Furthermore, garryfoline (II) has been related[5b] to the other *Garrya* alkaloids[16] as well as to members of the atisine class,[17] so that the complete absolute stereochemistry of these alkaloids is now known.

(16) K. Wiesner and Z. Valenta in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1958, Vol. XVI, pp. 26–89.

(17) S. W. Pelletier, *J. Am. Chem. Soc.*, **82**, 2398 (1960).

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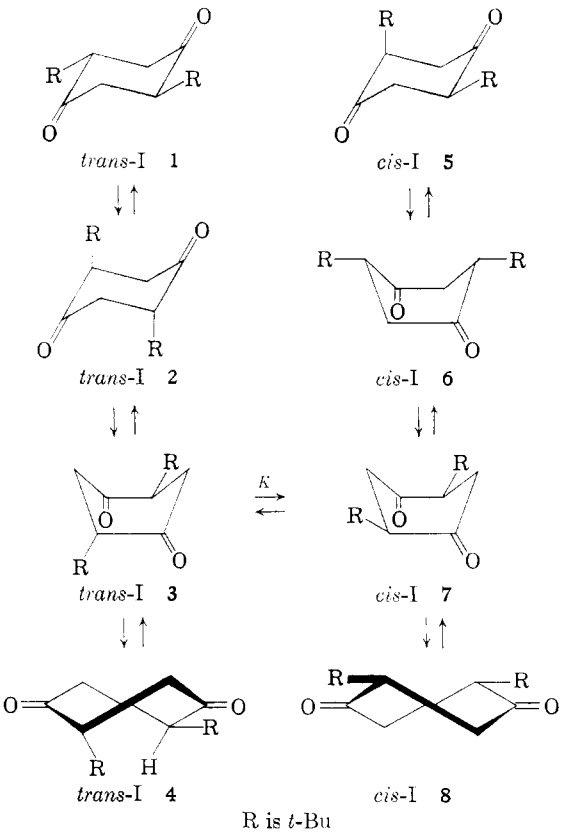
NON-CHAIR CONFORMATIONS. EQUILIBRATION OF *CIS*- AND *TRANS*-2,5-DI-*t*-BUTYL-1,4-CYCLOHEXANEDIONE

Sir:

Equilibrations of *cis*- and *trans*-1,3-di-*t*-butylcyclohexane[1] and of *cis*- and *trans*-2,4-di-*t*-butylcyclohexanone[2] demonstrate that in these molecules, the *t*-butyl groups prefer the equatorial orientation in chair conformations. This communication describes the equilibration of *cis*- and *trans*-2,5-di-*t*-butyl-1,4-cyclohexanedione (*cis*-I and *trans*-I). Although *trans*-I can exist in a chair conformation with both *t*-butyl groups equatorial (**1**), the equilibrium favors *cis*-I. We conclude that *cis*-I prefers a *nonchair* conformation such as **7**.

The diones, *cis*-I and *trans*-I, were prepared stereospecifically in good yield by the Jones oxidation[3] of two isomeric 2,5-di-*t*-butyl-1,4-cyclohexanediols, diol A (*t*-butyl groups *cis*) and diol B (*t*-butyl groups presumed *trans*). Oxidation of diol A,[4] m.p. 157.5–158.5°, yielded *cis*-I, m.p. 140–140.5°. Rapid reaction of 3 moles of hydrogen with 2,5-di-*t*-butylhydroquinone in acetic acid solution (containing one drop of concentrated hydrochloric acid) with platinum oxide catalyst at 75–80° under 2–4 atm. pressure gave a product mixture from which a 2,5-di-*t*-butyl-1,4-cyclohexanediol, diol B, m.p. 220–221°, was isolated by fractional recrystallization in *ca.* 5% yield.[5] Oxidation[3] of diol B yielded *trans*-I, m.p. 151.5–152°.[6]

Acid catalyzed equilibrations at 25–100° of the diones, *cis*-I and *trans*-I, 0.1–0.2 *M* solutions in acetic acid–water, 0.1–1 *N* in hydrogen chloride, and in carbon tetrachloride, 0.1 *N* in hydrogen chloride, gave mixtures containing 20 ± 10% *trans*-I and 80 ± 10% *cis*-I at equilibrium. The results of equilibrations in an acetic acid–water



solution 0.58 *N* in hydrogen chloride (prepared from 5.00 ml. of concentrated hydrochloric acid plus sufficient glacial acetic acid to bring the total volume to 100.0 ml.) are given in Table I.

