trans-1,5-cyclooctadiene in 30 ml of methylene chloride. Fractional crystallization of the complex from benzene–cyclohexane gave 0.58 g of a more soluble material, mp 106–108° (after further recrystallization from carbon tetrachloride), and $[\alpha]^{28}D$ +55.2° (*c* 2.5, methylene chloride).

Anal. Calcd for $C_{26}H_{38}Cl_4N_2Pt_2$: C, 34.28; H, 4.20; N, 3.08; Pt, 42.87. Found: C, 34.42; H, 4.05; N, 2.75; Pt, 43.22.

The least soluble diastereoisomer (0.62 g) had mp 155–157° and $[\alpha]^{28}D$ −18.3° (*c* 2.5, methylene chloride).

Anal. Calcd for $C_{26}H_{38}Cl_4N_2Pt_2$: C, 34.28; H, 4.20; N, 3.08; Pt, 42.87. Found: C, 34.10; H, 4.33; N, 3.06; Pt, 42.46.

The diene obtained on decomposition of the more soluble diastereoisomer had $[\alpha]^{28}D$ −26° (*c* 1.3, pentane); the diene from the least soluble diastereoisomer had $[\alpha]^{28}D$ +34° (*c* 1.2, pentane).

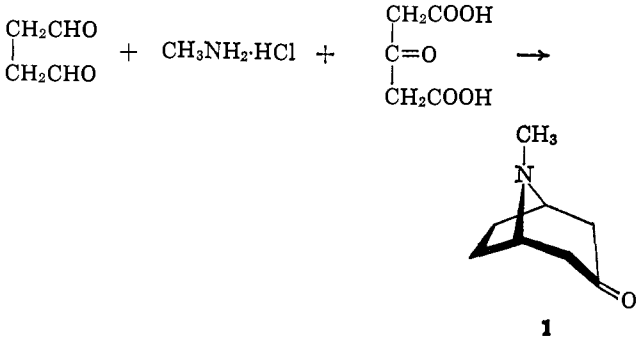
The Stereochemical Course of a Robinson–Schöpf Biogenetic-Type Reaction. The Conformation of Certain Tricyclic Tropane Congeners[1]

Leo A. Paquette[2a] and John W. Heimaster[2b]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received November 1, 1965*

Abstract: The Robinson–Schöpf reaction of *cis*-cyclopentane-1,3-dialdehyde, methylamine hydrochloride, and acetonedicarboxylic acid leads to a tricyclic amino ketone in which the nitrogen and carbon bridges are *anti* to each other. Furthermore, the N-methyl group is shown to exist almost totally, if not exclusively, in the axial conformation (with respect to the piperidone ring). The stereochemical course of the reduction of the amino ketone with various reagents has been studied and a variety of data is presented which contributes to the elucidation of the stereochemistry and conformational analysis of the resulting amino alcohols. The possible significance of the stereochemical outcome of the Robinson–Schöpf reaction on the mechanistic course of double Mannich reactions is discussed.

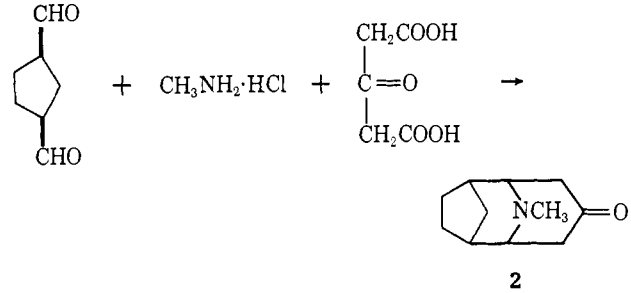
The elegant synthesis[3] of tropane alkaloids "under physiological conditions" ingeniously devised by Robinson[4] and later improved by Schöpf[5] has proved widely applicable, and is illustrated below for the



1

case of tropinone (**1**). The Robinson–Schöpf reaction is often cited as the epitome of a double Mannich condensation involving aldehydes other than formaldehyde,[6] although the actual mechanistic details (except for the nondescript lasso symbolism) of the process have never been discussed to the authors' knowledge and are undoubtedly not clearly understood.[7] In addition, the influence of steric factors on the course of Mannich reactions in general, and of the Robinson–Schöpf reaction in particular, has been little investigated.

Alder, Wirtz, and Koppelberg[8] have reported that the condensation of *cis*-cyclopentane-1,3-dialdehyde with methylamine hydrochloride and acetonedicarboxylic acid results in the formation of the tricyclic tropane congener **2**, but these workers were unable to determine the geometry of this amino ketone. We have reinvestigated the synthesis of **2** with a view to elucidating the stereochemical course of this reaction and in the anticipation that knowledge of the configuration of **2** will shed some light on the mechanistic course of the Robinson–Schöpf reaction.



2

Results

When a methyl acetate solution of *cis*-cyclopentane-1,3-dialdehyde was added to an aqueous phosphate-buffered solution of methylamine hydrochloride and

(1) We are indebted to the National Institutes of Health of the U. S. Public Health Service for financial support (Grant No. GM-11975).

