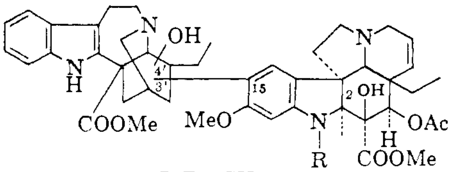
of cleavamine demonstrates the relationship of the indole portion of C_{46} alkaloids to catharanthine[13] (IX) since it was also obtained by a similar acid treatment of the latter.[14]

The mode of attachment of the indole moiety to the vindoline portion of VLB and LCR is apparent from the n.m.r. spectra of these compounds. The aromatic protons of the indole portion are unchanged; however, instead of the typical 1,2,4 pattern (6.9, 6.3, 6.08δ) present in vindoline,[1] the spectrum contains only two protons (δ6.16, 6.70) in a 1,4 relationship. A similar resonance pattern occurs also in vindoline derivatives substituted in the para position to the N(a) (*e.g.*, bromovindoline). *Therefore, the missing proton at C-15 (Fig. 1) represents the site of attachment of the indole portion.*

These data clearly indicate the partial structures I and III for VLB and LCR, respectively. On the basis of biogenetic considerations (free radical photosynthesis), as well as the mode of cleavage of these alkaloids, we are prompted to propose either C-3′ or C-4′ as the most likely site of attachment in the indole moiety and possible positions of the tertiary hydroxyl. The elucidation of this problem is at present in progress in these laboratories.



I, $R = CH_3$
III, $R = CHO$

We gratefully acknowledge helpful discussions with Prof. J. C. Martin, University of Illinois. Thanks are due to Dr. G. H. Svoboda for the sample of leurocristine, to Prof. K. Biemann, Massachusetts Institute of Technology, for mass spectra and their interpretation, and to Dr. J. N. Shoolery, Varian Associates, for n.m.r. spectra.

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[13] M. Gorman, N. Neuss and G. H. Svoboda, *J. Am. Chem. Soc.*, **81**, 4745 (1959), and N. Neuss and M. Gorman, *Tetrahedron Letters*, No. 6, 206 (1961).

[14] Cleavamine is believed to possess structure VIII and velbanamine appears to be its dihydrohydroxy derivative. The mass spectra indicate the same carbon skeleton for the two compounds and are consistent with the proposed structures. The rearrangements of catharanthine and related compounds under acidic conditions will be reported elsewhere, M. Gorman and N. Neuss, *Tetrahedron*, 1962 (in preparation).

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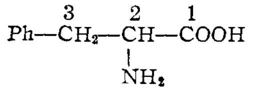
RECEIVED FEBRUARY 26, 1962

THE BIOSYNTHESIS OF TROPIC ACID[1]

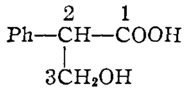
Sir:

We have established[2,3] recently by means of tracer experiments that phenylalanine (I) is a precursor of tropic acid (II), the acid moiety of the ester alkaloids hyoscyamine and hyoscine. In particular it was shown that C_2 and C_3 of the side chain of tropic acid were derived from C_3 and C_2, respectively, of the phenylalanine. The origin of the carboxyl group remained in doubt. Goodeve and Ramstad[4] obtained carboxyl-labeled tropic acid when tryptophan-3-C^{14} was fed to *Datura stramonium* plants. We attempted to explain this rather surprising result by suggesting[3] that the radioactive tryptophan was metabolized in the plant yielding radioactive carbon dioxide which was then incorporated into tropic acid by a hypothetical carboxylation of phenylpyruvic acid or related compound.



$$\mathrm{Ph{-}\overset{3}{C}H_2{-}\underset{\displaystyle NH_2}{\overset{2}{C}H}{-}\overset{1}{C}OOH}$$

I



$$\mathrm{Ph{-}\underset{\displaystyle 3CH_2OH}{\overset{2}{C}H}{-}\overset{1}{C}OOH}$$

