quantitative recovery) to give pure bicyclo[3.1.0]hexane-1-carboxamide having the same melting point as a sample sublimed for analysis, m.p. 161–162°, with softening at 155°. The infrared spectrum (potassium bromide pellet) contains an inflection at 3.32 μ and a band at 3.23 μ (calcium fluoride prism) as well as a strong band at 9.94 μ, characteristic of the three-membered ring.[18]

Anal. Calcd. for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.29; H, 8.98; N, 11.37.

Methyl 3-cyclohexenecarboxylate. Butadiene and methyl acrylate were condensed in a Diels-Alder reaction by a published procedure[41] to give a 91% yield of methyl 3-cyclohexenecarboxylate, b.p. 80° (20 mm.), n_{D}^{25} 1.4589 (reported,[41] b.p. 70° at 13 mm.).

3-Cyclohexenecarboxamide was prepared by heating 0.69 g. of the ester and 10 ml. of a saturated methanolic-ammonia solution in a sealed tube at 100° for 2 days. Removal of the solvent and crystallization of the crude product from cyclohexane-benzene gave 0.48 g. (78%) of 3-cyclohexenecarboxamide having the same melting point as a sample sublimed for analysis, m.p. 155.5–156.5°.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.43; H, 9.00; N, 11.34.

Methyl 3,4-epoxycyclohexanecarboxylate (XIVa). A solution of 0.10 mole of commercial peracetic acid in 30 ml. of methylene chloride was shaken with 4.0 g. of sodium acetate trihydrate, separated, and added dropwise with stirring over a 10-min. period to a cold solution of 7.0 g. (0.05 mole) of methyl 3-cyclohexenecarboxylate in 28 ml. of methylene chloride. When the addition was complete, the reaction mixture was allowed to stand at room temperature for 2 days. A 40% solution of sodium hydroxide was added dropwise, with cooling, to neutralize the excess acid. The solid material was separated, dissolved in water and extracted with methylene chloride. The combined methylene chloride solutions (which gave a negative starch-iodide test) were dried.[31] Distillation of the product through a semimicro column gave 2.8 g. of unchanged ester, b.p. 80–82° (22 mm.), and 3.6 g. (77%, based on recovered starting material) of methyl 3,4-epoxycyclohexanecarboxylate, b.p. 115–117° (22 mm.), n_{D}^{25} 1.4626. Large scale preparations gave comparable yields. An analytical sample had b. p. 109.5–110.5° (17 mm.), n_{D}^{25} 1.4625.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.49; H, 7.56.

Reaction of methyl 3,4-epoxycyclohexanecarboxylate with potassium t-butoxide. (a) *Short reaction time.* A solution of 0.047 mole of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol was added dropwise, with stirring, over a 5-min. period to a solution of 7.41 g. (0.047 mole) of methyl 3,4-epoxycyclohexanecarboxylate and 50 ml. of *t*-butyl alcohol. The reaction mixture was heated under reflux for 1 hr., cooled, treated with sodium chloride solution, and extracted with ether. The dried ether solution was concentrated on the steam bath and the residue was distilled through a semimicro column giving 6.63 g. (71%) of *t-butyl 3,4-epoxycyclohexanecarboxylate* (XIVb), b.p. 82.5–85.5° (1.3 mm.), n_{D}^{25} 1.4525–1.4534. An analytical sample had b.p. 80.5–81.5° (1.4 mm.), n_{D}^{25} 1.4525.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.91; H, 9.09.

The infrared spectrum of the product contains the bands characteristic of a *t*-butyl group (7.22 and 7.33 μ)[42] and does not contain bands characteristic for a hydroxyl group or a cyclopropane ring. Lithium aluminum hydride reduction gave as a product a viscous oil whose infrared spectrum did not contain the characteristic bands of a *t*-butyl group. This demonstrates that the *t*-butyl group must be present in an ester rather than an ether function.