(2) (a) Alfred P. Sloan Foundation Research Fellow; (b) undergraduate research participant.

(3) Once characterized by Willstätter as "von bewundernswerter Eleganz": E. Winterstein and G. Trier, "Die Alkaloide," Gebrüder Borntraeger, Berlin, 1931, p 295.

(4) R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

(5) For early extensive reviews of such reactions see C. Schöpf, *Angew. Chem.*, 50, 779, 797 (1937).

(6) See, for example, H. O. House "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 233.

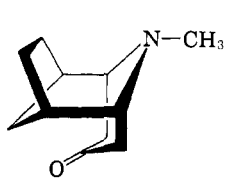
(7) Our understanding of the mechanism of simple Mannich condensations is much more complete: (a) ref 6, p 230; (b) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (c) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960); (d) M. Brown and W. S. Johnson, *ibid.*, 27, 4706 (1962); (e) H. O. House and B. M. Trost, *ibid.*, **29** 1339 (1964).

(8) K. Alder, H. Wirtz, and H. Koppelberg, *Ann.*, **601**, 138 (1956).

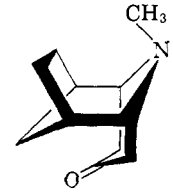
acetonedicarboxylic acid, there could be isolated in 60–70% yield after 2 days at room temperature a *single* highly crystalline, easily sublimed, white solid, mp 103–104°. It was clear from the various spectral data obtained on this material (see below) that the product was indeed a conformer of **2** of which there are eight distinct possibilities as depicted in Table I.

Table I. Possible Conformers of 6,9-*endo*-Methylenehomopseudopelletierine (**2**)

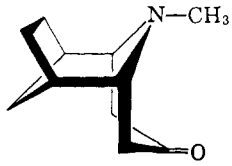
Series A



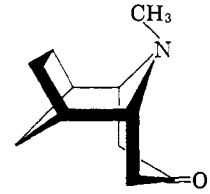
3
μ calcd 2.7 D



4
μ calcd 2.7 D

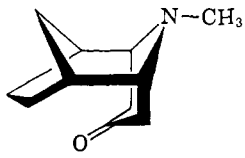


5
μ calcd 2.7 D

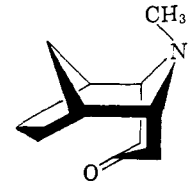


6
μ calcd 3.85 D

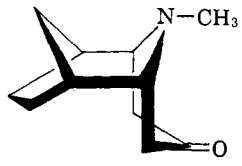
Series B



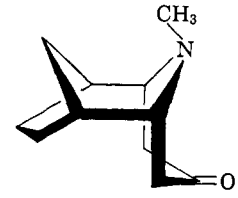
7
μ calcd 2.7 D



8
μ calcd 2.7 D



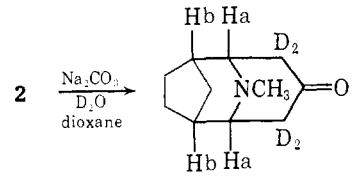
9
μ calcd 2.7 D



10
μ calcd 3.85 D

These eight structures are grouped most readily into two series, labeled A and B, which are characterized by the *anti* and *syn* relationship of the one-carbon bridge to the nitrogen bridge, respectively.

Our initial experiments were directed to the elucidation of the actual nature of the ring fusion in **2** and for this purpose we had recourse to nuclear magnetic resonance (nmr) spectroscopy. Examination of Dreiding models of the structures in series A suggested that the dihedral angle formed by the C–Ha and C–Hb bonds (see **11**) was approximately 45° and would therefore be expected to give rise to a proton coupling constant (J_{HaHb}) of 4.5–5 cps. In contrast, models of the structures of the B series indicated a dihedral angle between Ha and Hb of about 10° which would produce a rather large J_{HaHb} of 8–8.5 cps.[9] In order to simplify the nmr spectrum of the amino ketone, it was necessary to replace the hydrogen atoms α to the carbonyl group with deuterium, and this was readily accomplished in the usual manner.[10] In **11**, the two protons at Ha differed magnetically from the remainder of the protons



11

of the molecule to a degree sufficient to permit a first-order analysis. The observed J_{HaHb} was 4.5 cps (see Figure 1). We interpret this result to mean that the conformation of **2** can only be represented by one of the structures in series A, and that the two one-atom bridges are not *syn* to each other.

With the removal of **7**–**10** as the correct structures of the Robinson–Schöpf adduct, it remained to derive the proper structural assignment from among formulas **3**–**6**. The dipole moments expected for these four conformers are shown in Table I.[11] It is apparent that the calculated moments remain unchanged when the A ring passes from a chair (**3** and **4**) to a boat conformation (**5**), except when the N-methyl substituent is equatorial (with respect to the A ring) as in **6**. This exception, however, led to the ready exclusion of conformer **6** from consideration since the observed dipole moment of **2** in benzene solution (2.67 D.) was at wide variance with the value calculated for **6**.

