Base-catalysed Deuterium Exchange Reactions of 6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane [Pin-2(10)-ene] and 6,6-Dimethylbicyclo[3.1.1]heptan-2-one (Nopinone)

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Deuterium exchange reactions of nopinone with NaOD–D$_2$O–dioxan and of pin-2(10)-ene with NaH–[^{2}H$_6$]DMSO during isomerization to pin-2-ene were monitored by mass and ^{1}H n.m.r. spectral means after separating the products by g.l.c. In both cases, there was relatively rapid uptake of one deuterium atom, followed by the slower incorporation of a second. The first deuterium was shown to be on C-3 and *trans* to the 6,6-*gem*-dimethyl bridge, by reducing the exchanged ketone or olefin to the corresponding alcohol and examining the ^{1}H n.m.r. spectra of mixtures of the purified alcohols with an n.m.r. shift reagent. From analysis of the rate equations for each species, these results were rationalized in terms of base and solvent mainly approaching C-3 from the side *trans* to the *gem*-dimethyl group to abstract a hydrogen atom and donate a deuterium atom to the intermediate. Attack on the *cis*-face is precluded by steric hindrance.

It has been reported that pin-2(10)-ene, and 6,6-dimethylbicyclo[3.1.1]heptan-2-one (nopinone) and -3-one (isopinone) are attacked by various reagents at a hydrogen adjacent to the C=C or C=O double bond. Except for a few reactions, the products were found to have substituents only *trans* to the 6,6-dimethyl group.[1]

However, no attempt has been made to carry out the reactions in basic media, in which anionic species will be intermediates. In this paper, the deuterium exchange reactions of nopinone and pin-2(10)-ene, as well as the mechanism of isomerization between pin-2- and -2(10)-ene over basic catalysts, are investigated by means of a technique which determines the number and position of the deuterium atoms in each product.

EXPERIMENTAL

Reagents.—Pin-2-ene (Wako Pure Chemicals Co.) and pin-2(10)-ene (Takasago Perfumery Co.) were purified by distillation over sodium and passage through a preparative gas chromatograph (Perkin-Elmer F-21) using a 3-m × 8-mm column containing 20% polyethylene glycol 1500 on Chromosorb W. Nopinone synthesized from ozone oxidation of pin-2(10)-ene according to the method of Meinwald and Gassman [2] was purified by distillation. Sodium hydride (Metal Hydride Inc.) was washed twice by pentane to remove oil. Sodium [^{2}H]hydroxide [40% (w/w) in 98% D$_2$O], dimethyl [^{2}H$_6$]sulphoxide (99.5% D), and deuterium oxide (99.7% D) were purchased from Merck, Sharp, and Dohme and other reagents were used without further purification.

Reaction Procedures.—The exchange reaction of nopinone was carried out by mixing dioxan (5 g), nopinone (1 g, 7 mmol), and NaOD (0.04 g) in deuterium oxide (4 g, 220 mmol) and stirring at 0 °C. Exchange and isomerization reactions of pin-2(10)- or -2-ene were performed by mixing a solution prepared in advance at 60—70 °C from sodium hydride (10 mmol) and dimethyl [^{2}H$_6$]sulphoxide (80 mmol) with pin-2(10)- or -2-ene (15 mmol) and stirring at 50—80 °C under nitrogen. From the concentration of each compound, the proportion of exchangeable deuterium to total exchangeable hydrogen can be estimated as 97 and 92% for the reactions of nopinone and pin-2(10)-ene, respectively, assuming that the number of exchangeable hydrogens is one for sodium hydride, two for pin-2(10)-ene, nopinone, and deuterium oxide, and six for dimethyl sulphoxide. After an appropriate reaction time, a portion of the mixture was removed and quenched by water. The product was extracted with ether and the ether layer was analysed for its composition, deuterium content, and deuterium position.

