the ester residue was hydrolyzed with methanolic potassium hydroxide and the resulting carboxylic acid was characterized. Properties of the acid are summarized in Table III. In all cases involving 5,5-diarylsubstituted pyrazolines nearly quantitative yields of cyclopropanes were obtained.

Partial Decomposition of 3 and 4.—A sample of each pure 2-pyrazoline (≈0.6 g) was dissolved in 50 ml of decalin in which 0.3 ml of triisoamylamine had been mixed. This solution was placed in a constant-temperature oil bath at 150° until about 50% of the calculated amount of nitrogen had been evolved. The solution was then removed from the bath and allowed to cool. Five milliliters of acetic anhydride and 3 drops of concentrated sulfuric acid were added. The liquids formed a two-phase mixture which was heated overnight at 60°. The two layers were then separated and the anhydride layer was worked up in the usual manner. This work-up gave a pale yellow oil. The infrared spectrum (plates) of this oil gave peaks at 5.78, 5.80, 5.95, 11.4, and 12.6 μ, and was virtually identical with the spectrum of an authentic mixture of the two acetyl derivatives.

The infrared spectrum of the decalin solution remaining showed a single carbonyl peak indicating the possible presence of cyclopropane products.

Removal of the decalin under reduced pressure gave an oil which was hydrolyzed with alcoholic potassium hydroxide at room temperature. Following acidification and reaction of the product with diazomethane, a colorless oil was obtained. The infrared spectrum of this oil was virtually superimposable on the spectrum of a known mixture of *cis*- and *trans*-3-phenyl-1,2-dicarbomethoxycyclopropane.

Registry No.—**3**, 10036-65-4; N-acetyl derivative of **3**, 10036-66-5; **4**, 10036-67-6; N-acetyl derivative of **4**, 10036-68-7; **6**, 10036-69-8; N-acetyl derivative of **6**, 10036-70-1; **7**, 10036-71-2; N-acetyl derivative of **7**, 10036-72-3; **8**, 10036-73-4; N-acetyl derivative of **8**, 10036-74-5; **10**, 10036-75-6; N-acetyl derivative of **10**, 10036-76-7; **11**, 10036-77-8; N-acetyl derivative of **11**, 10036-78-9; **12**, 10036-79-0; N-acetyl derivative of **12**, 10036-80-3; **5**, 10036-81-4; **9**, 10036-82-5.

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Bicyclo[3.3.1]nonanes. II. Synthesis and Reactions of Simple Derivatives

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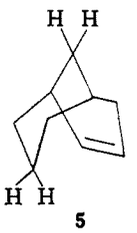
The preparation of numerous bicyclo[3.3.1]nonane derivatives from available starting materials is described. Conversion of 2-N-morpholinobicyclo[3.3.1]nonan-9-one (**2**) to 2-N-morpholinobicyclo[3.3.1]nonane (**3**) and reaction of the latter with hydrogen peroxide gave the N-oxide **4** which on pyrolysis produced bicyclo[3.3.1]non-2-ene (**5**) in good over-all yield. Hydroboration of **5** gave a 2:3 mixture of *exo*-bicyclo[3.3.1]nonan-2-ol (**6**) and *exo*-bicyclo[3.3.1]nonan-3-ol (**7**). Oxidation of **7** produced bicyclo[3.3.1]nonan-3-one (**8**) which on reduction yielded *endo*-bicyclo[3.3.1]nonan-3-ol (**9**). Oxidation of **5** with selenium dioxide gave *exo*-bicyclo[3.3.1]non-3-en-2-ol (**10**), which could be further oxidized with manganese dioxide to bicyclo[3.3.1]non-3-en-2-one (**11**). Reduction of **11** with sodium borohydride produced *endo*-bicyclo[3.3.1]non-3-en-2-ol (**12**); catalytic hydrogenation of **11** gave bicyclo[3.3.1]nonan-2-one (**13**). Ketone **13** could also be synthesized from β-(3-carboxycyclohexyl)-propionic acid (**20**) by pyrolysis of the barium salt or through a Dieckmann condensation of the corresponding diethyl ester.

Although the bicyclo[3.3.1]nonane structure is a potentially interesting framework for the investigation of structure–reactivity relationships, a detailed study of the chemistry of the system has not yet been reported due, in part, to the relative inaccessibility of suitable simple derivatives. As a prelude to a study of the solvolytic reactivity of certain bicyclo[3.3.1]nonane derivatives, we have investigated several synthetic approaches to the parent system and have developed two practical routes which are versatile and adaptable to the synthesis of large quantities of these compounds.

In 1956, Stork and Landesman[2] reported that a high yield of 2-N-pyrrolidinobicyclo[3.3.1]nonan-9-one (**1**) resulted from the reaction of the pyrrolidine enamine of cyclohexanone with acrolein. The ease of formation of the bridged bicyclic compound made it an attractive starting material for the synthesis of other bicyclo[3.3.1]nonane derivatives. Chart I outlines the synthetic routes which we have used to prepare numerous derivatives from the morpholine analog (**2**) of **1**.

Reduction of **2** by the Wolff–Kishner method gave 2-N-morpholinobicyclo[3.3.1]nonane (**3**) in 74% yield. Oxidation of **3** with hydrogen peroxide and pyrolysis of the resulting amine oxide **4** produced bicyclo[3.3.1]-non-2-ene (**5**) in an over-all yield of 51%. Hydroboration of **5** using the procedure of Brown and Subba Rao[3] gave a 3:2 ratio of two isomeric alcohols. These alcohols were separated chromatographically, and the minor component was shown to be the known *exo*-bicyclo[3.3.1]nonan-2-ol (**6**).[4]



5

The major alcohol formed on hydroboration of **5** was identified as *exo*-bicyclo[3.3.1]nonan-3-ol (**7**) (Figure 1) on the basis of its infrared and nuclear magnetic resonance (nmr) spectra and its subsequent reactions. The nmr spectrum of **7** showed a nine-line pattern (A_2B_2X system) centered at τ 5.77 for the carbinyl proton at C-3; the coupling constants were 11.3 and 5.9 cps. These features are characteristic of an axial proton in a rigid cyclohexane ring.[5] Oxidation of **7** gave bicyclo[3.3.1]nonan-3-one (**8**) in good yield. Re-

(1) For the first paper in this series, see J. P. Schaefer and J. C. Lark, *J. Org. Chem.*, **30**, 1337 (1965).

