at 85–90° for 90 min. The mixture was cooled in an ice bath and methanol was added. After the excess sodium and alkylsodium had been destroyed, the mixture was decanted into a 250-ml separatory funnel containing 50 ml of water. The organic layer was separated, washed once with 50 ml of water, and dried over anhydrous magnesium sulfate. Vapor phase chromatographic analysis of the dried organic phase on column A revealed only one product peak, and this peak had a retention time identical to that of a mixture of the allylcyclopentenes. The infrared spectrum indicated some methyl absorption near 1380 cm^{-1}, suggesting some isomerization. There was no evidence of any bicyclic isomers and a 33% recovery of unreacted allylcyclopentenes was obtained.

Registry No.—I, 14564-95-5; II, 14564-96-6; III, 14564-97-7; IV, 765-99-1; V, 930-99-4; VI, 823-02-9.

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Bicyclo[3.3.1]nonanes. III. Preparation and Reactions of Bicyclo[3.2.2]nonanes

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The reaction of bicyclo[2.2.2]oct-2-ylcarbinylamine with nitrous acid gave a mixture of alcohols which consisted of bicyclo[3.2.2]nonan-2-ol (62%), bicyclo[3.2.2]nonan-3-ol (22%), and bicyclo[3.3.1]nonan-2-ol (16%). Dehydration of bicyclo[2.2.2]oct-2-ylmethanol at 165° with phosphoric acid produced only bicyclo[3.3.1]non-2-ene. Mechanisms for these transformations are suggested. The reaction of bicyclo[3.2.1]oct-2-en-8-one with diazomethane gave a 3:2 mixture of bicyclo[3.2.2]non-3-en-6-one and bicyclo[3.2.2]non-2-en-6-one which could be hydrogenated to bicyclo[3.2.2]nonan-6-one; the latter ketone could also be obtained from the reaction of bicyclo[3.2.1]octan-8-one with diazomethane. Reduction of bicyclo[3.2.2]nonan-6-one with lithium aluminum hydride gave an 87:13 mixture of *endo*-bicyclo[3.2.2]nonan-6-ol and *exo*-bicyclo[3.2.2]nonan-6-ol. Solvolysis of the *p*-nitrobenzenesulfonates of these alcohols produced bicyclo[3.3.1]nonan-2-ol and what is believed to be *exo*-bicyclo[4.2.1]nonan-2-ol. Solvolysis of the tosylate of bicyclo[3.2.2]nonan-2-ol yielded the unrearranged alcohol (52%), bicyclo[3.2.2]nonan-3-ol (16%), and bicyclo[3.3.1]nonan-2-ol (32%). Stereoelectronic influences governing the reactions of these bridged bicyclic compounds are discussed.

In a recent paper we described the synthesis of a series of bicyclo[3.3.1]nonane derivatives.[2] To compare the chemistry and the solvolytic reactivity of compounds in this series to those in the bicyclo[3.2.2]nonane system, we undertook to prepare the four possible secondary alcohols of the latter bicyclic framework. Although a number of diverse approaches for the preparation of the bicyclo[3.2.2]nonane system have been reported,[3-13] we decided that the method outlined by Alder[6-8] and his co-workers was the most promising, since the starting materials were easy to obtain and the conversions have been reported to be efficient.

Bromination of cyclohexene at low temperatures followed by dehydrohalogenation with potassium hydroxide in triglyme gave cyclohexa-1,3-diene of excellent purity in about 40% over-all yield. Reaction of the diene with acrylonitrile yielded 5-cyanobicyclo[2.2.2]oct-2-ene which was readily reduced to bicyclo[2.2.2]oct-2-ylcarbinylamine (**1**). Reaction of **1** with nitrous acid using Alder's conditions[7] gave a complex mixture of products from which three alcohols could be separated chromatographically. The components of the alcohol fractions were present in relative yields of 62, 22, and 16% as ascertained by integration of the vapor phase chromatograms of the mixture. To identify the components of this mixture, both bicyclo[3.2.2]nonan-2-ol (**2**) and bicyclo[3.2.2]nonan-3-ol (**3**) were synthesized by unambiguous routes for purposes of comparison.

Acylation of ethyl hydrocinnamate produced ethyl 3-(4-acetylphenyl)propionate in 75% yield, and oxidation and saponification of the latter gave 3-(4-carboxyphenyl)propionic acid (78% yield). Catalytic hydrogenation using Raney nickel followed by the addition of cerous chloride resulted in the formation of the cerous salt of 3-(4-carboxycyclohexyl)propionic acid (**4**) which upon pyrolysis produced bicyclo[3.2.2]nonan-2-one (**5**) in 22% yield (isolated as its semicarbazone). Reduction of **5** with lithium aluminum hydride yielded **2**, and a comparison of physical properties indicated that this compound corresponded to the major product formed in the Demjanov reaction of **1**.

Acylation of ethylbenzene followed by cautious oxidation of the product with potassium permanganate produced *p*-diacetylbenzene in 63% over-all yield. A Willgerodt reaction converted the diketone to *p*-benzenediacetic acid (69%). Catalytic hydrogenation of the diacid (using 50% rhodium on alumina as the catalyst) gave a mixture of the *cis* and *trans* isomers of 1,4-cyclohexane diacetic acid (**6**) in quantitative yield,

(1) Abstracted from the Ph.D. Thesis of L. S. Endres, University of Arizona, Tucson, Ariz., 1967.

