The Stereochemistry of Febrifugine. I. The Equilibrium between *cis*- and *trans*-(3-Substituted 2-piperidyl)-2-propanones

DONALD F. BARRINGER, JR., GERALD BERKELHAMMER,* SPENCER D. CARTER, LEON GOLDMAN, AND ANTHONY E. LANZILOTTI

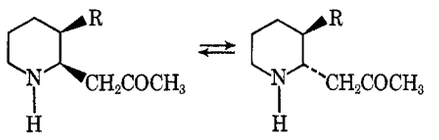
Chemical Research and Development Laboratories, Agricultural Division, American Cyanamid Company, Princeton, New Jersey 08540, and Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

Received October 24, 1972

A facile thermal equilibration of *cis*-(3-methoxy-2-piperidyl)-2-propanone and some analogous *cis*-(3-substituted 2-piperidyl)-2-propanones with their trans isomers is reported. The effects on the equilibrium of temperature, solvent, pH, and the size of the 3 substituent were investigated. Chemical and nmr spectral data and conformational free-energy calculations are presented to support the assignment of the trans configuration to the more stable isomer. A revised synthesis of the title compounds is reported. The title compounds are intermediates in the synthesis of febrifugines.

The hydrangea alkaloid, febrifugine, and many of its synthetic analogs have been extensively investigated because of their antimalarial[1] and anticoccidial[2] activity. In the course of the synthesis of some febrifugines using a route first developed by Baker, *et al.*,[3] it was discovered that the intermediate **1a** readily undergoes isomerization. It was subsequently found that the analogous compounds **1b–d** undergo a similar isomerization.

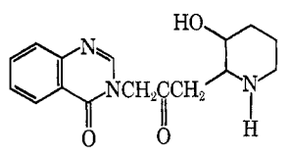
It would be expected that the compounds **1**, which are synthesized by hydrogenation of the corresponding



1 **2**

a, R = OCH_3; b, R = OC_2H_5; c, R = $OCH(CH_3)_2$; d, R = CH_3

pyridines (**5**), would possess the cis configuration and that they would equilibrate to mixtures favoring the trans isomers (**2**). However, our initial thinking on this subject was complicated by the fact that Baker had assigned the cis configuration to febrifugine (**3**).

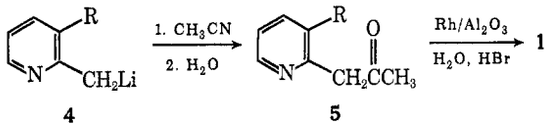


3

He was unaware of the easy isomerization of **1a** and interpreted his results as further confirmation of the cis configuration, originally assigned on the basis of other work.[4] Because of this conflicting evidence we studied the isomerization in some detail. In this paper we will present the evidence that the configurations of **1** and **2** are as expected, and part II[5] will present the evidence that febrifugine (**3**) has the isomerized or trans configuration.

We found it convenient to synthesize *cis*-(3-alkoxy-2-piperidyl)-2-propanones (**1a–c**) and *cis*-(3-methyl-2-piperidyl)-2-propanone (**1d**) *via* Scheme I. This sequence is more convenient than the longer route of Baker, *et al.*,[3] involving condensation of **4** with acetaldehyde followed by hydrogenation and chromic acid oxidation of the secondary alcohol. Rhodium on alumina in water in the presence of 1 equiv of hydrobromic acid at 3–4 atm and ~50–70° is quite selective for the reduction of the pyridine ring in the presence of the ketone. A high degree of selectivity is achieved only when the (3-substituted 2-pyridyl)-2-propanones (**5**) are carefully purified by distillation. Otherwise the impurities present act as catalyst poisons, and, as the rate of hydrogenation diminishes, the selectivity is also lost.[6] The hydrogenation product is a single isomer to the limits of detectability by nmr (>95%), and the available evidence in the literature[7] suggests that under these conditions the cis isomer would predominate. Our observations on the isomerization also support this conclusion. Additionally, we tried hydrogenation of the free base in methanol over rhodium on carbon, of the free base in acetic acid over rhodium on alumina or palladium on carbon, and of the hydrobromide salt in methanol or the free base in acetic acid over platinum oxide, but none of these systems gave a rapid selective reduction.