Consideration of structures **3** and **4** will show readily that they differ only in configuration about the nitrogen atom. In relatively unstrained and sterically unhindered amines, such inversion of substituents on trivalent nitrogen is usually a process of low activation energy.[12] However, in the present instance Dreiding models indicated that the N-methyl group in **4** is subject to substantially more steric crowding than the same moiety in **3**; this observation led to the unavoidable conclusion that **3** and **4** are of distinctly different energy. In fact, it can be stated further that the steric demands in **4** are probably sufficient to favor **3** almost

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); Karplus recently (*J. Am. Chem. Soc.*, **85**, 2870 (1963)) has emphasized that other factors also may affect the coupling constants and that reliable quantitative results can be expected only with closely related species. However, in the present instance where a measured value of **5** is compared with two theoretical ones, and where the calculated values differ so greatly, it appears safe to apply the method as an absolute test of conformation. Furthermore, in this particular case a number of good experimental models are available from the tropane alkaloid field (see various references to be cited later in the text) to provide a substantial degree of confirmatory evidence.

(10) For a similar conversion of tropinone to 2,2,4,4-tetradeuteriotropinone, see G. L. Closs, *ibid.*, **81**, 5456 (1959).

(11) In these calculations, we have utilized the customary assumption of tetrahedral angles at carbon and at nitrogen: N. J. Leonard, D. F. Morrow, and M. T. Rogers, *ibid.*, **79**, 5476 (1957); see also J. M. Eckert and R. J. W. Lefevre, *J. Chem. Soc.*, 3991 (1962).

(12) For a discussion of this topic, see ref 10 and pertinent references cited therein. For other leading references to the problem see J. McKenna, J. White, and A. Tully, *Tetrahedron Letters*, No. 24, 1097 (1962); W. L. Meyer and N. Sapianchiay, *J. Am. Chem. Soc.*, **86**, 3343 (1964); J. McKenna, *et al.*, *J. Chem. Soc.*, 1711, 1726, 1729, 1733 (1965); A. T. Bottini, *et al.*, *J. Org. Chem.*, **30**, 575 (1965); *J. Am. Chem. Soc.*, **87**, 3250 (1965).

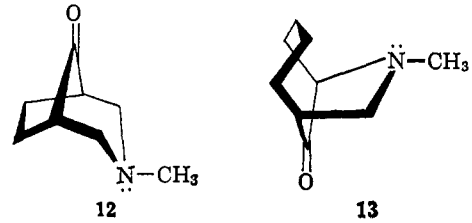
exclusively, and that the position of the N-methyl substituent is perhaps even locked into the axial direction (with respect to the piperidone ring). A direct method for the examination of the ground-state inversion frequency of this N-methyl group was available from the knowledge that amines and their protonated salts have the same conformation.[10,13] To ascertain the degree to which this inversion occurs in **2**, the deuterated amino ketone **11** was dissolved in 3 *N* deuterium chloride solution and an nmr spectrum of the solution was obtained. Since protonation (or in this case deuteration) of the amine function is a process of much lower energy than the configurational inversion of the N-methyl group a reasonable estimate of the equilibrium constant for inversion might be expected from the relative intensities of the nonequivalent methyl resonance peaks.[14] The nmr spectrum of the acidified solution displayed a lone methyl singlet, thus confirming the high-energy requirements for inversion of the N-methyl substituent.

Some measure of further support for this conclusion came from the finding that **2** did not react when refluxed with methyl iodide in methanol solution for prolonged periods or when heated at 100° with excess methyl iodide in the absence of solvent for 2 days in a sealed tube (90% recovery); no methiodide was isolated.[15,16] From these results, it is clear that, for reasons of pronounced steric compression, the nitrogen electron pair is not permitted to enter into carbon–nitrogen bond formation. When the energetics of the possible transition states for quaternization of **3**, **4**, and **5** are compared, it becomes clear that conformer **4** is not subject to steric inhibition of reaction (in actual fact, the transition state model for quaternization of **4** resembles closely those of the more common tropane derivatives); therefore, our data are consistent with the fact that **4** is not an important ground-state contributor to the structure of **2**.

The pK^*_{mcs} value[17] of **2**, 5.68, is likewise in accord with the fact that the nitrogen atom is undergoing protonation from the hindered top side in conformer **3** and/or **5**. Thus, it is a weaker base than tropinone

Figure 1. Proton nmr spectra (in CCl_4) of H_a region of isotopically normal (**2**) and of tetradeuterated tricyclic amino ketone (**11**) (δ units from TMS).

