, 149, —; 9, 74.7%, 12.5%, —, —; 10, 74.9%, 12.5%, 111, .763; 11, 74.9%, 12.5%, —, —; 12, 73.6%, 12.3%, —, —; theoretical (calculated for $C_8H_{16}O$, octenol): 75.0%, 12.6%, 125, 0.771. Fraction 6 was treated with phenyl isocyanate and 1 drop of pyridine on a steam bath for 48 hr. The mixture was diluted with isopentane and filtered to remove the diphenylureas. The filtrate was vacuum distilled to remove solvent and unchanged alcohol. The viscous residue was chromatographed over neutral alumina and the eluate yielded colorless crystals. Recrystallization three times from isopentane yielded phenyl carbamate derivatives melting at 67–72°.

Anal. Calcd. for phenylurethane of fraction 6 ($C_{15}H_{21}NO_2$): C, 72.9; H, 8.65, N (Kjeldahl), 5.67. Found: C, 73.0; H, 8.6; N (Kjeldahl), 5.7.

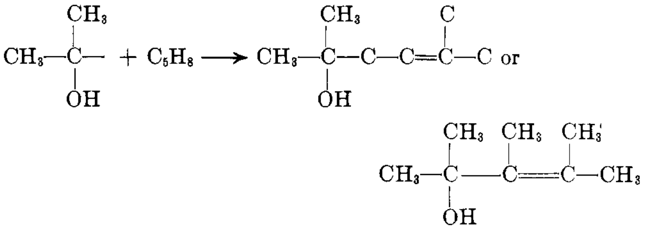
A similar treatment of fraction 10 gave a urethane which was much more difficult to purify (melting point criterion). Recrystallization six times from isopentane yielded material melting at 52–59°.

Anal. Calcd. for phenylurethane of fraction 10 ($C_{15}H_{21}O_2N$): C, 72.9; H, 8.65; N, 5.67. Found: C, 72.6; H, 8.5; N, 5.7.

The alcohol fractions were examined by g.l.c. on a 5-ft. UCON Polar/acid-washed Chromosorb at 113°. There were three important constituents with emergence times: A (10.7 min.), B (14.8 min.), and C (18.1 min.). Fraction 5 contained all three constituents in the approximate ratio A:B:C as 1:5:1. In fraction 7 the ratio was 1:5:7; in fraction 9, 1:1:5; and fraction 10, 2:30:1.

Ozonolysis studies indicated further that the fractions contained more than one component. The compounds were ozonized in methylene chloride at −78°. The methylene chloride solution was then added to a mixture of zinc in 50% aqueous acetic acid and the methylene chloride distillate condensed in an ice bath. Acetaldehyde and acetone were analyzed by g.l.c. on a 10-ft. oxydipropionitrile column at 42°. The emergence times were: methylene chloride, 5.6 min.; acetaldehyde, 3.3 min.; and acetone, 9.5 min. Formaldehyde was determined by weighing the methone derivative formed from the aqueous mother liquors. The estimates of the yields of these three carbonyl components are as follows: fraction, formaldehyde, acetaldehyde, acetone: 5, 13%, 20%, 7%; 6, —, 7%, —; 8, 23%, 20%, 6%; 10, 25%, 1%, 13%; 11, 15%, 4.2%, 9%.

The positive identification of acetone in these ozonolyses indicate the presence of an isopropylidene end group, which can arise only if the addition of the hydroxy isopropyl moiety is added to isoprene at the 3- or 4-position.



$$CH_3-\underset{OH}{\overset{CH_3}{C}}- + C_5H_8 \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-C-C=\overset{C}{C}-C \text{ or }$$

$$CH_3-\underset{OH}{\overset{CH_3}{C}}-\overset{CH_3}{C}=\overset{CH_3}{C}-CH_3$$

Since mechanistically it is difficult to rationalize addition at the 3-position, structure 3,5-dimethylhexen-4-ol-2 was preferred for the isomer yielding acetone on ozonolysis.

2:1 **Adducts.**—The mixture of adducts consisting of two acetone and one isoprene units boiled at 84–95° (2 mm.) and was not resolved into its components. Its structure was presumably predominantly that of the 1,4-adduct, 2,4,7-trimethyloctene-4-diol-2,7.

