at −78 °C by the standard method[19] gave 9-phenyl-9,10-dihydrophenanthrene (200 mg, 99%) as a colorless oil which solidified on standing, mp 80–82 °C. Chromatography on Florisil gave the analytical sample, mp 82–83 °C.

9-Benzyl-9,10-dihydrophenanthrene. 9-Benzylphenanthrene was prepared from 9-bromophenanthrene through reaction of the Grignard derivative with benzyl chloride.[24] Reduction of 9-benzylphenanthrene with lithium in ammonia in the presence of colloidal iron under conditions similar to those employed with the 9-methyl analogue[16] gave 9-benzyl-9,10-dihydrophenanthrene (94%) as oil. Chromatography on silica gel effected removal of residual starting material and furnished the pure title compound.

9-*tert*-Butyl-9,10-dihydrophenanthrene. 9-*tert*-Butylphenanthrene was synthesized through reaction of phenanthrene 9,10-oxide[23] with *tert*-butyllithium followed by acid-catalyzed dehydration. Complete purification required several chromatographies on silica gel impregnated with trinitrofluorenone.[25] The pure 9-*tert*-butylphenanthrene had mp 64–65 °C (lit.[26] 64–65 °C).

Reduction of 9-*tert*-butylphenanthrene (234 mg, 1 mmol) with lithium in ether and ammonia by the standard method have an oil containing 9-*tert*-butyl-9,10-dihydrophenanthrene and recovered starting material (7:3). Chromatography twice on neutral alumina and elution with hexane gave pure 9-*tert*-butyl-9,10-dihydrophenanthrene (86 mg, 35%) free of the parent aromatic hydrocarbon.

5-Methyl- and 5,6-Dimethyl-5,6-dihydrochrysene. The method for the reductive methylation of chrysene previously reported[27] was modified to improve the yield. A solution of chrysene (2.74 g, 12 mmol) in THF (200 ml) was added to 100 ml of refluxing ammonia. Sodium metal (220 mg, 14 mmol) was added, and the resulting deep blue solution was stirred for 4 min, then methyl bromide was bubbled into the solution for 2 min, followed by NH_4Cl (20 g). Conventional workup afforded 2.31 g of a solid. Chromatography on neutral alumina eluted with hexane gave initially 5,6-dimethyl-5,6-dihydrochrysene as a minor product. Recrystallization from chloroform–hexane gave the pure dimethyl compound as a white solid, mp 104–106 °C. Further elution with hexane furnished pure 5-methyl-5,6-dihydrochrysene (1.57 g, 93%) as a colorless solid, mp 132–133 °C.

Acknowledgment. Support of this research by grants from the U.S. Public Health Service CA-11968 (R.G.H.) and the Indiana University Office of Research and Advanced Studies (P.W.R.) is gratefully acknowledged. The Hx-270 Bruker superconducting NMR spectrometer was provided through the University of Chicago Cancer Research Center Grant CA-14599. We also wish to thank Dr. Frederick Beland for synthesis of the sample of pure 9-*tert*-butylphenanthrene, Mr. Walter Flack for modification of the LAOCN 3 program to run on the IBM 360, and Mrs. Sarah Land for testing the program.

Registry No.—9-Cyanophenanthrene, 2510-55-6; 9-acetylphenanthrene, 2039-77-2; 9-(ethylenedioxyethyl)-9,10-dihydrophenanthrene, 60084-40-4; methyl phenanthrene-9-carboxylate, 1217-49-8; phenanthrene-9-carboxylic acid, 837-45-6; ethyl phenanthrene-9-carboxylate, 4895-92-5; 9-trimethylsilylphenanthrene, 18209-95-5; 9-bromophenanthrene, 573-17-1; phenanthrene 9,10-oxide, 585-08-0; 9-*tert*-butylphenanthrene, 17024-05-4; chrysene, 218-01-9; 5,6-dimethyl-5,6-dihydrochrysene, 60084-41-5; 5-methyl-5,6-dihydrochrysene, 34908-52-6; 9-phenyl-9,10-dihydrophenanthrene, 5235-80-3; 9-phenylphenanthrene, 844-20-2; 9-benzyl-9,10-dihydrophenanthrene, 60084-42-6; 9-benzylphenanthrene, 605-05-0.

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Syntheses and Absolute Configurations of Tricyclo[4.3.0.0^{3,7}]nonane ("Brexane"), 3-Oxatricyclo[4.3.0.0^{4,9}]nonane ("3-Oxabrexane"), and Tricyclo[4.2.0.0^{3,7}]octan-2-one ("Norbrexan-2-one")[1]

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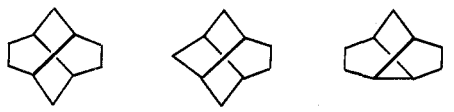
(−)-(1*S*,3*S*,6*R*,7*R*)-Brexane (tricyclo[4.3.0.0^{3,7}]nonane) (**3**) was prepared from (+)-(1*R*,4*R*,7*S*)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (**12**). Examination of the circular dichroism curve of the intermediate, (−)-brexan-2-one (tricyclo[4.3.0.0^{3,7}]nonan-2-one) (**4**), which exhibited a (−) Cotton effect, confirmed the absolute configuration. Starting from (−)-(1*S*,4*S*,7*R*)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (**16**), 3-oxabrexane (3-oxatricyclo[4.3.0.0^{4,9}]nonane) (**5**), and norbrexan-2-one (tricyclo[4.2.0.0^{3,7}]octan-2-one) (**6**) were synthesized in optically active forms.