(2) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(3) E. M. Mil'Vitskaya and A. F. Platte, *Zh. Obshch. Khim.*, **32**, 2566 (1962); *Chem. Abstr.*, **58**, 8927e (1963).

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(5) O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.*, **81**, 3696 (1959).

(6) K. Alder, S. Hartung, and G. Hausmann, *Ber.*, **89**, 1972 (1956).

(7) K. Alder, H. Krieger, and H. Weiss, *ibid.*, **88**, 144 (1955).

(8) K. Alder and R. Reubke, *ibid.*, **91**, 1525 (1958).

(9) J. A. Berson and M. Jones, *J. Am. Chem. Soc.*, **86**, 5019 (1964).

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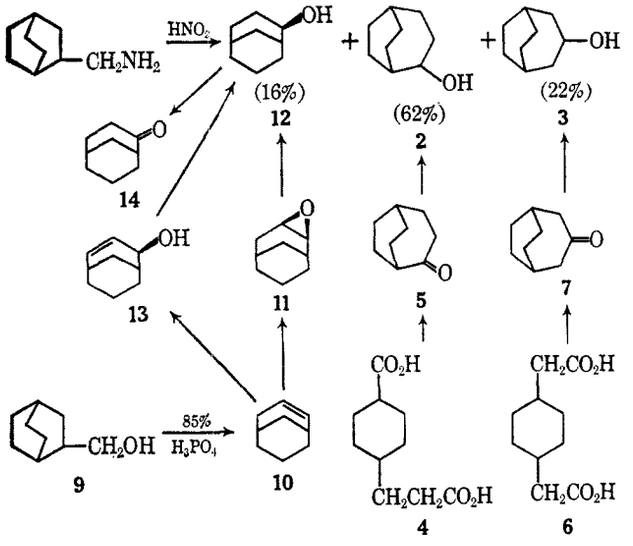
(11) L. T. Mann, Ph.D. Dissertation, Columbia University, New York, N. Y., 1951. (Doctoral Dissertation Series, Publication No. 9528, University Microfilms, Ann Arbor, Mich.)

(12) V. Ioan, M. Popovici, E. Mosanu, M. Eliean, and C. D. Nenitescu, *Rev. Roumaine Chim.*, **10**, 185 (1965).

(13) C. W. Jefford, S. Mahajan, J. Waslyn, and B. Waegell, *J. Am. Chem. Soc.*, **87**, 2183 (1965).

CHART I

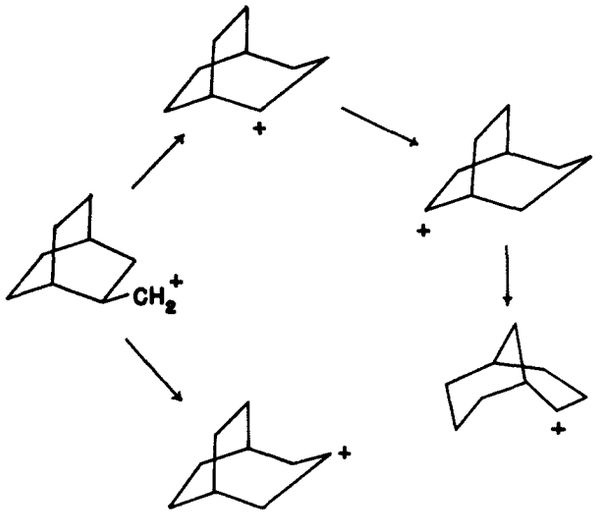


but the ratio of the two isomers was a sensitive function of the reaction conditions. When the hydrogenation of *p*-benzenediacetic acid was carried out at 90° and 1000 psi, reduction was rapid and exothermic; chromatography of the esters of the product showed an isomer distribution of 6:94 in order of retention times. At 25° and a pressure of 95 psi the reaction was quite slow, and the product isomer distribution was 86:14. Pyrolysis of the cerous salt of the former mixture produced no bicyclic ketone whereas the latter mixture produced bicyclo[3.2.2]nonan-3-one (**7**) in very low yield. Reduction of **7** with lithium aluminum hydride yielded **3**; from a comparison of retention times, the isomer formed from **1** in 22% yield was found to correspond to **3**.

Because the mixture of alcohols which we obtained from **1** was difficult to separate into its components, we turned our attention to the preparation of bicyclo[3.2.2]non-2-ene (**8**). It was anticipated that oxygen could be readily and selectively introduced into **8** (*e.g.*, by selenium dioxide oxidation, hydroboration, or epoxidation) to provide us with suitable quantities of the desired products. The most practical source of **8** appeared to be bicyclo[2.2.2]oct-2-ylmethanol (**9**), since Alder[7] originally reported that dehydration of **9** resulted in the formation of **8** in high yield.[14]

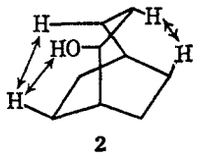
Dehydration of **9** gave a single olefin, **10**, which could be converted to an epoxide, **11**, upon reaction with peracetic acid. Reduction of **11** with lithium aluminum hydride produced a single alcohol, **12**, which did not correspond to either **2** or **3**, but to the third and minor component of the Demjanov reaction mixture. Since the epoxidation and reduction of **8** could have produced only **2** or **3**, it follows that the dehydration of **9** must have involved a carbonium ion rearrangement. Oxidation of **10** with selenium dioxide gave an allylic alcohol, **13**, which could be reduced to **12** using hydrogen in the presence of palladium on charcoal.