Anal. Calcd. for trimethyloctenediol ($C_{11}H_{22}O_2$): C, 70.9; H, 11.9; hydroxyl value (equiv./100 g.), 1.076; bromine no. (g./100 g.), 86. Found: C, 71.9, 71.4; H, 11.7, 11.7; hydroxyl value, 0.963; bromine no., 93.

1:2 **Adducts.**—The mixture of adducts consisting of one acetone and two isoprene units boiled at 95–125° (2 mm.) and was a mixture of several isomers. A possible structure is related to 2,4,8-trimethyldecadien-4,8-ol-2.

Anal. Calcd. for trimethyldecadienol ($C_{13}H_{24}O$): C, 79.4; H, 12.3; hydroxyl value, 0.51; bromine no., 172. Found: C, 79.8, 77.6; H, 11.0, 11.7; hydroxyl value, 0.452; bromine no., 150.

Analysis for Nondistillable Residues (Polyisoprene) (C_5H_8)$_n$.—The infrared spectra of these residues showed the presence in varying degrees of intensity hydroxyl absorptions (2.95 μ).

Anal. Calcd. for C_5H_8: C, 88.2; H, 11.8. Found: C, 87.0, 86.5; H, 11.8, 11.9.

Reaction of Mesityl Oxide and Butadiene with Sodium in Tetrahydrofuran.—Sodium wire (30 g.) and 350 ml. of tetrahydrofuran were cooled to −80° and 300 ml. of butadiene and 80 ml. of mesityl oxide added. The reaction was allowed to warm to 0° and an additional 70 ml. of mesityl oxide was added dropwise (20 min.). The reaction was stirred for 40 min. at 0° and 80 min. at 6°. To the light yellow fairly mobile solution was added 200 ml. of isopropyl alcohol and the whole poured onto a mixture of 80 g. of sulfuric acid and an ice-water slurry. The ether extracts after washing with sodium bicarbonate were dried with sodium sulfate and distilled. Fraction, pressure (mm.), boiling range, $n^{25}\text{D}$, weight, C, H: 5, 30, 36–50°, 1.4266, 11.9 (mesityl oxide); 6, 30, 55–55°, 1.4406, 17.6 (mesityl oxide); 7, 3, 55–66°, 1.4581, 11.1, 76.5, 11.6; 8, 3, 66–67°, 1.4652, 23.6, 75.7, 11.4; 9, 2, 67–69°, 1.4688, 11.4, 74.3, 11.1; 10, 2, 70–94°, 1.4758, 5.5, 75.4, 11.2; 11, 2, 94–119°, 1.4806, 7.9, 76.2, 11.2; 12, 2, 119–

122°, 1.4817, 3.4, 76.1, 11.4; 13, 2, 122–150°, 1.4848, 2.8, 76.7, 11.5; residue, —, —, 1.4981, 5.6, 82.3, 11.3.

Fractions 8, 9, 10, and 11 were quite similar and showed the presence of hydroxyl (2.95 μ) and carbonyl (5.95, 6.05 μ) bands in the infrared spectra.

Fractions 9 and 10 crystallized partially. After filtering, the solid recrystallized from petroleum ether to yield colorless solid (m.p. 73–74°). The infrared spectrum in carbon tetrachloride showed important absorption bands at 2.90, 5.95, 8.60, 9.43, 9.75, 10.62, 11.00, and 12.00 μ.

Anal. Calcd. for hydroxy ketone ($C_{12}H_{20}O_2$): C, 73.5; H, 10.3; hydroxyl value ($LiAlH_4$) (equiv./100 g.), 0.510; carbonyl value (equiv./100 g.), 0.510. Found: C, 73.5, 73.6; H, 10.3, 10.3; hydroxyl value, 0.557; carbonyl value, 0.393.

Reaction of Methyl Propionate with Sodium in Tetrahydrofuran.—Sodium wire (23 g.) in 500 ml. of tetrahydrofuran was cooled to 20° and a solution of 100 g. of methyl propionate in 100 ml. of tetrahydrofuran added dropwise. The temperature was maintained at 20–25° (1.5 hr.). Acetic acid (80 g.) and water were added to the clear homogeneous solution and the reaction mixture then poured into a large excess of water. It was extracted several times with ether, washed with sodium bicarbonate, and dried over sodium sulfate. Distillation yielded 12.1 g. of material boiling at 64–66° at 15.5 mm. ($n^{25}D$ 1.4252).

