ferred into a separatory funnel, acidified with hydrochloric acid, and shaken. The slightly yellow organic phase was separated, the aqueous solution was washed with 60 ml. of chloroform, and the chloroform was combined with the carbon tetrachloride solution. The resulting liquid was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from petroleum ether at −5° C. to give 1.273 g. of white crystals, m.p. 88–89° C. Further crystallization raised the melting point to 90–91° C. The melting point was undepressed upon admixture with libocedrol *p*-methoxythymol adduct. The material was separated using the previously described procedure[1] into libocedrol, m.p. 86–87° C., and *p*-methoxythymol characterized as its *p*-nitrobenzoate, m.p. 126–127° C.; both melting points were undepressed on admixture with authentic samples.

The filtrate was diluted to 30 ml. with petroleum ether and extracted with 150 ml. of 5% sodium hydroxide in 3 portions. The petroleum ether solution was dried and evaporated to dryness. The residue was heated on a steam bath with 1.0 g. of *p*-nitrobenzoyl chloride in 5 ml. of pyridine, cooled, and treated with 25 ml. of 10% bicarbonate solution and 50 ml. of ethyl ether. The ethyl ether solution was washed with 50 ml. of 10% sodium carbonate and 50 ml. of 10% hydrochloric acid, dried, and evaporated to dryness. The residue was crystallized from methanol to give 244 mg. of libocedrol *p*-nitrobenzoate, m.p. 165–170° C. (8%). Further crystallization from isooctane followed by crystallization from methanol raised the melting point to 174–175° C., undepressed on admixture with an authentic sample.

The sodium hydroxide extracts were combined, acidified with hydrochloric acid, and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate, filtered, evaporated to dryness, and *p*-nitrobenzoylated in the usual manner to give a very small amount of material of indefinite melting point which was not further investigated.

Thus, the reaction gave 1.020 g. (49%) of libocedrol and 0.425 g. (20%) of the original material.

Comparison of the infrared spectra of the synthetic libocedrol and the naturally occurring material revealed that they were identical. Also the benzoylation of the synthetic libocedrol[11] gave a benzoate, m.p. 137–138° C., which did not depress the melting point of the naturally occurring libocedrol benzoate.

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FOREST PRODUCTS LABORATORY
UNIVERSITY OF CALIFORNIA
RICHMOND, CAL.

Bromination Rates of Some Norcamphor Derivatives[1]

WILLIAM G. WOODS[2] AND JOHN D. ROBERTS

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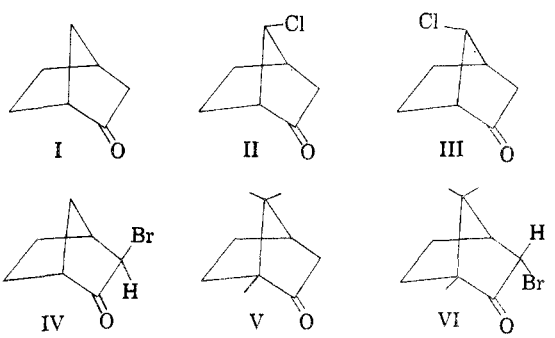
In continuation of earlier work on the effect of structure on reactivity in the norbornyl system,[3] a study has been made of the sodium acetate-catalyzed rates of bromination of norcamphor (I), *syn*- and *anti*-7-chloronorcamphor (II and III), *exo*-3-bromonorcamphor (IV), *d*-camphor (V) and *endo*-3-bromo-*d*-camphor (VI).

Ketones I, II, and III were prepared from the corresponding *exo*-norborneols by chromic acid oxidation, a method found to be superior to nitric acid oxidation.[4] I–III were purified by regeneration from their pure semicarbazones by steam distillation from oxalic acid solution. *d*-Camphor (V) was brominated under acid-catalyzed conditions[5] to give



VI, whose structure has been unequivocally established by an x-ray crystal structure determination.[6,7] *exo*-3-Bromonorcamphor (IV) was prepared by a similar method. In addition to the kinetic argument given below, the *exo*-configuration assigned to the bromine atom of IV was consistent with a comparison of its ultraviolet absorption with those of VI and its *exo*-isomer (Table I).