(b) *Long reaction time.* The reaction was carried out as in part (a) using 7.91 g. (0.051 mole) of methyl 3,4-epoxycyclohexanecarboxylate in 100 ml. of anhydrous *t*-butyl alcohol and a solution of 0.052 mole of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol. The reaction mixture was stirred and heated under reflux for 8.5 hr., then worked up as in part (a). Fractional distillation through a semimicro column gave 4.38 g. (44%) of *t*-butyl 3,4-epoxycyclohexanecarboxylate, b.p. 75–105° (1.2 mm.), n_{D}^{25} 1.4533–1.4559 and 2.54 g. (22%) of a fraction distilling mostly at 113–114° (1.2 mm.), n_{D}^{25} 1.4577 which was identified as *t-butyl 3,4-methoxyhydroxycyclohexanecarboxylate* (XVII). An analytical sample had b.p. 74° (0.03 mm.), n_{D}^{25} 1.4575.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; OCH_3, 13.47. Found: C, 62.60; H, 9.63; OCH_3, 15.15.

The infrared spectrum (calcium fluoride prism) of the *t*-butyl 3,4-methoxyhydroxycyclohexanecarboxylate contains the characteristic bands for associated (2.88 μ, broad) and unassociated hydroxyl (2.78 μ, sharp) and for the *t*-butyl group[42] (7.22 μ and 7.34 μ).

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(42) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 13, 22.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MEXICO]

Structure and Properties of Cyclic Compounds. X.[1] Dissociation Constants of Cyanohydrins of Some Bridged-Ring Ketones

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The dissociation constants of the cyanohydrins of norcamphor (XIII) and dehydronorcamphor (XIV) and of a number of methyl derivatives (XV–XVII) of the former have been measured. Methyl groups have a very large effect on reactivity in this system.

The bicyclo[2.2.1]heptane system of norcamphane (I) contains a cyclohexane ring (III) rigidly held in a boat form.[3] The one-carbon bridge distorts the ring and introduces considerable strain which has been estimated to amount to about 6 kcal.[4] In forming this ring from the boat form of cyclo-

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(3) (a) C. W. Shoppee, *Chemistry & Industry*, 86 (1952); (b) D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027.

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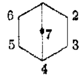
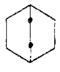
hexane by bridging the 1,4-carbon atoms (I) by a single methylene group these atoms must be brought closer together and all the internal angles of the bridge considerably opened. Bicyclo[2.2.2]-octane (II) with a two-methylene bridge is perfectly symmetrical and not strained.[5]

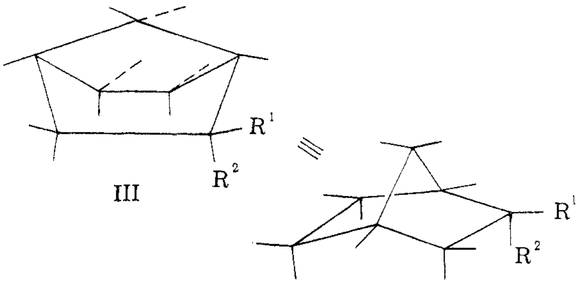
Placing a double bond inside a bicycloheptane ring will considerably increase the strain, since the preferred angle between carbon-carbon single and double bonds of 124° must be constrained to enter the ring and the original single bond (1.54 Å) is shortened to a double bond (1.35 Å). Chemical evidence in favor of this generalization is that the dehydration of tertiary methyl carbinols tends to take place exocyclically by loss of a primary methyl hydrogen atom rather than by loss of a secondary ring atom. Thus *tert.*-methyl borneol (V) gives β-methylcamphene (VI)[6] as well as α-methyl camphene (VII) formed by rearrangement, 3-methylepiborneol (VIII) gives 4-methyl-α-fenchene (IX)[7] and 2-methylisofenchol (X) gives 1-methyl-β-fenchene (XI) and only a little 1-methyl-γ-fenchene (XII).[8] Moreover the enol ether of camphor is very unstable, being hydrolyzed by water[9a] and both camphor-2-carbethoxylate[9b] and camphor[9c] have very small enol contents. In these respects the bicycloheptane ring is more similar to a cyclopentane ring than to a cyclohexane ring.[10a]