SCHEME I



4 **5**

a, R = OCH_3; b, R = OC_2H_5; c, R = $OCH(CH_3)_2$; d, R = CH_3

Equilibrium between **1** and **2** is established by heating for ~1 hr on a steam bath under nitrogen or in refluxing toluene. Equilibration occurs in ~3–4 weeks at room temperature, and it is essentially complete after 10 months' storage at 5°. Depending upon

(1) R. I. Hewitt, W. S. Wallace, E. R. Gill, and J. H. Williams, *Am. J. Trop. Med. Hyg.*, **1**, 768 (1952).

(2) E. Waletzky, G. Berkelhammer, and S. Kantor, U. S. Patent 3,320,124 (1967).

(3) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).

(4) R. B. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **18**, 153 (1953).

(5) D. F. Barringer, Jr., G. Berkelhammer, and R. S. Wayne, *J. Org. Chem.*, **38**, 1937 (1973).

(6) Unpublished work of Dr. J. R. Giacin, American Cyanamid Co., Agricultural Division.

(7) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Amer. Chem. Soc.*, **56**, 2425 (1934); R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951); J. Pliml, E. Knoblock, and M. Protiva, *Chem. Listy*, **46**, 758 (1952); F. Galinovsky, O. Vogl, and W. Moroz, *Monatsh. Chem.*, **83**, 242 (1952); F. Galinovsky and H. Langer, *ibid.*, **86**, 449 (1955); F. Bohlmann, A. Englisch, N. Ottawa, H. Sander, and W. Weise, *Chem. Ber.*, **89**, (1956); M. Freifelder, D. A. Dunnigan, and E. J. Baker, *J. Org. Chem.*, **31**, 3438 (1966); B. van de Graff, H. van Bekkum, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **87**, 777 (1968).

the pot temperature used, it can also occur during a vacuum distillation.

To study the isomerization, a convenient method for determining the isomeric composition was needed. The nmr spectrum turned out to be very well suited for this determination. Depending upon the solvent chosen, either the protons of the methyl group in the acetonyl substituent or the protons on the α carbon of the alkoxy group exhibit different chemical shifts in the two isomers. We used either benzene or toluene as the solvent, and in these solvents the protons of the methyl group on the acetonyl substituent appeared at 3 Hz higher field in the trans isomer. The two peaks were well resolved, and the results were quite reproducible. Unfortunately we were unable to determine the stereochemistry directly from the ring protons α to the substituents because of the complexity of the spectra.

The effects of temperature, solvent, pH, and the steric requirement of the 3 substituent on the equilibrium were studied. The temperature of the equilibration in toluene had no demonstrable effect on the position of the equilibrium. *cis*-(3-Ethoxy-2-piperidyl)-2-propanone (**1b**) was isomerized at 80°, reflux (110.6°), and 140° in a sealed tube to 68:32, 69:31, and 67:33 trans–cis mixtures, repectively.[8] These values are the same within experimental error. The isomerization required 23–31 hr, ~3 hr, and slightly more than 0.5 hr at the three temperatures.

The effects of various solvents on the equilibration are summarized in Table I. Only in the case of water

TABLE I

EFFECT OF SOLVENTS ON THE Cis ⇄ Trans EQUILIBRIUM OF (3-ETHOXY-2-PIPERIDYL)-2-PROPANONE

Solvent	Concn, %	Temp, °C	Time, hr[a]	% trans
Water[c]	5	98–102	20 min[d]	76
Cyclohexanol	10	98–100	1	67
tert-Butyl alcohol	10	Reflux (82.6)	4[e]	69
Neat		78–82	1.5[b]	51
Neat		96–101	0.5[b]	60
Neat		96–101	1[b]	67
Neat		96–101	1.5[b]	70
Toluene	10	95–100	22.5[f]	70
Toluene	10	Reflux (110.6)	3	69

[a] For runs in solution, this is the time after which no further change in isomer ratio occurred as was determined by at least one measurement after the time listed. For neat runs, see *b*. Started with 100% cis isomer. [b] Not necessarily complete equilibration. At 96–101° the 1-hr and 1.5-hr ratios are probably the same within experimental error. [c] pH 10.6 (pH meter). [d] 55% trans at 7 min, 75% trans at 30 min. [e] 52% trans at 1.5 hr, 65% trans at 3 hr. [f] Almost complete at 6.5 hr.

is the isomer ratio significantly different from that obtained in toluene or in the absence of solvent. The increase in the proportion of trans isomer in water solution is probably due to coordination of the solvent with the ether oxygen and/or the nitrogen, which would increase the steric interactions in the cis isomer.

