cyclopropyl cyanide has been ascribed by Walborsky[7b] to nonplanarity of the carbanion. If steric effects on flattening the carbanion were responsible for our 10^4 rate decrease in the cyclopropene exchange, then one would have expected a cyclopropene to show an even larger k_e/k_r, contrary to the results. On the other hand, antiaromatic interaction between the carbanion and the double bond should displace charge into the cyano group, flattening the anion, and decreasing k_e/k_r, as is observed.

One must consider the possibility that Walborsky's retention data reflect asymmetric solvation[8] of a flat cyclopropane anion, although he has specifically rejected[7b] this alternative. Even if this were the explanation, our increased racemization would result from an increased tendency in the cyclopropene nitrile anion for protonation on nitrogen rather than on carbon, again because of electronic antiaromatic interaction. It need hardly be added that the increased tendency for racemization in the cyclopropenes cannot be due to a *stabilizing* interaction of the flattened anion with the double bond, since the exchange rate is greatly decreased in the cyclopropene. Accordingly, our data on racemization *vs.* exchange rates are best interpreted as reflecting the same conjugative destabilization effect (antiaromaticity) we have invoked[3] to explain the exchange rates alone.[9]

(7) (a) Private communication from Professor Walborsky; (b) *cf.* H. M. Walborsky, A. A. Youssef, and J. M. Motes, *J. Am. Chem. Soc.*, **84**, 2465 (1962).

(8) D. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter III.

(9) Support of this work by the National Institutes of Health is gratefully acknowledged.

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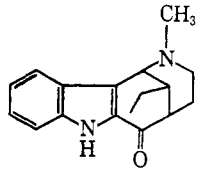
The Total Synthesis of (±)-Dasycarpidone and (±)-Epidasycarpidone

Sir:

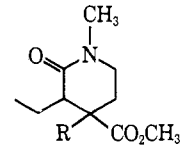
Both dasycarpidone[1] (**1**) and its epimer[2] have been isolated from natural sources along with the closely related alkaloids (in which the carbonyl oxygen is exchanged for a methylene) uleine[3] and epiuleine.[2]



1

We have now completed the total synthesis of dasycarpidone and its epimer, the first 2-acylindole alkaloids to be obtained by total synthesis. The approach taken in the present work is entirely different from the sequence used in the synthesis of desethyldasycarpidone.[4]

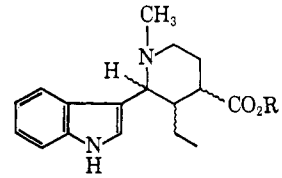
The action of N-methylaziridine on α-bromobutyryl chloride afforded N-methyl-N-(2-chloroethyl)-α-bromobutyramide which was condensed directly with dimethyl malonate using 2 equiv of sodium methoxide to afford 1-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone, mp 79–80°, $\nu_{max}^{CHCl_3}$ 1730 and 1640 cm^{-1}, in 65% yield.[5] Treatment of the piperidone **2** with sodium cyanide in hot N,N-dimethylformamide removed one carbomethoxy group to yield 1-methyl-3-ethyl-4-carbomethoxy-2-piperidone (**3**), bp 120–130° (1.5 mm), as a mixture of diastereomers in 70% yield.



2, R = CO_2CH_3
3, R = H

Condensation of the piperidone **3** with indole was effected by phosphorus oxychloride.[6] The reaction mixture was diluted with aqueous methanol, basified, and treated with sodium borohydride to yield a mixture of stereoisomers of the amino ester **4** in 70% yield. One isomer of the amino ester **4** was isolated in crystalline form: mp 140–141°; $\nu_{max}^{CHCl_3}$ 1730 and 3530 cm^{-1}; nmr ($CDCl_3$) δ 0.64 (triplet, J = 6 cps, 3 H), 2.01 (singlet, 3 H), and 3.72 ppm (singlet, 3 H); normal indole ultraviolet absorption.

The total crude ester was suitable for the following steps. Normal saponification afforded the amino acid



4, R = CH_3
5, R = H

5 which was heated with polyphosphoric acid at 80–90° for 75 min to yield a mixture of 2-acylindoles. Chromatographic separation of this mixture afforded (±)-dasycarpidone in low yield and (±)-epidasycarpidone in 55% yield. The identity of the synthetic dasycarpidone, which was not obtained in crystalline form,[7] was established by comparison of the infrared and nmr spectra with those of authentic material.[8] Mass spectral comparison[9] with the published spectrum[1] futher confirmed the identity of the synthetic dasycarpidone which yielded a crystalline picrate, mp 240° dec. The mass spectrum of (±)-epidasycarpidone, mp 168–169°, was identical with that of dasycarpidone, and the nmr absorptions coincided with those reported for epidasycarpidone.[2] This result agrees with the previous report that

(1) J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, **21**, 1717 (1965).

(2) A. J. Gaskell and J. A. Joule, *Chem. Ind.* (London), 1089 (1967). These authors conclude from nmr studies that the ethyl group of dasycarpidone and uleine is *syn* to the indole moiety. See also M. Shamma, J. A. Weiss, and R. J. Shine, *Tetrahedron Letters*, 2489 (1967).

(3) G. Büchi and E. W. Warnhoff, *J. Am. Chem. Soc.*, **81**, 4433 (1959).

(4) A. Jackson and J. A. Joule, *Chem. Commun.*, 459 (1967).

(5) Satisfactory analytical data have been obtained on all crystalline compounds.

(6) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DeVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, 7, 415 (1964).

(7) Natural dasycarpidone was obtained in amorphous form.[1]

(8) We are grateful to Professor Carl Djerassi for sending us nmr and infrared spectra of dasycarpidone.

