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Reduction of Alkyl-Substituted Butadienes by Sodium in Liquid Ammonia

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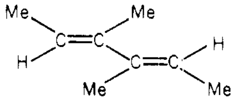
Six alkyl-substituted butadienes have been reduced by sodium in liquid ammonia to determine the relative importance of 1,2 and 1,4 reduction pathways and, for the latter, whether the cisoid or transoid state of the butadiene preferentially is reduced. The 1,4 reduction predominates in all cases and especially so when a terminal methylene is present. For alkylbutadienes which have no steric constraints preventing the cisoid conformation, 1,4 reduction of the cisoid conformation is preferred.

It is known that butadiene can be reduced by using sodium in liquid ammonia to give 87% *trans*-2-butene and 13% *cis*-2-butene at −33 °C.[1] No 1-butene was obtained. The stereochemical course of the reduction is temperature dependent; at −78 °C, 50% *cis*-2-butene was obtained.[1] Bauld postulated that a developing cis anion radical accounts for the formation of cis olefin, and electron releasing groups stabilizing this should increase the amount of cis isomer found. Thus, 1,3-pentadiene gave 68% *cis*-2-pentene at both −33 and −78 °C.[1] The sodium in liquid ammonia reduction of butadienes with three or four alkyl substituents has not been reported, at least not since identification of products by VPC and NMR became possible.

The objective of the present work was to study the sodium in liquid ammonia reduction of the six alkylated butadienes (**1**–**6**) obtained by dehydrating the pinacol 3,4-dimethyl-3,4-hexanediol. The preparation and identification of these alkylated butadienes has been described.[2] In the reduction of butadienes, both the relative amounts of 1,2 vs. 1,4 reduction and the stereochemical course of the reduction must be considered.



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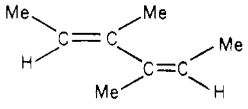

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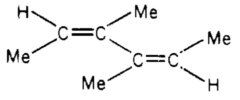

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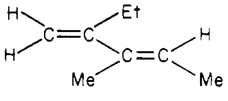

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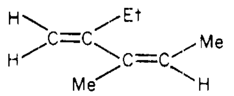

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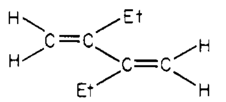

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1,2 vs. 1,4 Reduction. In all cases, 1,4 reduction predominated. However, the three butadienes (**1**, **2**, and **3**) alkylated on carbons one and four of butadiene gave 10–25% 1,2 reduction whereas the three butadienes with at least one terminal methylene group gave 0–4% 1,2 reduction, i.e., 96–100% 1,4 reduction (Table I), with the 1,2 reduction always occurring at the methylene group. The products were isolated by VPC and identified by their NMR and IR spectra.

The above results are in agreement with the earlier work of Levina,[3] who found that 2,3-dimethylbutadiene undergoes 1,4 reduction almost exclusively to 2,3-dimethyl-2-butene. Butadienes substituted in the 1 and 4 positions are known to give increased amounts of 1,2 reduction.[4]

Table I. 1,2 Reduction of Alkylated Butadienes to 3,4-Dimethyl-2-hexene (7)

butadiene	% 1,2 reduction with Na/liq NH_3	% 1,2 reduction with Li/liq NH_3	product
1	25	27	(*E*)-7
2	17	21	7[a]
3	10		(*Z*)-7
4	4		(*E*)-7
5	2		(*Z*)-7
6	near zero		

[a] Stereochemistry not established. Olefins (*E*)-7 and (*Z*)-7 could not be separated by VPC.

Table II. Formation of *cis*- and *trans*-3,4-Dimethyl-3-hexenes from Six Octadienes with Sodium in Liquid Ammonia

diene	% olefin formed		diene conformn giving cis olefin	reaction pathway	existence of model of diene as	
	cis	trans			cisoid	transoid
1	64	11	cisoid	84% from cisoid	yes	yes
2	54	29	cisoid	65% from cisoid	difficult	difficult
3	20	70	cisoid	78% from transoid	no	no
4	14	82	transoid	86% from cisoid	yes	yes
5	49	49	transoid	50% from each	difficult	difficult
6	56	44	cisoid	56% from cisoid	yes	yes

Stereochemistry of 1,4 Reductions. All six of the dienes on reduction with sodium in liquid ammonia undergo 1,4 reduction to give a mixture of *cis*- and *trans*-3,4-dimethyl-3-hexenes (Table II) in 70 to almost 100% yield, depending on the ratio of 1,2 to 1,4 reduction. The ratio of cis to trans product and the reasons for the varying ratios are of considerable interest.