(8) Febrifugines synthesized from trans–cis mixtures such as these for **1a–c** usually contained 90% or more trans isomer, as was determined by quantitative thin layer chromatography. The difference in trans content between the intermediates and the febrifugine products is probably due to the preferential solubility of salts of the *cis*-febrifugines in ethanol, the solvent used for purification.

Apparently the two alcohols do not bond tightly enough to have a measurable effect. All three polar hydroxylic solvents enhanced the rate of the isomerization compared with toluene. The minimum time for equilibration in toluene is probably not very much greater than 6.5 hr (footnote *f*, Table I), while the minimum in cyclohexanol is 1 hr or less and in water 20 min or less. The demonstrated effect of solvent polarity would be expected where charge separation is present in the transition state.

The effect of pH on the position of the equilibrium in water solution was examined. A 5% solution of equilibrated (3-ethoxy-2-piperidyl)-2-propanone (**2b**, 68% trans) in water had a pH of 10.6. The pH of the other samples was adjusted up or down with aqueous sodium hydroxide or hydrochloric acid. The solutions were heated in a bath at 94–100°, and the free base was isolated and dissolved in toluene for nmr measurements (see Experimental Section).

The results are shown in Table II. The % trans isomer decreases with decreasing pH in the range

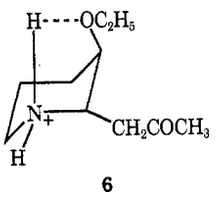
TABLE II

EFFECT OF pH ON THE Cis ⇄ Trans EQUILIBRIUM OF (3-ETHOXY-2-PIPERIDYL)-2-PROPANONE

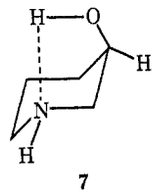
	% recovery		% trans isomer		
pH[a]	3 hr	5.5 hr	20 min	3 hr	4 hr	5.5 hr
0.5 *N* NaOH[b]	92			75		
0.1 *N* NaOH	91	86		76		75
10.6[c]			76[c]			
9.9	88	84		72		71
8.0[d]					56[d]	
6.9	94	79		46		47
5.9	91	87		61		48[e]
4.8[a]	76	88		63		48

[a] The pH remained constant during each run except the one at 4.8, which increased to 6.4 after 5.5 hours, presumably owing to loss of HCl. [b] Not completely homogeneous. Ir after run showed evidence of decomposition. [c] Started with cis isomer. Equilibrium reached in 20 min. [d] Run at 105–110°. [e] 5.5-hr sample redissolved in water at pH 6.0 and heated for 3 hr more at 98–99°. No further change in % trans isomer.

where the proportions of free base and hydrochloride salt are varying, and it remains fairly constant above and below this range. The probable explanation for this effect is transannular hydrogen bonding in the salt **6**. This would reduce the conformational free



6



7

energy penalty for the axial ethoxy group in the cis isomer. Similar hydrogen bonding has been observed in 3-piperidinol (**7**) and its *N*-alkyl derivatives.[9] Hydrogen bonding would be expected to be much less important in the free base of **6** since the evidence at this time favors the hypothesis that a proton bonded to nitrogen has greater steric requirements than an

(9) G. Hite, E. E. Smissman, and R. West, *J. Amer. Chem. Soc.*, **82**, 1207 (1960); R. E. Lyle, D. H. McMahon, W. E. Grueger, and C. K. Spicer, *J. Org. Chem.*, **31**, 4164 (1966).

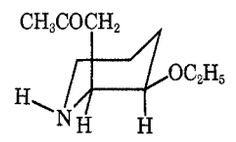
electron pair,[10] and ammonium ions would be expected to form stronger hydrogen bonds than free amines. The rate of isomerization is less at pH values below 7 than above 7, in agreement with a base-catalyzed mechanism.