II

We also considered that the branched three-carbon side chain of tropic acid might arise by a rearrangement of the phenylalanine side chain. This hypothesis was tested by feeding L-phenylalanine-1-C^{14} [5] (1.21 mg., 50 μc.) to ten two-month old *Datura stramonium* plants[6] growing in soil using a wick arrangement.[7] After two weeks hyoscyamine and hyoscine were isolated without dilution by established methods[2] and had specific activities of 3.6×10^6 and 3.0×10^6 d.p.m./mM.,[8] respectively. Hydrolysis of the radioactive hyoscyamine yielded inactive tropine and tropic acid (3.6×10^6 d.p.m./mM.). Dehydration of the tropic acid with 50% aqueous potassium hydroxide[9] afforded atropic acid which was oxidized in alkaline solution with sodium metaperiodate and a catalytic amount of osmium tetroxide yielding formaldehyde collected as its dimedone derivative (inactive) and phenylglyoxylic acid isolated as its oxime (3.4×10^6 d.p.m./mM.)[10]. The oximino acid was refluxed in water when decarboxylation occurred yielding benzonitrile.[11] The evolved carbon dioxide was collected as barium carbonate (3.5×10^6 d.p.m./mM.). The benzonitrile was hydrolyzed yielding inactive benzoic acid. Benzoic acid obtained by the direct oxidation of the radioactive tropic acid was also completely inactive. This degradation thus established that the tropic acid was labeled solely on its carboxyl group. The relatively high incorporation[12] (0.25%) of tracer into the tropic acid, with specific labeling, favors the hypothesis that the side chain of tropic acid is indeed produced by a novel intramolecular

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[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**, 612 (1960).

[3] E. Leete and M. L. Louden, *Chemistry and Industry*, 1405 (1961).

[4] A. M. Goodeve and E. Ramstad, *Experientia*, **15**, 124 (1961).

[5] Purchased from Nichem Ind., Bethesda, Maryland.

[6] We thank Robert C. McLeester of the Botany Department of the University of Minnesota for the cultivation of the *Datura* plants.

[7] C. L. Comar, "Radioisotopes in Biology and Agriculture," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p. 151.

[8] Radioactivity measurements were carried out in a Nuclear Chicago Model C-115 low background Q gas flow counter. Determinations were carried out on samples of finite thickness, making corrections for efficiency and self absorption.

[9] J. W. Baker and A. Eccles, *J. Chem. Soc.*, 2125 (1927).

[10] This slightly low value may be due to contamination with benzonitrile which is formed in small amount on sublimation of the oxime.[11]

[11] A. Ahmad and I. D. Spenser, *Can. J. Chem.*, **39**, 1340 (1961).

[12] Incorporation is defined as the total amount of radioactivity found in the isolated natural product divided by the total amount of tracer fed to the plant.

rearrangement of the phenylalanine side chain. A close biochemical analogy is the recently discovered methylmalonyl-coenzyme A $\leftrightarrows$ succinyl-coenzyme A isomerization.[13]

A less likely explanation of our results would involve a carboxylation reaction utilizing carbon dioxide produced by decarboxylation of the phenylalanine-1-C^{14}. If this were the case one would expect a much more general labeling of the alkaloids by the radioactive carbon dioxide. This expectation was realized in subsequent tracer experiments. Sodium bicarbonate-C^{14} (24.8 mg., 1.0 mc.) was fed to *Datura* plants as previously described and two weeks later radioactive hyoscyamine (5.5×10^5 d.p.m./mM.) and hyoscine (4.2×10^5 d.p.m./mM.) were isolated, representing a 0.008% incorporation of tracer into the alkaloids. Hydrolysis of the hyoscyamine yielded tropine (2.4×10^5 d.p.m./mM.) and tropic acid (3.1×10^5 d.p.m./mM.). Systematic degradation of the tropic acid as previously described indicated that it was non-specifically labeled, the percentage activity at C_1, C_2, C_3, and on the aromatic carbons being 16, 4, 16, and 65%, respectively.

We could speculate on the mechanism of the rearrangement of the phenylalanine side chain. However, we feel that scientific journals are currently being filled with far too many incontinent biogenetic hypotheses, and we will withhold our ideas until the completion of additional experimental work.

[13] *Cf.* R. Stjernholm and H. G. Wood, *Proc. Natl. Acad. Sci.*, **47**, 303 (1961), and ref. cited therein.