Oxidation of **12** with chromic acid gave ketone **14**, which was shown to have three exchangeable protons. A comparison of the physical and chemical properties of **14** and its semicarbazone with those of an authentic sample[2] of bicyclo[3.3.1]nonan-2-one showed that these substances were identical. Subsequent comparisons of physical and chemical properties with those of authentic samples[2] showed that **12** was *exo*-bicyclo[3.3.1]nonan-2-ol, **13** was *exo*-bicyclo[3.3.1]non-3-en-2-ol, **10** was bicyclo[3.3.1]non-2-ene, and **11** was the corresponding *exo* epoxide. These results are summarized in Chart 1. Reasonable pathways for the transformation of the bicyclo[2.2.2]oct-2-ylcarbinyl cation to the bicyclo[3.3.1]non-2-yl cation and to the cationic precursors of **2** and **3** are given below.

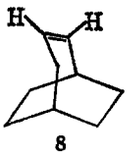


The findings cited above indicate that, under conditions that approach equilibrium control, the primary fate of the bicyclo[2.2.2]oct-2-ylcarbinyl cation is rearrangement to the bicyclo[3.3.1]non-2-yl cation. Further evidence supporting this suggestion stems from the fact that **2** was converted almost completely to **10** (99%) when **2** was added to 2 *N* sulfuric acid and heated at 100°. Small amounts of alcohol **12** were also detectable by chromatography of the product; this may arise from hydration of **10** or directly from the rearranged cation. The driving force for this rearrangement probably has its origin in the unfavorable conformational interactions which are inherent in the bicyclo[3.2.2]nonane framework.

In **2**, three serious eclipsing interactions exist which serve to destabilize this molecule over and above the usual destabilization energy which is associated with the presence of the boat conformation of a cyclohexane ring. These interactions could be relieved to a signif-



2



8

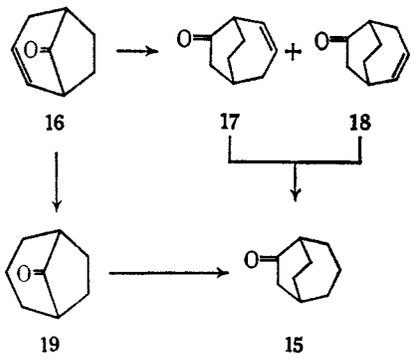
icant degree if an elimination of a proton from C_3 to form bicyclo[3.2.2]non-2-ene (**8**) were to occur. However, even in **8**, serious nonbonded interactions exist which serve as a destabilizing factor. These sources of strain can be eliminated by a 1,3-hydride migration in the 2-bicyclo[3.2.2]nonyl cation followed by an alkyl shift to give the 2-bicyclo[3.3.1]nonyl cation; elimina-

(14) On further investigation[6] into the chemistry of bicyclo[3.2.2]nonanes, Alder synthesized bicyclo[3.2.2]nonan-6-one by an unambiguous route and reduced this to bicyclo[3.2.2]nonane through a Wolff–Kishner reaction. Catalytic hydrogenation of what he previously formulated as **8**[7] gave a saturated hydrocarbon which was clearly not the same as the product derived from the ketone. He was unable to resolve this incongruency.

tion of a proton from C_3 would result in **10**. In **10**, both the cyclohexane and cyclohexene rings can adopt relatively strain-free conformations, and we believe that the relative stabilities of **10** and **8** probably account for the observations cited above.

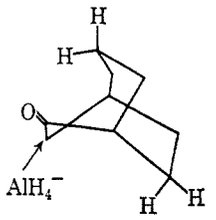
An approach to the synthesis of medium-sized rings which has been successful in recent years involves formation of the ring through a Dieckmann condensation using sodium hydride and high-dilution conditions. To develop our reaction techniques, the preparation of cycloheptanone from dimethyl suberate was studied using a variety of reaction conditions until consistently good yields of ketone could be obtained. However, when we used these reaction conditions and variations on the dimethyl ester of **4**, we were able to detect only traces of ketonic product (presumably **5**). Since the Dieckmann condensation is an equilibrium process, the failure of the cyclization of the diester is probably a consequence of the strain inherent in the bicyclo[3.2.2]nonane nucleus. After these studies were completed, Berson[9] reported a convenient synthesis of **5** through an oxy Cope rearrangement, and we have since used this method to prepare the ketone in quantity.

Bicyclo[3.2.2]nonan-6-one (**15**) was prepared from bicyclo[3.2.1]oct-2-en-8-one (**16**) by treating **16** with diazomethane and reducing the mixture of products which was obtained. From the ring-expansion step, a 3:2 mixture of bicyclo[3.2.2]non-3-en-6-one (**17**) and bicyclo[3.2.2]non-2-en-6-one (**18**) was isolated. These products could be separated by vapor phase chromatography, and **17** was identified on the basis of the presence of an absorption maximum in the ultraviolet region of the spectrum (λ_{max} 298 mμ, log ϵ 2.03) which is characteristic of homoconjugated unsaturated ketones.[15] Hydrogenation of both **17** and **18** using palladium on charcoal yielded **15**. This ketone could also be prepared by reducing **16** to bicyclo[3.2.1]octan-8-one (**19**) and treating **19** with diazomethane.