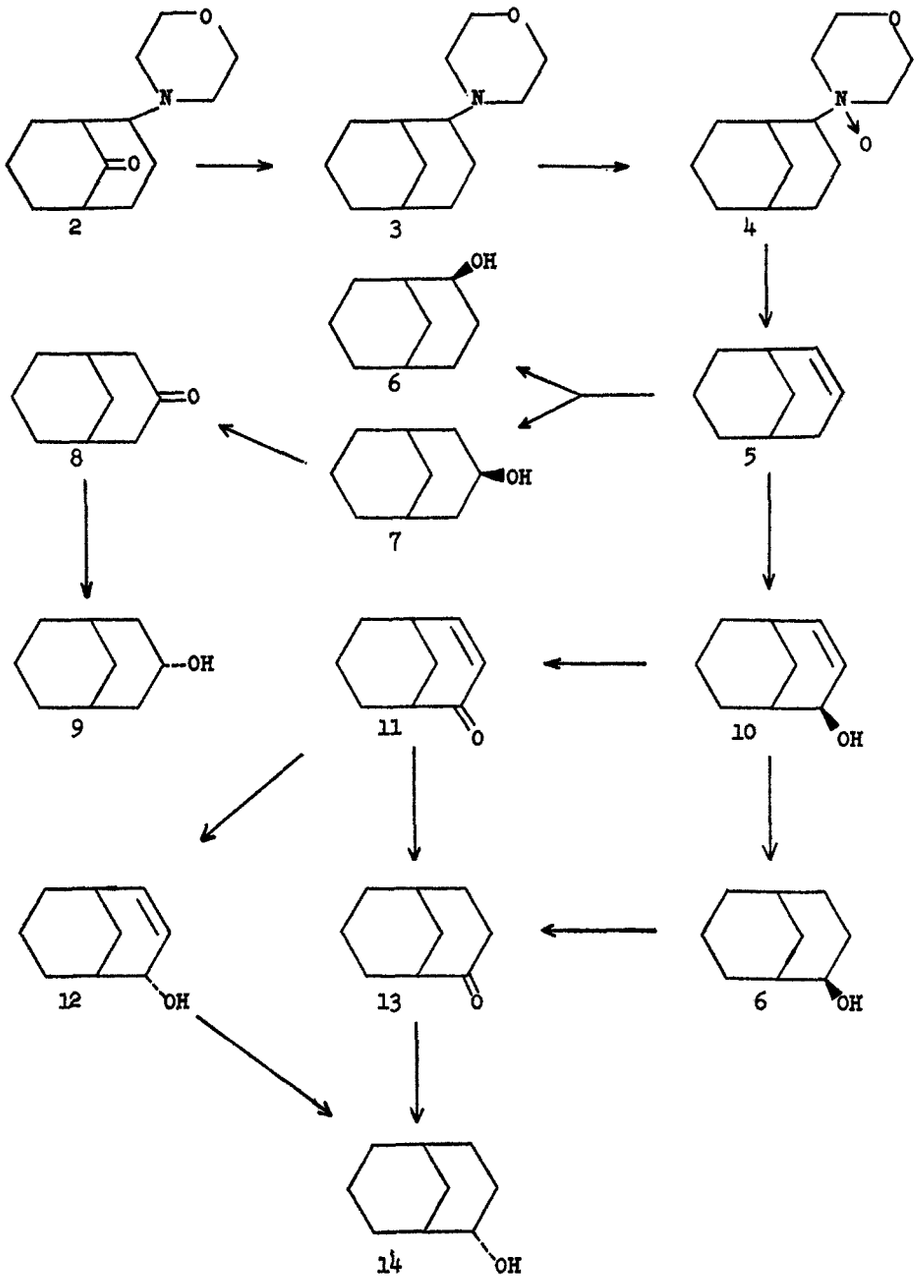
(2) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956).

(3) H. C. Brown and B. C. Subba Rao, *ibid.*, **78**, 5694 (1956); *ibid.*, **81**, 6428 (1959).

(4) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *ibid.*, **87**, 3130 (1965).

(5) F. A. L. Anet, *ibid.*, **84**, 1053 (1962).

CHART I
PREPARATION OF BICYCLO[3.3.1]NONANE DERIVATIVES



duction of **8** with sodium borohydride in methanol gave a new alcohol (**9**) which must be *endo*-bicyclo[3.3.1]-nonan-3-ol. From an examination of Dreiding models of **5**, it is apparent that the least hindered approach to the double bond by an attacking reagent should occur from the *exo* face of the molecule and that attack at C-3 should be slightly more favored on steric grounds. In view of the demonstrated sensitivity of the hydroboration reaction to steric effects, it is not unreasonable that both of the alcoholic products should be the *exo* isomers.[6,7]

Oxidation of **5** with selenium dioxide in aqueous dioxane gave an unsaturated alcohol in moderate yield. Recent work in these laboratories has indicated that in solvents of high ionizing power the product-forming intermediate from the selenium dioxide oxidation of an olefin is an allylic carbonium ion.[8] Again, in view of the relative shielding effects of the methylene and propylene bridges between C-1 and C-5, attack on the allylic cation by water should favor the production of *exo*-bicyclo[3.3.1]non-3-en-2-ol, and the oxidation product **10** has, therefore, been assigned this structure. Hydrogenation of **10** yielded **6**; this fact provides further confidence in the stereochemistry assigned to the unsaturated alcohol.

Oxidation of **10** with manganese dioxide produced bicyclo[3.3.1]non-3-en-2-one (**11**) in high yield. Reduction of **11** with sodium borohydride in methanol gave a new unsaturated alcohol (**12**) which, in view of its origin and subsequent reaction, must be *endo*-bicyclo[3.3.1]non-3-en-2-ol. Hydrogenation of **11** gave bicyclo[3.3.1]nonan-2-one (**13**), whereas **12** produced

(6) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

(7) Similar findings for the 1,5-dimethyl analog of **8** have recently been reported by W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Letters*, No. 30, 2589 (1965).

(8) J. P. Schaefer and B. Horvath, *ibid.*, **30**, 2023 (1964).