A feature common to tricyclo[4.4.0.0^{3,8}]decane ("twistane")[2] (**1**) and tricyclo[4.3.0.0^{3,8}]nonane ("twist-brendane")[3] (**2**), whose preparations in optically active forms have been recently reported from our laboratory, is the "twist carbon frame" inherent to their gyrochiral[4] cage-shaped molecules (D_2 and C_2 symmetry, respectively). These twisted carbon

skeletons are undoubtedly responsible for their rather large optical rotations for hydrocarbon,[5] and we have been successful at correlating their signs of rotation to the senses of twist in their carbon frameworks.[6] In highly symmetrical twistane (1), we find five "frozen" twist-boat six-membered rings with identical direction of twist and two types of methylene group. Removal of one of these methylene groups gives



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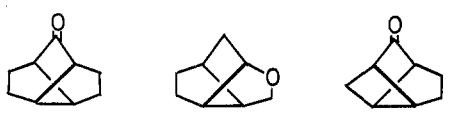

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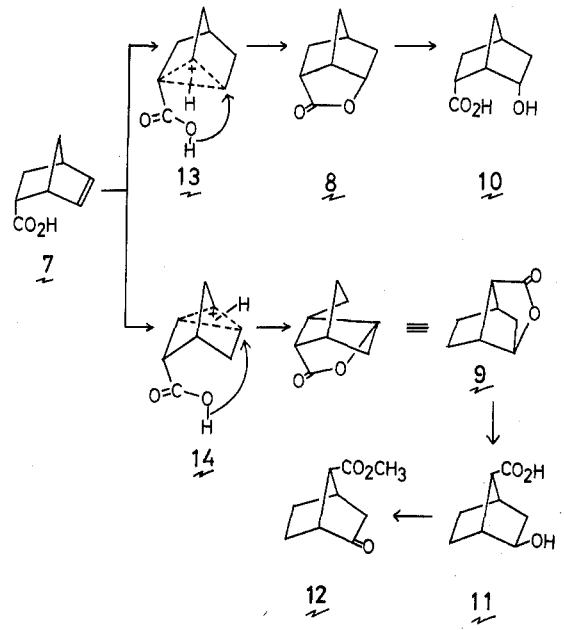
rise to two lower homologues: twist-brendane (2) and tricyclo[4.3.0.0^{3,7}]nonane ("brexane")[7] (3), respectively. Although these cage-shaped tricyclic compounds (2 and 3) share a similar geometrical feature, both belonging to C_2 point group, twist-brendane (2) has a twisted seven-membered ring along C_2 axis interlocked with an oppositely twisted six-membered ring along the axis perpendicular to the C_2 axis, whereas brexane (3) has a five-membered ring twisted along the C_2 axis with an eight-membered ring of the opposite sense of twist. As a part of our continuing effort toward syntheses of high symmetry chiral cage-shaped molecules[8] in optically active forms as well as determination of their absolute configurations, we are interested in comparison of the chiroptical properties between these two types of cage-shaped compounds. Moreover, these stereochemical interests, information on the absolute configuration of (−)-brexan-2-one (4), which is one of the precursor of our synthesis of (−)-brexane (3), is indispensable for our recent investigation on the phytochemical conversion of cage-shaped compounds.[9] In this paper we describe the syntheses and absolute configuration determinations of optically active (−)-brexane (3) and (−)-brexan-2-one (4) together with the preparation of 3-oxatricyclo[4.3.0.0^{4,9}]nonane ("3-oxabrexane")[10] (5) and tricyclo[4.2.0.0^{3,7}]octan-2-one ("norbrexan-2-one")[11] (6) in optically active forms.

Results and Discussion

Synthesis of (−)-Brexane (3). Isomerization with 75% sulfuric acid[12] converted (+)-(1*R*,2*R*,4*R*)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (7)[13] into a mixture of the endo and exo lactone (8 and 9) which was then hydrolyzed with 2 N sodium hydroxide to yield a mixture of sodium salts of the corresponding hydroxy acids (10 and 11).

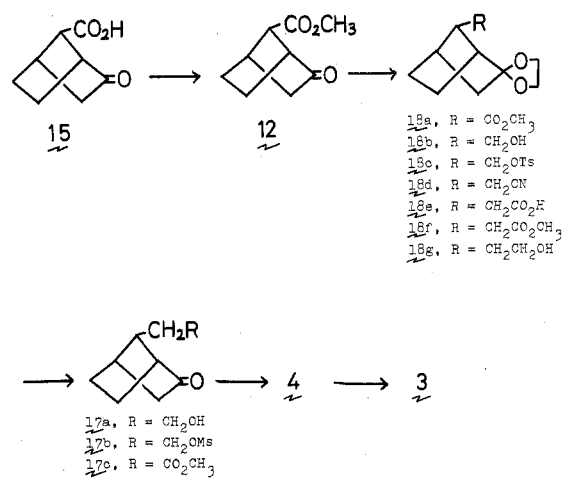
Marked difference observed in their lactonization rates furnished a means to their separation: adjustment of the pH of the hydrolysate to 5 made the endo acid (10) readily lactonize to give 8, $[\alpha]^{14}$D +2.2°, whereas the exo acid (11) remained intact. Permanganate oxidation followed by esterification with diazomethane converted the exo acid (11) into the keto ester (12), $[\alpha]^{13}$D +2.6°. Stereochemical correlations between the starting material (7) and the lactones (8 and 9) could be deduced by postulating (1) participation of the nonclassical ions (13 and 14)[14] and (2) their conversions into lactones (8 and 9), respectively, on intramolecular nucleophilic attack by carboxyl group via stereochemically most favored paths. This correlation indicated the (1*R*,4*R*,7*S*)-configuration for (+)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (12), and this assignment of configuration was supported by the circular dichroism curves of (−)-brexan-2-one (4) prepared from (+) keto ester 12 (vide infra).