TABLE I

ULTRAVIOLET SPECTRAL DATA[a]

Ketone	Solvent	λ_{max} Mμ	ε
d-Camphor(V)	95% EtOH	289.5[b]	32
	cyclo-C_6H_{12}	292[b]	23
exo-3-Bromo-*d*-camphor	*cyclo*-C_6H_{12}	312[b]	89
endo-3-Bromo-*d*-camphor(VI)	95% EtOH	306[b]	100
	cyclo-C_6H_{12}	307.5[b]	95.5
Norcamphor(I)	95% EtOH	287	30.9
exo-3-Bromo-norcamphor(IV)	95% EtOH	312	84.4
	cyclo-C_6H_{12}	317	73.2

[a] Determined with a Cary Model 11M recording spectrophotometer using 1-cm. quartz cells. [b] R. C. Cookson, *J. Chem. Soc.*, **1954**, 282 and references cited therein.

(1) Taken in part from the Ph.D. thesis of William G. Woods, California Institute of Technology, 1957.

(2) National Science Foundation Predoctoral Fellow, 1955–56. Present address: General Electric Research Laboratory, Schenectady, N. Y.

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Kinetic measurements. The kinetics of the ketone brominations were measured using the methods of Evans and coworkers.[8,9] Pseudo-first order rates of bromination were determined at 35° in 75% aqueous acetic acid containing 0.238*M* sodium acetate, prepared by diluting 750 ml. of purified acetic acid to 1000 ml. with conductivity water, all at 35°. The low reactivities of the ketones necessitated a correction for the bromine-solvent reaction. The rate of disappearance of bromine in the absence of ketone was cleanly first order and a least-squares fit of the data gave $2.656 \pm 0.056 \times 10^{-7}$ sec.$^{-1}$ for the rate constant at 35°.

Since the rate of the bromine-solvent reaction was of the same order of magnitude as the ketone bromination rates, the rate data were treated in the following semiempirical manner.

Let: [B] = concentration of bromine at time t.
[B_0] = initial concentration of bromine.
[K] = concentration of ketone at time t.
[K_0] = initial concentration of ketone.
k' = rate constant for the bromine-solvent reaction.
k = rate constant for the ketone bromination.

The total rate of disappearance of bromine is given by Equation 1 and that of ketone by Equation 2. Integration of Equation 2 yields Equation 3 for the concentration of ketone at time t. It was

$$\frac{d[B]}{dt} = -k'[B] - k[K] \quad (1)$$

$$\frac{d[K]}{dt} = -k[K] \quad (2)$$

$$[K] = e^{(\ln[K_0] - kt)} \quad (3)$$

found that plots of log ($[K_0] - [B_0] + [B]$) *vs.* times were strictly linear, except for a minor curvature in the early stages of the reaction. This linearity is expressed by Equation 4 which yields Equation 5 on integration.

$$\frac{d \ln ([K_0] - [B_0] + [B])}{dt} = -c \quad (4)$$

$$\ln \frac{[K_0] - [B_0] + [B]}{[K_0]} = -ct \quad (5)$$

Rearrangement and differentiation of Equation 5 gives Equation 6 for the slope at any time t. Substituting Equation 3 and Equation 6 into Equation 1 gives Equation 7, which allows the evaluation of k

$$\frac{d[B]}{dt} = -[K_0]ce^{-ct} \quad (6)$$

$$ke^{(\ln[K_0] - kt)} = [K_0]ce^{-ct} - k'[B] \quad (7)$$

for various pairs of [B] and t values, since [K_0] c and k' are known. A typical set of data is given in Table II.