Analysis of Nopinone.—The ether extracts were directly injected on to a Hitachi M-52 g.l.c.–m.s. apparatus with a 1-m × 3-mm column coated with OV-1 operating at 80 °C with helium (1 atm) as carrier. From mass spectra, the deuterium distribution corrected for factors derived from the spectrum of non-deuteriated nopinone, was deduced. The position and stereochemistry of deuterium incorporated in nopinone were determined by reducing nopinone with LiAlH$_4$ to α-nopinol and measuring the ^{1}H n.m.r. spectrum (Jeorco PS-100 or Hitachi R-20B) in the presence of Eu(fod)$_3$ in chloroform.

Analysis of Pinenes.—The mole fraction of pin-2- and -2(10)-ene were determined from chromatograms measured by a Hitachi–Perkin-Elmer F-6D gas liquid chromatograph with a 45-m capillary column of Ucon LB-550-X. In cases where a large quantity of compound was needed, preparative g.l.c. as above was used. The deuterium distributions were measured as for nopinone. From the distribution, the deuterium content per molecule of pinene, ϕ, was calculated from the equation, $\Sigma i \times d_i$, where d_i is the mole fraction of pinene with i atoms of deuterium. To estimate the position of deuterium, it was assumed that only the hydrogens attached to C-3, -4, and -10 (allylic and vinylic) could participate in the exchange reaction and their signals did not overlap each other in the n.m.r. spectra, as was actually the case. The carbon to which the hydrogen(s) is attached and the chemical shifts are as follows: pin-2-ene, C-3, δ 4.9—5.35; C-4, δ 1.75—2.6; C-10, δ 1.45—1.75; pin-2(10)-ene, C-3, δ 2.15—2.80; C-4, δ 1.55—2.15, C-10, δ 4.35—4.70. The assignment of the shifts was based on the reported n.m.r spectral parameters of pinenes.[3] Furthermore, the stereochemistry of the incorporated deuterium was determined from lanthanide-induced ^{1}H n.m.r. measurements of *cis*-myrtanol, which was produced by hydroboration of pin-2(10)-ene with LiBH$_4$ and acetic acid and by oxidation of the borane according to the method of Brown *et al.*[4a] modified by Uzarewicz and Uzarewicz.[4b] All g.l.c. and mass measurements are accurate to within ±10%.

RESULTS AND DISCUSSION

Nopinone.—The results for the deuteriation of nopinone are shown in Figure 1, where each mole fraction of non-, mono-, and di-deuteriated nopinone is plotted against reaction time. There was rapid uptake of one deuterium atom into nopinone with a half-life of <10 min, followed by the slower incorporation of a second deuterium. To accelerate the second incorporation, the reaction was carried out at ambient temperature. The rate for the first deuterium uptake was 14.1 times faster than that for the second in the mole fraction range of [$^2H_1$]nopinone between 0.6 and the inflection point. There is little [$^2H_2$]nopinone formed in the range below 0.6.

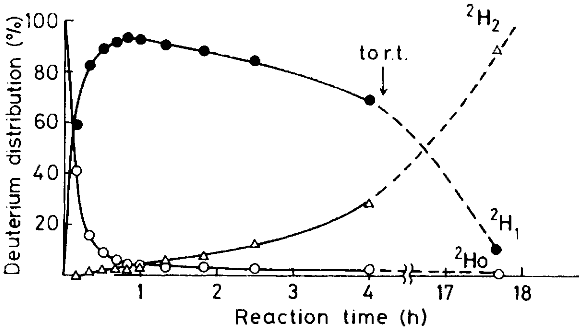


FIGURE 1 Exchange reaction of nopinone. Deuterium distribution of [$^2H_0$]- (○), [$^2H_1$]- (●), and [$^2H_2$]-nopinone (△)

The stereochemistry of deuterium incorporation was examined by means of the lanthanide-shifted n.m.r. spectra of α-nopinol, after the close agreement of the deuterium distributions in nopinone and α-nopinol had been confirmed. The n.m.r. spectra clearly shows that the first deuterium atom occupies the 3β-position, and the second the 3α-position.