It is known that butadiene itself exists almost entirely in the transoid conformation,[5] and reduction of this conformation must lead to *trans*-2-butene. Actually, 13% *cis*-2-butene is formed at −33 °C, presumably because the reduction using sodium in liquid ammonia proceeds through a radical anion, and interaction of this with the counterion favors a cisoid conformation which gives rise

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to *cis*-2-butene.[1] Our results are in agreement with Bauld's postulate[1] that alkylated butadienes stabilize the radical anion in the cisoid conformation and that the radical anion provides the preferred pathway for olefin formation, always providing that steric restraints do not prevent the radical anion from existing in the cisoid conformation. A study of Stuart–Hershfelder molecular models of the dienes allows one to estimate the relative ease with which the olefins, and presumably the radical anions, can exist in the cisoid and transoid forms. Our results are easily interpreted in terms of Bauld's radical-anion explanation. Radical and dianion intermediates may also exist, but the radical-anion intermediate provides a simpler explanation and explains all the known facts.

The results with the first three dienes in Table II illustrate the importance of the cisoid conformation of the diene or radical anion in determining the stereochemical reaction pathway. The percentages of olefin formed from the cisoid conformations are 84, 65, and 22% as the ease of having the molecular models of the dienes in the cisoid state varies from easy to impossible. The fourth diene gives 82% trans olefin, but this corresponds to 86% going through the cisoid conformation of the diene or radical anion.

The first two dienes in Table II were also reduced with lithium in liquid ammonia, and similar results were obtained: from 1, 56% cis, 17% trans; from **2**, 47% cis, 32% trans.

Proof of Structure of Dienes and Olefins. Proof of the structure of the dienes follows from their IR, UV, and ^{1}H NMR spectra.[2] For the *cis*- and *trans*-3,4-dimethyl-3-hexenes, proof of the structure goes back to the *dl*-3,4-dimethyl-3,4-hexanediol of melting point 52 °C.[6] This was converted by Corey's thionocarbonate method[7] to *trans*-3,4-dimethyl-3-hexene.

Experimental Section

Melting and boiling points are corrected. The infrared spectra were determined with a Perkin-Elmer Model 337 spectrophotometer and the ^{1}H NMR spectra with a Varian Model A-60A. Chemical shift values are expressed as δ values (parts per million) downfield from tetramethylsilane as internal standard. Elemental microanalyses were performed by Dr. F. J. Kasler.

General Procedure for Reduction. Sodium (0.12 g, 0.005 mol) was allowed to dissolve (1 h) in 25 mL of distilled, liquid ammonia, and an ether solution containing 0.25 mL of the diene (~0.002 mol), purified by VPC, was added by syringe. The reaction mixture was stirred with a magnetic stirrer for 75 min, and more ammonia was added to maintain the original volume. Solid ammonium nitrate was added to discharge the blue color, most of the liquid ammonia was allowed to evaporate, and 30 mL of ether was added. After the ethereal solution was washed with water and dried ($CaCl_2$), it was analyzed by VPC.

VPC Analyses. The analyses reported in Tables I and II were carried out on F&M Model 300 (using helium) and Hewlett-Packard Model 5751 (using nitrogen) vapor-phase chromatographs. The former was used to purify the diene and olefin samples. The columns used included a 2 m × 0.25 in. copper tube packed with 10% Carbowax 1000 on 80/100-mesh silanized Anakrom P and a similar 2 m × 0.13 in. column packed with 15% 2,4-dimethyltetrahydrothiophene 1,1-dioxide (dimethylsulfolane) on silanized 80/100-mesh A/W Chromosorb P (see Table III).

The dimethylsulfolane column gave an amost base-line separation of the *cis*- and *trans*-3,4-dimethyl-3-hexenes.

Table III. Relative Retention Times (min) of Octenes

olefin	Carbowax 1000 at 50 °C	dimethylsulfolane at 28 °C
3,4-dimethyl-2-hexene	6.3	28
cis-3,4-dimethyl-3-hexene	7.0	41
trans-3,4-dimethyl-3-hexene	7.0	37
2-ethyl-3-methyl-1-pentene[a]	5.7	25

[a] A small peak was observed on VPC following reduction of 2,3-diethylbutadiene and was assumed to be 2-ethyl-3-methyl-1-pentene. There was too little to collect and identify.