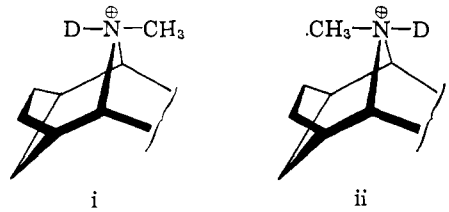
(**1**), pK^*_{mcs} = 6.49,[17a] and **12**, pK^*_{mcs} = 7.59, but is of comparable basicity to **13**, pK^*_{mcs} = 5.03,[13] where the steric demands may be considered somewhat similar.



Two conformations, namely **3** and **5**, remain to be considered. At this point, it should be noted that these structures may be regarded as derivatives of the bicyclo[3.3.1]nonane system which recently has become the object of considerable study from the point of view of conformational and configurational analysis.[18] More specifically, attempts to deduce the preferred conformation of bicyclo[3.3.1]nonane derivatives through the use of nmr spectroscopy have been made. Although some of these approaches have been moderately successful, most lack a rigorous evaluation of all the coupling constants utilized in the analysis. The nmr spectrum of **2** is of a complexity such that the

(13) H. O. House, P. P. Wickham, and H. C. Muller, *J. Am. Chem. Soc.*, 84, 3139 (1962).

(14) It is known that the two possible orientations of the methyl group are nonequivalent in a large variety of related amino ketone salts.[10,13] Although the methiodide of **2** has not yet been prepared, it is assumed that the methyl absorptions of the isomeric deuteriochlorides i and ii would be clearly nonequivalent.



i ii

(15) This datum is to be contrasted with the observations that tropinone, pseudopelletierine, and homopseudopelletierine were converted quantitatively to their methiodides when refluxed for 2 hr in an ethanolic solution of methyl iodide.

(16) It is to be specifically noted that the desired $>\overset{+}{N}(CH_3)_2$ grouping would require one methyl group to be equatorially oriented (with respect to the piperidone ring).

(17) The pK^*_{mcs} values are the apparent p*K*a values in a mixture of 80% Methyl Cellosolve and 20% water: (a) W. Simon, G. H. Lyssy, A. Mörikofer, and E. Heilbronner, "Zusammenstellung von Scheinbaren Dissoziation Konstanten in Lösungsmittelsystem Methylcellosolve/Wasser," Julius Verlag, Zurich, 1959; (b) W. Simon, *Helv. Chim. Acta*, 41, 1835 (1958).

(18) (a) N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (London), 1903 (1963); (b) W. A. C. Brown, G. Eglington, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (c) E. N. Marvel, and S. Provant, *J. Org. Chem.*, 29, 3084 (1964); (d) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, 47, 695 (1964); (e) C.-Y. Chen and R. J. W. LeFevre, *Chem. Ind.* (London), 306 (1965); (f) C.-Y. Chen and R. J. W. LeFevre, *Tetrahedron Letters*, 737 (1965); (g) W. D. K. Macrosson, J. Martin, and W. Parker, *ibid.*, 2589 (1965); (h) R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.* (London), 356 (1965); (i) G. Eglington, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

data do not permit the luxury of a complete and accurate analysis of the chair (*i.e.*, **3**)–boat (*i.e.*, **5**) equilibrium.[19] However, because the band width and splittings of the resonance peaks associated with Ha and Hb (see **2**) are observed to vary considerably in passing from carbon tetrachloride to chloroform and benzene, we have concluded that the tricyclic ketone in question is best described as a mobile equilibrium of conformers **3** and **5**, with the former in highest concentration.

The conformation of this tricyclic tropane congener in the crystalline state is presently under active study by Professor Michael Laing, University of Natal, Durban, South Africa. His X-ray results will be reported independently.

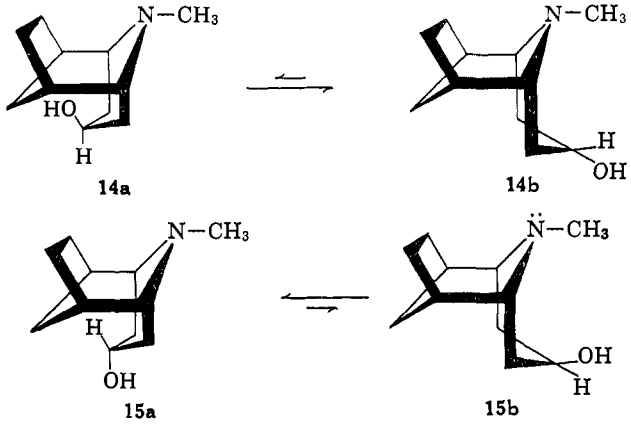
The stereochemical course of the reduction of **2** under various conditions was next examined[20] and the results are summarized in Table II.[21] Relatively

Table II. Reduction of Azatricyclic Ketone **2**

Reducing agent	Yield, %	Composition of the amino alcohol mixture, % β isomer **14**, %	α isomer **15**, %
$LiAlH_4$, Et_2O	91.4	100	...
$NaBH_4$, H_2O–MeOH	*ca.* 65[a]	100	...
Na, *i*-PrOH, $PhCH_3$	79.5	48	42[b]

