The optical purity of two peptides (with side-chain blocking groups removed), H-(Ala)$_2$-Lys-Phe-OMe (IV) and H-Ser-Thr-Ser-(Ala)$_2$-OH (V), was investigated by enzymic hydrolysis. Peptide IV was incubated with aminopeptidase M,[12] and peptide V was treated with leucine aminopeptidase.[13] Amino acid analysis and paper and thin layer chromatograms of the hydrolysates showed that both peptides were completely hydrolyzed, thus indicating that no detectable racemization occurred during synthesis.

The results reported above indicate that the use of polymeric NHS esters combines high reactivity and steric homogeneity in peptide synthesis with the facile work-up of polymer reagent and support systems. Application of this method to the synthesis of higher peptides is being investigated.[14]

Acknowledgments. We thank Dr. Elizabeth R. Simons for valuable assistance in enzymic hydrolyses and Miss Mary Jane Becherer for amino acid analyses. This work was supported in part by the U. S. Public Health Service, Grants AM 07300 and AM 10794, and by the Office of the Surgeon General, Department of the Army.

(12) G. Pfleiderer and P. G. Celliers, *Biochem. Z.*, **339**, 186 (1963); K. Hoffmann, F. M. Finn, M. Limetti, J. Montibeller, and G. Zannetti, *J. Am. Chem. Soc.*, **88**, 3633 (1966).

(13) K. Hofmann and H. Yajima, *ibid.*, **83**, 2289 (1961); K. Hofmann, H. Yajima, T.-Y. Liu, N. Yanaihara, C. Yanaihara, and J. L. Humes, *ibid.*, **84**, 4481 (1962).

(14) Subsequent to the completion of the manuscript we noted a brief reference to the use of the polymer reported here: A. Patchornik, M. Fridkin, and E. Katchalski, "Proceedings of the Eighth European Peptide Symposium," John Wiley and Sons, Inc., New York, N. Y., 1967, p 92.

(15) National Institutes of Health Postdoctoral Fellow 1965–1966.

(16) National Science Foundation Postdoctoral Fellow 1965–1967.

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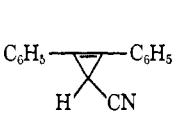
Antiaromatic Effects in Cyanocyclopropenyl Anions

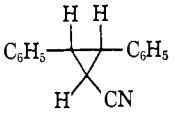
Sir:

We have reported[1-3] evidence for conjugative destabilization in some cyclopropenyl anions. The most convincing data involve a comparison[3] of deuterium exchange rates for cyclopropyl and cyclopropenyl ketones, sulfones, and esters; in spite of the greater formal conjugation in the related anions, exchange in the cyclopropenes is considerably slower. This striking effect may result from antiaromaticity in the cyclopropenyl anions, or various steric differences which might make rehybridization to a trigonal carbon more difficult in the cyclopropene case. Previous arguments[3] indicated that the steric explanation is less likely. We wish now to report further evidence which supports antiaromaticity as the major factor in these rate differences.

Evidence similar to that we have already reported comes from a comparison of the rate of exchange[4] of diphenylcyclopropenyl cyanide[5] (I) with that of the corresponding cyclopropane derivative[6] (II). Some of the steric effects cited[3] for the corresponding benzoyl derivatives should be smaller with a cyano group, but PPP–SCF calculations predict that the antiaromaticity effect should be larger. This results essentially from less effective charge removal by the cyano group than by a benzoyl group. Experimentally, the exchange of I was carried out at 60.3° in 40% dimethoxyethane and 60% *t*-butyl alcohol-O-*d* with 0.06 *M* potassium *t*-butoxide, with aliquots analyzed by mass spectroscopy. Good reproducible pseudo-first-order data were obtained, $k_I = 1.86 \times 10^{-6}$ sec^{-1}. The much faster exchange of II was examined in the same medium at three lower temperatures and extrapolated to 60.3°: $k_{II}(-0.8°) = 1.82 \times 10^{-4}$ sec^{-1}, $k_{II}(6.9°) = 3.84 \times 10^{4}$ sec^{-1}, $k_{II}(16.4°) = 8.75 \times 10^{-4}$ sec^{-1}. The ratio at 60.3° is $k_{II}/k_I = 10{,}000$. As predicted by the MO calculations, this is larger than the corresponding number (6000) for ketone activation.