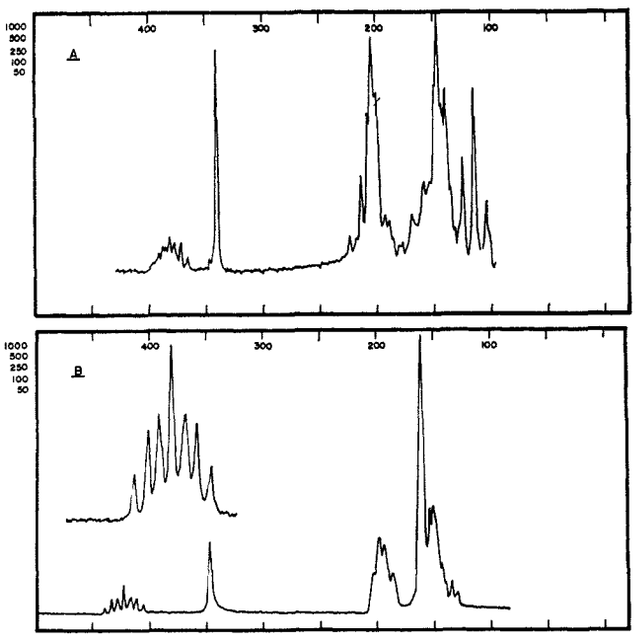


Figure 1.—Nmr spectra (HA 100) of *endo*-bicyclo[3.3.1]nonan-3-ol (A) and *exo*-bicyclo[3.3.1]nonan-3-ol (B).

endo-bicyclo[3.3.1]nonan-2-ol (**14**). Chromic acid oxidation of **6** also gave **13**, and reduction of **13** with sodium borohydride in methanol yielded **14**. This series of interrelated reactions firmly establishes the proposed structures of the products and removes the possibilities of complications which might have resulted from skeletal rearrangements.

Most of the previous approaches to the bicyclo[3.3.1]nonanes[9-14] have involved the preparation of an appropriate 1,3-disubstituted cyclohexane derivative which was subsequently converted to the bicyclic structure by an acid- or base-catalyzed ring closure. Therefore, a second approach which we attempted was concerned with the synthesis of β-(3-carboxycyclohexyl)-propionic acid (**15**) since it was anticipated that a Dieckmann condensation of a diester of **15** would provide a convenient source of **13**. Chart II summarizes several straightforward routes to **15**.

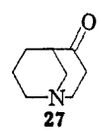
Toluic acid (**16**) was converted to its acid chloride, brominated, and added to absolute ethanol to give **17** in good yield. A Sommelet reaction on **17** produced ethyl isophthalaldehydate (**18**) which was readily converted to the cinnamic ester **21** by reaction with malonic acid and subsequent esterification. Catalytic hydrogenation of **21** in the presence of Adams catalyst was difficult owing to a pronounced tendency of the catalyst to coagulate during the reduction, but, with persistence, high yields of **20** were obtained. Rhodium on alumina was subsequently found to be a superior catalyst for these reductions.

An alternative source of **20** from **17** involved a base-catalyzed reaction of **17** with diethyl malonate followed by hydrolysis, decarboxylation, esterification, and hydrogenation; this too proved to be an efficient source of the desired intermediate. Another route to **20**, which was slightly less efficient, utilized *m*-nitrobenzaldehyde (**23**) as the starting material. Reaction of **23** with the half-ester of malonic acid followed by catalytic hydrogenation gave **24** in excellent yields; diazotization of **24** and reaction of the diazonium salt with cuprous cyanide gave fair yields of **25** which was readily converted to **26**.

Saponification of **20** produced **15** which readily formed a barium salt. When the dried barium salt was heated in Wood's metal bath at 175–200° in a nitrogen atmosphere, the ketone **13** sublimed out of the reaction mixture. Yields of **13** obtained by this technique were variable and ranged up to 31%, although yields of 20% were more typical.[15]

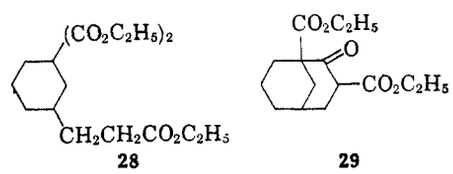
When **20** was subjected to the Dieckmann condensation using potassium *t*-butoxide as the catalyst in refluxing xylene under high-dilution conditions, **22** was isolated in moderate yield; hydrolysis and decarboxylation of **22** also gave **13**. Although we are still studying the effect of variables on the course of the Dieckmann reaction, at the present time this is the most consistent and reliable source of **13**.

The difficulties encountered during closure of the second ring of the bicyclic skeleton require further comment. Earlier workers,[16-17] who were concerned with the synthesis of **27**, obtained the bicyclic ketone in

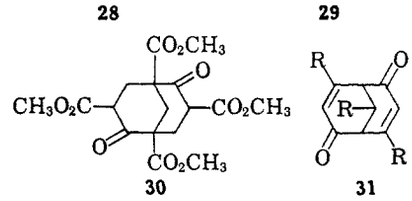


27

yields varying from 6 to 23% using the Dieckmann condensation. Similarly, cyclization of compound **28** utilizing sodium hydride produced **29** in a maximum yield of 21%.[18] In contrast, compounds such as **30** and **31**, which also rely upon acid- or base-