16 **17** **18** **19** **15**

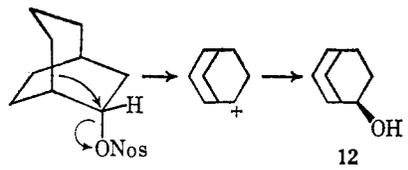
Reduction of **15** with lithium aluminum hydride gave a mixture of alcohols **20** and **21** which were present to the extent of 13 and 87%, respectively, as determined chromatographically. An inspection of Dreiding models indicates that four conformational modifications of **15** are possible; of these, the conformation shown should be the most stable, since nonbonded interactions are at a minimum when the molecule is in this form. In this conformation the *endo* face of the carbonyl group is almost completely shielded by the C_3 methylene group, and approach of the reducing agent from the exposed *exo* face would be expected to be favored if steric approach control of the reagent is the determining factor.[16] That this is probably the case was shown by the following experiment.



15

20 **21**

Although the mixture of **20** and **21** could not be separated conveniently on a large scale, the reduction mixture was readily converted to a mixture of *p*-nitrobenzenesulfonate esters. Solvolysis of this mixture produced two alcohols which were present to the extent of 10 and 90%. By comparison with an authentic sample,[2] the minor component of the solvolysis mixture was shown to be **12**. If we draw the reasonable conclusion that **12** arises from the minor component of the reduction mixture, then the latter alcohol must be *exo*-bicyclo[3.2.2]nonan-6-ol (**20**). On mechanistic grounds, only this epimer would be expected to produce **12** on solvolysis (eq 1).



12 (1)

Careful comparison of the retention time of the major component of the solvolysis reaction with those of all of the known bicyclo[3.3.1]nonanols and bicyclo[3.2.2]nonanols (see Table I) indicated that **22** had

TABLE I
RETENTION TIMES OF BICYCLONONANOLS[a]

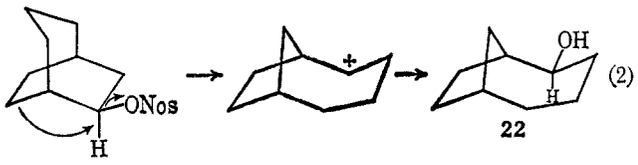
Compd	Retention time, min
exo-Bicyclo[3.3.1]nonan-2-ol	22.6
endo-Bicyclo[3.3.1]nonan-2-ol	25.2
exo-Bicyclo[3.3.1]nonan-3-ol	25.6
exo-Bicyclo[4.2.1]nonan-2-ol (?)	27.5
Bicyclo[3.2.2]nonan-2-ol	28.0[b]
endo-Bicyclo[3.2.2]nonan-6-ol	28.0[b]
exo-Bicyclo[3.2.2]nonan-6-ol	28.0[b]
Bicyclo[3.2.2]nonan-3-ol	29.5

[a] A 10 ft × 0.25 in. 5% Carbowax 20M on 80/100 mesh Chromosorb P column operating at 120° and a flow rate of 100 cc/min was used for these measurements. [b] When analyzed simultaneously, these can be detected as shoulders.

none of these structures; therefore, a new, bridged bicyclic skeleton must have been formed during the solvolysis reaction (eq 2). On mechanistic grounds we regard *exo*-bicyclo[4.2.1]nonan-2-ol to be a likely structure for **22**. Compound **22** was also detected as a product obtained from the dehydration of **21** with sulfuric acid. We plan to investigate these reactions in more detail.

(15) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

(16) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).



22 (2)

Since the reactions of **16** and **19** with diazomethane provided a useful entry into the bicyclo[3.2.2]nonane framework, we explored the reaction of norbornen-7-one with an excess of this reagent. The major product from this reaction was bicyclo[2.2.2]oct-2-en-5-one, which was isolated in 79% yield, and only trace amounts of bicyclo[3.2.2]non-6-en-2-one could be detected by vapor phase chromatography. Reaction of bicyclo[2.2.2]octanone with diazomethane gave only traces of bicyclo[3.2.2]nonan-2-one, and the starting material was recovered. Evidently the success of the ring expansion in these bicyclic systems is determined to a large extent by the degree of strain in the starting ketone, and the bicyclo[2.2.2]octane system is not very reactive toward this reagent.

Experimental Section

1,2-Dibromocyclohexane.—A modification of the procedure of Snyder and Brooks[17] was used. A solution of cyclohexene (384 g, 4.68 moles), 500 ml of carbon tetrachloride, and 45 ml of absolute ethanol was cooled to −35° with a Dry Ice–isopropanol bath. The solution was stirred rapidly, and 630 g (3.94 moles) of bromine dissolved in 120 ml of carbon tetrachloride was added from an addition funnel at such a rate that the temperature could be maintained below −25°. After the addition was completed, the reaction mixture was distilled; 815 g (85.5%) of 1,2-dibromocyclohexane was obtained, bp 111° (30 mm) [lit.[17] bp 108–112 (25 mm)].