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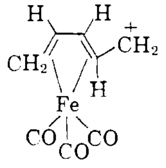
RECEIVED FEBRUARY 15, 1962

PENTADIENYL AND HEXADIENYL CARBONIUM IONS AS LIGANDS IN STABLE COMPLEX CATIONS

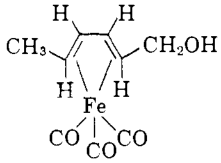
Sir:

Recently several cyclic unsaturated carbonium ions, *e.g.*, the tropylium,[1] cyclopentadienyl,[2] cyclohexadienyl,[3] cycloheptadienyl,[4] and cyclooctatrienyl[5] cations, have been found to bond with certain metal carbonyl groups in the formation of remarkably stable organo-metallic cations. Two major factors concerning the stability of these complex cations appear to be the donor properties of the π electrons and the "back donation" of electrons from the metal atom to the organic ligand through interaction of filled d orbitals of the metal with vacant π molecular orbitals of the carbonium ion ligand. This latter interaction is particularly important for, at the same time, it increases the metal–ligand bonding, decreases the electron density on the metal, and decreases the electrophilicity of the carbonium ion moiety. In each of the cyclic carbonium ions mentioned above, the sp^2 hybridized carbon atoms are fixed in a completely cisoid configuration and each presumably is involved directly in bonding to the metal atom.

It is of interest then to determine whether linear unsaturated carbonium ions can act as ligands in similar complexes; such carbonium ions possess the required vacant, low energy molecular orbitals but, in contrast to the cyclic systems above, in certain *trans* configurations not all of the unsaturated carbon atoms can be simultaneously bonded to the metal. This may be the reason then why we have been unable to prepare the *trans*-pentadienyl-ion tricarbonyl cation (I) by direct hydride abstraction from *trans*-1,3-pentadiene-iron tricarbonyl using triphenylmethyl perchlorate. This reaction proceeds readily for the cyclic diene complexes.[3] Salts of two of the complexed linear carbonium ions have, however, been obtained from the corresponding alcohols. *trans-trans*-2,4-Hexadien-1-ol and $Fe(CO)_5$ reacted to form *trans-trans*-2,4-hexadien-1-ol-iron tricarbonyl (II).[6] (*Anal.* Calcd. for $C_9H_{10}O_4Fe$: C, 45.41; H, 4.23. Found: C, 45.67; H, 4.15.) Treatment of this alcohol with $HClO_4$ in acetic anhydride afforded a yellow crystalline precipitate of hexadienylium-iron tricarbonyl perchlorate in almost quantitative yield. (*Anal.* Calcd. for $C_9H_9O_7ClFe$: C, 33.73; H, 2.83; Cl, 11.07. Found: C, 33.49; H, 2.87; Cl, 10.89.) The structure (III) is assigned to this cation for several reasons. The salt reacted with $NaBH_4$ to produce hexadiene-iron tricarbonyl. Reaction of (III) with water gave a complex alcohol (IV), isomeric with (II). (*Anal.* Calcd. for $C_9H_{10}O_4Fe$: C, 45.41; H, 4.23. Found: C, 45.40; H, 4.57.) This new alcohol also generated the perchlorate of salt III when liberated with $HClO_4$. Decomposition of (IV) with $FeCl_3$ in alcoholic sodium acetate solution liberated a hexadienol which, on catalytic hydrogenation, absorbed 1.9 mole of hydrogen to give 2-hexanol. Compound (IV) must therefore be 1,3-hexadien-5-ol-iron tricarbonyl. Now since only dienes in the cisoid configuration produce stable diene–iron tricarbonyl complexes, carbon atoms 1 and 4 must now be *cis* with respect to the C_2–C_3 bond in (IV). Although it has not yet been definitely proven it would seem most likely that the geometrical inversion has taken place during



I



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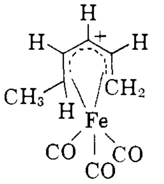
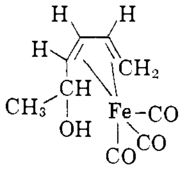


III



IV

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[1] H. J. Dauben and L. R. Honnen, *J. Am. Chem. Soc.*, **80**, 5570 (1958).

[2] A. Davison, M. L. H. Green and G. Wilkinson, *J. Chem. Soc.*, 3172 (1961).

[3] E. O. Fischer and R. D. Fischer, *Angew. Chem.*, **72**, 919 (1960).

[4] H. J. Dauben and D. J. Bertelli, *J. Am. Chem. Soc.*, **83**, 497 (1961).

[5] G. W. Schrauzer, *J. Am. Chem. Soc.*, **83**, 2966 (1961).

[6] Decomposition of this complex by treatment with $FeCl_3$ in alcoholic sodium acetate regenerated the starting alcohol.