I

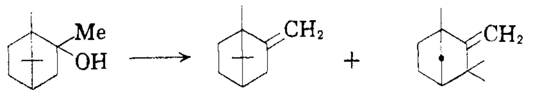


II



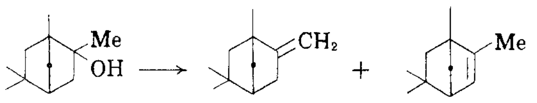
III

IV



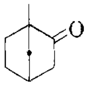
V VI VII

VIII IX

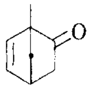


X XI XII

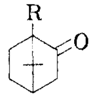
A double bond exocyclic to the ring will produce a little extra strain since the preferred double bond internal angle is about 116° and this will have to be diminished to enter a ring, which has its angle a little less than the carbon tetrahedral angle. Thus addition to a ketone group might be favored since it will result in a small decrease in I-strain.[10b] However in the boat-form of cyclohexane the two pairs of bonds on either side of the ring are eclipsed and addition to the keto group in XIII will introduce unfavorable eclipsing interactions (IV). In this respect, too, the bicycloheptane ring is similar to a cyclopentane ring.[10] To test this hypothesis the dissociation constant of the cyanohydrin of norcamphor (XIII) has been measured (Table I) and found to be little different from that of cyclopentanone, but quite different from the high reactivity of cyclohexanone in its free chair-form. In the case of dehydronorcamphor (XIV) the double bond will introduce additional strain at the ketone group and facilitate an addition reaction. However there is an electronic effect of the double bond across the ring, which is manifest in the ultraviolet[11a] and infrared absorption[11b] of the ketone, and the inductive effect will decrease the ketone reactivity.[12] The net result of the opposing effects is an observed increase of about a factor of 3 in reactivity.



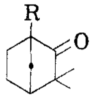
XIII



XIV



XVa, R = H
b, R = Me



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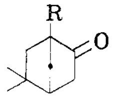
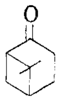
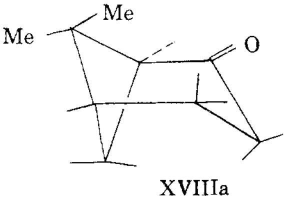
b, R = Me



XVIIa, R = H
b, R = Me



XVIII



XVIIIa

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Methyl groups have a considerable effect on the reactivity of cyclohexanone[13] and in order to investigate their effect in this system a number of methylated ketones (XV–XVII) were prepared and the dissociation constants of their cyanohydrins measured (Table I). α-Fenchocamphorone (XVa), which has two methyl groups on the bridge methylene groups, is 13 times less reactive than norcamphor (XIII) and camphor (XVb), with an extra methyl group on the bridgehead adjacent to the keto-group, is 18 times less reactive. This large effect of the methyl groups results from the fact that one of them is placed over the ketone group[3a] and interferes considerably with the cyano (or hydroxyl) group of the cyanohydrin. This effect is analogous to the axial-crowding effect observed in 3-substituted cyclohexanones.[13a] When the pair of methyl groups is placed adjacent to the carbonyl group as in camphenilone (XVIa) and fenchone (XVIb) the effect is much greater, these compounds being 90 and 130 times less reactive than norcamphor. In these cases both the methyl groups will be eclipsed with the cyano and hydroxyl groups of the cyanohydrin. However when this pair of methyl groups is across the ring as in isofenchone (XVIIb) they exert no steric effect at all. The large difference in reactivity of fenchone (XVIb) and isofenchone (XVIIb) of 226/1 is noteworthy.