[a] The remainder of the material was unreduced ketone. [b] In addition a small amount of a mixed fraction was obtained.

unhindered approach of a reducing agent to **3** would be expected to lead to the β isomer **14**, whereas steric shielding in **5** would favor the formation of the α isomer **15**.[22] In actual fact, hydride reduction of **2** gave rise exclusively to the β isomer **14** and may be indicative of the preferred existence of conformer **3** at least in the 30–40° temperature range. At higher temperatures, such as those employed in the sodium–alcohol reduction, approximately equal amounts of both alcohols are formed presumably because of a more equitable concentration of the two conformers under these reaction conditions.[23]



The configurations of these epimeric amino alcohols were established by their different modes of reaction with *p*-nitrobenzoyl chloride in chloroform solution.[20]

The infrared spectra of **14** and **15** in dilute (*ca.* 5×10^{-3} *M*) carbon disulfide solution exhibited no indication of intramolecular hydrogen bonding.[24] The infrared spectrum of **15** in 10% chloroform solution did, however, display definite absorption at 3020 cm^{-1} which may be attributed to hydrogens perturbed by severe nonbonded interactions.[18b,g,i,25] These data would seem to suggest that the piperidinol ring of **15** exists to a high degree in the chain conformation, and further corroborate the evidence that conformer **3** is favored for the amino ketone.[26]

The nuclear magnetic resonance spectra of **14** and **15** proved to be quite complex especially in the X segment of the A_2B_2X portion attributable to the C-3 proton (the proton on the carbon bearing the hydroxyl group). These observations are in marked contrast to several recently documented spectra for certain closely related compounds,[27] and may perhaps be ascribed to a high incidence of long-range and virtual couplings in the tricyclic alcohols. Since an analysis of mobile systems in conformational equilibria relies heavily on precise nuclear spin coupling and chemical shift parameters for each of the various possible conformational isomers, and because the complexity of our spectra made the derivation of such data at best qualitative, the problem of the conformational analysis of **14** and **15** by nmr alone is reduced to the semiquantitative level at best.

It is, on the other hand, difficult to envisage conformers **14a** and **15b** as major contributors to the equilibria under discussion because of the severe (especially in **14a**) nonbonded interactions acting in these molecules. However, **14b** and **15a** are not totally free of steric interactions in their own right. Accordingly, on the basis of all the spectral data recorded above, we propose that both alcohols are best described

(19) For the purposes of simplicity and brevity, we are ignoring possible contributions of slightly distorted forms of the piperidone rings of both **3** and **5**.

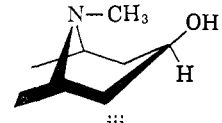
(20) Previous studies regarding the stereochemical outcome of reductions of a variety of azabicyclic ketones have been summarized: H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, 28, 2407 (1963).

(21) In addition, catalytic reductions of **2** with hydrogen and platinum in a variety of solvents over the temperature range 30–65° were tried without success.

(22) This argument implies that the products are formed under conditions of kinetic control wherein the reducing agent attacks the carbonyl atom from the less hindered side. This concept is in agreement with results obtained in general with hydride reducing agents.[20]

(23) In appropriate control experiments **14** and **15** were found to equilibrate only very slowly when refluxed in benzene solution containing fluorenone and the alkoxide derived from the alcohol.

(24) Although **14** exists predominantly in conformation **14b** (as evidenced from nmr data presented later in this paper), no associated hydroxyl band is seen in this spectrum because of the unfavorable configuration of the N-methyl group (see iii) forced upon the system by steric compressions of the type alluded to earlier.



iii

(25) L. deVries and P. R. Ryason, *J. Org. Chem.*, **26**, 621 (1961).

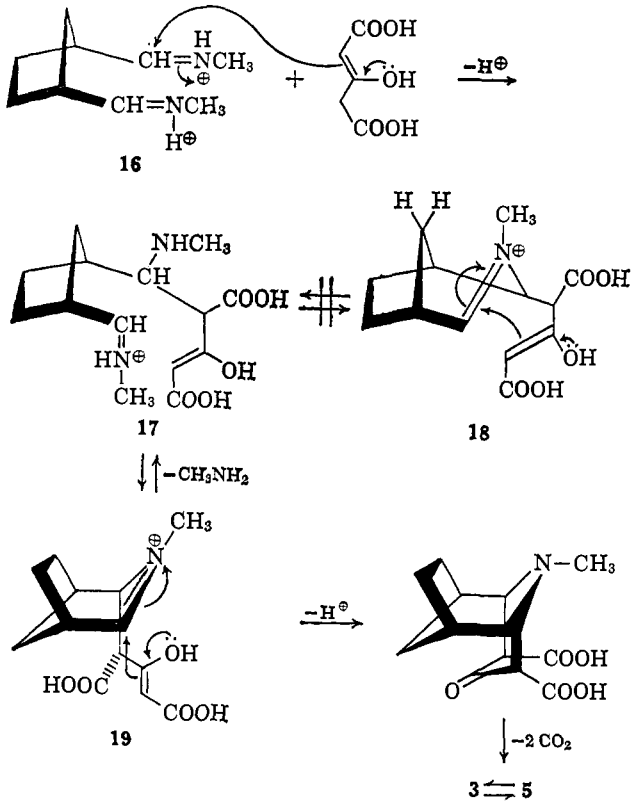
(26) It is readily seen that in **3** nonbonded hydrogen interactions favoring the boat conformation are diminished (when compared to **15**), while those favoring the chair conformation remain.