Based on the above results, the ratios of the rate constants were calculated by formulating rate equations based on Scheme 1. In Scheme 1, it should be understood that the base concentration is included in all the k values, the protium donor concentration in k_{-1}, k_{-4}, and k_{-5}, and the deuterium donor concentration in k_{-2}, k_{-3}, and k_{-6}. It can be plausibly assumed that (1) k_{-1}, k_{-4}, and k_{-5} can be neglected, since 97% of exchangeable hydrogen in the system consisted of deuterium, (2) k_1 is equal to the sum of k_4 and k_5, if secondary isotope effects can be neglected, and (3) the ratios of k_5 to k_2 and k_4 to k_3 are the same, since both correspond to the primary isotope effect. Furthermore, it was assumed that the rate of formation for each species obeyed the mass-action law and the variation in concentration for the enol intermediates can be neglected, compared with that for nopinones (steady state assumption). Thus, the rate of formation of [$^2H_1$]nopinone (equal to $D_1{}^t + D_1{}^c$) can

$$d[D_1]/dt = k_1[D_0] - k_4[D_1{}^t] - k_5[D_1{}^c] \qquad (1)$$

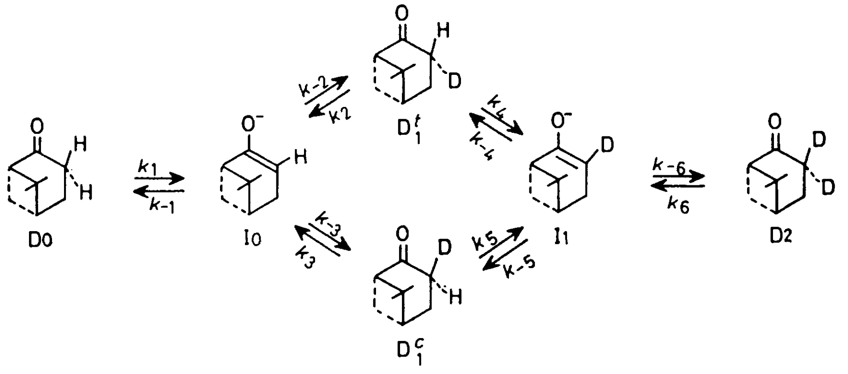
be calculated from equation (1). Applying the same type of treatment to $d[D_2]/dt$, the ratio $d[D_2]/d[D_1]$ is given

$$\frac{d[D_2]}{d[D_1]} = \frac{k_4[D_1{}^t] + k_5[D_1{}^c]}{k_1[D_0] - k_4[D_1{}^t] - k_5[D_1{}^c]} \qquad (2)$$

by equation (2). Since $d[D_2]/d[D_1]$ is $1/14.1 = 0.071$ in the mole fraction range of [$^2H_1$]nopinone between 0.6 and the inflection point, k_4/k_1 is expressed by equations (3) and (4), in which x and y denote $[D_1{}^c]/[D_1{}^t]$ and $[D_1]/[D_0]$, respectively.

$$\frac{k_4}{k_1} = \frac{0.071(1 + x) - (1 + 0.071)xy}{(1 + 0.071)y(1 - x)} \qquad (3)$$

$$= \frac{0.142 - 1.071y}{1.071y(1 - x)} - \frac{0.071 - 1.071y}{1.071y} \qquad (4)$$



SCHEME 1 Reactions of nopinone

Since k_4/k_1 is positive, the denominator of equation (3) is positive, and, thus, the numerator is positive. The value of x at the inflection point, x_i was estimated to be <0.003 1 from the equation $0.071/(1.071y_i - 0.071)$, where y_i took the value 0.935/0.043 from the results in Table 1. Furthermore, since $(0.142 - 1.071y)/1.071y$ of equation (4) is negative, because $[D_1]$ is between 0.6 and 0.935, and the value of x was less than unity (n.m.r.), equation (4) shows that the smaller the value of x, the larger is k_4/k_1. Thus, k_4/k_1 was calculated at the inflection point to be less than 0.003 0, from 0.071/ $1.071y_i$, obtained by substituting $x = 0$ in equations (3) and (4).