Anal. Calcd. for propionoin ($C_6H_{12}O_2$): C, 62.1; H, 10.42. Found: C, 62.2, 61.9; H, 10.3, 10.3.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–water mixtures (m.p. 124.0–125.5°; lit.[3] m.p. 154°).

Anal. Calcd. for propionoin DNP ($C_{12}H_{16}N_4O_5$): C, 48.7; H, 5.45; N, 18.9. Found: C, 48.9, 48.5; H, 5.4, 5.2; N, 18.7, 19.0.

Reaction of Methyl Propionate and Butadiene with Sodium in Tetrahydrofuran.—Butadiene (300 ml.) was added to a mixture of 30 g. of sodium wire and 350 ml. of tetrahydrofuran at −10°. Methyl propionate (130 g.) was added dropwise at a temperature of approximately 15° (1.5 hr.). The reaction was allowed to stir at 15° for 4 hr. and then poured into a mixture of ice slurry and 80 g. of sulfuric acid. The ethereal extracts were washed with sodium bicarbonate and water, dried with sodium sulfate, and distilled. Fraction, pressure (mm.), boiling range, $n^{25}D$, weight, C, H: 5, 760, 143–145°, 1.4319, 4.1, 72.8, 10.7; 6, 40, 68–72°, 1.4348, 8.8, 74.3 and 73.5, 10.7 and 10.6; 7, 40, 72–74°, 1.4365, 11.6, 73.7 and 73.7, 10.6 and 10.6; 8, 40, 74–78°, 1.4369, 6.1, 74.0 and 74.2, 10.7 and 10.7; 9, 40, 83–118°, 1.4442, 5.8, 73.3, 10.4; 10, 2, 100–103°, 1.4613, 8.0, 73.9, 10.3; 11, 2, 103–119°, 1.4658, 3.3, 73.5, 10.2; 12, 2, 126–150°, 1.4798, 6.8, 74.3, 10.5; 13, 2, 148–150°, 1.4842, 1.3, 75.0, 10.5; residue, —, —, 1.4971, 18.8, 75.3, 11.7.

Fraction 7 is fairly pure heptenone. It reacted with 2,4-DNP reagent to form an amorphous derivative with, however, correct analysis for heptenone–DNP.

Anal. Calcd. for heptenone DNP ($C_{13}H_{16}N_4O_4$): C, 53.4; H, 5.53; N, 19.15. Found: C, 53.0, 52.7; H, 5.5, 5.6; N, 19.0, 18.3.

Hydroxyl value (0.725 equiv./100 g.) and bromine number (127 g./100 g.) are in fair agreement with theory, 0.89 and 143, respectively.

Reaction of Methyl Propionate and Isoprene with Sodium in Ether.—Sodium (15 g.) was dispersed in 50 ml. of xylene. The xylene was decanted and the sodium pellets washed with absolute ether several times. Ether (200 ml.) was added and the mixture cooled to −25° and 50 ml. of isoprene added. A solution of 39 g. of methyl propionate in 50 ml. of ether was added and the reaction refluxed simultaneously (30 min.). The reaction was refluxed an additional hour and poured into a mixture of 35 g. of sulfuric acid and water. The upper layer was decanted and washed with sodium bicarbonate and dried with potassium carbonate. Fraction, pressure (mm.), boiling range, $n^{25}D$ weight: 1, 2.5, 34–40°, 1.4473, 8.7; 2, 2.5, 40–47°, 1.4485, 11.3; 3, 2.0, 49–62°, 1.4526, 2.5; 4, 1.0, 54–68°, 1.4686, 1.3; 5, 1.0, 68–102°, 1.4732, 1.4; 6, 1.0, 102–128°, 1.4850, 2.3.

The lower boiling fractions (1–4) from several runs were combined and redistilled at 12 mm. Fraction, boiling range, $n^{25}D$, weight, C, H: 1, 45–62°, 1.4530, 2.9, —, —; 2, 62–64°, 1.4478, 4.8, 75.3, 11.0; 4, 65–66°, 1.4498, 4.4, 74.7, 10.8; 4, 66–67°, 1.4516, 4.0, 74.1, 10.9; 5, 67–68°, 1.4520, 4.1, —, —; 6, 68–74, 1.4480, 3.7, 70.7, 10.4; 7, 74–87°, 1.4332, 3.9, —, —.