Scheme I



Since carrying out the synthesis of optically active brexane required the optically active keto ester 12 in substantial quantity, we divert attention from the above approach to the second one in which optical resolution was performed on the racemic 7-*syn*-carboxybicyclo[2.2.1]heptan-2-one (15). The acid (15) was prepared from a mixture of racemic endo and exo isomers of 2-carboxybicyclo[2.2.1]hept-5-ene (7) by the same procedure described above. Optical resolution of the bicyclic carboxylic acid (15) was accomplished via cinchonidine salts, and the separated enantiomeric acids were esterified with diazomethane to afford (−) methyl ester (16), $[\alpha]^{17}$D −11.6°, and (+) methyl ester (12), $[\alpha]^{13}$D +3.47°. Since our plan to build the tricyclic framework was the intramolecular alkylation of the bicyclic keto mesylate (17b), modification of the carboxylate group was our next step, which was straightforwardly carried out as depicted in Scheme II.[15]

Scheme II

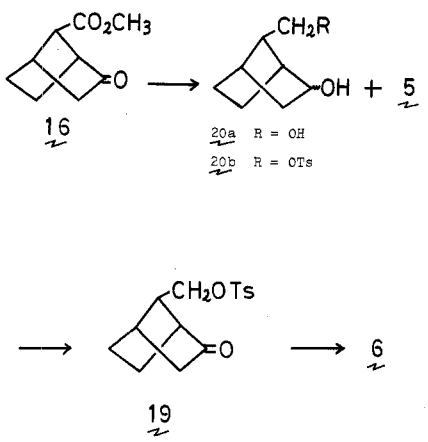


After protection of the keto group of the (+) methyl ester (12) by ketalization with ethylene glycol, the resultant ketal ester (18a) was reduced with lithium aluminum hydride to afford the alcohol (18b) which was further converted into the

nitrile (**18d**) via the tosylate (**18c**). Heating of the nitrile (**18d**) with potassium hydroxide in ethylene glycol led to the formation of the carboxylic acid (**18e**) which was not isolated but was converted into the methyl ester (**18f**) with diazomethane. Hydride reduction of **18f** and removal of the protecting group with 5% sulfuric acid furnished the keto alcohol (**17a**). After the keto mesylate (**17b**) derived from **17a** was heated with sodium hydride in dimethylformamide for 17 h, the ring closure product was purified by chromatography to give (−)-tricyclo[4.3.0.0^{3,7}]nonan-2-one ("brexan-2-one") (**4**), bp 116 °C (20 mm), $[\alpha]^{14}D$ −201°. Wolff–Kishner reduction of (−)-brexan-2-one (**4**) completed the synthesis of (−)-brexane (**3**), $[\alpha]^{15}D$ −94.3°.

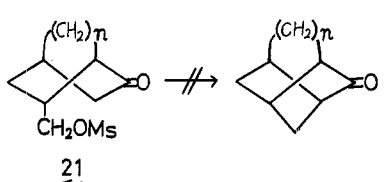
Syntheses of 3-Oxabrexane (5) and Norbrexan-2-one (6). We now divert our attention from the tricyclo[4.3.0.0^{3,7}]-nonane series of compounds to preparation of optically active norbrexan-2-one (**6**), a lower homologue of brexan-2-one (**4**). This time again, our choice among synthetic approachs was intramolecular alkylation of the bicyclic keto tosylate (**19**).

Scheme III



After lithium aluminum hydride reduction of (−)-(1*S*,4*S*,7*R*) keto ester (**16**) (the enantiomer of **12**), the resulting diol (**20a**) was treated with 1 equiv of tosyl chloride in cold pyridine to secure the monotosylate (**20b**). Silica gel chromatography of the reaction mixture revealed, besides the expected monotosylate (**20b**), the formation of a compound $C_8H_{12}O$, mp 63–64 °C, $[\alpha]^{20}D$ −168°. The ir, NMR, and mass spectral evidences all indicate that this compound is (−)-3-oxabrexane (**5**) whose racemate[10] was reported to melt at 64–65°C. Oxidation of the monotosylate (**20b**) with Jones reagent to the keto tosylate (**19**) and treatment of the latter with sodium hydride in dimethylformamide gave an oil, bp 60 °C (20 mm), whose parent peak in the mass spectrum was 122. The CD spectrum (to be discussed later) and the ir spectrum, which lacked olefinic peaks and showed a carbonyl peak at 1754 cm^{-1}, indicated the tricyclic structure **6** for this product. Although the yield of this cyclization was found to be rather low (yield 3.5%), it is relevant to note here that similar attempted intramolecular alkylations have failed in the compounds **21** (n = 1 and 2).