28 **29**



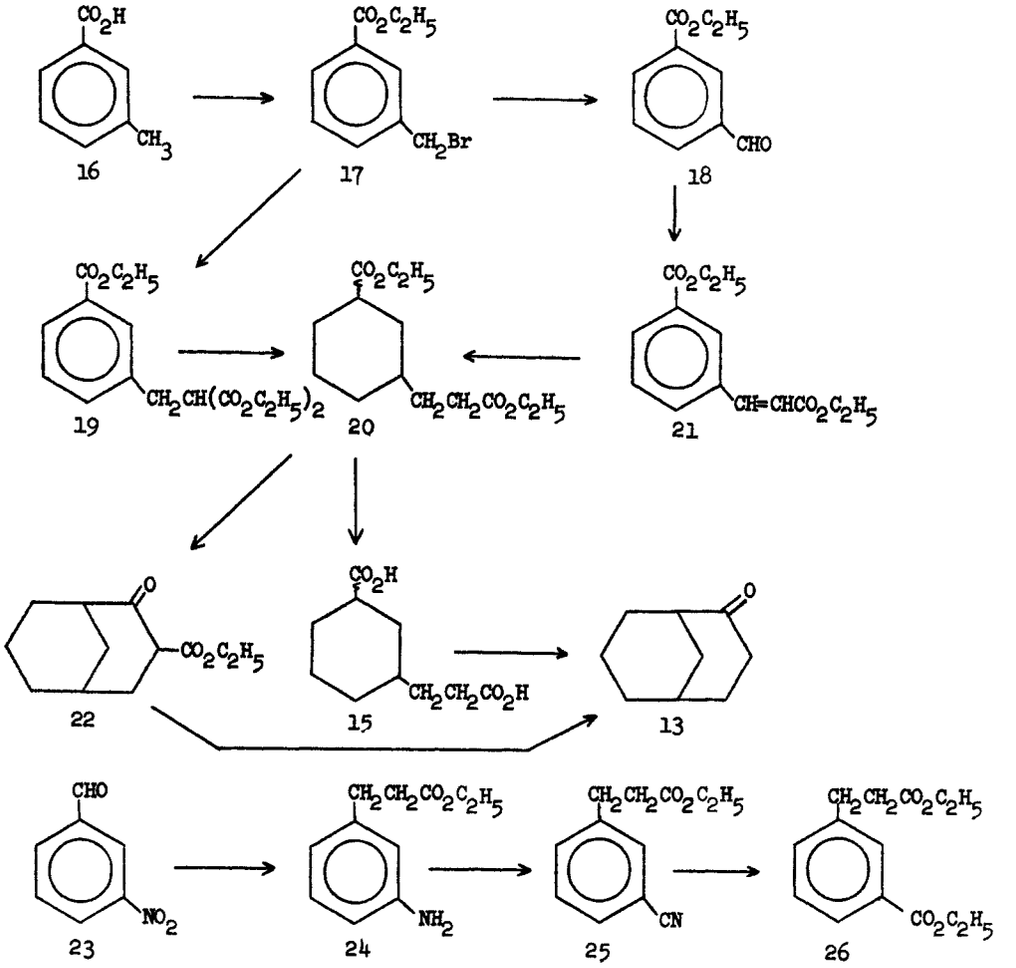
30 **31**

catalyzed ring closures to form the bridged bicyclic rings, are formed in high yields and require no unusual reaction conditions.[9,19] These results are readily interpreted on the basis of conformational effects.

Recent crystallographic studies[20-22] have shown that in the solid state the preferred conformation of the

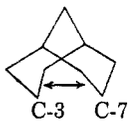
(9) H. Meerwein and W. Schurman, *Ann.*, **398**, 196 (1913); H. Meerwein, F. Kiel, G. Klösgen, and E. Schoch, *J. Prakt. Chem.* [2], **104**, 161 (1922).
(10) S. Julia, *Bull. Soc. Chim. France*, 780 (1954).
(11) A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950).
(12) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1379 (1959).
(13) P. Rabe and K. Appuhn, *Ber.*, **76**, 982 (1943).
(14) R. D. H. Murray, W. Parker, and R. H. Raphael, *Tetrahedron*, **16**, 74 (1961).
(15) Hartmann has just reported that pyrolysis of the magnesium salt at 475° gave the ketone in 42% yield. M. Hartmann, *Z. Chem.*, **6**, 182 (1966).
(16) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).
(17) L. H. Sternbach and S. Kaiser, *ibid.*, **74**, 2215 (1952).
(18) J. P. Ferris and N. C. Miller, *ibid.*, **85**, 1325 (1963).
(19) E. Knoevenagel, *Ann.*, **281**, 25 (1964).
(20) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964).
(21) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. H. Sim, *Proc. Chem. Soc.*, **57** (1964).
(22) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

CHART II
SYNTHESIS OF BICYCLO[3.3.1]NONAN-2-ONE[a]



[a] Aromatic route.

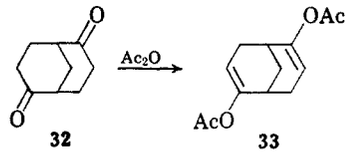
simple bicyclo[3.3.1]nonanes is the chair–chair arrangement. However, the interactions between the C-3 and C-7 methylene groups are serious enough to



bring about a flattening of the two rings and to increase the bond angles at carbon atoms 2, 3, 4, 6, 7, and 8 to about 114° to compensate for the resulting repulsion between these moieties. Furthermore, from a comparison of infrared spectral bands observed for the solid and for the compound in solution, it is apparent that this conformation is also an important one in solution.[6, 23]

In condensations which are equilibrium processes, the formation of the bicyclic system will be hindered when significant repulsive interactions exist and side reactions, such as intermolecular condensations, will be favored. Where these interactions are negligible, as in **31** or in the dianion of **30**, cyclization is remarkably facile. The behavior of bicyclo[3.3.1]nonan-2,6-dione (**32**) is also instructive.

Meerwein[9] found that when **32** is warmed for a short period of time with acetic anhydride, it is readily converted to the dienol acetate (**33**). In view of the above discussion, it seems probable that a significant driving force for this reaction is provided by substantial relief of strain present in the parent diketone.



32 **33**

Further studies concerning conformational aspects and reactivities of bicyclo[3.3.1]nonanes are in progress and will be reported in the near future.

Experimental Section

2-N-Morpholinobicyclo[3.3.1]nonan-9-one (2).—To a 1-l. flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 83.5 g (0.500 mole) of 1-N-morpholinocyclohexene[24] and 400 ml of benzene. This solution was cooled to 0–5° and 28 g (0.50 mole) of acrolein was added over a period of 30 min. Stirring of the cold solution was continued for an additional 1 hr, after which the mixture was heated at reflux for 3 hr. The product was collected by distillation [bp 150–160° (2.8 mm)] and weighed 83 g (75%).