When a pyridine solution of the hydrochloride of 68% *trans*-(3-ethoxy-2-piperidyl)-2-propanone (**2b**) was heated on a steam bath for 3.5 hr, the equilibrium shifted slightly toward the cis isomer, giving a trans:cis ratio of 1.83:1 (65% trans). Presumably this reflects a small contribution from structure **6** in this medium.

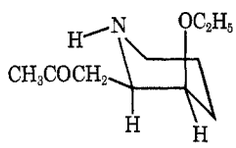
There were no significant differences in the extent of isomerization of the (3-alkoxy-2-piperidyl)-2-propanones (**1a**, **1b**, and **1c**) studied (69, 68, and 67%). This is what one would expect, since the conformational free energies for methoxy, ethoxy, and isopropoxy groups are about the same. When a methyl group (*vide infra*) was placed in the 3 position, however, there was a large shift in favor of the trans isomer (**2d**). This can be explained by the larger conformational free energy of a methyl group and the lack of any stabilization of the cis isomer by transannular hydrogen bonding.

The theoretical position of the cis $\rightleftarrows$ trans equilibrium of (3-ethoxy-2-piperidyl)-2-propanone (**1b** $\rightleftarrows$ **2b**) can be approximated using conformational free-energy differences determined for substituents on cyclohexane systems.[11] The conformational free-energy difference for an acetonyl substituent apparently has not been determined, but the value of 1.7 kcal/mol for a methyl group can be used as a minimum value. The value for an ethoxy group is 0.9 kcal/mol.

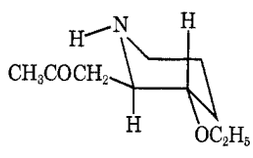
To simplify the computations, two conformations (**8** and **9**) were considered for the cis isomer and one



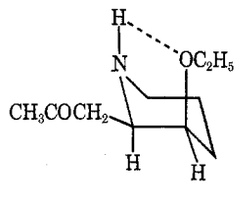
8



9



10



11

(**10**) for the trans isomer. The other conformation for the trans isomer has the two large groups axial and would be expected to be essentially absent. Only conformations with the proton on the nitrogen in the equatorial position were considered. Since an axial group in the 3 position of piperidine has only one 1,3-diaxial interaction with hydrogen, the conformational free energy was reduced by one-half to a value of 0.45. It is probably true that the hydrogen-bonded conformation (**11**) contributes some extra stability to the cis isomer, but, since we have no data from which to estimate the contribution of **11**, it was ignored in the computation.

On the basis of these assumptions the equilibrium mixture of the isomeric (3-ethoxy-2-piperidyl)-2-propanones (**1b** and **2b**) was calculated to contain 73% trans at 25° and 69% trans at the boiling point of toluene (111°). These values compare well with the experimentally observed trans concentration of about 70%.

cis-(3-Methyl-2-piperidyl)-2-propanone (**1d**) was synthesized and isomerized as an intermediate for a febrifugine analog. A similar calculation on this equilibrium predicts 85% trans at 25° and 79% at 111°. The amount of cis isomer in the mixture is too small to be determined accurately by the nmr method, but it appears to be ~10% in the crude product and considerably less after distillation. Since in this case there is no opportunity for transannular hydrogen bonding to give unusual stability to the cis isomer, it is quite certain that the more stable isomer is trans. Since the synthesis route and equilibrium results with the (3-alkoxy-2-piperidyl)-2-propanones were analogous, initial formation of the cis isomers followed by predominant isomerization to trans must also have occurred in this series. The differences in the compositions of the equilibrium mixtures also agree well with the predictions based on conformational free energies.

A further confirmation of the stereochemistry of the (3-methyl-2-piperidyl)-2-propanones can be found in the nmr resonance of the 3-methyl group. In the cis isomer this resonance is a doublet (J = 6.5 Hz) centered at δ 0.96. In the trans isomer it is a partly resolved, unequal doublet (J = 3.5 Hz) centered at δ 0.82. This same effect was reported in the case of the isomeric 2,3-dimethylpiperidines,[12] and it was attributed to the effect of the strong upfield shift of the proton on the adjacent ring carbon on going from the cis to the trans configuration.