The large interference effect of methyl groups on the bridgehead accounts for the reversed stability of the isomeric alcohols formed by reduction of norcamphor (XIII) and camphor (XVb).[3a] Thus norisoborneol (III, IV; $R^1 = OH$, $R^2 = H$) with the hydroxyl group in the more stable exo or equatorial position, is more stable than norborneol (III, IV; $R^1 = H$, $R^2 = OH$) in which the hydroxyl group is in an endo or axial position.[14] However in the camphor series borneol (hydroxyl endo) is more stable than isoborneol (hydroxyl exo),[15] because of the *gem* dimethyl group in the latter isomer. Such interference also leads to low reactivity of camphor in a number of addition reactions. Catalytic reduction proceeds very slowly[16] giving isoborneol (exo) formed by attack from the less hindered underside of the molecule, and reduction with aluminum isopropoxide also proceeds slowly giving 70% isoborneol.[17]

Extension of these above observations allows possible steric assignments to be made to a number of pairs of alcohols of unknown configuration. Since the methyl groups in isofenchone (XVIIb) have no effect on the ketone-cyanohydrin equilibrium, the more stable of the two α and β isofenchols should have an exo hydroxyl group as in the norcamphor series. α-Isofenchol is uneffected by sodium ethoxide in xylene, whereas β-isofenchol is partially converted to the α-isomer.[14,18] Also reduction of isofenchone with sodium in alcohol gives largely the α-isomer.[18] Such procedures give the more stable isomer[3b] and this α-isomer must have the hydroxyl group exo.[19] Catalytic reduction proceeds by absorption of the ketone grouping on the catalyst from the less hindered side,[3b] which in this case is from the exo direction, and it is observed that β-(endo)-isofenchol is formed in over 90%.[18] Similarly since reduction of β-fenchocamphorone (XVIIa) with sodium and alcohol gives β-fenchocamphorol with less than 10% of iso-β-fenchocamphorol,[20a] these must be the exo- and endo-isomers respectively.

Reduction of epicamphor (3-ketocamphane) with sodium and alcohol gives epiborneol,[16b,20b] while catalytic hydrogenation gives epi-isoborneol,[16b] and by analogy with camphor these should have the endo and exo configurations respectively. In the case of the fenchols (from XVIb) one of the methyl groups in position 3 interferes with the hydroxyl group in either configuration and since at position 7 there is only hydrogen atom, there will probably be little difference between the isomers, and sodium catalyzed isomerization of either alcohol gives a mixture of both.[21a] Infrared evidence[19] suggests that β-fenchol is the exo-isomer.

The camphenilols, I and II, derived from camphenilone (XVIa) are probably the exo and endo isomers since they are formed by sodium-ethanol reduction[22a] and catalytic hydrogenation respectively.[22b]

An additional manner of bridging a cyclohexane ring is with a 1,3-bridge as in bicyclo[3.1.1]heptane derivatives (XVIII) and in this case the cyclohexane ring has the form of a distorted chair.[23] However in the case of nopinone (XVIII), because of the distortion of the ring and the shielding effect of one of the methyl groups on the ketone grouping, the reactivity will be less than that of cyclohexanone and it in fact has the same reactivity towards cyanohydrin formation as norcamphor (XIII). Of the corresponding nopinols, the α-

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isomer has been shown to be equatorial and the β-isomer axial,[24a] and as expected sodium reduction gives principally the α-isomer.[24b]

EXPERIMENTAL

Ketones. Norcamphor was prepared by chromic acid oxidation[25] of norborneol[26] and dehydronorcamphor by oxidation of dehydronorborneol[26] using only a slight excess (10%) of oxidant.

TABLE I

Dissociation Constants of Cyanohydrins[a]

	$K_D \times 10^2$	Ratio[b]
Cyclopentanone	2.05[c]	0.67
Cyclohexanone	0.059[c]	.019
Norcamphor (XIII)	3.07	1.0
Dehydronorcamphor (XIV)	1.11	.36
α-Fenchocamphorone (XVa)	38.5	13
Camphor (XVb)	54.0	18
Camphenilone (XVIa)	285	90
Fenchone (XVIb)	397	130
Isofenchone (XVIIb)	1.76	.58
Nopinone (XVIII)	3.07	1.0

[a] In 96% ethanol at 25.0 ± 0.2°. [b] Ratio of dissociation constants to norcamphor = 1.0. [c] O. H. Wheeler and J. Z. Zabicky, ref. 13a, and unpublished results.