(9) We are indebted to Professor William Epstein and Mr. Leonard Wojcik of the University of Utah for the mass spectra.

dasycarpidone and epidasycarpidone show the same mass spectrum.[2] Professor J. A. Joule has kindly informed us that he and his coworkers have synthesized (±)-dasycarpidone and (±)-epidasycarpidone by another route. A sample of (±)-epidasycarpidone provided by Professor Joule shows the same behavior on tlc as our material.

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Paramagnetic Proton Nuclear Magnetic Resonance Shifts of Metmyoglobin, Methemoglobin, and Hemin Derivatives[1]

Sir:

We present here preliminary results of studies of paramagnetic proton nmr shifts in hemin and related compounds, chlorohemin, chloromesohemin, chlorodeuterohemin, metmyoglobin,[2] and methemoglobin. Our results suggest that the isotropic hyperfine interaction is transmitted principally through the σ-bond system of the porphyrin ring. Moreover, a comparison of the metmyoglobin and methemoglobin spectra may indicate the effect of nonequivalent heme groups in hemoglobin.

The 100-MHz proton nmr spectra of the hemin derivatives are shown in Figure 1; those of metmyoglobin and methemoglobin are shown in Figure 2. Spectra were measured both at 60 MHz, with a Varian DP-60 spectrometer, and also at 100 MHz, with a Varian HA-100 spectrometer modified to give the required large frequency-sweep ranges and sweep offsets in a field-frequency controlled mode.[3] Samples of the hemin derivatives, taken as ~0.06 *M* solutions of the free acid in DMSO-d_6, and those of methemoglobin and metmyoglobin, taken as ~0.01 *M* solutions in 0.1 *M* deuterated phosphate, pD 7,[3] were run at ambient temperature (27.0 ± 0.5°).

The spectra in Figures 1 and 2 show lines shifted far downfield (30–90 ppm) from the normal range of chemical shifts in diamagnetic porphyrins.[4-6] No lines were observed shifted upfield by comparable amounts. A comparison of line positions and relative intensities in these spectra leads to the tentative assignments for the chlorohemin derivatives shown in Table I, and the numbering scheme is shown in Figure 3. The large downfield shifts of lines assigned to the 2a,4a methylene protons in mesohemin and to the 2,4 protons of deuterohemin suggests that the isotropic hyperfine interaction is transmitted through the σ-bond system. Were the unpaired electron spin in the porphyrin ring system distributed over π-type orbitals in a strictly planar ring system, one would expect the isotropic hyperfine constants for the 2a,4a methylene protons in mesohemin to be of opposite sign to those for the 2,4 protons in deuterohemin.[7,8]

Several of the lines in the methemoglobin and metmyoglobin spectra may arise from histidine and/or water, bonded to the heme group in the fifth and sixth coordination positions. Further, there are large differences in relative intensities and line widths, the lines of the metmyoglobin spectra generally being sharper. The greater line widths of the hemoglobin spectra may be due to a nonequivalence of the four heme groups or to the larger rotational correlation time of the methemoglobin molecule.

We have taken the contribution of the pseudo-contact term in the isotropic hyperfine interaction to be negligible, as indicated by calculations to the second

Table I. Assigned Line Positions for Paramagnetic Proton Nmr Shifts in Chlorohemin Derivatives at 100 MHz and 300°K[a]

	Assignments[b]					
Compound	$H_{\alpha,\beta,\gamma,\delta}$	CH_3(1a,-3a,5a,8a)	CH_2-(2a,4a)	CH_2-(6a,7a)	-CH=CH_2 (2a,4a)(2b,4b)	H(2,4)
Chlorohemin	62.61[c]	50.75		46.80	57.53	
				40.51	54.23	
				37.18	44.51	
Chloromesohemin	61.96	50.15	44.02	44.02		
	60.17	49.05	39.59	39.59		
Chlorodeuterohemin	64.42	49.34		41.92		
	61.18	46.98		39.68[d]		72.29[e]
	60.01					
	57.44					

[a] The numbering scheme used is shown in Figure 3. [b] Shifts are in parts per million downfield from DMSO; the precision of the measurements is better than ±0.05 ppm, or better than the line width (~2–3 ppm). [c] A slight splitting was observed here, ~0.06 ppm. [d] Broadening, indicating the presence of additional lines, can be observed here. [e] This shift is approximately the same as that found for pyrrole protons in $\alpha,\beta,\gamma,\delta$-tetraphenylporphyriniron(III) chloride (D. R. Eaton and E. A. LaLancette, *J. Chem. Phys.*, **41**, 3534 (1964)).

(1) This paper was presented in part to the 12th Annual Meeting of the Biophysical Society, Feb 19–21, 1968, Pittsburgh, Pa.

(2) A. Kowalsky (*Biochemistry*, **4**, 2382 (1965)), in a related proton nmr study of cytochrome *c* and heme polypeptides, has mentioned the occurrence of large downfield shifts in the proton nmr spectra of metmyoglobin; however, no values were cited for these shifts or spectra given.

(3) Details of this modification as well as the preparation and sources of materials will be published elsewhere.

(4) R. J. Abraham, A. H. Jackson and G. W. Kerner, *J. Chem. Soc.*, 3468 (1961).

(5) E. D. Becker, R. B. Bradley, and C. J. Watson, *J. Am. Chem. Soc.*, 83, 3473 (1961).

(6) W. S. Caughey and W. S. Koski, *Biochemistry*, 1, 923 (1962).

(7) D. R. Eaton and W. D. Phillips, *Advan. Magnetic Resonance*, 1, 119 (1965).

(8) A. Forman, G. N. Murrell, and L. E. Orgel, *J. Chem. Phys.*, 31, 1129 (1959).