phenyl radicals generated in this manner attack the neutral ferrocene molecule (eq. 3) seems improbable on energetic grounds,[7] and Little and Clark[2] accordingly formulated the phenylation reaction as proceeding by radical substitution of the ferricenium ion (eq. 4).

$$FcH + Ph\cdot \longrightarrow FcPh + H\cdot \quad (3)$$

$$FcH^+ + Ph\cdot \longrightarrow FcPh + H^+ \quad (4)$$

Recently, these suggestions have been discounted by Rosenblum and his co-workers,[4] who claim that neither ferrocene nor the ferricenium ion reacts with free phenyl radicals derived from phenylazotriphenylmethane, and who suggest that the mechanism of the phenylation reaction involves intermediate formation and intramolecular rearrangement of a ferrocene–diazonium salt charge-transfer complex. Nevertheless, the most recent work has demonstrated the high reactivity of ferricenium ion toward attack by free alkyl radicals[6] and has verified the production of free aryl radicals during the arylation reaction,[5,6] both of which observations provide indirect evidence for the mechanism suggested by Little and Clark.[2] In support of this mechanism we now describe the first unequivocal example of free-radical phenylation of ferricenium ion.

When ferricenium borofluoride (0.011 mole) and phenylazotriphenylmethane (0.011 mole) in acetic acid were maintained at 75° for 1.5 hr. nitrogen was evolved and the characteristic color of the ferricenium ion faded. The products isolated were phenylferrocene (0.002 mole) and triphenylcarbinol (0.006 mole) together with small amounts of tritylferrocene,[8] triphenylmethane, and tetraphenylmethane. Some ferrocene (0.004 mole) was recovered. Since it has been demonstrated previously that phenylazotriphenylmethane is without effect on neutral ferrocene,[4,6,9] there can be little doubt that the formation of phenylferrocene in the present instance represents an authentic example of free-radical phenylation of ferricenium ion.

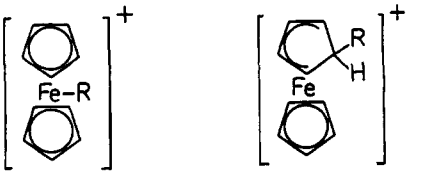
The mode of formation of tritylferrocene is less obvious. The production of triphenylcarbinol suggests that ferricenium ion and triphenylmethyl radical participate in the following oxidation–reduction equilibrium (eq. 5), the occurrence of which in the reverse direction has been observed earlier by Hawthorne.[10]

$$FcH^+ + Ph_3C\cdot \rightleftharpoons [FcHCPh_3]^+ \rightleftharpoons FcH + Ph_3C^+ \quad (5)$$

If, as seems possible, formation of tritylferrocene represents an alternative and irreversible mode of decomposition of the intermediate complex in the above equilibrium, it is no longer meaningful to distinguish between free-radical and electrophilic substitution in this system.

It may be significant that our experiment when carried out for 24 hr. afforded 1,1′-ditritylferrocene[8] but no triphenylcarbinol. Other products were unchanged.

Little[5] has suggested that either of the structures (I or II) may represent the intermediate complex in free-radical substitution of ferricenium ion. Both are of special interest in that, as drawn, they are identical with hypothetical intermediates in electrophilic substitution of the neutral ferrocene molecule.[11] Whether, in fact, free-radical and electrophilic substitution of ferricenium ion and ferrocene, respectively, proceed through the same intermediate, and whether this intermediate plays a part in oxidation–reduction equilibrium reactions (*e.g.*, eq. 5), are problems currently undergoing investigation in these laboratories.



I II

Ferricenium ion also undergoes substitution by free phenyl radicals generated oxidatively from phenylhydrazine.[12] When the latter (0.023 mole) was slowly added with stirring to the blue solution obtained by mixing ferrocene (0.007 mole) and silver oxide (0.022 mole) in acetic acid, phenylferrocene and 1,1′ diphenylferrocene were obtained in yields of 37% and 2% (based on unrecovered ferrocene), respectively. The yield of disubstituted product was increased to 9% when a large excess of phenylhydrazine and silver oxide was employed. In benzene the reaction proceeded less efficiently but the concomitant formation of biphenyl and terphenyl verified the presence of free phenyl radicals in the reaction mixture. Other oxidizing agents, *e.g.*, mercuric oxide, benzoquinone, also afforded phenylferrocene in small yield.