TABLE I

EQUILIBRATION: *trans*-I ⇌ *cis*-I

T, °C.	Time, hr.	% *cis*[a]	*K*[b]	Δ*F*
44.9	37	81.5 ± 0.4	4.41 ± 0.2	−0.94 ± 0.04
85.0	3.0	79.1 ± 0.2	3.78 ± 0.1	−0.95 ± 0.02

[a] Analyses by gas chromatography were carried out in duplicate at 180° with a 10 ft. 0.25 in. copper column packed with 20% silicone gum rubber on 60–80 mesh firebrick. The analyses were calibrated against known mixtures, one containing 79.1% *cis*-I. [b] From a graph of ln *K* as a function of 1/*T*, the approximate values of the enthalpy and entropy of equilibration were determined: Δ*H*, −0.87 ± 0.3 kcal./mole; Δ*S*, 0.2 ± 0.7 e.u.

For *cis*-I and *trans*-I, the three different possible chair conformations (**1**, **2** and **5**) and three of the nine different possible boat conformations (**3**, **6** and **7**) are illustrated. The other possible boat conformations are predicted to have higher energies than **3**, **6** and **7** because of stronger repulsions between nonbonded groups. In addition, other conformations, such as twist[7] conformations **4** and **8**, require consideration.

A simple argument can be given in support of the conclusion that *cis*-I prefers a non-chair conformation. If a *t*-butyl group preferred an equatorial orientation when 1,4-cyclohexanedione was in the chair conformation, then **1** (the diequatorial chair conformation of *trans*-I) would be more stable than **5**.

(1) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).

(2) N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961).

(3) R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(4) R. D. Stolow, *J. Am. Chem. Soc.*, **83**, 2592 (1961). Assignment of the *cis* configuration to the *t*-butyl groups in diol A is considered to be unequivocal, and is based upon the observation that diol A exhibits intramolecular hydrogen bonding.

(5) Diol B does not exhibit intramolecular hydrogen bonding.

(6) The diones, *cis*-I and *trans*-I, gave acceptable carbon and hydrogen analyses and have been characterized further by their infrared, ultraviolet and nuclear magnetic resonance spectra, as well as by gas chromatography.

(7) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

However, if the axial orientation were preferred, **2** (the diaxial chair conformation of *trans*-I) would be more stable than **5**. In either case, the chair conformation of *cis*-I (**5**), with one axial and one equatorial *t*-butyl group, would be expected to be intermediate in stability between **1** and **2**. If this reasoning is valid, then because *cis*-I proved to be more stable than *trans*-I (Table I), *cis*-I must be able to exist in non-chair conformations which are more stable than **1**, **2** or **5**. Possible non-chair conformations for *cis*-I include **6**, **7** and **8**.

Allinger[8] has reported calculations which suggest that the chair, boat and twist conformations of 1,4-cyclohexanedione (**2**, **3** and **4** with R = H) have comparable energies (perhaps within ±0.2 kcal./mole). Assuming such to be the case, one can estimate the relative energy change resulting from substitution of a *t*-butyl group at each position of each of these conformations. The *t*-butyl groups appear to be most comfortably positioned in **7** for *cis*-I, and in **3** for *trans*-I, but with **7** somewhat more favorable than **3**.[9] Therefore, like *cis*-I, *trans*-I may prefer a non-chair conformation (such as **3**). The equilibration results are not inconsistent with this possibility, since *cis*-I and *trans*-I were found to have comparable entropies[2] (Table I).

The equilibration results clearly demonstrate that the diequatorial chair conformation of *trans*-2,5-di-*t*-butyl-1,4-cyclohexanedione (**1**) does not enjoy the special stability possessed by the diequatorial chair conformations of the related cyclohexane[1] and cyclohexanone[2] derivatives. The results are in accord with the description of 1,4-cyclohexanedione proposed by Allinger.[8] We are now exploring the possibility that non-chair conformations may also *predominate* for other simple 1,4-cyclohexanediones.

We are indebted to Dr. J. Casanova, Jr., for assistance with apparatus for gas chromatography. We wish to express our appreciation of support by the Research Corporation.

(8) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

(9) The boat **7** appears more stable than **6** because in **7** each carbonyl oxygen is skew (rather than opposed) to the adjacent *t*-butyl group. However, the most stable conformation of *cis*-I may be a non-chair conformation intermediate between **7** and **8**. Note that twist conformation **4** of *trans*-I is destabilized by a 1,4-repulsion between one *t*-butyl group and one hydrogen which can be relieved by rotation toward **3**.