The mechanism of the isomerization can be described as a base-catalyzed β elimination followed by a Michael addition, analogous to a mechanism proposed for the racemization of pelletierine (**12**)[13] (Scheme II).

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord Model 137. Nmr spectra were recorded on a Varian A-60.

(3-Methoxy-2-pyridyl)-2-propanone (5a).—The reaction was run in a stirred flask under a nitrogen atmosphere. A hexane solution (397.4 g) containing 0.924 mol of *n*-butyllithium was introduced into the flask along with 909 g of absolute ether. 3-Methoxy-2-picoline (103.3 g, 0.840 mol) was added dropwise at 0–5°. The 3-methoxy-2-picolyllithium partially precipitated as a yellow solid. The mixture was allowed to warm briefly to 10°, and 37.9 g (0.924 mol, 48.4 ml) of acetonitrile was added dropwise at 4° over a 1.5-hr period. The mixture was allowed

(10) P. J. Brignell, A. R. Katritzky, and P. L. Russell, *Chem. Commun.*, 723 (1966); N. L. Allinger, J. G. Carpenter, and F. M. Karkonski, *Tetrahedron Lett.*, 3345 (1964); *J. Amer. Chem. Soc.*, **87**, 1232 (1965); F. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 218 (1961); *J. Chem. Soc.*, 2637 (1962); N. W. Pumphrey and M. J. Robinson, *Chem. Ind. (London)*, 1903 (1963). However, J. B. Lambert and R. G. Keske [*J. Amer. Chem. Soc.*, **88**, 621 (1966)] have presented evidence that the hydrogen may have smaller steric requirements than the electron pair.

(11) E. Eliel, N. Allinger, S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 11, 44.

(12) A. Silhankova, D. Doskocilova, and M. Ferles, *Collect. Czech. Chem. Commun.*, **34**, 1976 (1969).

(13) F. Galinovsky, G. Bianchetti, and O. Vogl, *Monatsh. Chem.*, **84**, 1221 (1953).

TABLE III

(3-SUBSTITUTED 2-PYRIDYL)-2-PROPANONES (5)

R	Yield, %	$n^{25}D$	Bp, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
OC_2H_5	72	1.5179	94 (0.4)	67.02	7.31	7.82	66.94	7.62	8.25
$OCH(CH_3)_2$	69		32 (0.2)	68.37	7.82	7.25	68.59	7.88	7.40
CH_3	72	1.5338	68 (0.15)	Not analytically pure					

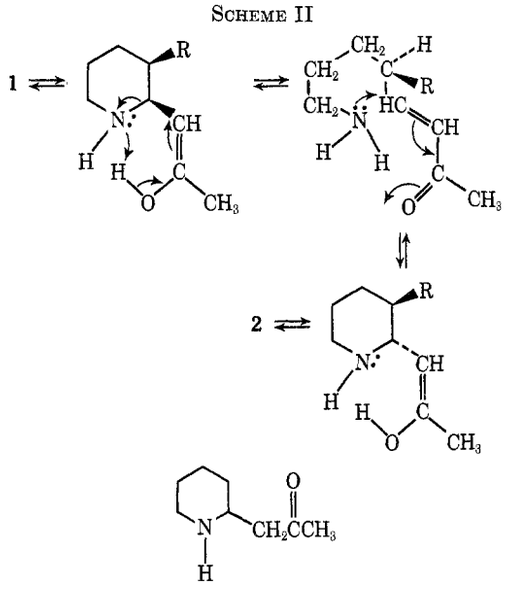
TABLE IV

TRANS-RICH (3-SUBSTITUTED 2-PIPERIDYL)-2-PROPANONES (2)

R	Yield, %	Bp, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Br	Found, % C	Found, % H	Found, % N	Found, % Br
OC_2H_5[a]	68	88–93 (1.25)	45.11	7.47	5.26	30.01	45.39	7.70	5.21	29.79
$OCH(CH_3)_2$	95+[b]									
CH_3[c]		54–61 (0.4)	69.63	11.04	9.02		69.67	10.99	9.11	

[a] Analyzed as the hydrobromide, mp 164–167°, prepared by passing HBr into a toluene solution of the free base, followed by trituration in and recrystallization from acetone. Isolation of the free base from this salt gave samples containing 85–95% trans isomer. [b] Crude yield. Structure assigned on the basis of nmr spectrum and subsequent conversion to a *trans*-febrifugine. [c] Analyzed as the free base.