In view of the recent report[13] that oxidation of ferrocene with phenylmercuric acetate in the presence of perchloric acid affords phenyl radicals and ferricenium ion, we repeated this reaction in expectation of obtaining phenylferrocene. However, when the reactants were mixed in acetic acid–toluene, the only products were benzene and ferricenium ion and no phenylferrocene was formed. We were unable to detect bibenzyl and other compounds characteristically formed by attack of phenyl radicals on toluene.[14] Also, the reported formation of benzene *in quantitative yield* in this reaction is inconsistent with a free-radical mechanism. It thus appears that reduction of phenylmercuric acetate with ferrocene does not involve generation of free phenyl radicals.

(7) *Cf.* C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 482.
(8) E. W. Neuse and D. S. Trifan, *J. Am. Chem. Soc.*, **84**, 1850 (1962).
(9) C. D. Broadhead and P. L. Pauson, *J. Chem. Soc.*, 367 (1955).
(10) M. F. Hawthorne, *J. Org. Chem.*, **21**, 363 (1956).
(11) M. Rosenblum, J. O. Santer, and W. G. Howells, *J. Am. Chem. Soc.*, **85**, 1450 (1963).
(12) R. L. Hardie and R. H. Thomson, *J. Chem. Soc.*, 2512 (1957).
(13) C. H. Wang, *J. Am. Chem. Soc.*, **85**, 2339 (1963).
(14) D. H. Hey, B. W. Pengilly, and G. H. Williams, *J. Chem. Soc.*, 6 (1955), 1463 (1956); C. S. Rondestvedt and H. S. Blanchard, *J. Am. Chem. Soc.*, **77**, 1769 (1955).

DEPARTMENT OF ORGANIC CHEMISTRY
UNIVERSITY OF ADELAIDE
ADELAIDE, SOUTH AUSTRALIA
A. L. J. BECKWITH
R. J. LEYDON

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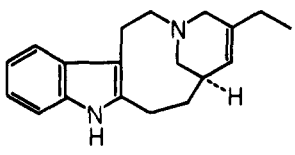
The Chemistry of Cleavamine: A Novel Transannular Cyclization Relating to Biosynthesis of Aspidosperma Alkaloids

Sir:

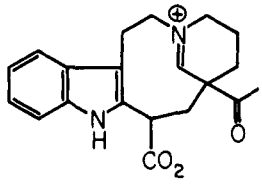
Recently, in connection with our interests in alkaloids from *Vinca rosea* Linn, we established the structure of cleavamine (I)[1] as one of the acid rearrangement products of catharanthine.[2] The close structural relationship of cleavamine to the known alkaloid quebrachamine[3] suggested its use as an excellent model for evaluating some of the reactions proposed in the biosynthesis of Aspidosperma alkaloids.

(1) J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind.* (London), 648 (1963).
(2) N. Neuss and M. Gorman, *Tetrahedron Letters*, 206 (1961).
(3) K. Biemann and G. Spiteller, *J. Am. Chem. Soc.*, **84**, 4578 (1962), and references cited therein.

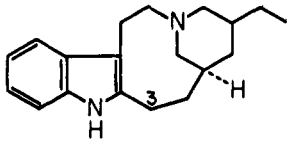
Wenkert[4] proposed an elegant scheme for this class of alkaloids and his postulate involved the transannular cyclization of an ionic intermediate such as II. This attractive proposal is of considerable interest but up to this time it has received no experimental verification.[5] We wish now to report the first laboratory realization of such a cyclization to provide the Aspidosperma skeleton in very reasonable yield.