Fractions 2 and 4 were treated with 2,4-dinitrophenylhydrazine reagent and yielded solid derivatives. They were both recrystallized twice from ethanol–water solutions but yielded material melting over a range (fraction 2, DNP, m.p. 80–85; fraction 4, DNP, m.p. 80–90°). They both had correct analyses for an octenone.

Anal. Calcd. for DNP of octenone ($C_{14}H_{18}N_4O_4$): C, 55.0; H, 5.93; N (Dumas), 18.3. Found (fraction 2, DNP): C, 54.9; H, 6.3; N, 18.0. (Fraction 4, DNP): C, 55.0; H, 6.1; N, 18.3.

Reaction of Benzalacetone and Butadiene with Sodium in Tetrahydrofuran.—A mixture of 23 g. of sodium ribbon in 350 ml. of tetrahydrofuran was cooled to −60° and 300 ml. of butadiene added. The temperature was raised to −10° and a solution of 90 g. of benzalacetone in 100 ml. of tetrahydrofuran was added at such a rate to maintain the temperature at 12–14° (1 hr.). The reaction was stirred for 3 hr. at 14° and became quite viscous. It was poured into ice–water and separated as a very viscous, ether soluble, mass. It was not worked up.

Reaction of Acrolein and Butadiene with Sodium.—Sodium wire (30 g.) in 350 ml. of tetrahydrofuran was cooled to −70° and 350 ml. of butadiene added. A solution of 100 ml. acrolein in 100 ml. of tetrahydrofuran solvent was added dropwise at −70° and the addition continued until the temperature reached −10° (30 min.). The solution became opaque and as the acrolein was added a solid material separated (disacryl?). The sodium was not apparently consumed as evidence by its dull surface.

Reaction of Acetaldehyde and Butadiene with Sodium.—Sodium wire (30 g.) in 350 ml. of tetrahydrofuran was cooled to −70° and 350 ml. of butadiene added. An aliquot (20 ml.) of a solution of 100 ml. of acetaldehyde and 100 ml. of tetrahydrofuran was added and the reaction allowed to warm to −10°. The surface of the sodium was shiny, but, as the addition of the acetaldehyde solution was continued, the solution became opaque and the sodium surface became dull. After all the aldehyde had been added the sodium was less than 10% consumed. Addition of more acetaldehyde did not appear to activate the sodium. The reaction was stirred for 1 hr. at room temperature at which time most of the sodium wire remained unchanged. It was worked up in the usual manner by decanting the solution into ice–water. It yielded no material boiling where hexenol is expected.

The reaction was repeated with the simultaneous addition of acetic acid (100 ml.) with the acetaldehyde solution. After approximately half the solution was added (temperature, 0°, 1 hr.) the solution became opaque. After the acetaldehyde and acetic acid were added approximately 50% of the sodium was still unchanged. The reaction was stirred for an additional hour at 5°, but no visible reaction occurred. Approximately 10 g. of 3-mm. diameter glass beads was added and the reaction became exothermic (temperature rise to 20°). The mixture was cooled to 10° and after 0.5 hr. of stirring the sodium was completely dissipated. It was poured into sulfuric acid–ice mixture and extracted with ether. The ethereal extract, after washing three times with sodium bicarbonate and drying over sodium sulfate, was distilled to remove the ether. The residue (approximately 50 ml.) was vacuum distilled. Fraction, pressure, boiling range, $n^{25}D$, weight, C, H: 1, 70, 31–41°, 1.4192, 1.5, —, —; 2, 70, 45–46°, 1.4282, 3.5, 81.1, 12.4; 3, 30, 39–42°, 1.4322, 4.6, 82.8, 12.6; 4,[20a] 10, 36–84°, 1.4362, 6.3, 73.8, 12.1; 5,[20b] 10, 84–92°, 1.4613, 1.0, 73.7, 11.2; residue, —, —, 1.5003, 1.2, —,—.