(27) For example, tropine (C.Y. Chen and R. W. LeFevre, *J. Chem. Soc.*, 3473 (1965)) X portion is a pseudo-triplet; 3β-granatonol,[18f] X portion is a quintet; *endo*-1,5-dimethylbicyclo[3.3.1]nonan-3-ol,[18g] X part is a nine-line pattern; *exo*-bicyclo[3.2.1]octan-3-ol (C. W. Jefford, J. Gunsher, and B. Waegell, *Tetrahedron Letters*, 3405 (1965)), X part is a septuplet; *endo*-bicyclo[3.2.1]octan-3-ol (C. W. Jefford, J. Gunsher, and B. Waegell, *ibid.*, 3405 (1965)), X portion is a quintuplet; 3,3,5,5-tetramethylcylohexanol (C. W. Jefford, J. Gunsher, and B. Waegell, *ibid.*, 3405 (1965)), X portion is a triplet of triplets.

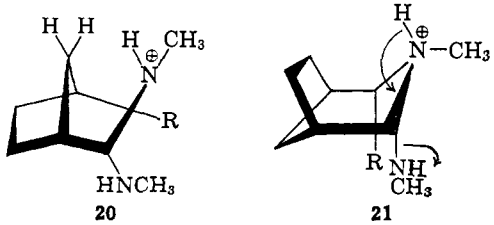
by mobile equilibria of pairs of conformational isomers with **14b** and **15a** preferred to the extent of greater than 70%.

Discussion

The gross mechanistic picture of the Robinson–Schöpf reaction derived from these studies is in agreement with the concept of a double Mannich reaction.[6] The high configurational stereospecificity observed in the condensation of *cis*-cyclopentane-1,3-dialdehyde speaks for a stepwise process in which the intermediate cyclization step (*i.e.*, **17** → **19**) is strongly influenced by nonbonded interactions. Thus, it seems reasonable to postulate that electrophilic attack of the bisiminium salt **16** on the enol of acetonedicarboxylic acid leads initially to **17**, which *a priori* may undergo cyclization to **18** (by topside attack) or to **19** (by underside attack).[28] Closer scrutiny of the mechanism of such cyclizations reveals that the intermediate involved in the reaction leading to **18**, *i.e.*, **20**, suffers from steric



compressions sufficient to severely retard its rate of formation. Intermediate **21**, which is presumed to lead *via* **19** to the amino ketone which is ultimately



isolated, is reasonably less sterically crowded. The large difference in nonbonded strain in **20** and **21**, readily discerned upon examination of Dreiding models, is advocated as the cause of the favored formation of **21**.

(28) The precise timing of the loss of carbon dioxide from any of these intermediates is, of course, unknown. For the sake of simplicity we have implied by the formulas that the decarboxylation occurs as the final step.

Experimental Section[29]

Materials. *endo,cis*-Bicyclo[2.2.1]hept-5-ene-2,3-diol, mp 199–201°, was prepared by the Diels–Alder addition of vinylene carbonate to cyclopentadiene, followed by hydrogenation and saponification of the adduct.[30] Lead tetracetate oxidation of this diol according to the published procedure[8] and rapid distillation of the crude product afforded *cis*-cyclopentane-1,3-dialdehyde. For our purposes, distillation of the dialdehyde was unnecessary. In actual fact, the over-all yield for the cleavage and suqsequent Robinson–Schöpf reactions could be improved by an average 25–30% by elimination of this troublesome manipulation.

The procedure of Alder, Wirtz, and Koppelberg[8] for the preparation of **2** was modified as follows. A solution of 19.4 g (0.154 mole) of crude, undistilled cyclopentane-1,3-dialdehyde in 200 ml of methyl acetate was added in one portion to a solution of 26.4 g (0.39 mole) of methylamine hydrochloride, 53.2 g (0.364 mole) of acetonedicarboxylic acid, 25.6 g of sodium monohydrogen phosphate, and 15.0 g of potassium dihydrogen phosphate in 1800 ml of distilled water. The resulting solution was stirred in a nitrogen atmosphere at room temperature for 2 days. The solution was evaporated under reduced pressure to a volume of approximately 700 ml, brought to pH 10 with 10% sodium hydroxide solution, and extracted with seven 100-ml portions of chloroform. The combined organic layers were washed with water, dried, filtered, and evaporated. The dark solid residue was sublimed directly to give 19.2 g (69.8%) of pale yellow solid, mp 90–100°. Recrystallization of this material from ether–hexane afforded long, white rods of 6,9-*endo*-methylenehomopseudopelletierine (**2**), mp 103–104° (lit.[8] mp 106°).