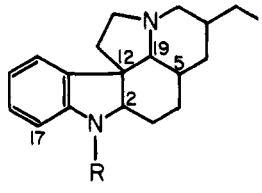
I



II



III



IV, R=H

V, R=Ac

Dihydrocleavamine (III)[1] on reaction with mercuric acetate in acetic acid at room temperature (81% recovery of mercurous acetate by weight) followed by reflux provided a crude mixture (λ_{max}^{MeOH} 222, 278 (very broad), and shoulder at 288 mμ), which was not purified further but immediately subjected to reduction with lithium aluminum hydride. The latter mixture by chromatography on alumina afforded a crystalline material as the major product (30% yield), m.p. 128–129° (from acetone), $[\alpha]^{23}D$ −105° ($CHCl_3$). The cyclic structure IV was established for this substance on the basis of the following evidence: $C_{19}H_{26}N_2$, mol. wt. 282 by mass spectrometry[6]; λ_{max}^{MeOH} 242 mμ (log ε 3.78) and 294 (3.42), λ_{min}^{MeOH} 223 mμ (log ε 3.52) and 269 (2.99, unsubstituted dihydroindole); n.m.r. spectrum[7] showed a complex pattern of lines between 6.4 and 7.3 p.p.m., area = 4H (aromatic protons, in excellent agreement with known systems),[8] 0.9 p.p.m. (triplet, area = 3H); mass spectrum showed significant peaks at *m/e* 282 (M^+), 281 (M − 1), 254 (M − 28), 152, 144, 138, 130, and a very strong peak at *m/e* 124. The mass spectrum, with the exception of the intensity of the M − 1 peak (discussed later), was virtually identical with that of aspidospermidine (alkaloid 282A).[9] Further evidence for the Aspidosperma skeleton (IV) was obtained from the N-acetyl derivative V, $C_{21}H_{28}N_2O$, m.p. 99–100° (petroleum ether, b.p. 60–80°). The expected alteration in the ultraviolet spectrum was indeed observed [λ_{max}^{MeOH} 253 mμ (log ε 4.15), 280 (3.61), and 289 (3.53); λ_{min}^{MeOH} 226 mμ (log ε 3.52), 276 (3.59), and 287 (3.47)] so that the spectrum was now in excellent agreement with that of demethoxypalosine.[10] The n.m.r. spectrum of the acetylated product indicated the expected change in the aromatic region. The complex pattern originally observed in the spectrum of IV had collapsed to form a broad unresolved peak (area corresponding to three protons) centered at 7.15 p.p.m., while a single proton signal (C-17 hydrogen) was evident downfield at 8.15 p.p.m. (poorly resolved multiplet). These data are again in excellent agreement with those of vindolinine[8] and demethoxypalosine.[10] Most important, the typical quartet (centered at 4.02 p.p.m.) associated with the C-2 hydrogen atom and the "aspidospermine fingerprint" (2.9–3.3 p.p.m.) shown to be characteristic of the Aspidosperma skeleton by Djerassi and co-workers[11] was also evident.

Any definite conclusions regarding the stereochemistry in IV must await an X-ray analysis which we hope to initiate in the near future, but some tentative proposals may be made from the above evidence. One significant feature evident in the mass spectrum of IV is the relative intensity of the M − 1 peak, which is considerably stronger than observed in the spectra of most Aspidosperma alkaloids.[9] It is interesting that very recently Djerassi[12] has observed a strong M − 1 peak in an isomeric deacylcylindrocarpine derivative and suggests the loss of the C-19 hydrogen atom assisted by a *trans* electron pair on N_b. Also, in the n.m.r. spectrum of V, the quartet for the C-2 hydrogen atom occurs at higher field than normally observed.[11] This suggests *either* a different stereochemistry at this position or at other asymmetric centers so that the over-all conformation of V provides for increased shielding of the C-2 proton as compared with that of the aspidospermine or the antipodal pyrifolidine series.[13,14] Finally if one *assumes* that the stereochemistry previously established for cleavamine[1] remains unaltered during the cyclization, then the stereochemical center denoted by C-5 is already defined.

We feel that the laboratory demonstration of this transannular cyclization has numerous interesting facets both from a biogenetic and a synthetic standpoint. It certainly provides strong support for Wenkert's biogenetic proposals for the Aspidosperma alkaloids.[4] The obvious extension of this reaction to the quebrachamine series is anticipated when we obtain sufficient quantities of this alkaloid.

Finally, it is apparent from the nature of the above cyclization that a carbomethoxydihydrocleavamine derivative possessing a carbomethoxy group at C-3 (see III) could lead *directly* (*i.e.*, prior to reduction with lithium aluminum hydride) to the unsaturated ester system present in such alkaloids as vincadifformine[15] and the related Akuamma alkaloids. We hope to present some evidence in this direction in the near future.

Acknowledgment.—We are greatly indebted to Professor Carl Djerassi, Stanford University, for the mass spectrometric measurements. Financial aid from the National Cancer Institute of Canada and the Na-

(4) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).

(5) Biemann and Spiteller[9] provide mass spectrometric evidence for a cyclization of quebrachamine during a high temperature zinc dust distillation. They visualize a participation of a free-radical process.

(6) Satisfactory elemental analyses were obtained for all substances reported

(7) All n.m.r. spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard using a Varian A60 spectrometer. All signals are reported as δ-units (c.p.s./60) in p.p.m.

