meric hydrogen in deuteriochloroform appears as a triplet at $\delta = 5.26$, being spin coupled to the axial C-2 hydrogen and to the C-1 hydroxyl hydrogen. The small spin coupling observed (2 to 3 cps.) indicates that the C-1 hydrogen in crystalline chalcose is equatorial,[2] as in II.

N.m.r. spectroscopy clearly demonstrates the configurational change at C-1 which accompanies the mutarotation of chalcose. In deuterium oxide (Fig. 1D), the equatorial C-1 hydrogen appears as a doublet at $\delta = 5.70$, $J_{a,e} = 2.7$ cps. The doublet signal at $\delta = 5.00$, being at higher field, is typical of an axial anomeric hydrogen[2,3]; the large spin coupling observed (7 cps.) indicates that in the newly formed anomer of chalcose the C-1 and C-2 hydrogens are axial.[2]

Oxidation of chalcose with nitric acid yielded a crystalline diacid, m.p. 179–182°, $[\alpha]^{24}D$ +47° (*c* 1.4%, water), [*Anal.* Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91; neut. eq., 81 (two titratable groups). Found: C, 36.54; H, 4.99; neut. eq., 81; p*K'*a (water), 2.7, 4.2], which was identical with a synthetic sample of O-methyl-L-tartaric acid (specific rotation, $R_f$ values, mixed melting point, infrared spectrum and X-ray diffraction pattern); the latter was synthesized by partial methylation of dimethyl L-tartrate[6] and saponification. The isolation of O-methyl-L-tartaric acid, which had originated from C-1 to C-4 of chalcose, confirmed the *trans*-relationship between the C-2 and C-3 hydrogens and established the absolute configuration of these two carbons as indicated in II, rather than in the mirror image of II.

According to Hudson's rules of isorotation,[7] the absolute configuration at C-1 of crystalline chalcose, as indicated in II, would result in a mutarotation the magnitude of which decreases with time. This behavior is exactly that observed.

Thus the C-1, C-2 and C-3 configurations of methyl chalcoside (I) and of chalcose (II) have been established by mutually consistent chemical, n.m.r. and rotational data; and the C-5 configuration has been deduced from n.m.r. data.

(6) From L-tartaric acid, $[\alpha]^{25}D$ +14.6° (*c* 10.1%, water).

(7) C. S. Hudson, "Advances in Carbohydrate Chemistry," **3**, 15 (1948).

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## THE EFFECT OF SUBSTRATE STERIC PROPERTIES ON THE STEREOCHEMICAL COURSE OF DIIMIDE REDUCTIONS[1]

*Sir:*

The action of diimide ($H_2N_2$) on organic substances has been the subject of recent investigations in this[2] and other[3] laboratories. Although it has been demonstrated that during reduction of olefins and acetylenes *cis* transfer of hydrogen is favored over *trans*,[3a] no examples are available which illuminate the role substrate steric features play in determining the relative configuration at an asymmetric center produced in the process.[4] Since it seemed that such information about this unusually selective, and therefore potentially useful, reagent[5] would be of general interest, we carried out a series of reductions on appropriate, representative olefins. Summarized below are results which indicate that in cases where bulk effects in the olefin are pronounced, reduction is markedly subject to steric approach control.[6] On the other hand, in examples where steric influences are moderate, much less stereochemical discrimination is observed; however, the product stability factor still does not entirely govern the stereochemical course of reaction in these cases.

Olefin cases selected for study were ones wherein approach of diimide from the less hindered side would afford the less stable of two possible reduc-

TABLE I

STEREOCHEMICAL RESULTS OF DIIMIDE REDUCTIONS

| | Olefin reduced | Diimide reduction Product (% *cis*:trans) | Catalytic reduction (Pt) product (% *cis*:trans) |
|---|---|---|---|
| 1 | α-Pinene | 99:1[a] | 93:7[d] |
| 2 | β-Pinene | 96:4[a] | 84:16[d] |
| 3 | 2,3-Dimethylcyclohexene | 24:76[b] | 71:29[e] |
| 4 | 2-Methylmethylenecyclohexane | 61:39[b] | 68:32[e] |
| 5 | 4-*t*-Butylmethylenecyclohexane | 49:51[c] | 83:17[f] |
| 6 | Camphene | 92(*endo*):8(*exo*)[a] | 75(*endo*):25(*exo*)[d] |
| 7 | 2-Norbornene-2,3-dicarboxylic acid | *endo-cis* (by isolation of single product in 40% yield) | (*endo-cis*) |