$$d[D_1{}^t]/dt = \frac{k_{-2}}{k_{-2} + k_{-3}}(k_1[D_0] + k_2[D_1{}^t] + k_3[D_1{}^c]) - (k_2 + k_4)[D_1{}^t] \qquad (5)$$

On the other hand, the rate of formation of $D_1{}^t$ is given by equation (5). Since almost all D_1 consists of

D_1^t, both D_1 and D_1^t will have an inflection at almost the same reaction time. Thus, from $d[D_1]/dt = d[D_1^t]/dt = 0$ at the inflection point, k_{-3}/k_{-2} can be expressed as in equation (6). Equation (6) is converted into (7) by using the assumptions described before, *i.e.* $k_1 = k_4 + k_5$ and $k_5/k_2 = k_4/k_3$. Since equation (7) indicates that the larger the values of k_5/k_2 and x_i and the smaller that of k_4/k_1, the larger is k_{-3}/k_{-2}, k_{-3}/k_{-2} was given as <0.022 by setting k_5/k_2, x_i, and k_4/k_1 equal to 7,[5] 0.003 1, and 0, respectively. From these calculations, the main reaction pathways in Scheme 1 are a forward reaction from [$^2H_0$]nopinone to I_0, in which the 3β-hydrogen of nopinone is picked up by base 330 times * (1/0.003 0) or more faster than 3α-hydrogen, and a reversible reaction between I_0 and D_1^t, in which a deuterium is donated to I_0 at the 3β-position 46 times * (1/0.022) or more faster than that at the 3α-position and 3β-deuterium of D_1^t is removed 47 times * [calculated from (1 − 0.003 0)/(0.003 0 × primary isotope effect taken as 7)] or more faster than the 3α-hydrogen. This causes accumulation of D_1^t. Once D_1^c is formed, it produces I_1 1 300 times * [calculated from (1 − 0.003 0/0.003 0) × (primary isotope effect taken as 4 [5])] or more faster than I_0.

$$\frac{k_{-3}}{k_{-2}} = \frac{(k_3 + k_5)}{(k_2 + k_4)}\, x_i \qquad (6)$$

$$\frac{k_{-3}}{k_{-2}} = \frac{\dfrac{k_5}{k_2} - \dfrac{k_4}{k_1}\left(\dfrac{k_5}{k_2} - 1\right)}{1 + \dfrac{k_4}{k_1}\left(\dfrac{k_5}{k_2} - 1\right)}\, x_i \qquad (7)$$

TABLE 1

Deuterium uptake in nopinone [a-c]

Reaction time (h)	0.17	0.33	0.52	0.68	0.83	1.00	1.33	1.83	2.50	4.00	17.70
$[D_0]$ [d]	0.410	0.159	0.090	0.059	0.043	0.034	0.034	0.034	0.028	0.027	0.005
$[D_1]$ [d]	0.590	0.823	0.889	0.918	0.935	0.927	0.905	0.886	0.845	0.692	0.108
$[D_2]$ [d]	0.000	0.017	0.021	0.023	0.022	0.039	0.061	0.079	0.127	0.281	0.887

[a] The reaction was carried out at 0 °C except the last sample (of which the reaction time was shown to be 17.70), whose reaction temperature was raised to ambient after keeping 0 °C for 4 h. [b] Errors of the above data are at most ±10%. [c] No [$^2H_3$]nopinone was observed within experimental error. [d] $[D_0]$, $[D_1]$, and $[D_2]$ are the mole fractions of [$^2H_0$]-, [$^2H_1$]-, and [$^2H_2$]-nopinone, respectively.