TABLE II

ANALYSIS OF KINETIC DATA FOR THE BROMINATION OF NORCAMPHOR AT 35° IN 75% ACETIC ACID (0.238*M* IN SODIUM ACETATE)

10^5t, sec.	10^2[B], mol. l.$^{-1}$	10^9d[B]/dt, mol. l.$^{-1}$ sec.$^{-1}$	10^7k, sec.$^{-1}$
0.000	(1.1066)[a]	−5.619	0.98
0.012	1.1055	...	...
0.037	1.0995	...	...
0.133	1.0935	−5.611	0.99
1.800	1.0025	−5.413	1.03
3.586	0.9095	−5.219	1.07
5.301	0.8314	−5.038	1.10
6.971	0.7384	−4.868	1.15

[a] Evaluated by least squares, $c = 2.058 \times 10^{-7}$ sec.$^{-1}$.

As expected from the results of other workers,[9] the k values are found to increase slowly with time, presumably due to further bromination. However, the rate constants could be evaluated with assurance at zero time and are reported in Table III for ketones I–VI.

It has been well established[10] that the rate-determining step in the base-catalyzed bromination of ketones is the removal of the α-hydrogen by the base to give an enolate ion. This enolate ion then rapidly reacts with bromine to give the α-bromoketone. The results in Table III appear to reflect the

TABLE III

PSEUDO-FIRST ORDER BROMINATION RATE CONSTANTS AT 35° IN 75% ACETIC ACID CONTAINING 0.238*M* SODIUM ACETATE

Ketone	K_0, *M*	10^5k, sec.$^{-1}$	Rel. *k*
Norcamphor(I)	0.0273	9.8 ± 0.7	1.00
syn-7-Chloro-norcamphor(II)	0.0173	3.2 ± 0.5	0.3
anti-7-Chloro-norcamphor(III)	0.0174	11.5 ± 0.6	1.2
exo-3-Bromo-norcamphor(IV)	0.0181	2.7 ± 0.4	0.3
d-Camphor(V)	0.0217	<0.28[a]	0.03
endo-3-Bromo-*d*-camphor(VI)	0.0161	5.2 ± 0.7	0.5

[a] Upper limit of experimental error.

importance of steric effects in determining the reactivity of the α-hydrogen atoms of norcamphor derivatives towards acetate ion.

The *exo*-α-hydrogens are apparently attacked faster than the *endo*-α-hydrogens since II is substantially less reactive than either I or III. If the *endo*-α-hydrogens were attacked initially, I, II, and

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III would be expected, in the absence of polar effects, to react at about the same rate. The slightly increased rate of III relative to I is consistent with a small polar effect of the remote *anti*-7-chlorine atom. The threefold decrease in the rate of II relative to I is most simply interpreted as the result of steric shielding of the *exo*-3-hydrogen atom by the *syn*-7-chlorine atom. Partial substantiation of this interpretation is given by the extremely low relative rate of V, presumably due to steric inhibition of *exo*-attack by the *syn*-7-methyl group and the combined inductive (+I) effect of all three methyl groups.

The very high rate of VI relative to V is in agreement with the observation[11] that the introduction of one α-bromine atom generally greatly increases the base-catalyzed rate of bromination of aliphatic ketones. However, IV is found to be less reactive than I, which indicates that steric interference has overcome the accelerating effect expected from the α-bromine atom. Taken with the previous discussion, this result leads to the conclusion that IV is, indeed, *exo*-3-bromonorcamphor.

Although one might find it difficult to predict *a priori* that the *exo*-hydrogens should be more easily removed by base than *endo*-hydrogens, it is of interest to note that the additions of chlorine, hypochlorous acid and bromine[4,12] to norbornene are initiated by *exo* attack on the double bond. A similar *exo* attack of bromine on the enol of I accounts for the formation IV as the acid-catalyzed bromination product of norcamphor (see Experimental).

In an effort to evaluate the relative reactivities of *exo*- and *endo*-hydrogens to attack by base, an attempt was made to prepare *endo*-3-bromonorcamphor(VII). Brief boiling of an ethanolic solution of IV with a catalytic amount of sodium ethoxide[13,14] gave a solution whose ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 307.4 mμ, ϵ 70–79 was different from that of IV and suggested (See Table I) that isomerization to VII had occurred. However, experiments on a preparative scale yielded only impure material of unknown composition.