(8) See, for example, C. Djerassi, S. E. Flores, H. Budzikiewicz, J. M. Wilson, L. J Durham, J. Le Men, M. M. Janot, M. Plat, M. Gorman, and N. Neuss, *Proc. Natl. Acad. Sci. U. S.*, **48**, 113 (1962).

(9) K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *J. Am. Chem Soc.*, **85**, 631 (1963).

(10) B. Gilbert, J. A. Brissolese, J. M. Wilson, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Chem. Ind.* (London), 1949 (1962).

(11) C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, *Experientia*, **16**, 532 (1960).

(12) K. S. Brown, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters*, 1731 (1963).

(13) C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson, and K. Biemann, *Experientia*, **17**, 162 (1961).

(14) M. Plat, J. Le Men, M. M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakegawa, and C. Djerassi, *Tetrahedron Letters*, 271 (1962).

(15) C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men, and M. M. Janot, *ibid.*, 235 (1962).

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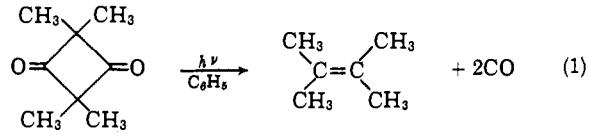
CHEMISTRY DEPARTMENT
UNIVERSITY OF BRITISH COLUMBIA
VANCOUVER 8, CANADA
JAMES P. KUTNEY
EDWARD PIERS

RECEIVED DECEMBER 27, 1963

Photolysis of Tetramethyl-1,3-cyclobutanedione

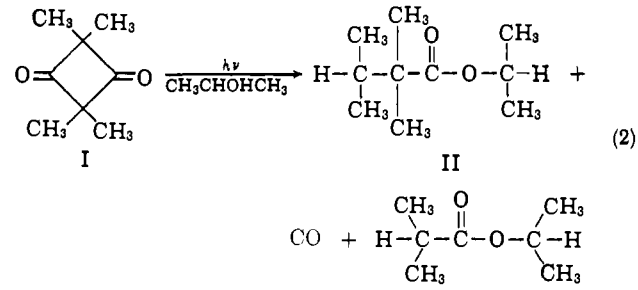
Sir:

Potentially, the photolytic decarbonylation of tetrasubstituted 1,3-cyclobutanediones in solution or in the gas phase is an attractive and simple route to substituted cyclopropanones, either as stable species or as intermediates. Photodecarbonylation reactions are well known in the gas phase,[1] but they usually occur with very low efficiencies in solution.[2] However, irradiation of a benzene solution of tetramethyl-1,3-cyclobutanedione (I) through Pyrex leads to the rapid evolution of carbon monoxide and the formation of tetramethylethylene in 80% net yield. The quantum yield for disappearance of I under these conditions is 0.4 at 3660 Å. Apparently, a small amount of dimethyl ketene is also produced since the photolyzed solution quickly develops a yellow color and a strong band in the infrared[3] at 4.7 μ. Addition of a few drops of isopropyl alcohol to the irradiated solution results in disappearance of both the yellow color and the 4.7 μ band.



I (1)

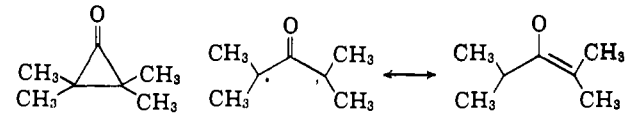
Irradiation of I in isopropyl alcohol leads to rather different results, as no tetramethylethylene is produced (although carbon monoxide is still formed), and several products appear in the vapor chromatogram of the irradiated solution. The quantum yield for the disappearance of I in this case is 0.5. The two major products of the photolysis, both formed in about 30% net yield, are isopropyl isobutyrate (presumably formed by addition of isopropyl alcohol to dimethyl ketene) and compound II. The latter was obtained pure by preparative v.p.c. and possesses an n.m.r. spectrum[4] consisting of two septets centered at 4.8 (one proton) and 1.65 p.p.m. (one proton), two doublets centered at 1.10 (six protons) and 0.70 p.p.m. (six protons), and a singlet at 0.90 p.p.m. (six protons). This spectrum, as well as the infrared spectrum of the compound, is completely consistent with II being the ester isopropyl 2,2,3-trimethylbutyrate. *Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.6; H, 11.7. Found: C, 69.2; H, 11.8. In methanol, competing reactions similar to both eq. 1 and 2 take place, with formation of both tetramethylethylene in about 5% net yield and, as the major



I II (2)

product, the methyl ester III (methyl 2,2,3-trimethylbutyrate), the quantum yield for disappearance of I being 0.5. III possesses an n.m.r. spectrum consisting of a sharp singlet at 3.40 p.p.m. (3 protons), a septet centered at 1.6 p.p.m. (one proton), a sharp singlet at 0.82 p.p.m. (6 protons), and a doublet centered at 0.60 p.p.m. (6 protons). *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.2. Found: C, 66.7; H, 11.2. Methyl isobutyrate is also formed as a major product upon irradiation of I in methanol.