Pinenes.—A deuterium exchange reaction of pin-2-ene with dimethyl [$^2H_6$]sulphoxide catalysed by sodium methylsulphinylmethide, produced from sodium hydride and dimethyl sulphoxide,[6] was carried out, but the exchange rate was so slow that only 0.12 molecules of deuterium per pin-2-ene were incorporated after 56 h. On the other hand, pin-2(10)-ene did pick up deuterium in the same media. Figure 2 shows plots of mole fractions mono- and di-deuteriated pin-2- and -2(10)-ene against the mole fraction of pin-2-ene. A 70% mole fraction of pin-2-ene corresponds to a reaction time of 24 h. Pin-2-ene produced from pin-2(10)-ene by the isomerization reaction, picks up almost one deuterium at the beginning of the reaction. For pin-2(10)-ene, there was a rapid uptake of a first deuterium, followed by the slower incorporation of a second. These results are analogous to the case of nopinone. The rate ratio of the second to the first uptake was calculated at 0.073 in the mole fraction range of [$^2H_1$]pin-2(10)-ene between 0.4 and the inflection point. By using the results in Figure 1, one also can calculate the total deuterium content in pin-2- and -2(10)-ene from the expression [deuterium content per molecule of a pinene(φ)] × (mole fraction for the pinene). The ratios of the total deuterium content of pin-2(10)- and -2-ene extrapolated to zero % pin-2-ene was 1.95. This value suggests that an intermediate collapses about twice as fast to pin-2(10)-ene than to pin-2-ene. From this value and the equilibrium constant for pin-2(10)-ene/pin-2-ene measured to be 0.02 by Bank *et al.*[7] at 55 °C using 0.7M-KOBu^t in DMSO, the rate constant for the formation of an intermediate from pin-2(10)-ene can be estimated to be *ca.* 100 times larger

$$\text{pin-2(10)-ene} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{intermediate} \underset{k_b}{\overset{k_{-b}}{\rightleftharpoons}} \text{pin-2-ene}$$

$$k_{-a}/k_{-b} = 1.95,\ (k_{-a}/k_a)(k_b/k_{-b}) = 0.02,\ \text{then } k_a/k_b = 98$$

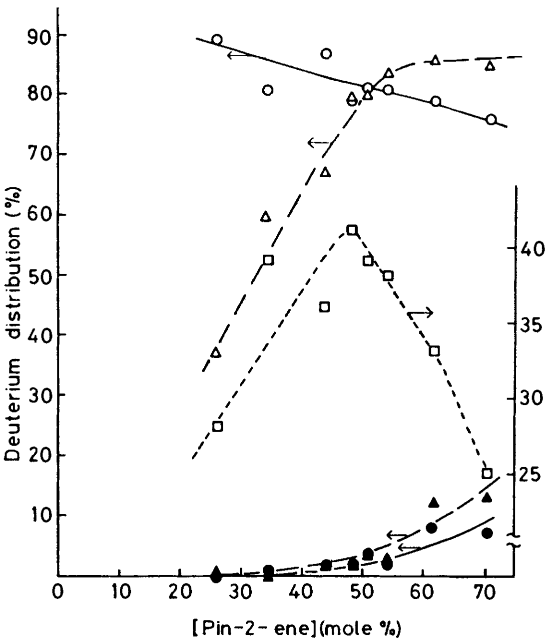


FIGURE 2 Exchange and isomerization reactions of pin-2(10)-ene. Deuterium distribution of [$^2H_1$]- (△) and]$^2H_2$]-pin-2(10)-ene (▲) and [$^2H_1$]- (○), and [$^2H_2$]-pin-2-ene (●). Mole fraction of [$^2H_1$]-pin-2(10)-ene (□)