***trans*-3,4-Dimethyl-3-hexene.** To 5 g (0.034 mol) of *dl*-3,4-dimethyl-3,4-hexanediol (mp 53 °C)[8] in 50 mL of dry dioxane was added 2.5 g (0.064 mol) of potassium, and the magnetically stirred mixture was refluxed under a nitrogen atmosphere for 12 h. After 3 h a fine white precipitate began to form, but traces of potassium metal could be seen even after 12 h. After the mixture was cooled to room temperature, 2 mL (0.033 mol) of carbon disulfide was injected through the rubber septum into the reaction mixture, and it was heated at 70 °C for 15 min. The mixture was cooled in an ice bath, 2.4 mL (0.038 mol) of methyl iodide was added, and the mixture was again heated at 70 °C for 5 min and then cooled. Ten milliliters of methanol was added to destroy the unreacted potassium. Most of the dioxane was distilled off under reduced pressure, and the orange solid residue was partitioned between 80 mL of benzene and 100 mL of ice–water containing 5 g of ammonium chloride. The dark red aqueous layer was extracted with 50 mL of benzene, and the combined benzene layers were washed with water until neutral and then with sodium chloride solution, dried (Na_2SO_4), and evaporated to yield 3.5 g of impure ***dl*-4,5-dimethyl-4,5-diethyl-1,3-dioxolane-2-thione**. Chromatography on a 60 × 2.6 cm column of 100 g of 0.05–0.2 mm (70–325 mesh) ASTM (E. Merck) silica gel suspended in freshly distilled benzene followed by elution with about 1 L of benzene gave a yellow middle fraction containing 1 g (15% of theory) of the dioxolane product. The elution was followed by taking IR spectra of the fractions. The product had no carbonyl band at 1800 cm^{-1} and a very strong C=S band around 1300 cm^{-1}.

A similar series of reactions was carried out by using *m*-xylene as a solvent instead of dioxane, but the final purified product was obtained in 12% instead of 15% yield. The thionocarbonate from either preparation was an oil that slowly crystallized at −17 °C but melted as soon as it was exposed to room temperature: IR (film) 2970, 2930, 2870, 1450, 1380, 1300 (br), 1200, 1120 (br), 1085, 1050, 1030, 1000, 935, 925, 900, 875 cm^{-1}; NMR (CCl_4) δ 1.75 (q, 4, $J = 7$ Hz, CH_2), 1.38 (s, 6, CCH_3), 1.08 (t, 6, $J = 7$ Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.40; H, 8.57; S, 17.03. Found: C, 57.32; H, 8.36; S, 17.28.

The purified *dl*-4,5-dimethyl-4,5-diethyl-1,3-dioxolane-2-thione (0.60 g, 0.0032 mol) and 5 mL of triethyl phosphite were refluxed under a nitrogen atmosphere for 48 h with stirring by a magnetic stirrer. During this time the product was swept out of the reaction mixture by a slow nitrogen stream into a collection trap containing ether and cooled in dry ice. The ethereal solution was washed several times with water and dried over calcium chloride. Purification was by VPC using a Carbowax 1000 column at 50 °C. The ***trans*-3,4-dimethyl-3-hexene** had a micro boiling point of 119.5 °C: IR (film) 3000–2850, 1460, 1380, 1160, 1070, 970, 775 cm^{-1}; NMR ($CDCl_3$) δ 2.02 (q, 4, $J = 7.5$ Hz, CCH_2CH_3), 1.62 (s, 6, CCH_3), 0.92 (t, 6, $J = 7.5$ Hz, CCH_2CH_3).

Enriched *cis*-3,4-Dimethyl-3-hexene. This may be prepared from the enriched liquid *meso*-3,4-dimethyl-3,4-hexandiol by the same procedure as above, but a 60% cis/40% trans mixture is the best that can be obtained due to the composition of the starting pinacol.

A better procedure is to reduce *cis,cis*-3,4-dimethyl-2,4-hexadiene (1) with sodium in liquid ammonia and separate the 3,4-dimethyl-3-hexene from the 3,4-dimethyl-2-hexene by VPC using a Carbowax 1000 column. The final mixture consists of 85% *cis*-3,4-dimethyl-3-hexene together with 15% of the trans isomer. The boiling point, IR spectra, and NMR spectra are the same as

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those for the trans isomer. VPC using the dimethylsulfolane column distinguishes between them.

Anal. Calcd for C_8H_{16} (85% cis/15% trans sample): C, 85.64; H, 14.36. Found: C, 85.79; H, 14.02.

3,4-Dimethyl-2-hexene (7) was prepared by the sodium in liquid ammonia reduction of *cis,cis*-3,4-dimethyl-2,4-hexadiene (1). The 3,4-dimethyl-2-hexene was separated from the 3,4-dimethyl-3-hexenes by VPC on a Carbowax 1000 column: micro boiling point 113 °C; IR (film) 3000–2850, 1660, 1460, 1380, 1090, 1025, 1010, 960, 825 cm^{-1}; NMR (CCl_4) δ 5.20 (q, 1, J = 7 Hz, $=CHCH_3$), 2.00 (m, 1, allylic CH), 1.58 (d, 3, J = 7 Hz, $=CHCH_3$), 1.50 (s, 3, $C(CH_3)=$), 1.36–0.60 (m, 8).

Anal. Calcd for C_8H_{16}: C, 85.64; H, 14.36. Found: C, 85.37; H, 14.08.