Scheme IV



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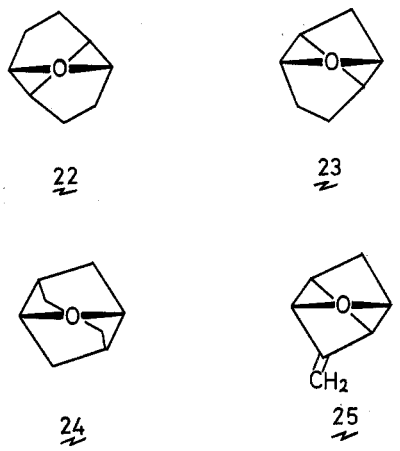
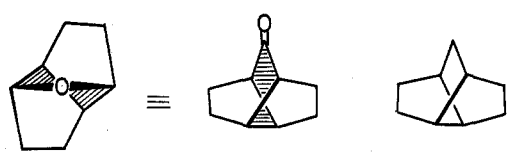
Chiroptical Properties and Absolute Configurations. CD spectral analyses of the various tricyclic ketones (**22**,[2] **23**,[3a] **24**,[3b] and **25**[16]), prepared in our laboratory from the intermediates with known absolute configurations, indicated that



the sign of the CD curve due to n–π^* transition around 300 nm can be predicted by applying the octant rule to the "outer ring"[17] in the projection formula which holds the carbonyl group at the "point of twist".[18] Applying this generalization to (−)-brexan-2-one (**4**) with CD absorptions at 294 ($[\theta]$ −7.24 × 10^3) and 300 nm ($[\theta]$ −7.36 × 10^3), we had the absolute configuration **26** for this tricyclic ketone, which was found



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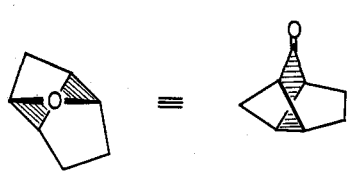
compatible with our assignment of (1*R*,4*R*,7*S*) configuration to the (+) bicyclic keto ester (**12**) by chemical correlation. These facts eventually lead to the absolute configuration **27**, (−)-(1*S*,3*S*,6*R*,7*R*)-tricyclo[4.3.0.0^{3,7}]nonane, for (−)-brexane (**3**), and the absolute configurations **5** and **6**, respectively, to (−)-3-oxabrexane and norbrexan-2-one both prepared from (−)-(1*S*,4*S*,7*R*) bicyclic keto ester (**16**) as shown in Scheme III.

The conclusion was further supported by the (+) sign observed in the CD curve of norbrexan-2-one (**6**), which is compatible with the prediction derived from application of the octant rule to its projection formula **28**.



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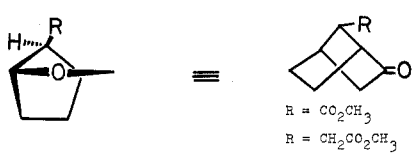
Finally, attention is called to the Cotton effects of the intermediate bicyclic keto carboxylates (**12** and **17c**). Application of the octant rule to the projection formula **29**, with a



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plausible assumption that the substitution at C_7 should make a predominant contribution, suggests that these bicyclic ke-

tones would give positive Cotton effects, which was found in agreement with our observations.

Experimental Section

Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-20 spectropolarimeter with a CD attachment. Elemental analyses were determined on a Yanagimoto CHN-Corder type II. All melting points and boiling points are uncorrected.

Hydration of (+)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (7). (+)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (7), $[\alpha]^{15}D$ +72.1° (10.0 g, 0.0724 mol), was mixed with 75% sulfuric acid and the mixture was agitated for 4 h at room temperature. After pouring onto 1 kg of ice, it was extracted continuously for 3 days with ether and the extract was washed with saturated sodium bicarbonate solution. This alkaline solution was extracted continuously for 2 days with ether. Both ethereal extracts were combined, washed with water, and dried over magnesium sulfate. Removal of the solvent gave a mixture of lactones (8 and 9) (3.46 g, yield 34%). This mixture (2.52 g, 0.0182 mol) was mixed with 13 ml of 2 N sodium hydroxide solution and it was agitated for 1 h at room temperature. The pH of the clear solution was adjusted to 5 with concentrated sulfuric acid. After the solution had stood for 10 min at room temperature, the pH of the solution was then adjusted to 8 with solid sodium bicarbonate. The slightly alkaline solution was extracted continuously for 3 days with ether. The extract was dried over magnesium sulfate and removal of the solvent gave endo lactone (8) which was purified by sublimation to yield 1.65 g of 8, mp 148–151 °C (racemate[12] mp 157–158 °C), $[\alpha]^{14}D$ +2.2° (*c* 1.58, ethanol).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.35; H, 7.32.

The alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave hydroxy acid 11 (0.77 g). This was used for the succeeding reaction without further purification.