A reaction was also run in which acetic anhydride (80 ml.) was used to replace the acetic acid in the previous reaction (23 g. of sodium, 75 ml. of acetaldehyde, 300 ml. of butadiene in 350 ml. of tetrahydrofuran). The products were distilled into the following fractions. Fraction, pressure (mm.), boiling range, weight (g.), $n^{25}D$, C, H: 3, 3, 25–42°, 2.9, 1.4341, —, —; 4, 2, 42–49°, 8.6, 1.4426, 66.8, 9.8; 5, 2, 52–66°, 5.3, 1.4469, 64.4, 9.3; 6, 2, 66–83°, 1.5, 1.4576, 64.3, 8.7; 7, 2, 83–91°, 7.8, 1.4574, —, —; 8, 2, 91–99°, 4.9, 1.4663, 64.4, 8.8; 9, 2, 100–106°, 4.8, 1.457, —, —; residue, —, —, 32.2, 1.5012, 71.7, 9.4.

Reaction of Ethyl Acetate and Butadiene with Sodium and Acetic Anhydride in Tetrahydrofuran.—A mixture of 30 g. of sodium wire in 350 ml. of tetrahydrofuran reacted with 350 ml. of butadiene and 122 ml. of acetic anhydride in the usual manner. The addition took approximately 1 hr. and the reaction was stirred an additional 2 hr. at 5°. The consumption of the sodium occurred very slowly. The work-up yielded products distilling over a wide range. Fraction, pressure, boiling range, weight, $n^{25}D$, C, H: 1, 8, 26–28°, 1.5, 1.4279, —, —; 2, 5, 28–37°, 2.1,

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[20] (a) Hydroxyl value (equiv./100 g., acetic anhydride), 0.86, 0.88; (b) hydroxyl value (equiv./100 g., acetic anhydride), 0.66, 0.64.

1.4492, 68.5, 9.1; 3, 2.5, 41–42°, 17.9, 1.4632, 69.5, 9.0; 4, 2; 42–47°, 10.6, 1.4697, 69.5, 9.0; 5, 2, 47–58°, 1.9, 1.4670, —, —; 6, 2, 58–70°, 2.5, 1.4662, —, —; 7, 2, 70–84°, 4.1, 1.4700, —, —; 8, 2, 84–117°, 1.9, 1.4832, —, —; 9, 2, 117–124°, 7.9, 1.5035, —, —; residue, —, —, 32.6, 1.5150, 70.6, 8.7.

Fraction 4 on treatment with 2,4-DNP reagent yielded an orange-red DNP (recrystallized from absolute ethanol), m.p. 158–160°.

Anal. Calcd. for hexenone DNP ($C_{12}H_{14}N_4O_4$): C, 51.8; H, 5.07; N, 20.1. Found: C, 51.9, 52.1, 51.6; H, 4.9, 4.9, 5.0; N, 19.8, 19.8, 19.7. That fraction 4 was not pure hexenone also was indicated by its bromine number (137) and hydroxyl value (208).

Reaction of 2-Methylbutene-1 and Hexene-1 and Acetone with Sodium in Tetrahydrofuran.—A mixture of 30 g. of sodium wire and 400 ml. of tetrahydrofuran was chilled to −20° and 150 ml. of 2-methylbutene-1 was added. Acetone was added dropwise at such a rate to maintain the temperature at 30° (2.5 hr.). The clear homogeneous solution was quenched with 100 ml. of acetic acid and water and poured into an ice–water slurry. The mixture was extracted three times with ether and the ethereal solutions washed with sodium bicarbonate and dried over sodium sulfate. The distillation of the ethereal extracts yielded in addition to isopropyl alcohol, mesityl oxide, and isophorone. In addition there was formed a high boiling ketonic product(s) (b.p. 98–147° (1 mm.); n^{25}D 1.5053–1.5231; 7.1 g.) which showed hydroxyl absorption in the infrared spectrum (2.80, strong; 5.80, strong, 6.05, strong; 6.4, weak μ). The distillation pattern from the reaction of acetone with 2-methylbutene-1 is given below. Boiling range, n^{25}D, weight (g.), C, H, hydroxyl value: 49.3–53.0°, 1.4705, 6.5, —, —, —; 53.0–53.5°, 1.4745, 8.5, 76.2, 10.2, —; 53.5–62.0°, —, 3.3, 77.5, 10.3, 0.624; 84–86°, 1.5089, 2.4, —, —, —; 86–88°, 1.5122, 3.0, —, —, —; 88–89°, 1.5158, 2.8, 79.9, 10.2, 0.500; 89–98°, 1.5156, 1.5, 79.2, 10.2, —; 98–128°, 1.5053, 3.3, —, —, —; 128–147°, 1.511, 3.0, —, —, —. A similar spectrum of products was obtained from the reaction of hexene-1 with acetone and sodium.