Cyclohexa-1,3-diene.—A stirred solution of potassium hydroxide (600 g, 10.7 moles) and 1900 ml of triglyme was heated to 150° in a 3-l., three-necked flask which was fitted with a mechanical stirrer and an addition funnel and equipped for a simple vacuum distillation. The pressure was reduced by means of an aspirator to 200–500 mm, and 1,2-dibromocyclohexane (910 g, 3.85 moles) was added in a steady stream with vigorous stirring. As soon as the products began to distil from the reaction mixture, the addition rate was adjusted so that the distillation rate did not become too rapid. Upon completion of the distillation, the distillate was washed with brine, dried with magnesium sulfate, and fractionally distilled to give 126 g (40.0%) of cyclohexa-1,3-diene, bp 77° (lit.[18] bp 80°), which contained only trace amounts (<2%) of benzene, cyclohexene and the 1,4-diene.

Deamination of Bicyclo[2.2.2]oct-2-ylcarbinylamine.—The hydrochloride salt of bicyclo[2.2.2]oct-2-ylcarbinylamine[19] was prepared by adding 150 ml of concentrated hydrochloric acid to a cooled ethereal solution of 55.7 g (0.424 mole) of the amine. The product was filtered and dissolved in 100 ml of water containing 40.0 g (0.580 mole) of sodium nitrite. The solution was stirred and heated to reflux, and 40 ml of glacial acetic acid was slowly added. After heating at reflux for 1 hr, 40 ml of 50% aqueous sodium hydroxide was added; after 3 hr at reflux, the products were isolated by steam distillation. The crude product (46.6 g) was crystallized from pentane to give 39.8 g (67.0%) of a mixture with five major components. Three of these, which accounted for about 80% of this mixture, were alcohols. Vapor phase chromatography indicated that these alcohols were bicyclo[3.3.1]nonan-2-ol (16%), bicyclo[3.2.2]-nonan-2-ol (62%), and bicyclo[3.2.2]nonan-3-ol (22%); their retention times are reported in Table I. These compounds were isolated by preparative vapor phase chromatography and were identified by a comparison of their physical and chemical properties with those of the compounds described below.

Dehydration of Bicyclo[2.2.2]oct-2-ylmethanol.—In a flask fitted with a short-path distillation adapter were placed 16 g (0.11 mole) of bicyclo[2.2.2]oct-2-ylmethanol,[7] 9 g of 85% phosphoric acid, a few crystals of hydroquinone, and a few copper granules. The flask was heated to 160–180°; when distillation of the dehydration product ceased, the distillate was dissolved in pentane. The pentane solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and refluxed with several small cubes of sodium metal to remove any unreacted alcohol. Distillation gave 4.4 g (32%) of an olefin, mp 89–93° (lit.[2] mp 96.5–97°), which was subsequently identified as bicyclo[3.3.1]non-2-ene.

Epoxidation of Bicyclo[3.3.1]non-2-ene.—To a cooled solution of 7.0 g (0.058 mole) of bicyclo[3.3.1]non-2-ene in 90 ml of chloroform was added over a 1-hr period a mixture of 25 ml of 40% peracetic acid (Becco) and 2.0 g of sodium acetate. The temperature was kept at 0° for 3 hr and then at room temperature for 4 hr. The chloroform solution was washed with dilute aqueous potassium hydroxide, dried, and concentrated. Sublimation (100°, 30 mm) yielded 5.6 g (71%) of the epoxide, which melted at 155–162°.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.02; H, 10.28.

Bicyclo[3.3.1]nonan-2-ol.—A mixture of 2.1 g (0.015 mole) of the epoxide, 2.0 g (0.053 mole) of lithium aluminum hydride, and 60 ml of tetrahydrofuran was refluxed for 2 days. Isolation of the product in the usual manner and crystallization from pentane gave 1.6 g (77%) of *exo*-bicyclo[3.3.1]nonan-2-ol, mp 174.5–176° (lit.[2] mp 175–177°), which was shown to be identical (infrared and nmr spectra, retention time) with an authentic sample.[2]

Bicyclo[3.3.1]nonan-2-one.—*exo*-Bicyclo[3.3.1]nonan-2-ol (0.80 g, 0.0057 mole) in 15 ml of acetone was oxidized with Jones reagent. Sublimation afforded 0.35 g (44%) of the ketone, mp 136–139° (lit.[2] mp 135–137°). The semicarbazone derivative was prepared in the usual manner, mp 179–180° (lit.[2] mp 179–180°). A deuterium exchange experiment led to the incorporation of 17.80 atom % of excess deuterium (2.49 atoms of deuterium per molecule).[20]

Selenium Dioxide Oxidation of Bicyclo[3.3.1]non-2-ene.—The olefin was converted to *exo*-bicyclo[3.3.1]non-3-en-2-ol by the procedure described previously.[2] Catalytic reduction of the product to *exo*-bicyclo[3.3.1]nonan-2-ol was carried out in the presence of 5% palladium on charcoal. The physical and chemical properties of the alcohol obtained in this way were identical to those of an authentic sample (*vide supra*).