2-N-Morpholinobicyclo[3.3.1]nonane (3).—To 83 g (0.38 mole) of 2-N-morpholinobicyclo[3.3.1]nonan-9-one were added 520 ml of diethylene glycol, 71 g of potassium hydroxide, and 51 ml of 85% hydrazine hydrate. This mixture was refluxed in a

(23) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

(24) S. Honig, E. Benzing, and E. Lucke, *Ber.*, **90**, 2833 (1957).

flask fitted with a Dean–Stark trap and condenser until no more water separated and nitrogen evolution ceased. Then the temperature was raised to 195° and kept there for 4 hr. The solution was cooled, poured onto 1000 g of ice, and extracted with diethyl ether. Drying, filtration, and concentration of the combined extracts were carried out. Distillation gave 60 g (74%) of the desired product, bp 120–123° (3 mm).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.53; H, 11.57; N, 6.90.

Bicyclo[3.3.1]non-2-ene (5).—To a solution of 62.7 g (0.300 mole) of 2-N-morpholinobicyclo[3.3.1]nonane, 150 ml of 95% ethanol, and 150 ml of methanol was added 100 ml of 30% hydrogen peroxide. The resulting solution was heated at 70–72° for 36 hr. The excess hydrogen peroxide was decomposed by stirring the solution overnight at 40° in the presence of platinum black. The solution was then filtered and concentrated to a syrup at aspirator pressure; after further drying at 1-mm pressure and 80°, the brown mass crystallized. The flask was fitted for a simple distillation, flushed with nitrogen, and heated slowly to 110–115°, at which temperature pyrolysis began. After 1 hr at 110–115°, the flask was heated at 145° for 3 hr. Water was then added to the flask and steam distillation was carried out in order to recover any remaining traces of olefin. Filtration of the distillate gave a crude product. Purification by sublimation at 75° afforded 18.7 g (51.0%) of pure olefin, mp 96.5–97° (lit.[25] mp 96–100°). Hydrogenation over palladium on charcoal gave the known bicyclo[3.3.1]nonane, mp 143–144° (lit.[9] mp 145–146°).

Hydroboration of Bicyclo[3.3.1]non-2-ene (5).—Bicyclo[3.3.1]-non-2-ene (3.6 g, 30 mmoles) and 2 g (5 mmoles) of sodium borohydride were dissolved in 50 ml of freshly distilled triglyme. The system was flushed with nitrogen and 8.3 g (59 mmoles) of freshly distilled boron trifluoride etherate dissolved in 10 ml of triglyme was added dropwise over a period of several hours. A slight positive gas pressure was maintained by inserting the outlet tube into an 8-in. test tube filled with mercury. The solution was stirred with a magnetic bar for 3 hr. Then 10 ml of water and 10 ml of 3 *N* sodium hydroxide were added; the addition of 10 ml of 30% hydrogen peroxide ensued. The solution was poured onto 300 ml of ice water and extracted with five 75-ml portions of ether. The combined ether extracts were washed with five 100-ml portions of water, dried, and filtered. After removal of the ether by distillation, the residue was purified by crystallization from pentane at −80° and subsequent sublimation at 100°. The yield of alcohol was 2.6 g (61%) and the product had a melting range of 126–134°.

Analysis by gas chromatography using a 10-ft Carbowax 20 M column heated to 150° showed that the product consisted of a 3:2 mixture of isomeric alcohols. The minor alcohol was collected and found to be *exo*-bicyclo[3.3.1]nonan-2-ol (**6**), mp 176–177° (lit.[4] mp 180–192°). The major product was identified as *exo*-bicyclo[3.3.1]nonan-3-ol (**7**), mp 100–101°. The nmr spectrum of **7** is shown below. The infrared spectrum of **7** was characterized by strong absorption at 1050 cm^{-1}, which is indicative of an equatorial hydroxyl group on a cyclohexane ring.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.92; H, 11.66.

Bicyclo[3.3.1]nonan-3-one (8) and *endo*-Bicyclo[3.3.1]nonan-3-ol (9).—A solution of 1 g (7 mmoles) of **7** and 5 ml of acetone was cooled to below 5° with an ice bath. A solution of 1.05 g of chromic oxide and 0.89 ml of concentrated sulfuric acid, diluted with water to a total volume of 4 ml, was slowly added dropwise. After 3 hr, 5 ml of methanol was added to reduce the excess chromic acid. The mixture was filtered, added to a saturated solution of potassium carbonate, and extracted with diethyl ether. The ether extract was dried over anhydrous sodium sulfate and filtered.

Removal of the solvent from a portion of the oxidation product solution and subsequent sublimation of the residue afforded a white, crystalline, ketonic product, mp 170–176° (lit.[26] mp 180–182°). Only one component was revealed by gas–liquid partition chromatography (glpc) (Carbowax 20 M, 150°). An nmr spectrum showed four protons (τ 7.60) adjacent to a carbonyl group. This product was identical with the ketone produced by pyrolysis of the barium salt of cyclohexane-1,3-diacetic acid.[26]

The solvent from the bulk of the oxidation product solution was replaced with methanol (*ca.* 100 ml), and 2 g of sodium borohydride was added. This solution was allowed to stand overnight before water was added to decompose the excess hydride. Extraction with diethyl ether was carried out. The extract was dried over anhydrous sodium sulfate and filtered. Removal of the solvent by distillation, followed by crystallization of the residue from pentane at −80° and sublimation at 85°, gave 0.413 g of alcohol, mp 121.5–124°. No impurities could be detected by glpc (Carbowax 20 M, 150°). Assignment of the structure corresponding to *endo*-bicyclo[3.3.1]nonan-3-ol to this product is consistent with its nmr and infrared spectra.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.56; H, 11.93.

***exo*-Bicyclo[3.3.1]non-3-en-2-ol (10).**—To 110 ml of freshly distilled dioxane were added 15.2 g (0.125 mole) of bicyclo-[3.3.1]non-2-ene, 20 ml of water, and 18.5 g (0.165 mole) of selenium dioxide. The solution was refluxed for 24 hr, cooled, and filtered; 200 ml of pentane was added. The resulting solution was washed with water to remove the dioxane, dried with anhydrous potassium carbonate, filtered, and concentrated. Sublimation of the residue gave 8.39 g (48.6%) of the allylic alcohol, mp 103–103.5°.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.51; H, 10.19.

The *p*-nitrobenzoate, mp 85–86°, was prepared.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.96; H, 6.15; N, 4.75.