Reaction of Styrene and Methyl Propionate with Sodium in Ether.—To a mixture of 30 g. of sodium wire in 400 ml. of ether at −40° was added 10 ml. of methyl propionate and 150 ml. of styrene. Methyl propionate (150 ml.) was then added dropwise at 5–10° (0.5 hr.) and the reaction allowed to stir at 30–40° for 2 hr. (12 g. of unchanged sodium remained). The solution was decanted into a mixture of acetic acid and water and worked up in the usual manner. Distillation of the ether left approximately 100 g. of material which on distillation was primarily styrene. The reduction products although not isolated were probably monomeric products such as ethyl benzene and propanol. There was less than 3 g. of material boiling higher than styrene. It appeared thus that no condensation between methyl propionate and styrene occurred.

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Steroids. CCXXI.[1] Syntheses of Some Steroid Dienes

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Novel syntheses are outlined of $\Delta^{1,3}$- and $\Delta^{2,4}$-androstadien-17β-ols, $\Delta^{2,4}$-pregnadien-20-one, and $\Delta^{2,5}$-pregnadien-17α-ol-20-one 17-acetate. $\Delta^{2,5}$-Pregnadiene-11β,17α,21-triol-20-one 21-acetate was obtained, but with the $\Delta^{3,5}$-isomer as a contaminant. Diagnostic features of ultraviolet absorption, infrared absorption, and nuclear magnetic resonance spectra, and optical rotatory dispersion are discussed.

Until very recently an oxygen atom at C-3 of the steroid nucleus was considered mandatory for biological activity. However, in 1959 biological activity was demonstrated for steroids carrying either no substituent at C-3[2] or a nitrogen substituent.[3] There rapidly followed reports of other active steroids devoid of a C-3 oxygen atom,[4-6] and further extensive investigations were initiated in the Syntex Laboratories. As a result there was discovered a new class of highly active androstenes, sp² hybridized at C-2 or C-3, or at both positions.[7] Substitution at the C-2 position of these steroid ring A olefins by methyl[8] or substituted methyl[9,10] led to further variations in activity, and some of these derivatives displayed an unusually favorable separation of androgenic and anabolic (myotrophic) activity. It was of distinct interest, therefore, to study the activity coincident upon the introduction of further unsaturation into the electron-rich ring A of these steroid olefins.

Accordingly, syntheses of such compounds have been developed by routes which also should prove applicable to other cyclic systems.

3β-Chloro-Δ^{1}-androsten-17β-ol acetate[7b] (Ia), from the reaction of the 3β-alcohol Ib with thionyl chloride, was converted smoothly in 80% yield into $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa) by treatment with boiling dimethylformamide containing calcium carbonate or a little pyridine. Alternatively, boiling dimethyl sulfoxide alone, or in conjunction with a small quantity of pyridine, eliminated hydrogen chloride from Ia to give IIa. Earlier preparations of steroid $\Delta^{1,3}$-dienes proceeded in substantially inferior yields.[11] Hydrolysis of the acetate IIa furnished the corresponding 17β-alcohol IIb, which on oxidation with chromic acid[14]

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[11] Henbest and Wilson[12] reported $\Delta^{1,3}$-cholestadiene as a minor non-isolated contaminant of Δ^{1}-cholestene formed through reductive dehalogenation of 3β-chloro-Δ^{1}-cholestene. Our synthesis of Δ^{1}-androstenes by the same experimental method furnished no trace of a $\Delta^{1,3}$-diene elimination reaction product.[7b] $\Delta^{1,3}$-Cholestadiene was obtained in 4.3% yield by the action of alumina on, or pyrolysis of, Δ^{1}-cholestene-3β-ol benzoate.[13]

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