Ring Expansion of Bicyclo[3.2.1]oct-2-en-8-one.—A solution of 12 g (0.12 mole) of N-nitroso-N-methylurea in 350 ml of ether was converted to diazomethane in the usual way.[21] To the ethereal solution of diazomethane were added 10 g (0.082 mole) of bicyclo[3.2.1]oct-2-en-8-one,[22] 10 ml of methanol, and 0.2 g of lithium chloride. The mixture was stirred for 3 days, and analysis of a small sample of the reaction mixture by vapor phase chromatography indicated that the reaction had gone to only 60% of completion. Additional diazomethane (from 10.0 g of N-nitroso-N-methylurea) was added, and the solution was stirred for another 3 days at which time analysis indicated that little starting material remained. The ether solution was washed with a saturated solution of sodium bicarbonate, dried, and concentrated. Distillation gave a total of 7.5 g of product, which contained some starting material; the yield of bicyclo-[3.2.2]nonenones was about 61%. A small sample was separated by gas phase chromatography to give bicyclo[3.2.2]non-2-en-7-one, mp 84–86.5°, (60% of the mixture) and bicyclo-[3.2.2]non-2-en-6-one, mp 90–93 (40% of the mixture). The lower melting isomer had an absorption maximum at 298 mμ (log ε 2.03) while the higher melting isomer had an absorption maximum at 293 mμ (log ε 1.33). The infrared spectra of both compounds were characterized by maxima at 2950 and 1715 cm^{-1}. Catalytic hydrogenation of the mixture of unsaturated ketones in the presence of 5% palladium on charcoal gave bicyclo[3.2.2]-nonan-6-one in quantitative yield. The product had the same retention time as a sample of the ketone prepared from the ring expansion of bicyclo[3.2.1]octan-8-one.

Ring Expansion of Bicyclo[3.2.1]octan-8-one.—Reaction of bicyclo[3.2.1]octan-8-one with diazomethane, using the procedure described above, yielded bicyclo[3.2.2]nonan-6-one in

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85% yield. Chromatographic analysis showed that the product was contaminated with traces of starting material. The compound melted at 157–160° (lit.[6,12] mp 169–170°) and the semicarbazone melted at 208–210° (lit.[6,12] mp 209–210°).

Reduction of Bicyclo[3.2.2]nonan-6-one.—Reduction of 1.0 g (0.0072 mole) of ketone in 80 ml of tetrahydrofuran with 1.0 g (0.026 mole) of lithium aluminum hydride gave 0.5 g of a mixture of alcohols in the ratio of 87:13 as indicated by vapor phase chromatographic analysis. The mixture melted over the range of 183–194°.

Anal. Calcd for $C_9H_{16}O$: C, 77.07; H, 11.52. Found: C, 77.31; H, 11.79.

Solvolysis of *exo*- and *endo*-Bicyclo[3.2.2]non-6-yl *p*-Nitrobenzenesulfonate.—Reaction of 0.22 g (0.0015 mole) of the mixture of alcohols obtained from the reduction of bicyclo[3.2.2]-nonan-6-one with 0.40 g (0.0018 mole) of *p*-nitrobenzenesulfonyl chloride yielded 0.38 g of mixed ester. This was added to 8 ml of acetic acid containing 0.2 g of sodium acetate, and the solution was heated at 100° for 5 hr. The solution was poured into cold water and extracted with ether. The dried ether extracts were treated with an excess of lithium aluminum hydride. After reaction had ceased, water was added, the solid was removed by filtration, and the concentrated ether extracts were analyzed by vapor phase chromatography. *exo*-Bicyclo[3.3.1]-nonan-2-ol was found to be present to the extent of 10% of the product mixture, and a new compound believed to be *exo*-bicyclo[4.2.1]nonan-2-ol was present to the extent of 90%. Insufficient material was present to allow further characterization of the latter substance.

Cerous Salt of 3-(4-Carboxycyclohexyl)propionic Acid.—To an aqueous solution of 3-(4-carboxyphenyl)propionic acid (117 g, 0.605 mole) was added 10% sodium hydroxide solution until neutrality was achieved. The resulting solution was hydrogenated at 180° and an initial hydrogen pressure of 2000 psi for 24 hr using Raney nickel W-5 catalyst. The hydrogenation was complete as shown by nmr analysis (deuterium oxide) of the sodium salt of the product. After the hydrogenation, the catalyst was removed and a cerous chloride solution was added until no more precipitate formed on further addition. The precipitate was collected by filtration, pressed dry, and dried further at 110° to give 137 g (66.8% over-all) of the cerous salt of the diacid.

Bicyclo[3.2.2]nonan-2-one Semicarbazone.—Infusorial earth (101 g) was added to the powered cerous salt of 3-(4-carboxycyclohexyl)propionic acid (137 g, 0.472 mole) in a large bottle which was shaken vigorously for several minutes to obtain a nearly homogeneous mixture. This mixture (in 60-g batches) was placed in a pyrolysis oven (60 mm × 35 cm) and heated to 400–420° while a slow stream of nitrogen flowed through the system and finally through two 95% ethanol bubblers. The bubblers were used both to meter the gas flow and to trap traces of ketonic product which might otherwise pass into the atmosphere. At first, water condensed on the cooler portions of the pyrolysis system. As the temperature approached 390°, a yellow-brown oil began to emerge from the hot oven. The mixture was heated at the reaction temperature for 6 hr after the oil started to form. After the pyrolysis system had cooled to room temperature, the oil was washed from it thoroughly using the ethanol in the bubbler traps.

To the combined ethanol solution was added an aqueous solution of semicarbazide hydrochloride (8 g per batch) and sodium acetate trihydrate (15 g per batch). The resultant solution was heated to boiling in an erlenmeyer flask until most of the ethanol had boiled out. The solution was decanted from a dark brown oil that settled to the bottom and was allowed to cool, and the semicarbazone derivative was allowed to crystallize. After filtration and drying, 7–8 g (29–35%) of crude semicarbazone (probably contaminated with much biurea) was obtained. A total of 29 g (32%) of crude semicarbazone was obtained from the four pyrolyses. A portion was recrystallized from chloroform with poor recovery to give a white powder, mp 199–201° dec (lit.[11] mp 200–201° dec).