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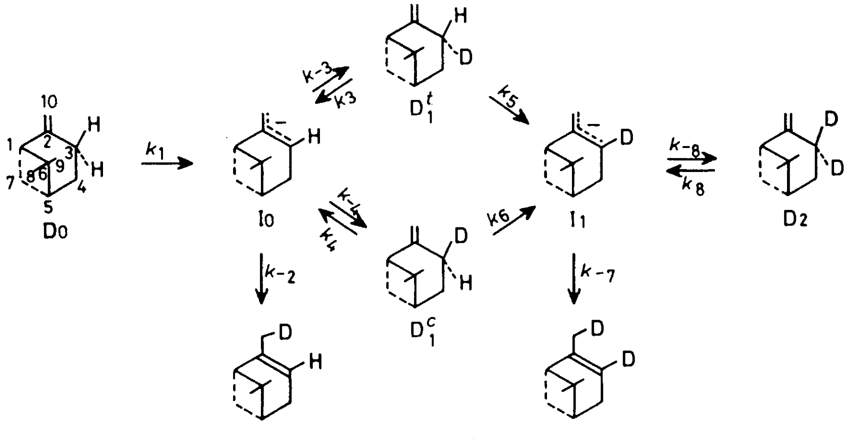
* The errors are at most ±18%.

than that from pin-2-ene. This explains why deuterium is not incorporated into pin-2-ene, but is into pin-2(10)-ene.

The position of deuterium in pin-2(10)- and -2-ene was estimated by the procedures described in the Experimental section and is shown in Table 2. In spite of the large errors Table 2 clearly demonstrates that pin-2-ene formed from pin-2(10)-ene takes up deuterium at C-10, and pin-2(10)-ene at C-3, showing that the isomerization between pin-2(10)- and -2-ene proceeds through an allylic anion intermediate. Pin-2(10)-ene is converted into an allyl anion by removal of an allylic hydrogen at C-3 and the allyl anion accepts a deuterium either at C-3 to produce [$^2H_1$]pin-2(10)-ene or at C-10 to give [$^2H_1$]pin-2-ene. The stereochemistry of [$^2H_1$]pin-2(10)-ene was determined by converting it into *cis*-myrtanol without loss of deuterium and measuring the lanthanide-induced n.m.r. chemical shifts. The n.m.r. spectra show that [$^2H_1$]pin-2(10)-ene, which has 0.62 molecules of deuterium per pinene according to the mass spectrum, has no deuterium at the 3α-position, but does have 0.59 molecules of deuterium at the 3β-position, as in the case of nopinone.



SCHEME 2 Reactions of pin-2(10)-ene

The rate of each step in Scheme 2 was formulated by the same procedures as described for nopinone. Equation (8) corresponding to equation (2) for nopinone is obtained, in which *f* shows a value of $(k_{-3} + k_{-4})/(k_{-2} + k_{-3} + k_{-4}) = k_{-a}/(k_{-a} + k_{-b}) \equiv 0.661$. k_5/k_1 is expressed

$$\frac{d[D_2]}{d[D_1]} = \frac{f\{(k_3 + k_4)[D_2] + k_5[D_1{}^t] + k_6[D_1{}^c]\} - (k_3 + k_4)[D_2]}{f\{k_1[D_0] + k_3[D_1{}^t] + k_4[D_1{}^c]\} - (k_3 + k_5)[D_1{}^t] - (k_4 + k_6)[D_1{}^c]} \tag{8}$$

$$\frac{k_5}{k_1} = \frac{\frac{1-f}{z}[D_2] - \frac{[D_1]}{1+x}\left\{x(f + 0.073) + 0.073\,\frac{1-f}{z}\right\} + 0.073f[D_0]}{\frac{1-x}{1+x}[D_1]\left\{(f + 0.073) - 0.073\,\frac{1-f}{z}\right\}} \tag{9}$$