This amino ketone was further characterized as its perchlorate salt, mp 256° dec (from aqueous ethanol), according to the usual procedure of treating an ethereal solution of **2** with an equivalent amount of ethanol–70% perchloric acid (1:1).

Anal. Calcd for $C_{11}H_{18}ClNO_5$: C, 47.23; H, 6.48; N, 5.01. Found: C, 47.35; H, 6.50; N, 5.11.

Deuterium Exchange of 2. A mixture of 2.0 g of **2**, 100 mg of potassium carbonate, 15 ml of deuterium oxide, and 1 ml of dioxane was refluxed with stirring for 25 hr. The cooled solution was extracted with ether and the combined ether extracts were dried, filtered, and evaporated. The resulting solid was reprocessed as above to give, after sublimation, 1.7 g (85.0%) of white solid, mp 75–93°. The crude sublimate was recrystallized three times from ether–hexane to give long, white needles, mp 101–101.5°.

Anal. Calcd: D, 4.0. Found: D, 3.94.

Reduction of 2. A. With Lithium Aluminum Hydride. To a cooled, stirred slurry of 1.0 g (0.0264 mole) of lithium aluminum hydride in 30 ml of anhydrous ether was added 2.0 g (0.0115 mole) of **2** in several portions. The mixture was refluxed for 1 hr and cooled. With vigorous stirring, there was added 1 ml of water, 1 ml of 30% sodium hydroxide solution, and 3 ml of water, in that order. The precipitated solids were removed by filtration, and the filtrate was evaporated. The residual solid was sublimed to yield 1.9 g (91.4%) of white solid, mp 84–85.5°.

A solution of 1.74 g (9.62 mmoles) of this amino alcohol and 1.90 g (10.25 mmoles) of *p*-nitrobenzoyl chloride in 25 ml of chloroform was allowed to stand at room temperature for 61 hr. The solvent was evaporated under reduced pressure and the residual solid was triturated with three 50-ml portions of ether to remove unreacted acid chloride. The white solid was recrystallized from ethanol to give a single material, mp 270° dec. Further recrystalli-

(29) Melting points are uncorrected. Infrared spectra were determined with a Beckman IR-9 spectrometer. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The nmr spectra were determined with a Varian A-60 spectrometer made available through funds donated by the National Science Foundation. The deuterium analysis (falling-drop method) was performed by J. Nemeth, Urbana, Ill. The pK^*_{mcs} determinations were carried out by Professor Dr. W. Simon, Zurich, Switzerland. The dipole moment value was measured with the aid of General Radio Co. Type 1610-A Capacitance Measuring Assembly and calculated by means of a computer program.

(30) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **75**, 1263 (1953); **77**, 3789 (1955).

zation from ethanol–ether gave pure *endo* alcohol hydrochloride, mp 270° dec.

Anal. Calcd for $C_{11}H_{20}ClNO$: C, 60.67; H, 9.26; N, 6.43. Found: C, 60.76; H, 9.25; N, 6.48.

A sample of the hydrochloride salt was dissolved in water and the solution was basified with 30% sodium hydroxide solution. The solution was extracted with chloroform, and the combined organic layers were dried, filtered, and evaporated to give a white solid. Sublimation of this material gave white needles of pure *endo* alcohol **14**, mp 87.5–88.5°.[31]

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.94; H, 10.61; N, 7.71; $pK^*_{mcs} = 8.11$.

B. With Sodium Borohydride. A solution of 2.0 g (0.0115 mole) of **2** in 45 ml of methanol was added to a solution of 455 mg (0.012 mole) of sodium borohydride in 40 ml of water and the resulting mixture was slowly stirred at room temperature for 3 hr. After the excess of borohydride had been destroyed by the addition of acetic acid, 3 ml of concentrated hydrochloric acid was added and the mixture was concentrated, made basic with aqueous sodium hydroxide, and extracted with ether. The ethereal extract was dried, filtered and evaporated, and the residue was sublimed to give 1.85 g of solid, mp 43–49°.

A solution of 1.72 g (9.50 mmoles) of this crude solid and 1.90 g (10.25 mmoles) of *p*-nitrobenzoyl chloride in 25 ml of chloroform was allowed to stand at room temperature for 61 hr. The same work-up as above afforded a white solid which could be fractionally crystallized from ethanol to give 350 mg of **2** hydrochloride (from incomplete reduction), mp 235–240° dec, and 1.3 g of *endo* alcohol hydrochloride, mp 250–265° dec. The latter substance was further recrystallized from ethanol–ether to give pure *endo* alcohol hydrochloride, mp 270° dec, identical in all respects with the sample of part A.