(+)-7-*syn*-Methoxycarbonylbicyclo[2.2.1]heptan-2-one (12). Hydroxy acid 11 (0.77 g, 4.93 mmol) was dissolved in water (8 ml) with potassium hydroxide (0.40 g). A solution of potassium permanganate (1.10 g, 7.00 mmol) in water (13 ml) was added to the solution and then it was stirred for 3 h at room temperature. A few milliliters of ethanol were then added to the mixture to decompose excess of potassium permanganate and manganese dioxide was filtered off. The filtrate was acidified with sulfuric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. After filtration of magnesium sulfate, the ethereal solution was treated with excess of diazomethane in ether. After working up as usual, the solvent was evaporated and the residue was distilled to give keto ester 12 (0.36 g, yield 43%): bp 98 °C (5 mm); $[\alpha]^{13}D$ +2.6° (*c* 1.17, ethanol); CD (*c* 1.01×10^{-2}, isooctane) $[\theta]$ (nm) 0 (265), $+3.10 \times 10^2$ sh (293), $+4.71 \times 10^2$ (302), $+3.62 \times 10^2$ (313), 0 (330).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.37; H, 7.19. Found: C, 64.05; H, 7.27.

Optical Resolution of 7-*syn*-Carboxybicyclo[2.2.1]heptan-2-one (15). Racemic 7-*syn*-carboxybicyclo[2.2.1]heptan-2-one (15) was prepared by the procedure reported previously.[12] A salt from the carboxylic acid (62.5 g, 0.405 mol) with cinchonidine (119 g, 0.405 mol) was systematically recrystallized from acetone. The levorotatory salt (50.2 g, yield 28%), mp 155–157° dec, $[\alpha]^{15}D$ −72.5° (*c* 0.614, ethanol), was obtained as a sparingly soluble crystal, which was treated with 5% sodium hydroxide solution at room temperature. After filtration of cinchonidine, the filtrate was acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave a solid which was esterified with diazomethane in ether by the usual manner. The methyl ester was distilled to yield (+) methyl ester 12 (16.8 g): bp 138–141 °C (13 mm); $[\alpha]^{13}D$ +3.47° (*c* 1.60, ethanol); ir (neat film) 1750, 1725, 1440, 1298, 1200, and 1145 cm^{-1}; NMR (CCl_4) δ 1.4–2.0 (m, 5 H), 2.1–2.4 (m, 1 H), 2.62–2.72 (m, 2 H), 2.75–2.88 (m, 1 H), and 3.64 (s, 3 H); CD (*c* 8.23×10^{-3}, isooctane) $[\theta]$ (nm) 0 (264), $+4.01 \times 10^2$ sh (292.5), $+5.89 \times 10^2$ (302), $+4.62 \times 10^2$ (313), 0 (332); uv max (isooctane) 284 nm (ε 17.0), 290 (17.5), 300 sh (16.0).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.26.

Condensation of the mother liquor of the cinchonidine salt gave the levorotatory salt (21.1 g, yield 12%), mp 193–195 °C dec, $[\alpha]^{18}D$ −89.7° (*c* 0.836, ethanol). This was treated by the same manner described above to yield (−) methyl ester 16 (6.05 g), bp 109–111 °C (5 mm), $[\alpha]^{17}D$ −11.6° (*c* 1.08, ethanol).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.91; H, 7.29.

(+)-2-Ethylenedioxy-7-*syn*-methoxycarbonylbicyclo[2.2.1]-heptane (18a). To a boiling solution of (+) methyl ester 12 (16.4 g, 0.0976 mol) and *p*-toluenesulfonic acid (100 mg) in benzene (500 ml) was added dropwise ethylene glycol (13 ml) during 2 h, and the mixture was refluxed for an additional 7 h. After cooling to room temperature, the reaction mixture was washed with saturated sodium bicarbonate solution and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield 18a (18.6 g, yield 90%): bp 124–128 °C (5 mm); $[\alpha]^{14}D$ +27.2° (*c* 1.10, ethanol); ir (neat film) 1730, 1335, 1218, 1190, and 958 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.50; H, 7.64.

(+)-2-Ethylenedioxy-7-*syn*-hydroxymethylbicyclo[2.2.1]-heptane (18b). A solution of (+) ketal ester 18a (18.6 g, 0.0877 mol) in dry ether (350 ml) was added dropwise to a suspension of lithium aluminum hydride (3.40 g, 0.0894 mol) in dry ether (200 ml). After refluxing for 5 h, the reaction complex was decomposed with saturated ammonium chloride solution with ice cooling. Inorganic solids were filtered off, and the filtrate was dried over magnesium sulfate. After removal of the solvent, the residue was distilled to yield 18b (15.7 g, yield 97%): bp 136–138 °C (5 mm); $[\alpha]^{16}D$ +0.26° (*c* 3.08, ethanol); ir (neat film) 3350, 1330, 1118, 1080, 1020, and 950 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.93; H, 8.86.

(−)-2-Ethylenedioxy-7-*syn*-cyanomethylbicyclo[2.2.1]heptane (18d). To a stirred solution of (+)-18b (15.7 g, 0.0853 mol) in dry pyridine (50 ml) was added *p*-toluenesulfonyl chloride (21.1 g, 0.110 mol) with ice cooling, and stirring was continued for 6 h at this temperature. The mixture was poured onto ice and acidified with hydrochloric acid, followed by extraction with ether. The extract was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water and dried over magnesium sulfate. Removal of the solvent gave an oily tosylate (18c) which was dissolved in dry dimethyl sulfoxide (85 ml). After addition of sodium cyanide (8.00 g, 0.163 mol), the reaction mixture was stirred for 18 h at 90 °C. A solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield 18d (12.4 g, yield 75%): bp 135–138 °C (5 mm); $[\alpha]^{16}D$ −8.19° (*c* 0.830, ethanol); ir (neat film) 2250, 1335, 1118, 1082, 1015, and 950 cm^{-1}; NMR (CCl_4) δ 1.3–1.9 (m, 6 H), 1.95–2.22 (m, 3 H), 2.45 (s, 1 H), 2.58–2.60 (d, 1 H), and 3.73–3.88 (m, 4 H).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.07; H, 7.75; N, 7.31.