These results show that at least two paths for reaction are possible during the photolysis of I: (a) a bis-fragmentation without decarbonylation to yield dimethyl ketene[5]; and, more importantly (b) decarbonylation to yield products which are consistent with the intermediacy of either tetramethylcyclopropanone (IV), or the diradical resonance hybrid (V), or a combination of both. The intermediate decarbonylates in



IV V

inert solvents[6] to give good yields of tetramethylethylene, while in nucleophilic solvents, such as alcohols, addition to form the respective 2,2,3-trimethylbutyrate esters competes with decarbonylation. It is not clear at this time why isopropyl alcohol should be more efficient in this capacity than methanol.

Piperylene (0.3 *M*), a quencher of triplet states of energy greater than 55 kcal.,[7] has virtually no effect on the photolysis of the diketone in both benzene and alcohol solvents, and benzophenone was ineffective at sensitizing the photoreaction. Although we have not yet obtained a low temperature emission spectrum of the compound, these results (while not rigorously excluding the triplet) are consistent with the assumption that the above reactions occur only from the singlet state.

Preliminary experiments on the photolysis of I in the vapor phase reveal that tetramethylethylene, a lower boiling material, and carbon monoxide are the only isolable products. Further investigation of this and related systems as well as complete characterization of all products in the various solvents is in progress.

(1) W. A. Noyes, Jr., G. Porter, and E. J. Jolley, *Chem. Rev.*, **56**, 49 (1956); J. N. Pitts, *J. Chem. Educ.*, **34**, 112 (1957).

(2) Numerous reports concerning photodecarbonylations in solution have appeared recently: R. H. Eastman, J. E. Starr, R. St. Martin, and M. K. Sakata, *J. Org. Chem.*, **28**, 2162 (1963); O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962); D. C. England, *ibid.*, **84**, 2205 (1962); G. Quinkert, K. Opitz, and J. Weinlich, *Angew. Chem.*, **74**, 507 (1962); C. D. Gutsche and C. W. Armbruster, *Tetrahedron Letters*, **No. 26**, 1297 (1962); K. Mislow and A. J. Gordon, *J. Am. Chem. Soc.*, **85**, 3521 (1963); G. Quinkert, K. Opitz, and V. Weinlich, *Tetrahedron Letters*, 1863 (1963); P. A. Leermakers, P. C. Warren, and G. F. Vesley, *J. Am. Chem. Soc.*, in press.

(3) Dimethyl ketene possesses a strong infrared absorption at 4.7 μ. [R. A. Holroyd and F. E. Blacet, *ibid.*, **79**, 4830 (1957)].

(4) N.m.r. spectra were taken at 60 Mc. in carbon tetrachloride, employing tetramethylsilane as an external standard.

(5) It must be pointed out that while the yields of ketene adducts in alcohol solvents (the isobutyrate esters) account for 30–40% of the products, only 15–20% of the reaction proceeds by this path since *two* molecules of dimethyl ketene will be formed from one molecule of I. Several reports concerning photochemical elimination of ketene have appeared recently: J. C. Anderson and C. B. Reese, *Tetrahedron Letters*, 1 (1962); W. H. Urry, D. J. Trecker, and D. A. Winey, *ibid.*, 609 (1962); D. I. Schuster, M. Axelrod, and J. Auerbach, *ibid.*, 1911 (1963); G. O. Schenck and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963).

(6) The mechanism of the second decarbonylation is not known, but may be either a thermal reaction or secondary photolysis. Cyclopropanone itself appears to be stable in solution [A. Kende, Ph.D. Thesis, Harvard University, 1956], but a possible example of spontaneous decarbonylation has been reported [A. Kende, *Chem. Ind.* (London), 1053 (1956)]. We wish to thank a referee for pointing out the latter reference to us.

(7) G. S. Hammond, N. J. Turro, and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962).