Bicyclo[3.2.2]nonan-2-one (8).—The semicarbazone of bicyclo[3.2.2]nonan-2-one (8.0 g, 0.041 mole) which had been purified by crystallization from chloroform was added to a 1% phosphoric acid solution (100 ml), and steam distillation was carried out. The steam distillate was extracted with two portions of pentane; the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated by distillation through a Vigreux column (30 cm × 15 mm). The residue was sublimed to give 5.0 g (88%) of ketone, mp 161–165° after preparative vapor phase chromatography (lit.[9,11] mp 160.5–164.5°; 152.5–154.5°). When crude semicarbazone (22 g) was used, the yield of ketone was 3.3 g (21%).

Bicyclo[3.2.2]nonan-2-ol (5).—To a mixture of lithium aluminum hydride (0.4 g, 0.01 mole) and anhydrous ether (10 ml) was added a solution of bicyclo[3.2.2]nonan-2-one (0.7 g, 0.005 mole) in anhydrous ether (10 ml). After being stirred overnight, the solution was treated with water, filtered, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, the ether was removed by distillation, and 0.4 g (57%) of alcohol was obtained by sublimation (100°, 30 mm). The crude alcohol had a melting range of 166–184° with softening at 130°, whereas alcohol which had been recrystallized twice from pentane melted at 186–190° (lit.[11] mp. 186–190°).

Pyrolysis of Cerous 1,4-Cyclohexane Diacetate.—The pyrolysis of this cerous salt was carried out in the same manner as that described for the cerous salt of 3-(4-carboxycyclohexyl)propionic acid. A trace of semicarbazone, mp 198–200°, was obtained. The ketone, bicyclo[3.2.2]nonan-3-one, was regenerated by steam distillation from a 3% phosphoric acid solution. The 2,4-dinitrophenylhydrazone derivative was prepared and recrystallized from 95% alcohol to give red-brown needles, mp 159–160° (lit.[13] mp 153°).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.69; H, 6.02; N, 17.88.

Bicyclo[3.2.2]nonan-3-ol.—The ketonic product from the pyrolysis of cerous 1,4-cyclohexane diacetate was reduced with an excess of lithium aluminum hydride to produce an alcohol, mp 105–107° with softening at 90°. The retention time of this material corresponded to that of the third alcohol obtained from the deamination reaction. The nmr spectrum of this compound showed a nine-line A_2B_2X pattern centered at δ 4.02 for the C_3 carbinyl proton with coupling constants of 5.5 and 11.1 cps. The mass spectrum showed a large peak at *m/e* 122 (P − 18), which would be expected for the title alcohol.

Bicyclo[3.2.2]non-2-yl Tosylate.—To a cooled solution of bicyclo[3.2.2]nonan-2-ol (1.02 g, 7.26 mmoles) in dry pyridine (10 ml) was added tosyl chloride (1.52 g, 8.00 mmoles). After all the tosyl chloride had dissolved, the solution was stoppered tightly and placed in the refrigerator (5°) for 24 hr. Cold water was added, and the resulting solution was extracted with ether (50 ml in three portions). The combined extracts were washed with 1 *N* sulfuric acid (100 ml in two portions), water (50 ml), and a saturated sodium bicarbonate solution (50 ml). After being dried over anhydrous magnesium sulfate and filtered, the ether solution was concentrated, and the residue was dissolved in pentane. Recrystallization at −20° afforded 1.09 g (51%) of white crystals, mp 46–48°.

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.26; H, 7.55. Found: C, 65.58; H, 7.83.

Solvolysis of Bicyclo[3.2.2]non-2-yl Tosylate.—A solution of 0.2 *N* sodium acetate in glacial acetic acid (16 ml) and bicyclo-[3.2.2]non-2-yl tosylate (0.94 g, 6.7 mmoles) were placed in a glass tube which was sealed and heated to 100° for 5 hr. The tube was opened, water was added, and the aqueous solution was extracted with ether (200 ml). The ether extracts were washed with water (200 ml in two portions) and dried over anhydrous magnesium sulfate. The filtered ether solution was concentrated to a volume of 50 ml and treated with an excess of lithium aluminum hydride. Analysis by vapor phase chromatography indicated the presence of bicyclo[3.3.1]nonan-2-ol (32%), bicyclo[3.2.2]nonan-2-ol (52%), and bicyclo[3.2.2]nonan-3-ol (16%).

Dehydration of Bicyclo[3.2.2]nonan-2-ol.—To 15 ml of 4 *N* sulfuric acid was added 0.4 g (0.003 mole) of bicyclo[3.2.2]-nonan-2-ol and the mixture was heated in a sealed tube at 100° for 10 hr. Analysis of the reaction mixture using vapor phase chromatography and nmr indicated that the products were bicyclo[3.3.1]non-2-ene and *exo*-bicyclo[3.3.1]nonan-2-ol (less than 1% of the mixture).