(+)-2-Ethylenedioxy-7-*syn*-methoxycarbonylmethylbicyclo[2.2.1]heptane (18f). A mixture of (−)-nitrile 18d (12.4 g, 0.0604 mol) and potassium hydroxide (10.8 g, 0.193 mol) in ethylene glycol (80 ml) was heated for 6 h at 155 °C. After cooling to room temperature, it was diluted with water and washed with either to remove unsaponified materials. The water layer was acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave an oily product (12.8 g) which, without further purification, was dissolved in dry ether (300 ml). To this solution was added dropwise an excess of a solution of diazomethane in ether with ice cooling. After an usual working up, the product was distilled to yield 18f (13.2 g, yield 91%): bp 135–139 °C (5 mm); $[\alpha]^{14}D$ + 0.77° (*c* 2.05, ethanol); ir (neat film) 1735, 1435, 1330, 1210, 1170, 1080, 1020, and 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.44; H, 8.02.

(−)-7-*syn*-Methoxycarbonylmethylbicyclo[2.2.1]heptan-2-one (17c). A mixture of (+) ketal ester 18f (1.53 g, 6.77 mmol) and 5% aqueous sulfuric acid (10 ml) was stirred for 15 h at room temperature and then extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water, and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled to give 17c (789 mg, yield 64%): bp 125–127 °C (5 mm); $[\alpha]^{15}D$ −1.04° (*c* 1.92, ethanol); ir (neat film) 1735, 1438, 1290, 1255, and 1175 cm^{-1}; CD (*c* 3.60×10^{-2}, isooctane) $[\theta]$ (nm) -6.66×10 (274), 0 (283), $+4.05 \times 10^2$ sh (298), $+6.77 \times 10^2$ (308), $+6.00 \times 10^2$ (318.5), 0 (340); uv max (isooctane) 275 nm sh (ε 18.0), 283 (21.4), 296 (22.2), 305 nm (20.3).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.10; H, 7.72.

(−)-2-Ethylenedioxy-7-*syn*-(2-hydroxyethyl)bicyclo[2.2.1]-heptane (18g). A solution of (+) methyl ester **18f** (11.4 g, 0.0504 mol) in dry ether (200 ml) was added to a suspension of lithium aluminum hydride (1.90 g, 0.0500 mol) in dry ether (100 ml) over 90 min, and the mixture was refluxed for an additional 5.5 h. After saturated ammonium chloride solution was added to the chilled mixture, inorganic solid was filtered off and the filtrate was dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield **18g** (9.71 g, yield 97%): bp 143–146 °C (5 mm); $[\alpha]^{15}D$ −6.51° (*c* 1.92, ethanol); ir (neat film) 3400, 1330, 1118, 1080, 1050, and 1020 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.74; H, 9.29.

(+)-7-*syn*-(2-Hydroxyethyl)bicyclo[2.2.1]heptan-2-one (17a). A mixture of (−) ketal alcohol **18g** (4.56 g, 0.0231 mol) and 5% sulfuric acid (30 ml) was agitated for 15 h at room temperature and then extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled to give 17a (2.49 g, yield 70%): bp 146–150 °C (5 mm); $[\alpha]^{15}D$ +1.84° (*c* 1.23, ethanol); ir (neat film) 3400, 1735, and 1050 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.31.

(−)-Brexan-2-one (4). To a solution of (+) keto alcohol **17a** (2.28 g, 0.0148 mol) in dry pyridine (8 ml) was added methanesulfonyl chloride (3.38 g, 0.0295 mol) at 0–5 °C and then the mixture was stirred for 6 h at this temperature. After being kept overnight at room temperature, the mixture was poured onto ice. It was acidified with hydrochloric acid and extracted with chloroform. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. Removal of the solvent gave mesylate **17b** (2.63 g), which was, without further purification, dissolved in dimethylformamide (30 ml). This solution was added dropwise to a suspension of sodium hydride (1.00 g, 0.415 mol) in dimethylformamide (20 ml) and the mixture was stirred for 17 h at 60 °C under a nitrogen atmosphere. After cooling with ice, the reaction mixture was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). Fractions eluted with pentane–ether (9:1 volume) were distilled to yield (−)-brexan-2-one (**4**) (966 mg, yield 48% based on **17a**): bp 116 °C (20 mm); $[\alpha]^{14}D$ −201° (*c* 0.677, ethanol); ir (neat film) 1838, 1742, 1070, and 770 cm^{-1}; NMR (CCl_4) δ 1.56 (s, 1 H), 1.65–1.75 (m, 3 H), 1.75–1.85 (m, 1 H), and 2.24–2.35 (m, 4 H); CD (*c* 3.29 × 10^{-3}, isooctane) [θ] (nm) 0 (241), −7.24 × 10^3 (294), −7.36 × 10^3 (300), −4.56 × 10^3 sh (311.5), 0 (332); uv max (isooctane) 281 nm sh (ε 17.9), 290 (21.3), 300 (19.8).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.06; H, 8.85.