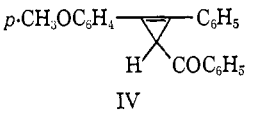


I

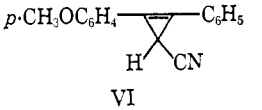


II

Evidence of a different sort comes from studies on racemization *vs.* exchange in optically active derivatives. 1-*p*-Anisyl-2-phenylcyclopropene-3-carboxylic acid[6] (III), mp 179–180°, was resolved with cinchonine, α_D(III) −20.3°. With phenyllithium this afforded optically active 1-*p*-anisyl-2-phenyl-3-benzoylcyclopropene[6] (IV), mp 100–102°, α_D −35.8°; the ORD shows a Cotton curve with α_{trough} −235°. Exchange with potassium ethoxide (0.2 *M*) in 1:1 dimethoxyethane and ethanol-O-*d* at 100.7° was followed by mass spectroscopy and ORD: $k_{exchange}/k_{racemization}$ was reproducibly 1.0 ± 0.1. For an optically active benzoylcyclopropane Walborsky has found $k_e/k_r = 1.6$ in methanol. We have also converted optically active III to the carboxamide V, mp 238–240°, and thence to optically active 1-*p*-anisyl-2-phenyl-3-cyanocyclopropene (VI), mp 95–96°. This was treated at 60.2° with 0.42 *M* potassium *t*-butoxide in *t*-butyl alcohol-O-*d* and aliquots were examined by mass spectroscopy and ORD. The ratio $k_{exchange}/k_{racemization}$ was 4.0 ± 0.2. By contrast, Walborsky has found $k_e/k_r = 77$ for optically active 2,2-diphenylcyclopropenyl cyanide in *t*-butyl alcohol with potassium *t*-butoxide.



IV
$k_e/k_r = 1.0 \pm 0.1$



VI
4.0 ± 0.2

Exchange in the cyclopropene system is thus accompanied by more racemization than in the cyclopropane series. The stereochemical retention for

(1) R. Breslow and M. Battiste, *Chem. Ind.* (London), 1143 (1958).

(2) R. Breslow and P. Dowd, *J. Am. Chem. Soc.*, **85**, 2729 (1963).

(3) R. Breslow, J. Brown, and J. Gajewski, *ibid.*, **89**, 4383 (1967).

(4) W. van Wijnen, M. van Wijnen, H. Steinberg, and Th. J. de Boer, *Tetrahedron*, **23**, 3763 (1967), suggest that the rate-determining step in this reaction comes after proton removal, but we feel their observed k_H/k_D of 1.9 in methanol is consistent with rate-determining ionization, as is expected in this solvent.

(5) R. Breslow, J. Lockhart, and H. W. Chang, *J. Am. Chem. Soc.*, **83**, 2375 (1961).

(6) New compounds had reasonable nmr, infrared, and ultraviolet spectra, and were further characterized by analysis or mass spectrum.

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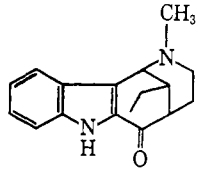
The Total Synthesis of (±)-Dasycarpidone and (±)-Epidasycarpidone

Sir:

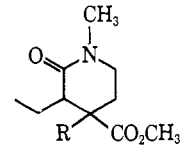
Both dasycarpidone[1] (**1**) and its epimer[2] have been isolated from natural sources along with the closely related alkaloids (in which the carbonyl oxygen is exchanged for a methylene) uleine[3] and epiuleine.[2]



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]

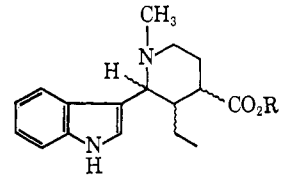
The action of N-methylaziridine on α-bromobutyryl chloride afforded N-methyl-N-(2-chloroethyl)-α-bromobutyramide which was condensed directly with dimethyl malonate using 2 equiv of sodium methoxide to afford 1-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone, mp 79–80°, $\nu_{max}^{CHCl_3}$ 1730 and 1640 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.