3,4-Dimethyl-2-hexene theoretically exists in cis and trans forms, but we could not separate them or distinguish between them by any method, including VPC. Thus the 3,4-dimethyl-2-hexenes from the reduction of either *cis,trans*- or *trans,trans*-3,4-dimethyl-2,4-hexadiene could not be distinguished from the above.

Registry No. 1, 18265-39-9; 2, 2417-88-1; 3, 21293-01-6; 4, 32388-98-0; 5, 32388-99-1; 6, 16356-05-1; (*E*)-7, 19550-82-4; (*Z*)-7, 19550-81-3; (*E*)-3,4-dimethyl-3-hexene, 19550-88-0; (*Z*)-3,4-dimethyl-3-hexene, 19550-87-9; 2-ethyl-3-methyl-1-pentene, 3404-67-9; *dl*-3,4-dimethyl-3,4-hexanediol, 32388-94-6; *dl*-4,5-dimethyl-4,5-diethyl-1,3-dioxolane-2-thione, 73367-88-1; *meso*-3,4-dimethyl-3,4-hexanediol, 32388-93-5.

Specific Enolates from α-Amino Ketones

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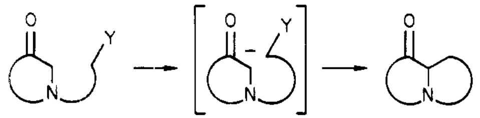
The enolization of 11 tertiary α-amino ketones was investigated under three different conditions (kinetic base, thermodynamic base, thermodynamic acid) to determine the directionality of such enolates for application to alkaloid synthesis. The ketone structural variables examined were the geometry of the amine nitrogen lone pair–carbonyl array and the electronic nature of the nitrogen substituent. With the exception of 3-pyrrolidinones, increasing the electron-withdrawing nature of the nitrogen increases the amount of enolization toward nitrogen (**3**, **6**, and **9** or **21**, **24**, and **27**). *N*-Alkyl-substituted amino ketones (**3**, **12**, **21**, **33**) under kinetic base conditions yield enolate distributions similar to those of the corresponding all-carbon compounds. *N*-Carbamato-substituted amino ketones (**6**, **24**, **27**, **30**) enolize predominantly toward nitrogen under all conditions. The 3-pyrrolidinones **12**, **15**, and **18** afford enolates away from nitrogen under all conditions.

A common structural feature of many alkaloids, including the pyrrolizidines, lycopodines, and aspidospermines, is a tertiary bridgehead nitrogen. A key step in one general synthetic approach to these diverse compounds might be an intramolecular ring closure of an N-substituted amino ketone enolate (**1** → **2**). Such specific enolates could also be useful in a variety of other applications in alkaloid synthesis. Little information is available regarding the effect of nitrogen on the directionality of ketone enolization, although numerous enolates have been studied in carbon systems[2-4] and with the α-heteroatoms halogen,[5] sulfur,[6] and oxygen.[7] We report the full details of our work with amino ketones communicated in 1978[8] as well as some additional information about the specificity of these enolate-forming reactions.



1 **2**

Ketone Variables. Of the numerous structural and electronic variables for α-amino ketones, the geometrical arrangement of the nitrogen-carbonyl group and the electronic nature of the nitrogen substituent are critical. Systematic examination of these features should establish general trends for synthetic application. The geometrical relationship of the nitrogen lone pair–carbonyl array was varied from freely rotating acyclic species (**3**, **6**, **9**) to fixed in a cisoid array (**30**, **33**) or in a transoid configuration (**12**, **15**, **18**, **21**, **24**, **27**). The nitrogen substituents were varied from alkyl to the synthetically versatile carbamate functionality. In all cases, the actual choice of ketone was based upon availability and spectroscopic simplicity.

Enolization and Product Identification. The enolization of the ketones was effected by three different methods: method A, excess lithium diisopropylamide in tetrahydrofuran (THF) at −78 °C; method B, 0.8 equiv of lithium hexamethyldisilazide in THF at 0 °C; method C, chlorotrialkylsilane and triethylamine in dimethylformamide (DMF) at 80 °C. The base in method B was chosen to eliminate potential carbonyl reduction (vide infra). All enolates were trapped with trialkylsilyl chlorides; some enolates were also trapped with acetic anhydride and with methyl iodide. These procedures were developed by House,[3] who was shown that methods B and C afford similar results in all-carbon compounds. The results for silyl trapping are summarized in Table I.

Many of the silyl enol ethers were identified by isolation either directly from the reaction mixture or by preparative GLC. All products exhibited the expected spectral properties, including a distinctive NMR shift of the olefinic protons. Silyl enol ethers formed by enolization away from nitrogen demonstrated olefin peaks in the 3.8–4.8-ppm region as observed by House in carbon systems.[3] Enol

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