by equation (9) using the fact that $d[D_2]/d[D_1] = 0.073$ in the limited range of [$^2H_1$]pin-2(10)-ene concentration. *x* and *z* represent $[D_1{}^c]/[D_1{}^t]$ and the isotope effect ($k_6k/_3$ and k_5/k_4), respectively. As shown in Figure 2, the mole fraction of [$^2H_1$]pin-2(10)-ene calculated by using the expression {deuterium distribution of [$^2H_1$]pin-2(10)-ene} × [mole fraction of pin-2(10)-ene], gives an inflection at mole fraction of [$^2H_0$]-, [$^2H_1$]-, and [$^2H_2$]-pin-2(10)-ene corresponding to 0.073, 0.414, and 0.016, respectively. By using these data and an isotope effect of 7 and analysing equation (9) by the same treatment as for equations (3) and (4), k_5/k_1 and x_i were computed to take the same value, <0.009 5.

TABLE 2

Deuterium position in pin-2- and -2(10)-ene [a, b]

Pin-2-ene (mole %)	$\phi^{2-P}(\phi^{2(10)-P})$ [c]	Deuterium position [d]		
		C-3	C-4	C-10
0.34	0.82	−0.16	0.26	0.73
	(0.60)	(0.68)	(0)	(−0.09)
0.48	0.82	−0.04	0.13	0.73
	(0.85)	(1.14)	(−0.08)	(−0.01)
0.53	0.85	0.01	0.02	0.82
	(0.89)	(1.18)	(−0.21)	(−0.07)
0.70	0.90	0.11	−0.05	0.84
	(1.11)	(1.22)	(−0.04)	(−0.07)

[a] Outer and inner values in parentheses correspond to the value for pine-2- and -2(10)-ene, respectively. [b] Limits of the error for deuterium position were calculated to be 0.17 (0.34), 0.34 (0.29), and 0.29 (0.24) for C-3, -4, and -10, respectively. [c] Deuterium content per molecule of pinene. [d] Number of deuterium atoms attached to specified carbon.

On the other hand, starting from equation (10) and analysing by the same procedures as for equations (6) and (7), k_{-4}/k_{-3} was calculated to be less than 0.066. Thus, it appears that the reaction proceeds as follows. (1) [$^2H_0$]Pin-2(10)-ene produces I_0, in which a 3β-hydrogen atom of pin-2(10)-ene is taken away by base 110 times * or more faster than a 3α-hydrogen atom. (2) A deuterium atom is donated to I_0 at C-10 to produce [$^2H_1$]pin-2-ene, at C-3 to give $D_1{}^t$, and at C-3 to give

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* The errors are at most ±22%.

D_1^c with a ratio of 1 : 1.83 * : 0.12 *, respectively. (3) D_1^t is converted into I_0 15 * times or more faster than into I_1. (4) D_1^c is changed into I_1 420 * times or more faster than into I_0.

$$\frac{d[D_1^t]}{dt} = \frac{k_{-3}}{k_{-2} + k_{-3} + k_{-4}}\{k_1[D_0] + k_3[D_1^t] + k_4[D_1^c]\} - (k_3 + k_5)[D_1^t] \quad (10)$$

Conclusions.—Nopinone and pin-2(10)-ene are exchanged with deuterium by the action of base catalysis. In both systems, there was a rapid uptake of a first deuterium atom at the 3β-position, followed by the slower incorporation of a second deuterium at the 3α-position. Pin-2(10)-ene isomerized into pin-2-ene through an allyl anion intermediate. Based on Schemes 1 and 2, the rate of formation for each species was formulated. It can be shown from the analysis of the rate equations that the preferential exchange of deuterium at the 3β-position is caused by two stereospecific reactions. (1) The base removes specifically the 3β-hydrogen atom of the reactant. (2) Deuterium is donated preferentially to the 3β-position of the intermediate. From these results and the other reports mentioned in the Introduction, it seems general that reagents preferentially attack the 3β-position in the 6,6-dimethylbicyclo[3.1.1]heptane system, because of steric hindrance by the 6,6-dimethyl group.

We thank Professor K. Tanabe for his critical reading of the manuscript and helpful discussions.

[9/046 *Received, 9th January*, 1979]

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* The errors are at most ±22%.

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