(−)-Brexane (3). A mixture of (−)-brexan-2-one (**4**, 480 mg, 3.53 mmol), potassium hydroxide (0.26 g), 80% hydrazine hydrate (0.4 ml), and triethylene glycol (4 ml) was heated for 1.5 h at 160 °C and then for an additional 3 h at 200–210 °C. After cooling to room temperature, the reaction mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over magnesium sulfate. After careful evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). The first fraction eluted with pentane was concentrated to give (−)-brexane (**3**, 90 mg, yield 21%): $[\alpha]^{15}D$ −94.3° (*c* 0.214, ethanol); ir (neat film) 2950, 2880, 1462, and 1308 cm^{-1}; mass spectrum *m/e* 122 (M^+).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.34; H, 11.56.

(−)-7-*syn*-Hydroxymethylbicyclo[2.2.1]heptan-2-ol (20a). A solution of (−) methyl ester **16** (2.55 g, 0.0152 mol) in dry ether (60 ml) was added dropwise to a suspension of lithium aluminum hydride (1.00 g, 0.0263 mol) in dry ether (30 ml), and the mixture was refluxed for 5 h. After cooling with ice, saturated ammonium chloride solution was added to the chilled reaction mixture and inorganic solids were filtered off. The filtrate was dried over sodium sulfate and the solvent was evaporated. The residue was distilled to give (−) diol **20a** (1.25 g, yield 58%), bp 138–140 °C (5 mm), $[\alpha]^{18}D$ −4.90° (*c* 1.62, ethanol).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.25; H, 9.94.

(−)-3-Oxabrexane (5) and (+) Tosylate (19). To a solution of (−) diol **20a** (2.69 g, 0.0189 mol) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (3.60 g, 0.0189 mol) at 0–5 °C, and the mixture was agitated for 3 h at this temperature. After being kept overnight at room temperature, the mixture was poured onto ice. It was acidified with hydrochloric acid and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel. The fractions eluted with pentane–ether (4:1 volume) gave a wax, which was sublimed at 38–45 °C (20 mm) to yield (−)-3-oxabrexane (**5**, 43 mg, yield 1.7%): mp 63–64 °C (in a sealed tube); $[\alpha]^{20}D$ −168° (*c* 1.10, ethanol); ir (KBr) 1305, 1100, 1028, 970, 932, 880, and 845 cm^{-1}; NMR ($CDCl_3$) δ 1.08–1.78 (m, 6 H), 2.10–2.35 (m, 3 H), 3.64–3.95 (m, 2 H), and 4.03–4.15 (m, 1 H); mass spectrum *m/e* 124 (M^+).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.13; H, 9.61.

From the fractions which came out with ether, an oily tosylate (**20b**, 3.33 g) was obtained. This was dissolved in acetone (45 ml) and 8 N Jones reagent was added dropwise to the solution at 0–5 °C until red-brown color persisted. After stirring for 1.5 h at this temperature, the mixture was diluted with water (50 ml) and extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water and dried over sodium sulfate. Evaporation of the solvent yielded (+) keto tosylate **19** (3.07 g, yield 55%): $[\alpha]^{21}D$ +8.7° (*c* 0.757, ethanol); ir (neat film) 1728, 1354, 1174, and 961 cm^{-1}.

This tosylate (**19**) was, without further purification, used for the cyclization reaction to norbrexan-2-one (**6**).

Norbrexan-2-one (6). A solution of (+) tosylate **19** (3.07 g, 0.0104 mol) in dimethylformamide (30 ml) was added under a nitrogen atmosphere dropwise to a suspension of sodium hydride (2.00 g, 0.0833 mol) in dimethylformamide (20 ml), and the mixture was stirred for 63.5 h at 60 °C and for an additional 13 h at 80 °C. After addition of methanol (7 ml) with ice cooling, the reaction mixture was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). The fractions eluted with pentane gave an oily product, which was distilled to give norbrexan-2-one (**6**, 44 mg, yield 3.5%): bp 60 °C (bath temperature) (20 mm); ir (neat film) 1754, 1100, 1030, 975, and 880 cm^{-1}; mass spectrum *m/e* 122 (M^+); CD (*c* 7.05 × 10^{-3}, isooctane) [θ] (nm) 0 (241), +3.73 × 10^3 sh (287), +3.98 × 10^3 (293), +4.00 × 10^3 (296), +2.46 × 10^3 sh (306), 0 (325).

Registry No.—**3**, 60133-47-3; **4**, 60133-48-4; **5**, 60133-49-5; **6**, 60133-50-8; **7**, 58001-99-3; **8**, 60133-51-9; **9**, 60133-52-0; **11**, 60104-05-4; **12**, 60133-53-1; (±)-**15**, 60104-06-5; (−)-**15** salt, 60133-55-3; **16**, 60133-56-4; **17a**, 60104-07-6; **17b**, 60133-57-5; **17c**, 60133-58-6; **18a**, 60104-08-7; **18b**, 60104-09-8; **18c**, 60104-10-1; **18d**, 60104-11-2; **18f**, 60104-12-3; **18g**, 60104-13-4; **19**, 60104-14-5; **20a**, 60104-15-6; **20b**, 60104-16-7.