Preliminary measurements were made of the rates of bromination of I and IV in aqueous sodium hypobromite solution.[11,15] The second order rate constant of I was found to drift upward as the reaction progressed while that of IV decreased with time. Although the kinetic data were of little value in evaluating relative reactivities, infinity titers showed that I ultimately consumed three moles of bromine per mole of ketone and IV consumed two moles of bromine. A preparative scale experiment with I afforded a liquid acidic compound which formed an amide containing bromine but was not investigated further.

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EXPERIMENTAL

Norcamphor (I). To an ice-cooled, stirred solution of 99.5 g. (0.338 mole) of potassium dichromate, 136 g. of concentrated sulfuric acid and 600 ml. of glacial acetic acid in 1500 ml. of water, was added 115 g. (1.025 mole) of *endo*-norborneol.[16] The mixture was stirred for 6 hr. and then allowed to stand at room temperature overnight. A cold solution of 500 g. of technical grade sodium hydroxide in 800 ml. of water was added slowly with cooling and the resultant green slurry was steam distilled. A total of 1500 ml. of steam distillate was collected, saturated with sodium chloride, and extracted with three 500-ml. portions of ether. The combined extracts were dried over magnesium sulfate and calcium sulfate, filtered, and the ether removed. The residue was distilled through a Vigreux column to give 84.5 g. (0.744 mole) of ketone, b.p. 89–119° (60–70 mm.). The semicarbazone had m.p. 195.7–196.7° (lit.,[17] m.p. 196–196.5°) and a mixture of 18.7 g. (0.112 mole) of the purified substance with a solution of 14.5 g. (0.115 mole) of oxalic acid dihydrate in 200 ml. of water was steam distilled until 350 ml. of distillate was collected. Sodium chloride was added and the milky suspension extracted with three 75-ml. portions of ether. The combined extracts were dried over magnesium sulfate and again over calcium sulfate. Most of the ether was removed on the steam bath and the residue was sublimed to give 10.4 g. (0.0945 mole, 84%) of waxy sublimate, m.p. 95.5–96.5° (lit., m.p. 91–92°;[18] 95°[19]).

syn-7-Chloronorcamphor (II). Prepared by the chromic acid oxidation of *syn*-7-chloro-*exo*-norborneol[4] as described above for norcamphor in 59% yield. Regeneration from its semicarbazone gave the pure ketone in 76% yield, m.p. 69–70°.

anti-7-Chloronorcamphor(III). Prepared as above from *anti*-7-chloro-*exo*-norborneol[4] in 43.5 to 65% yield. Regeneration from its semicarbazone gave the pure ketone in 73% yield, m.p. 68–70.5°.

exo-3-Bromonorcamphor(IV). The method of Kipping and Pope[5] was employed. Addition of 7.3 g. (0.0455 mole) of bromine to 5.0 g. (0.0455 mole) of norcamphor heated on the steam bath resulted in the evolution of copious quantities of hydrogen bromide. The reaction mixture was swirled and heated for 20 min. and then allowed to stand at room temperature for 30 min. The resulting yellow oil was taken up in 75 ml. of ether and the ethereal solution was washed with water, saturated sodium bicarbonate solution and then dried over magnesium sulfate. The ether was removed on the steam bath and the residue distilled through a semimicro column[20] to give a forerun of solid norcamphor, 0.4 g., b.p. 110° (53 mm.) followed by two intermediate liquid fractions, 0.80 g., b.p. 100–126.2° (23 mm.). The product was collected as 2.75 g. (38%) of liquid, b.p. 126.2–128.5° (23 mm.), n_D^{25} 1.5219, m.p. 30°.

Anal. Calcd. for C_7H_9OBr: C, 44.47; H, 4.80; Br, 42.27. Found: C, 44.27; H, 4.70; Br, 42.17.

CONTRIBUTION NO. 2234
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIF.

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