SCHEME II



12

to warm to 10° yielding a dark red solution. One liter of 3 *N* sulfuric acid was added cautiously at 20–30°. The layers were separated, and the aqueous layer was adjusted to pH 10 with 10% sodium hydroxide. The product was extracted with 4 × 500 ml of chloroform. Evaporation of the solvent yielded 173 g of an oil which was distilled under vacuum through a Vigreux column to yield 105.7 g (76%) of a yellow oil: bp 86–89° (0.1 mm); $n^{26.5}D$ 1.5284; principal ir bands at ν_{max}^{neat} ~2950 (five peaks), 1720, 1645, ~1675 (three peaks), 1455, 1430, 1355, 1280, 1120, 1025, 802 cm^{-1}. *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 64.9; H, 6.6; N, 8.9.

Other (3-substituted 2-pyridyl)-2-propanones (5) synthesized by this route are listed in Table III.

cis-**(3-Methoxy-2-piperidyl)-2-propanone (1a).**—A solution of 20.37 g (0.1235 mol) of (3-methoxy-2-pyridyl)-2-propanone in 250 ml of water was adjusted to pH 2 with 48% hydrobromic acid. This solution was hydrogenated over 2.0 g of 5% rhodium on alumina in a Parr apparatus at an initial pressure of 50.3 psi and a temperature of 55° measured in an external thermometer well. After 7.5 hr the mixture was cooled to room temperature. The pressure drop was 32.5 psi (101% of theory). The catalyst was filtered out, the solution was basified to pH >12 with sodium hydroxide, and the product was extracted with methylene chloride. The methylene chloride solution was dried and evaporated under vacuum to yield 18.87 g (0.1162 mol, 94%) of a yellow oil. This compound was not purified owing to its instability with respect to thermal isomerization. Principal infrared bands appeared at ν_{max}^{neat} 3330, 2930, 1710, 1460, 1440, 1360, 1100 cm^{-1} (broad). There is no absorption between 1710 and 1460 cm^{-1}. The spectrum is not very sensitive to small amounts of the corresponding secondary alcohol. This by-product is formed in the reduction of impure starting material, and its formation is accompained by a reduced rate of hydrogenation and spectral evidence for the presence of the pyridine ring (band at 1675 cm^{-1}) even after consumption of the theoretical amount of hydrogen.

Phenyl Isothiocyanate Derivative.—When 5 ml each of 0.2 *M* ether solutions of *cis*-(3-methoxy-2-piperidyl)-2-propanone and phenyl isothiocyanate were mixed and left standing for 15 min at room temperature and overnight in a refrigerator, a pale yellow crystalline derivative, mp 129–130°, was obtained in 40–60% yield: ir (mineral oil mull) ν_{max} 3260, 1590, 1330, 1080, 820 cm^{-1}; $\lambda_{max}^{0.1\ N\ NaOH}$ 214 nm (ϵ 19,700), 242 (broad, 19,300); λ_{max}^{MeOH} 225 nm (ϵ 17,700), 255 (15,300). *Anal.* Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.7; H, 7.24; N, 9.14; S, 10.5. Found: C, 62.7; H, 7.00; N, 9.31; S, 10.5.

The other *cis*-(3-substituted-2-piperidyl)-2-propanones (1) were prepared in similar fashion.