Dehydration of *endo*-Bicyclo[3.2.2]nonan-6-ol.—*endo*-Bicyclo-[3.2.2]nonan-6-ol was placed in a glass tube with 1 *N* H_2SO_4 (15 ml); the tube was sealed and heated to 100° for 18 hr. The tube was cooled and opened, and ether was added to its contents. The layers were separated, and the ether was dried over anhydrous magnesium sulfate and filtered. Analysis by vapor phase chromatography and nmr indicated the presence of olefin (*ca.* 50%), *endo*-bicyclo[3.2.2]nonan-6-ol (*ca.* 10%) and *exo*-bicyclo[4.2.1]nonan-2-ol (*ca.* 40%).

Treatment of Norbornen-7-one with Diazomethane.—Norbornen-7-one (5.0 g, 0.046 mole) was treated with an excess of diazomethane. A large amount of bicyclo[2.2.2]oct-2-en-5-one (79.0%) was formed. This product was identified by comparison of the retention time and infrared spectrum with those of an authentic sample. There was very little material formed which had the same retention time as bicyclo[3.2.2]non-6-en-2-one.

Treatment of Bicyclo[2.2.2]octan-2-one with Diazomethane.—Bicyclo[2.2.2]octan-2-one (5.5 g, 0.044 mole) was treated with an excess of diazomethane in the same fashion as bicyclo[3.2.1]-oct-2-en-8-one. Only a trace of new material was formed, which had the same retention time as bicyclo[3.2.2]nonan-2-one.

Cycloheptanone.—Using the apparatus and procedure described by Leonard,[23] 40.4 g (0.200 mole) of dimethyl suberate was converted to cycloheptanone in 58% yield using high-dilution conditions. The reaction time was 3 days. When the reaction was attempted with the dimethyl ester of **4**, starting material was obtained along with a trace of product which gave a positive 2,4-dinitrophenylhydrazine test but which was present in amounts insufficient to characterize.

Registry No.—**2**, 14565-01-6; **3**, 14638-73-4; **10**, 6671-66-5; **11**, 13366-99-9; **12**, 10036-15-4; **14**, 2568-17-4; **15**, 1614-77-3; **17**, 14565-07-2; **18**, 14565-08-3; bicyclo[3.2.2]non-2-yl tosylate, 14565-09-4; **20**, 14565-36-7; **21**, 14565-35-6; **22**, 14565-34-5.

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Synthesis of 8α- and 9β-B-Norestrone[1]

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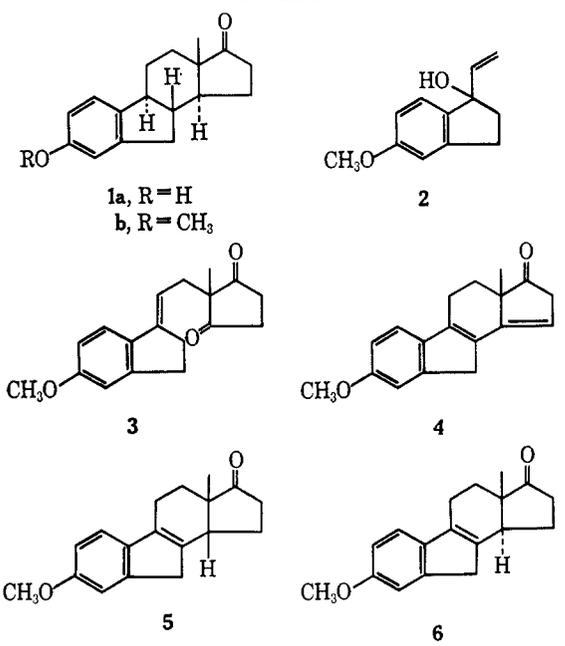
(±)-3-Methoxy-B-norestra-1,3,5(10),8-tetraen-17β-ol (**8a**) was prepared in five steps beginning with 5-methoxyindan-1-one. Metal–ammonia reduction of **8a** followed by chromic acid oxidation gave a mixture of (±)-3-methoxy-B-nor-9β-estra-1,3,5(10)-trien-17-one (**9a**) and (±)-3-methoxy-B-nor-8α-estra-1,3,5(10)-trien-17-one (**10a**), with **9a** as the predominant isomer. Catalytic reduction of **8a** gave a mixture of the same two products with **10a** predominating.

The synthesis of B-norestrone (**1a**) (Chart I) was undertaken as part of our continuing efforts to separate the lipodiatic and feminizing properties of estrone.[3,4] The synthetic approach was based on the recent method developed by Torgov[5] for steroidal total syntheses, which has since been extensively used by several laboratories.[3d,6] 5-Methoxyindan-1-one with vinyl magnesium bromide was readily transformed into allylic alcohol **2** (Chart I). Alkylation of 2-methylcyclopentane-1,3-dione with **2** in the presence of Triton B afforded diketone **3** in 70% over-all yield from the indanone.[7] Warm methanolic hydrochloric acid caused **3** to undergo cyclodehydration and tetracyclic ketone **4** was isolated in 92% yield. Selective reduction of the 14,15 double bond of **4** in the presence of 5% palladium on calcium carbonate afforded a 1:3 mixture (by nmr) of **5** and **6**, respectively, from which the *trans* ketone **6** was isolated in pure form in 25% yield. The configurations at C-14 were assigned on the basis of the shielding effect of the 8,9 double bond on the angular methyl group of **6** compared with that of **5**.[8] The poor yield of **6** was overcome by relying

CHART I



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