[a] In this case, the stereochemical assignment to reduction products was confirmed by hydroboration of starting olefins (H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959); thermal equilibration of the resulting alkyl borane; and then reductive hydrolysis to saturated hydrocarbon. The major product was considered to be also the more stable, *i.e.*, *trans*-pinane and *exo*-isocamphane (see J. C. Braun and G. S. Fisher, *Tetrahedron Letters*, No. 21, 9 (1960)). [b] Comparison with data supplied by the American Petroleum Institute. [c] Tentative assignment of configuration, which is based on application of the von Auwers–Skita rule (N. L. Allinger, *Experientia*, **10**, 328 (1954)) utilizing refractive index data (K. T. Serijan, P. H. Wise and L. C. Gibbons, *J. Am. Chem. Soc.*, **71**, 2265 (1949)), is not crucial here, in that nearly equimolar amounts of isomers were formed. [d] Determined in this laboratory (v.p.c.). [e] S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082 (1960). [f] S. Siegel, as quoted by J.-F. Sauvage, R. H. Baker and A. S. Hussey, *ibid.*, **82**, 6090 (1960).

(1) From the Ph.D. thesis (U. of W.) of R. J. Timmons.

(2) (a) E. E. van Tamelen, R. S. Dewey and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3725 (1961); (b) R. S. Dewey and E. E. van Tamelen, *ibid.*, **83**, 3729 (1961); E. E. van Tamelen, R. S. Dewey, M. F. Lease and W. H. Pirkle, *ibid.*, **83**, 4302 (1961).

(3) (a) E. J. Corey, D. J. Pasto and W. L. Mock, *ibid.*, **83**, 2957 (1961); (b) E. J. Corey, W. L. Mock and D. J. Pasto, *Tetrahedron Letters*, No. 11, 347 (1961); S. Hünig, H-R. Müller and W. Thier, *ibid.*, 353 (1961). See also F. Aylward and M. Sawistowska, *Chem. and Ind.*, 404 (1961), and previous papers by Aylward and co-workers.

(4) (a) The stereochemistry of the tetrahydrogibberellic acid produced by hydrazine–air reduction of gibberellic acid (B. E. Cross, *J. Chem. Soc.*, 3022 (1960)) has not been determined. (b) Cholesterol is converted by diimide to cholestanol (20%)[3b] which, however, is the expected product on the basis of either steric approach or product development control.

(5) For example, as noted in other laboratories, dideuteriodiimide ($D_2N_2$) reduces an isolated double bond with introduction of only the expected two deuterium atoms; whereas catalytic reduction with deuterium gas involves additional deuterium insertion through metal-catalyzed exchange.

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

tion products. In each case reduction was carried out by stirring an ethanolic solution of olefin and hydrazine hydrate in an oxygen atmosphere at 55° (camphene was reduced at 45°), and product composition was determined by analytical vapor phase chromatography (reproducibility ±0.5%). The results of the diimide reductions are summarized in Table I, along with, for comparison purposes, product ratios observed in catalytic reductions of the same olefins. In cases where substrate steric features are clearly important factors (no. 1, 2, 6 and possibly 7), greater than 90% of the less stable stereoisomer appears, resulting from reagent approach from the less hindered side. Of the other examples, perhaps the most instructive is 4-*t*-butylmethylenecyclohexane, where the six-membered ring itself is—for all practical purposes—the only steric contributor in the reduction; here, axial and equatorial attack by diimide are just counter-balanced. It should be noted that in no reduction did more than 76% of the more stable product result.

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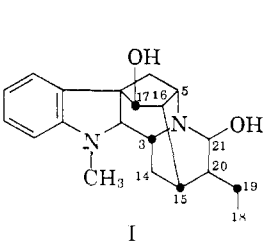
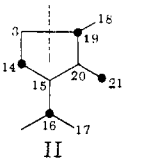
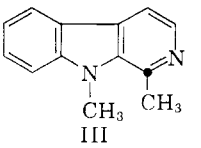
## BIOSYNTHESIS OF THE NON-TRYPTOPHAN DERIVED PORTION OF AJMALINE[1]