Isomerization of *cis*-(3-Methoxy-2-piperidyl)-2-propanone to *trans*-(3-Methoxy-2-piperidyl)-2-propanone.—This reaction was run either with or without a solvent (see Table I). The liquid was kept under a nitrogen atmosphere while hot to retard decomposition. The crude product was isolated from organic solvents by evaporation at moderate temperatures (<50°) on a rotary vacuum evaporator. Isolation from water solutions was effected by making the solution alkaline with sodium hydroxide and extracting with methylene chloride or chloroform. In a typical preparation 4.99 g (0.0292 mol) of *cis*-(3-methoxy-2-piperidyl)-2-propanone was dissolved in 100 ml of toluene, and the solution was heated under reflux for 3.5 hr. The solvent was evaporated under vacuum and the residue was distilled to yield 4.11 g (0.0240 mol, 82%) of the trans-rich equilibrium mixture as a nearly colorless oil: bp 88–93° (2.5 mm); principal ir bands at ν_{max}^{neat} 3380, 2940, 1704, 1460, 1440, 1360, 1100 cm^{-1} (broad). *Anal.* Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.18. Found: C, 63.5; H, 10.2; N, 8.57. The phenyl isothiocyanate derivative, prepared as for the cis ketone, had mp 165–169° and principal ir bands (mineral oil mull) at ν_{max} 3230, 1700, 1600, 1320, 1080 cm^{-1}; $\lambda_{max}^{0.1\ N\ NaOH}$ 214 nm (ϵ 20,100), 242 (broad, 19,000); λ_{max}^{MeOH} 224 nm (ϵ 17,800), 255 (14,400). *Anal.* Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.7; H, 7.24; N, 9.14; S, 10.5; OCH_3, 9.72. Found: C, 62.2; H, 7.34; N, 9.01; S, 10.2; OCH_3, 9.99.

Other trans-rich (3-substituted 2-piperidyl)-2-propanones (2) prepared in the same manner are listed in Table IV.

Determination of Isomer Ratios in (3-Alkoxy-2-piperidyl)-2-propanones and (3-Methyl-2-piperidyl)-2-propanone.—The isomer ratios were determined by comparing the nmr integrals for the methyl group α to the carbonyl in each of the isomers (Table V). The best solvents for this comparison were benzene or toluene. A 10% solution of the equilibrium mixture of the isomeric (3-ethoxy-2-piperidyl)-2-propanones gave nmr peaks at δ 1.76 and 1.82 for the trans and cis isomers. The peaks were well resolved when a 100-Hz sweep width was used on a Varian A-60.

TABLE V

PRINCIPAL NMR OF (3-SUBSTITUTED 2-PIPERIDYL)-2-PROPANONES

	Nmr[a]			
	Cis		Trans	
R	$COCH_3$	CCH_3	$COCH_3$	CCH_3
OCH_3	1.80		1.75	
OC_2H_5	1.82		1.76	
$OCH(CH_3)_2$	1.88		1.82	
CH_3	2.23	0.96	2.11	0.82

[a] 10% toluene solutions except for the 3-methyl compound which was 50% in chloroform. Chemical shifts given in δ (parts per million) from tetramethylsilane.

A 30% solution shows the peaks shifted to δ 1.84 and 1.88 with incomplete resolution. The results were similar in benzene and for the other alkoxy substituents. In the case of the 3-methyl analog, the peaks were at δ 2.11 and 2.23 in $CHCl_3$ for the trans and cis isomers. When toluene is the solvent, care must be taken to avoid interference from the spinning side bands of the solvent methyl group.

Registry No.—**1a**, 39037-79-1; **1a** phenyl isothiocyanate derivative, 39037-80-4; **1b**, 39037-81-5; **1c**, 39037-82-6; **1d**, 39037-83-7; **2a**, 39037-84-8; **2a** phenyl isothiocyanate derivative, 39037-85-9; **2b**, 39004-80-3; **2c**, 39037-86-0; **2d**, 39037-87-1; *cis*-**3**, 39037-92-8; *trans*-**3**, 39037-90-6; **4a**, 39049-96-2; **4b**, 39049-97-3; **4c**, 39049-98-4; **4d**, 39049-99-5; **5a**, 6652-00-2; **5b**, 6651-69-0; **5c**, 39050-02-7; **5d**, 39050-03-8; 3-methoxy-2-picoline, 26395-26-6; acetonitrile, 75-05-8.