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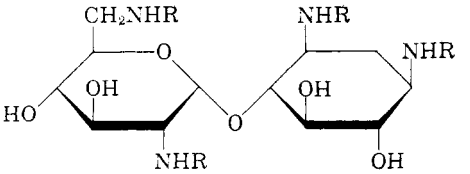
THE STRUCTURE OF NEAMINE

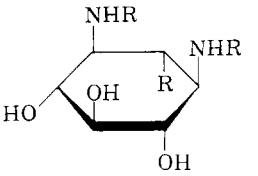
Sir:

On methanolysis in 0.4 *N* hydrochloric acid[1] neomycins B and C are approximately bisected to give the methyl glycosides of neobiosamines B and C, respectively,[1] together with the fragment neamine,[1,2,3,4] common to both. The structures of neobiosamines B[5] and C[6] have been assigned previously; the present report establishes the structure of neamine as I.



Neosamine C Deoxystreptamine

I, R = H (Neamine)
II, R = $COCH_3$
III, R = COC_6H_5



IV, R = H, R′ = H
V, R = COC_6H_5, R′ = H
VI, R = H, R′ = OH
VII, R = COC_6H_5, R′ = OH
(R′ inside ring)

Neamine ($C_{12}H_{26}N_4O_6$)[2] is hydrolyzed completely during 9 hours by refluxing 48% hydrobromic acid to give an 83% yield of deoxystreptamine (IV, $C_6H_{14}N_2O_3$),[7] whose gross 1,3-diamino-4,5,6-trihydroxycyclohexane structure was established by Kuehl, Bishop and Folkers from degradative evidence.[7] The all-*trans* stereochemistry of IV is assigned in the present study from these observations: (1) a *trans* OH–NH_2 relationship is indicated by the failure of N,N′-dibenzoyldeoxystreptamine (V),[7] m.p. 312–313°, to undergo N → O benzoyl migration under conditions (0.7 *N* hydrochloric acid in 95% ethanol, room temperature, two weeks) where *cis*-2-benzamidocyclohexanol undergoes N → O benzoyl migration, but the *trans* isomer does not.[8] Significantly, N,N′-dibenzoylstreptamine (VII),[9] m.p. 287–288°, which has been assigned the all-*trans* configuration on synthetic evidence,[10] also fails under the present conditions to undergo N → O benzoyl migration. (2) A *trans* OH–OH configuration is argued by the nearly equal rates of reaction with 0.1 *N* periodate of V (which is actually slightly *slower*) and the streptamine analog (VII).

Neamine was acetylated in the present study by acetic anhydride in methanol at 0–5° to the known[2] N,N′,N″,N‴-tetraacetylneamine (II). Hydrolysis of II in 3 *N* aqueous hydrochloric acid during 10 hours on a steam-bath gave a mixture of organic bases. Cellulose chromatography[11] (BAW 221 solvent system)[12] of the hydrolyzate from 975

(1) J. D. Dutcher, N. Hosansky, M. N. Donin and O. Wintersteiner, *J. Am. Chem. Soc.*, **73**, 1384 (1951).

(2) R. L. Peck, C. E. Hoffhine, Jr., P. Gale and K. Folkers, *ibid.*, **71**, 2590 (1949); **75**, 1018 (1953).

(3) B. E. Leach and C. M. Teeters, *ibid.*, **73**, 2794 (1951); **74**, 3187 (1952).

(4) J. D. Dutcher and M. N. Donin, *ibid.*, **74**, 3420 (1952).

(5) K. L. Rinehart, Jr., A. D. Argoudelis, T. P. Culbertson, W. S. Chilton and K. Striegler, *ibid.*, **82**, 2970 (1960).

(6) K. L. Rinehart, Jr., and P. W. K. Woo, *ibid.*, **80**, 6463 (1958).

(7) F. A. Kuehl, Jr., M. N. Bishop and K. Folkers, *ibid.*, **73**, 881 (1951). These authors, who established a *meso* configuration by optical inactivity, suggested the all-*trans* configuration for IV on the compound's presumed biogenetic relation to streptamine (VI).

(8) G. Fodor and J. Kiss, *Acta Chim. Acad. Sci. Hung.*, **1**, 130 (1951).

(9) H. E. Carter, Y. H. Loo and J. W. Rothrock, *J. Biol. Chem.*, **179**, 1027 (1949).

(10) M. L. Wolfrom, S. M. Olin and W. J. Polglase, *J. Am. Chem. Soc.*, **72**, 1724 (1950).

(11) Purification was also effected by gradient elution with hydrochloric acid from a Dowex 50 (Dow Chemical Co. strongly acidic cation exchange resin) ion exchange column.

(12) K. L. Rinehart, Jr., A. D. Argoudelis, W. A. Goss, A. Sohler and C. P. Schaffner, *J. Am. Chem. Soc.*, **82**, 3938 (1960).