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The Favorskii Rearrangement of 2-Bromobicyclo[3.2.1]octan-3-one. The Question of Bishomoantiaromaticity

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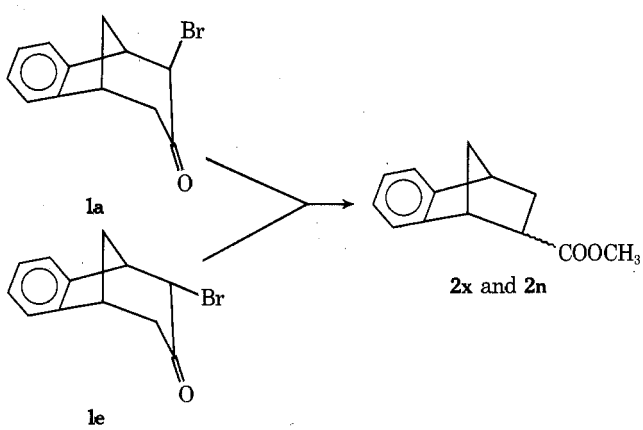
Bicyclo[3.2.1]octan-3-one (**4**) was brominated with *N*-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride to give axial 2-bromobicyclo[3.2.1]octan-3-one (**3a**) but no equatorial isomer (**3e**). The Favorskii rearrangement of axial bromo ketone **3a** with sodium methoxide in methanol gives only small amounts of Favorskii ring contraction compared to its benzo analogue 2-bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (**1a**). The major reaction of bromo ketone **3a** is halide displacement by methoxide ion. The facile rearrangement of **1a** is explained in two ways. Inductive withdrawal of the aromatic ring could stabilize enolate **7** and at the same time retard the solvolytic side reaction by destabilizing ion **15**. Secondly, bishomoantiaromaticity may contribute to the instability of ion **15**. Zwitterion **9** is also bishomoantiaromatic, causing a more rapid and less reversible ring closure to the cyclopropanone.

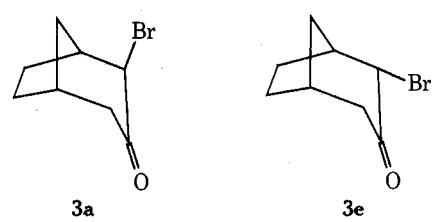
The Favorskii rearrangement has been the subject of intensive research since its discovery in 1894.[1] Monocyclic ring contraction in this base-catalyzed rearrangement of α-halo ketones is well known. However, rearrangement of bicyclic systems has been studied to a lesser extent, with some notable successful rearrangements[2] and other more negative results.[3] Until recently only bridgehead halogenated compounds have been tried. Wilt and Rasmussen[4] were the first to study a substrate having halogen at a position other than a bridgehead. Reaction of axial or equatorial 2-bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (**1a** and **1e**) with sodium methoxide in either methanol or 1,2-dimethoxyethane (glyme) proceeded smoothly to a mixture of exo and endo epimers of methyl benzonorbornene-2-carboxylate (**2x** and **2n**).



An examination of the literature of this rearrangement in bicyclic rings leaves one confused and unable to predict whether new examples might be synthetically viable. Previous work has not centered on a study of the synthetic usefulness and breadth of this rearrangement. Of the examples cited above, all except one[4] had bridgehead halogens. All of the carbonyl groups except two[2n,4] were located in a one-carbon bridge. Only a few ring sizes have been studied, especially the [3.3.1] and the [2.2.1] skeletons. With the exception of two papers[2o,4] very little mechanistic work has been reported.

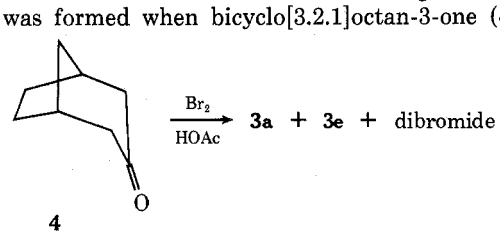
For these reasons we decided to embark on a study of this rearrangement in a number of different bicyclic bromo ketones to determine the effect of ring size, the effect of a bridgehead vs. a nonbridgehead α halogen or α' hydrogen, and the effect of unsaturation on the success of these rearrangements.

Succeeding papers will deal with the first two mentioned effects, but we wish to report an unusual result of unsaturation which appeared when we attempted a Favorskii rearrangement of the aliphatic analogue of bromo ketone **1a**, axial 2-bromobicyclo[3.2.1]octan-3-one (**3a**).



Results

Axial bromo ketone **3a** and its equatorial isomer **3e** have been prepared by Waegell and Jefford, but **3e** was said to be unstable. A mixture of these two isomers along with a dibromide was formed when bicyclo[3.2.1]octan-3-one (**4**) was



treated with bromine in acetic acid.[5] Since the benzo bromo ketone **1** gave essentially the same product composition whether the axial or equatorial isomer was used,[4] it was decided to prepare pure axial bromo ketone **3a** to simplify the study. These bicyclic bromo ketones probably equilibrate rapidly in basic solution, as evidenced by rapid deuteration of the parent ketones bicyclo[3.2.1]octan-3-one (**4**) and benzo[6,7]bicyclo[3.2.1]oct-6-en-3-one with sodium methoxide in methanol-d_4.