Camphor was an Eastman Kodak White Label sample and fenchone an Eastman Kodak Technical sample which was fractionated in a 20-plate column.

Camphenilone was prepared by ozonolysis of camphene in acetic acid[27] and nopinone by ozonolysis[28] of a fractionated sample (95% pure) of β-pinene.

Fenchone was reduced with lithium aluminum hydride to α-fenchol which was dehydrated with phthalic anhydride[29] to α-fenchene. Part of this was ozonized to α-fenchocamphorone[30] and part rearranged with acetic-sulfuric acid to isofenchyl acetate,[31] which was hydrolyzed and oxidized to isofenchone.[31]

Several ketones were purified through their semicarbazones and regenerated by steam distillation with phthalic anhydride.[32] The physical constants are given in Table II.

Cyanohydrins. The ketones were dissolved in purified 96% ethanol and an excess of hydrogen cyanide in the same solvent added together with 2% by volume of a 2% solution of tri-*n*-propylamine in ethanol. The solutions were allowed to equilibrate in a constant temperature bath mantained at 25.0 ± 0.2° for 24–30 hr. Samples were withdrawn, added to excess 0.1*N* aqueous silver nitrate, containing 0.5% nitric acid and the excess titrated with standardized potassium thiocyanate using ferric alum as indicator.

In the case of the more reactive ketones, samples of 0.4–0.2 g. were reacted in 50 ml. of solution and 10 ml. samples used for titration. The substituted ketones were very unreactive[33] and their dissociation constants were determined by using samples of 0.4–0.5 g. in 10 ml. of solution and titrating 2 ml. samples with a microburette. All the determinations were repeated 3 or more times and the mean values are reported in table I. Because of the small amount of reacted hydrogen cyanide in the cases of the substituted ketones, the results are only accurate to 5–8%, relatively.

TABLE II

Physical Constants of Ketones[a]

	M.P.	B.P.	n_D^{25}
Norcamphor (XIII)[b]	88–89°(92°)[c]	80°/25 mm.	
Dehydronorcamphor (XIV)[d]	—	72–76°/22 mm. (59–59.3°/18 mm.)[e]	1.4834 (1.4839)[e]
α-Fenchocamphorone (XVa)	108° (110°)[f]	95–100°/27 mm.	
Camphor (XVb)	174–175°	—	—
Camphenilone (XVIa)		85–88°/18 mm. (78°/12 mm.)[g]	1.4669
Fenchone (XVIb)		82–84°/25 mm.	1.4605 (1.4635)[h]
iso-Fenchone (XVIIb)		90–93°/21 mm.	1.4625 (1.4619)[i]
Nopinone (XVIII)[j]		98–99°/25 mm. (77–78.5°/8 mm.)[k]	1.4775 (1.4769)[k]

[a] Literature values in parenthesis. [b] From semicarbazone, m.p. 192.5–193°. Ref. 26 gives m.p. 198°. [c] Ref. 26. [d] From semicarbazone, m.p. 207–208°. P. D. Bartlett and B. E. Tate, Ref. 11b., give m.p. 205–206.8°. [e] Bartlett and Tate, *Loc. Cit.* [f] From semicarbazone, m.p. 218°, Ref. 30 gives m.p. 220°. [g] Ref. 22a. [h] At 18°. O. Wallach, *Ann.*, *263*, 131 (1891); [i] At 20°. Ref. 31. [j] From semicarbazone, m.p. 174.5–176°. [k] Ref. 24a.

Acknowledgments. The work was supported by financial grants from the Rockefeller Foundation, New York.

México, 20. D. F.

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