The Stereochemistry of Febrifugine. II. Evidence for the Trans Configuration in the Piperidine Ring

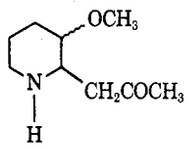
DONALD F. BARRINGER, JR., GERALD BERKELHAMMER,* AND RICHARD S. WAYNE

Chemical Research and Development Laboratories, Agricultural Division, American Cyanamid Company, Princeton, New Jersey 08540

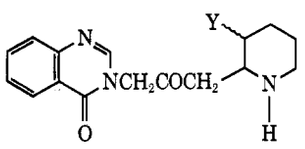
Received October 24, 1972

Evidence from nmr spectra and thin layer chromatography is presented pointing to the conclusion that the substituents on the piperidine ring of the hydrangea alkaloid, febrifugine, are in the trans configuration. The absolute stereochemistry proposed is (2′*S*,3′*R*)-3-[3-(3-hydroxy-2-piperidyl)acetonyl]-4(3*H*)-quinazolinone.

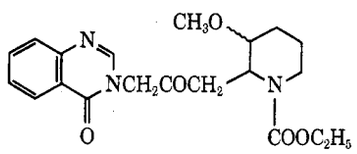
The discovery of the facile isomerization of (3-methoxy-2-piperidyl)-2-propanone (**1**),[1] a key intermediate in one synthesis of the hydrangea alkaloid, febrifugine (**2a**),[2] led to a reconsideration of the stereochemistry of the piperidine moiety of febrifugine. Baker, *et al.*, synthesized a second intermediate (**3**)[2]



1



2a, Y = OH, trans
b, Y = OH, cis
c, Y = $OCOCH_3$, trans



3

from (3-methoxy-2-piperidyl)-2-propanone (**1**) and showed that it was identical with a sample prepared by two other routes.[3] Compound **3** had previously been converted into febrifugine by removal of the blocking groups and had been assigned the cis configuration (**2b**). However, test results against coccidiosis in chicks with both synthetic isomers of febrifugine and some analogs with substituents on the aromatic ring clearly showed that the trans isomers possessed the expected biological activity. The *trans*-febrifugines are approximately ten times as effective as the *cis*-febrifugines against coccidia in chickens. The activity of the cis isomers is substantially, if not entirely, due to contamination with the trans isomer which is estimated to be present to the extent of 5–10% from thin layer chromatograms.

We isolated a sample of febrifugine dihydrochloride from hydrangea according to the procedure of Ablondi, *et al.*[4] The melting point, specific rotation, and ir spectrum all checked with the published data. The free base was prepared according to Hutchings, *et al.*,[5] and its melting point of 156.5–158.5° agreed well with the reported melting point of 154–156°[6] for the higher melting dimorph. The cis and trans racemic febrifugines (**2a,b**) were synthesized by published procedures[1,2] from the isomeric (3-methoxy-2-piperidyl)-2-propanones. Although *trans*-(3-methoxy-2-piperidyl)-2-propanone synthesized by our usual procedure contains from 25–35% of the cis isomer, purification of the febrifugine salts by recrystallization removes the cis isomer and affords the trans compound in high purity.

Thin layer chromatography (see Experimental Section) showed that the *trans*-febrifugine was pure, while the cis isomer contained a small amount of the trans. The compound isolated from hydrangea had the same R_f value as the synthesized *trans*-febrifugine. The melting point of the synthesized racemic *trans*-febrifugine, 178.5–180.5°, was higher than that of the naturally occurring dextrorotatory compound. The cis isomer melted at ~134–136°. It was impossible to obtain a precise melting point since the cis isomer underwent a rapid isomerization to the trans compound

(1) D. F. Barringer, Jr., G. Berkelhammer, S. D. Carter, L. Goldman, and A. E. Lanzilotti, *J. Org. Chem.*, **38**, 1933 (1973).
(2) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).
(3) (a) B. R. Baker, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 132 (1952); (b) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *ibid.*, **18**, 153 (1953).
(4) F. Ablondi, S. Gordon, J. Morton, II, and J. H. Williams, *J. Org. Chem.*, **17**, 14 (1952).
(5) B. L. Hutchings, S. Gordon, F. Ablondi, C. F. Wolf, and J. H. Williams, *J. Org. Chem.*, **17**, 19 (1952).
(6) J. B. Koepfli, J. F. Mead, and J. A. Brockman, Jr., *J. Amer. Chem. Soc.*, **71**, 1048 (1949).