*Sir:*

We have shown[2] previously that the administration of tryptophan-2-$C^{14}$ to *Rauwolfia serpentina* plants leads to the formation of ajmaline-5-$C^{14}$, strongly suggesting that this amino acid or closely related metabolite is a precursor of the reduced β-carboline moiety of ajmaline. The origin of the residual carbons of ajmaline and related indole alkaloids has been the subject of much controversy. Discussion of the various hypotheses will be simplified if we confine our attention to ajmaline (I). Woodward[3] and Robinson[4] suggested that $C_3$ and carbons 14 to 20 are derived from 3,4-dihydroxyphenylalanine. Wenkert[5] proposed that these carbons are derived from prephenic acid. In both these hypotheses $C_{21}$ is derived from a one carbon fragment and recent tracer studies[6] with sodium formate-$C^{14}$ support this idea. In a third hypothesis independently conceived by Thomas[7] and Wenkert[5c] all the non-tryptophan derived carbons are considered to arise from a monoterpene having the carbon skeleton II. The cyclopentane ring is cleaved at the dotted line and the carbons




are numbered as they would be expected to appear in ajmaline. The extra carbon at $C_{16}$ is absent in ajmaline but becomes the carbomethoxy group of serpentine, reserpine and related alkaloids.

We have tested these hypotheses by feeding various labeled compounds to *R. serpentina* plants by methods previously described.[2] Tyrosine is a known precursor of 3,4-dihydroxyphenylalanine and the administration of tyrosine-2-$C^{14}$ would be expected to yield ajmaline-3-$C^{14}$ if the Woodward–Robinson scheme were correct. However, the ajmaline, reserpine and serpentine obtained from the plant which had been fed this tracer (0.2 mc.) were completely inactive. The side chain of prephenic acid is derived from pyruvate,[8] which in turn can be formed rapidly from alanine by a transamination reaction. Thus if Wenkert's prephenic hypothesis were correct one would expect alanine-2-$C^{14}$ to yield prephenic acid labeled on the ketone group which ultimately becomes $C_3$ of ajmaline. Administration of DL-alanine-2-$C^{14}$ (0.36 mc.) led to the formation of radioactive ajmaline; however, the specific activity was quite low ($2.9 \times 10^4$ d.p.m./mM.) and degradation indicated that there was only about 2% of the radioactivity located at $C_3$. Ajmaline isolated from the plant which had been fed mevalonic acid-2-$C^{14}$ (0.1 mc.), an established precursor of terpenes,[9] was completely inactive. The administration of sodium acetate-1-$C^{14}$ (3.25 mg., 0.2 mc.) yielded radioactive ajmaline ($9.3 \times 10^5$ d.p.m./mM.). Kuhn–Roth oxidation of the ajmaline afforded radioactive acetic acid which on treatment with sodium azide and sulfuric acid yielded carbon dioxide assayed as barium carbonate ($2.4 \times 10^5$ d.p.m./mM.) and inactive methylamine (assayed as the platinochloride). On heating the ajmaline with soda-lime harman ($2.3 \times 10^5$ d.p.m./mM.) and N-(*ind*)-methylharman (III) ($2.4 \times 10^5$ d.p.m./mM.) were obtained.[10] The acetic acid obtained by the Kuhn–Roth oxidation of III was subjected to the Schmidt reaction yielding barium carbonate ($2.4 \times 10^5$ d.p.m./mM.) and inactive methylamine. These results indicate that approximately one half the total radioactivity of the ajmaline is located at $C_3$ and $C_{19}$ and equally divided between these positions. These results are incompatible with the monoterpene hypothesis since acetate-1-$C^{14}$ would produce mevalonate-1,3,5-$C^{14}$ which would afford

(1) This investigation was supported by a Research Grant MY-2662 from the National Institute of Mental Health, U.S. Public Health Service.

(2) E. Leete, *J. Am. Chem. Soc.*, **82**, 6338 (1960).

(3) R. B. Woodward, *Angew. Chemie*, **68**, 13 (1956).

(4) R. Robinson, *Festschrift Arthur Stoll*, Birkhäuser, Basel, 1957, p. 457.

(5) (a) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959); (b) E. Wenkert, *Experientia*, **15**, 165 (1959); (c) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).

(6) P. N. Edwards and E. Leete, *Chemistry and Industry*, 1666 (1961).

(7) R. Thomas, *Tetrahedron Letters*, 544 (1961).

(8) J. G. Levin and D. B. Sprinson, *Biochem. and Biophys. Research Comm.*, **3**, 157 (1960).

(9) A. J. Birch, D. Boulter, R. I. Fryer, P. J. Thomson, and J. L. Willis, *Tetrahedron Letters*, No. 3, 1 (1959).

(10) F. A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Chem. Soc.*, 1242 (1954).