C. With Sodium and Isopropyl Alcohol. To a stirred mixture of 1.73 g (0.075 g-atom) of sodium metal in 35 ml of toluene was added rapidly a solution of 3.0 g (0.0167 mole) of **2** in 11 g of isopropyl alcohol. After the resulting mixture had been refluxed for 3.5 hr (at which time all the sodium had reacted), it was cooled and extracted with three 30-ml portions of 4 *N* hydrochloric acid. The acid extracts were made basic by the addition of sodium hydroxide pellets and the resulting oily mixture was extracted with pentane. The pentane solution was dried, filtered, and evaporated, and the residual solid was sublimed to give 2.4 g of amino alcohol mixture, mp 82–101°.

A solution of 2.28 g (12.60 mmoles) of this solid and 2.50 g (13.45 mmoles) of *p*-nitrobenzoyl chloride in 30 ml of chloroform was allowed to stand at room temperature for 61 hr. The same work-up as above afforded a white solid which was fractionally crystallized from absolute ethanol to give three crops: A, 1.95 g of the *p*-nitrobenzoate ester hydrochloride of the *exo* alcohol **15**, mp 248–249° dec; B, 150 mg of a mixture, mp *ca.* 230° (indefinite melting region); C, 1.25 g of *endo* alcohol hydrochloride, mp 255–268° dec. Further recrystallization of the C fraction from ethanol–ether raised the melting point to 270° dec. This material was identical with the sample prepared above.

Fraction A was recrystallized several times from ethanol to give pure *exo* alcohol *p*-nitrobenzoate hydrochloride as white platelets, mp 253–254° dec.

Anal. Calcd for $C_{18}H_{23}ClN_2O_4$: C, 58.93; H, 6.32; N, 7.64. Found: C, 58.83; H, 6.36; N, 7.52.

A mixture of 1.2 g (3.27 mmoles) of this ester hydrochloride and 10 ml of 20% hydrochloric acid was refluxed for 6 hr and cooled. The precipitated *p*-nitrobenzoic acid was removed by filtration and the filtrate was basified with 30% sodium hydroxide solution and extracted with chloroform. The combined organic layers were dried, filtered, and evaporated to give a white solid. Sublimation of this material gave white needles of pure *exo* alcohol **15**, mp 104–104.5°.[32]

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.98; H, 10.61; N, 7.66; $pK^*_{mcs} = 8.09$.

(31) The reduction of **2** was also reported by Alder, *et al.*[5] The melting point of their amino alcohol (*ca.* 75°) is indicative of a mixture of epimers.

(32) All preliminary attempts to separate **14** and **15** on a variety of gas chromatographic columns were without success in our hands.

The Stereochemistry of Δ^2-Thiazoline Formation from Episulfides

James R. Lowell, Jr., and G. K. Helmkamp

Contribution from the Department of Chemistry, University of California, Riverside, California. *Received September 30, 1965*

Abstract: Stereochemical evidence is presented in support of the previously proposed mechanism for the acid-promoted reaction of episulfides with nitriles to form Δ^2-thiazolines. Ring opening of propylene sulfide by acetonitrile takes place at the more substituted carbon, resulting in the formation of 2,4-dimethyl-Δ^2-thiazoline without detectable amounts of the 2,5 isomer. That the ring opens in a *trans* manner is demonstrated by the preparation of *trans*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole from cyclohexene sulfide, which can only have the *cis* configuration. (4*R*:5*S*)-(−)-*cis*-2,4,5-Trimethyl-Δ^2-thiazoline has been prepared from (*SS*)-(−)-*trans*-2-butene episulfide, which was prepared from (*RR*)-(+)-*trans*-2,3-epoxybutane. The same epoxide can be converted to (*SS*)-(−)-*trans*-2,3-dimethylaziridine, from which the enantiomer of the above optically active thiazoline can be obtained by treatment with thioacetamide.

We have elsewhere reported[1] a general, stereospecific route to Δ^2-thiazolines, by treatment of an episulfide with a nitrile in the presence of a strong acid. At that time we proposed a mechanism for this reaction which involved protonation of the episulfide, ring opening by nucleophilic attack by the nitrile, and ring closure to form the thiazoline salt. We have now found the stereochemistry of this reaction to be in complete accord with the proposed mechanism.

To demonstrate that reaction involved one inversion, it was desirable to convert an episulfide of known configuration to one of a pair of isomers, both of which had been previously characterized. The preparation of *trans*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole from cyclohexene sulfide was admirably suited for these purposes. The episulfide can have only the *cis* configuration, and both the *cis* and *trans* thiazole isomers have been prepared[2] together with their picrates,[2]

(1) G. K. Helmkamp, D. J. Pettitt, J. R. Lowell, Jr., W. R. Mabey, and R. G. Wolcott, *J. Am. Chem. Soc.*, 88, in press.

(2) (a) T. Taguchi and M. Kojima, *ibid.*, 78, 1464, (1956); (b) M. Kojima, *Yakugaku Zasshi*, 79, 1 (1959); *Chem. Abstr.*, 53, 10183*h* (1959).