Bicyclo[3.3.1]non-3-en-2-one (11).—Oxidation of *exo*-bicyclo-[3.3.1]non-3-en-2-ol with manganese dioxide in pentane gave the conjugated ketone in 91.3% yield, mp 97.5–98.5°.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.83. Found: C, 78.88; H, 9.48.

The semicarbazone, mp 167–168°, was prepared.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.31; H, 7.99; N, 21.58.

***endo*-Bicyclo[3.3.1]non-3-en-2-ol (12).**—Reduction of bicyclo-[3.3.1]non-3-en-2-one with sodium borohydride produced the desired compound, mp 131.5–132.5°, in 94% yield.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.12; H, 10.36.

The *p*-nitrobenzoate of **12** had a melting point of 80–80.5° after crystallization from a mixture of ethanol and water.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.91; H, 5.99; N, 4.55.

***exo*-Bicyclo[3.3.1]nonan-2-ol (6).**—To a solution of **10** in ethyl acetate was added a small quantity of Adams catalyst. Reduction was carried out on a microhydrogenation apparatus at about 1 atm of hydrogen pressure. After hydrogen absorption ceased, the mixture was filtered and the ethyl acetate was removed by distillation. Crystallization of the residue from pentane at −80° and subsequent sublimation at 85° gave *exo*-bicyclo[3.3.1]-nonan-2-ol, mp 175–177°. The *p*-nitrobenzoate melted at 111.5–112.5° after crystallization from an alcohol–water mixture.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.11; H, 6.27; N, 5.12.

Ethyl *m*-Carbethoxycinnamate (21).—From *m*-toluic acid there was obtained *m*-toluyl chloride[27] in 90–96% yield. This acid chloride was converted to **17** by bromination in carbon tetrachloride followed by treatment with ethanol. The product, bp 140–145° (4 mm) [lit.[25] bp 160–161° (10 mm)], was obtained in 58% yield. Formation of the hexaminium salt[28] was quantitative; it was converted to ethyl isophthalaldehydate (**18**) by hydrolysis. Without further purification, crude **18** was treated with malonic acid. Esterification afforded **21**, bp 155–156° (0.8 mm) and $n^{25}D$ 1.5460, in 39% yield based on the amount of hexaminium salt used.

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.37; H, 6.60.

Diethyl *m*-Carbethoxybenzylmalonate (19).—To a solution prepared from 23.0 g (1.00 mole) of sodium and 200 ml of absolute ethanol under a nitrogen atmosphere was added 192 g (1.20 mole) of diethyl malonate. The mixture was stirred while 122 g (0.502 mole) of **17** was added dropwise over a period of 3 hr. After 5 hr at reflux, the solution was cooled, combined with 50 ml of water, and extracted with diethyl ether. The combined

(25) C. S. Foote, Ph.D. Thesis, Harvard University, 1962.

(26) H. K. Hall, Jr., *J. Org. Chem.*, **28**, 3213 (1963).

(27) W. Davies and W. H. Perkins, *J. Chem. Soc.*, **121**, 2202 (1922).

(28) S. J. Angyal, P. J. Morris, J. R. Tetaz, and J. G. Wilson, *ibid.*, 2141 (1950).

ether extracts were dried over anhydrous magnesium, sulfate, filtered, and concentrated at reduced pressure. Distillation afforded 104.5 g (68%) of product, bp 195–198° (4 mm) and $n^{33}D$ 1.4902.

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.25; H, 7.11.

Ethyl *m*-Nitrocinnamate.—From 11 g (0.084 mole) of ethyl hydrogen malonate, prepared according to the method described by Strube,[29] and 8.5 g (0.056 mole) of *m*-nitrobenzaldehyde was prepared 10 g (82%) of ethyl *m*-nitrocinnamate according to a modification of the procedure described by Galat.[30] After crystallization from 100% ethanol, the product melted at 72–72.9° (lit.[31] mp 78–79°).

Catalytic Reduction of Ethyl *m*-Nitrocinnamate.—Ethyl *m*-nitrocinnamate (716 g, 3.24 moles) was dissolved in 3 l. of 100% ethanol, and the catalyst, 5% rhodium on charcoal, was added. Hydrogenation was carried out in a high-pressure bomb for 24 hr at pressures ranging from 200 to 500 psi of hydrogen. The temperature rose spontaneously to 50–60°. Filtration and concentration on a rotary evaporator afforded 622 g (99.5%) of crude ethyl *m*-aminohydrocinnamate (**24**). An attempt to distill a portion of the product through a spinning-band column at reduced pressure was only moderately successful because the product tended to polymerize when heated. However, distillation did afford some pure **24**, bp 128–130° (1 mm) and $n^{21.5}D$ 1.5350.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.83; N, 7.25. Found: C, 67.97; H, 7.77; N, 7.57.

Ethyl *m*-Cyanohydrocinnamate (25).—Ethyl *m*-aminohydrocinnamate (50.0 g, 0.259 mole) was cooled in an ice bath and stirred while 62.5 ml of concentrated hydrochloric acid and sufficient cracked ice to keep the temperature between 0 and 5° were added concomitantly. Diazotization was effected when a solution of 19.0 g (0.275 mole) of sodium nitrite in 50 ml of water was added rapidly with stirring. Cracked ice was supplied as needed. Neutralization was achieved by the rapid addition of dry sodium bicarbonate. The cold, neutral diazonium salt solution was added immediately and rapidly to a 3-l. flask which contained a vigorously stirred mixture of cuprous cyanide (0.35 mole) in 200 ml of water and 65 ml of toluene. Cracked ice was added as required in order to keep the temperature of the reaction mixture below 5°. After the addition was complete, stirring was continued at 0° for 0.5 hr and then at room temperature for 5 or 6 hr. Finally, stirring was stopped and the mixture was heated to 50–60° by means of a hot water bath. The heat source was removed and the mixture was allowed to stand overnight. After the aqueous layer had been siphoned off, it was extracted with two or three 100-ml portions of benzene. The benzene extracts were combined with the toluene solution before drying, filtration, and concentration were carried out. The residue was distilled under reduced pressure through a spinning-band column. The product, which was obtained in 51.6% yield, had bp 133–136° (1.5 mm) and $n^{21}D$ 1.5129. An infrared spectrum (film) revealed nitrile absorption at 2240 cm^{-1} and strong carbonyl absorption at 1740 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.95; H, 6.45; N, 6.90. Found: C, 71.30; H, 6.64; N, 6.90.

Ethyl *m*-Carbethoxyhydrocinnamate (26). A.—Saponification and decarboxylation of **19** gave *m*-carboxyhydrocinnamic acid, mp 175–176° (lit.[32] mp 177°). Acid-catalyzed esterification of the diacid afforded the desired compound in 83% yield.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.60; H, 6.95.

B.—To a solution of ethyl *m*-cyanohydrocinnamate (36.0 g, 0.177 mole) in 42.3 ml of 95% ethanol was added 18.8 ml of concentrated sulfuric acid. This mixture was stirred and refluxed for 20 hr. After having been cooled to room temperature, the reaction mixture was filtered, and the filtrate was extracted with benzene. The combined benzene extracts were washed with saturated sodium bicarbonate solution, dried, filtered, and concentrated. Distillation of the residue gave the desired product, bp 150–155° (2 mm), in 77.8% yield.

Bicyclo[3.3.1]nonan-2-one (13). A.—Reduction of **21** in acetic acid utilizing Adams catalyst at 2000 psi of hydrogen and 25° gave **20** in quantitative yield. It was necessary to remove the catalyst by filtration and to add fresh catalyst several times during the hydrogenation in order to achieve complete reduction. After removal of the catalyst and the solvent, the product, bp 135° (1.5 mm) and $n^{33}D$ 1.4611, was purified by distillation. Ethyl carbethoxyhydrocinnamate was also reduced in this manner to give **20**. Saponification of **20** gave the corresponding diacid (**15**), mp 112.5–113.5°, in quantitative yield.

To 5.0 g (25 mmoles) of **15** in a 100-ml flask was added 3.0 g of barium hydroxide. The flask was fitted with a simple distillation head connected to a vacuum adapter and a receiving flask. A Wood's metal bath was used to heat the flask slowly to 175–200°; this temperature was maintained for 2 hr. The contents of the flask were steam distilled and a semicarbazone was prepared from the distillate. After crystallization from an ethanol–water mixture, the semicarbazone, mp 182–183° (lit.[9] mp 180–182°), weighed 1.5 g (31%). The semicarbazone was decomposed by steam distillation of the ketone from a 5% phosphoric acid solution; there was obtained 0.93 g (88%) of bicyclo[3.3.1]-nonan-2-one, mp 129–130° (lit. mp 135–137°[18] and 150°[9]), without further purification.

B.—Reduction of **26** in 100% ethanol was carried out in a Parr hydrogenation apparatus with 5% rhodium on alumina serving as catalyst. The initial hydrogen pressure was 60 psi; heat was supplied by a lamp. After separation of the catalyst by filtration and removal of the solvent at reduced pressure, the product (**20**), bp 123–124.5° (1 mm), was distilled through a spinning-band column.

A carefully dried, 2-l. Morton flask fitted with a cyclic high-dilution apparatus and a high-speed stirrer was flushed with dry nitrogen. A nitrogen atmosphere was maintained throughout the procedure. Approximately 700 ml of dry xylene was placed in the flask and then 70 ml of it was removed by distillation in order to ensure dryness. The contents of the flask were cooled slightly while 13.3 g (0.340 mole) of freshly cut potassium and 87.5 ml (0.647 mole) of dry *t*-butyl alcohol were added with stirring. Excess alcohol was removed by distillation. Reflux and stirring were continued while the addition of 35 g (0.14 mole) of ethyl β-(3-carbethoxycyclohexyl)propionate in 100 ml of dry xylene from a Hershberg funnel was carried out at the rate of 2–4 drops/min. Reflux was terminated 3 hr after the addition of diester was complete. When the reaction mixture had cooled to room temperature, 22 ml of glacial acetic acid was added slowly. The acidified mixture was stirred for several hours. Nitrogen flow was discontinued and sufficient water was added to dissolve the potassium acetate which had formed. The aqueous layer was separated and extracted with three 100-ml portions of xylene. The combined xylene extracts were washed with water and sodium bicarbonate solution, dried, filtered, and concentrated. To the residue was added ten times its volume of a mixture which consisted of 5.0 parts of glacial acetic acid, 1.15 parts of concentrated hydrochloric acid, and 1.5 parts of water. After 22 hr of reflux and stirring, the reaction mixture was cooled to room temperature, saturated with solid ammonium sulfate, and extracted exhaustively with diethyl ether. The combined extracts were washed with saturated sodium bicarbonate solution until neutrality was achieved. The ether solution was dried, filtered, and concentrated. Sublimation of the residue gave 6.5 g (34%) of ketone **13**, which melted at 124–133.5° (lit. mp 135–137°[18] and 150°[9]). The semicarbazone, mp 183.5–184.5° (lit.[9] mp 180–182°), was prepared. Pure ketone, mp 134–136.5°, was obtained after hydrolysis of the semicarbazone by steam distillation from oxalic acid solution.

Pure β-keto ester, bp 109–112.5° (2.5 mm), could be obtained by distillation of the condensation product.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.66; H, 8.78.

C.—Both *exo*-bicyclo[3.3.1]nonan-2-ol and its *endo* counterpart were oxidized to **12** in 50% yield by means of chromium trioxide in anhydrous pyridine. After 48 hr of stirring, sodium bisulfite solution was added to reduce the unreacted chromium trioxide. An excess of concentrated hydrochloric acid was added and steam distillation was carried out. The distillate was made basic with potassium carbonate, saturated with sodium chloride, and extracted with pentane. The pentane solution was dried, filtered, and concentrated. Sublimation of the residue afforded the desired ketone, mp 134–137° (lit. mp 135–137°[18] and 150°[9]).

D.—Bicyclo[3.3.1]non-3-en-2-one (**11**) (2.1 g, 15 mmoles) was dissolved in 20 ml of glacial acetic acid. Reduction was carried out in a Parr hydrogenation apparatus at approximately 25 psi of hydrogen with 10% palladium on carbon serving as catalyst. The mixture was filtered and the filtrate was poured into pentane.

(29) R. E. Strube, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 417.
(30) A. Galat, *J. Am. Chem. Soc.*, **68**, 376 (1946).
(31) R. Schiff, *Ber.*, **11**, 1782 (1878).
(32) A. F. Titley, *J. Chem. Soc.*, 2571 (1928).

The pentane solution was washed with water, dried, filtered, and concentrated. Sublimation gave 1.6 g (78%) of **13**, mp 133–137° (lit. mp 135–137°[18] and 150°[9]).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.02; H, 10.22.

endo-**Bicyclo[3.3.1]nonan-2-ol** (**14**). **A.**—To a solution of bicyclo[3.3.1]nonan-2-one (0.5 g, 4 mmoles) in 15 ml of anhydrous methanol was added 1.0 g of sodium borohydride over a period of 30 min. This mixture was stirred for 1 hr; 6 ml of water was added and stirring was continued for an additional 1 hr. The solution was poured into 70 ml of pentane. The pentane solution was washed with water, dried, and filtered. After the pentane was removed by distillation at atmospheric pressure, the alcohol was sublimed. The yield of product, mp 177–178°, was 0.45 g (90%).

B. *endo*-Bicyclo[3.3.1]non-3-en-2-ol (0.1 g, 0.7 mmoles) was dissolved in 5 ml of glacial acetic acid. Reduction was carried out in the presence of 10% palladium on carbon on a microhydrogenation apparatus. The mixture was filtered and the filtrate was poured into 50 ml of pentane. The pentane solution was washed with water, dried, and filtered. The solvent was removed by distillation and the residue was sublimed. The yield of alcohol, mp 175–176°, was 0.08 g (80%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.98; H, 11.87.

The *p*-nitrobenzoate was prepared and crystallized from an alchol–water mixture to a constant melting point of 100–101°.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.81; N, 4.72.

Registry No.—**2**, 10036-06-3; **3**, 10036-07-4; **7**, 10036-08-5; **8**, 10036-09-6; **10**, 10036-10-9; *p*-nitrobenzoate of **10**, 10036-11-0; **11**, 10036-12-1; semicarbazone of **11**, 10036-13-2; **12**, 10060-21-6; *p*-nitrobenzoate of **12**, 10036-14-3; **6**, 10036-15-4; *p*-nitrobenzoate of **6**, 10036-16-5; **21**, 10036-17-6; **19**, 10036-18-7; ethyl *m*-nitrocinnamate, 5396-71-4; **24**, 10039-64-2; **25**, 10036-20-1; **26**, 10036-21-2; **13**, 2568-17-4; **20**, 10036-23-4; **15**, 10036-24-5; **14**, 10036-25-6; *p*-nitrobenozate of **14**, 10036-26-7; **12**, 10036-27-8.

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Stereochemistry and Conformations of Reduced Quinoxalines, Phenazines, and Pteridines[1]

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The proton magnetic resonance spectra of *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline exhibit a chemical-shift difference in the signal for the protons adjacent to the nitrogen at C-2 and C-3. This difference of about 0.5 ppm reflects the unequal shielding of axial and equatorial protons resulting from the diamagnetic anisotropy of the carbon–nitrogen single bond. It is concluded that in both isomers interconversion of conformers is rapid down to −87° and that in the *trans* compounds this signal represents hydrogens which are predominantly axially oriented while in the *cis* compounds this is an average signal representing rapidly interconverting equivalent axial and equatorial hydrogens. Thus in the quinoxaline system in chloroform solvent, there is a chemical shift of about 1 ppm downfield in going from an axial to an equatorial proton. The demonstrated generality of this chemical shift permits the assignment of configurations to reduced triazanaphthalenes, phenazines, and pteridines.

Bouveault–Blanc reduction of 2,3-dimethylquinoxaline gives a mixture of *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (I and II, respectively), which can be separated by fractional crystallization *via* the oxalate salts. The stereochemical assignments are due to Gibson,[3] who resolved the lower melting *trans* isomer (II) into its optically active enantiomorphs, thereby distinguishing it from the nonresolvable *cis* isomer (I). Lithium aluminum hydride reduction of 2,3-dimethylquinoxaline[4] is stereospecific, giving the *cis* isomer (I). Similarly prepared were 2,3-dimethyl-1,2,3,4-tetrahydro-1,4,5-triazanaphthalene (III) and 2,3-dimethyl-1,2,3,4-tetrahydro-1,4,6-triazanaphthalene (IV) which were presumed to have the *cis* configuration. Since Gibson's method for proof of configuration by resolution of the *trans-dl* isomer cannot be utilized in the case of these reduced triazanaphthalenes (III and IV) or similar unsymmetrical molecules, the utility of nmr for this purpose has been investigated.

The proton magnetic resonance (pmr) spectra of I and II (Figure 1) are differentiated by a chemical shift in the signal assigned to the protons adjacent to the nitrogen atoms. The resonance signal for the C-2 and C-3 protons of the *trans* isomer (II) occurs 0.5 ppm upfield from the corresponding signal for the *cis* isomer (I) in deuteriochloroform (and about 0.4 ppm as the hydrochloride in deuterium oxide). Evidence for the generality of this chemical-shift difference is gained from examination of spectra of other isomeric pairs of known stereochemistry. Table I reports the chemical shift for the C-2 and C-3 protons of the *cis* and *trans* isomeric pairs (V and VI) from the reduction of 2,3-diphenylquinoxalines[5] and the corresponding phenazine[6] isomers (VII and VIII). In each case the protons (H_x) from the *trans* isomer are more shielded than those from the corresponding *cis* isomer, and this shielding difference is manifest in the observed chemical shift difference of about 0.5 ppm.

A comparison of the chemical shifts of the signals from the C-2 and C-3 protons of reduced triazanaphthalenes III (3.52 ppm) and IV (3.50 ppm) and reduced pteridine IX (3.43 ppm) to the corresponding signals from I (*cis*, 3.48 ppm) and II (*trans*, 2.98 ppm) of established configuration, strongly supports the *cis* con-

(1) Taken in part from the Ph.D. Dissertation of R. A. Archer, Stanford University, 1963.

(2) Parke, Davis Fellow, 1960–1963.

(3) C. S. Gibson, *J. Chem. Soc.*, 342 (1927).

(4) R. C. DeSelms and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 3762 (1960).

(5) C. S. Gibson, *J. Chem. Soc.*, 1570 (1923).

(6) G. R. Clemo and H. McIlwain, *ibid.*, 258 (1936).