Photochemical Synthesis of Isoquinoline Alkaloids

TETSUJI KAMETANI* AND KEIICHIRO FUKUMOTO

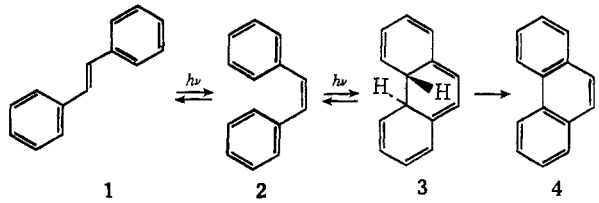
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Received July 26, 1971

The photochemical reactions of organic compounds started to be investigated in the early years of this century,[1] but only in the last decade has photochemistry become a sophisticated field.[2,3] The improved methods for the isolation of products and for the determination of structure which have been developed since World War II have overcome the former reluctance of organic chemists to utilize photochemical methods of synthesis. Photochemical syntheses of strained or complicated molecules are widely employed. In particular, a number of alkaloids have been synthesized by photochemical reactions, often from starting materials of rather simple structure. Such syntheses are the subject of this Account.

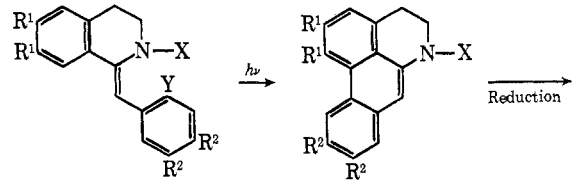
Photolytic Electrocyclic Reaction[2]

Conjugated polyene systems often undergo photolytic electrocyclization. Thus, *trans*-stilbene (**1**) undergoes a rapid cis–trans isomerization under the influence of ultraviolet light, and *cis*-stilbene (**2**) then cyclizes to the *trans*-dihydrophenanthrene (**3**) upon further irradiation. Mild oxidation of the latter with air or iodine produces phenanthrene (**4**).[4,5] This type of hexatriene–cyclohexadiene isomerization has been widely applied to the synthesis of several types of isoquinoline alkaloids.

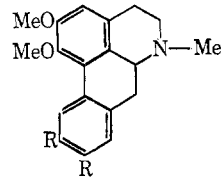


1 **2** **3** **4**

Aporphine Alkaloids. 1-Benzylidene-1,2,3,4-tetrahydroisoquinoline is a substituted stilbene, and may undergo photolytic electrocyclization to give a dehydroaporphine system which is easily converted into the aporphine. Thus, ultraviolet irradiation of 1-benzylidene-2-ethoxycarbonylisoquinoline (**5**) in the presence of iodine gave in 35% yield the dehydronuciferine analog (**6**)[6,7] which was converted into nuciferine (**7**) by a standard method.



5, R^1 = OMe; R^2 = H; X = CO_2Et; Y = H
6, R^1 = OMe; R^2 = H; X = CO_2Et
8, R^1 = R^2 = H; X = Me; Y = H
9, R^1 = R^2 = H; X = Me
10, R^1 = R^2 = H; X = CO_2Et; Y = H
11, R^1 = R^2 = H; X = CO_2Et
12, R^1 = R^2 = OMe; X = CO_2Et; Y = H
13, R^1 = R^2 = OMe; X = CO_2Et
15, R^1 = OMe; R^2 = H; X = CO_2Et; Y = Cl
16, R^1 = R^2 = OMe; X = CO_2Et; Y = Br



7, R = H
14, R = OMe

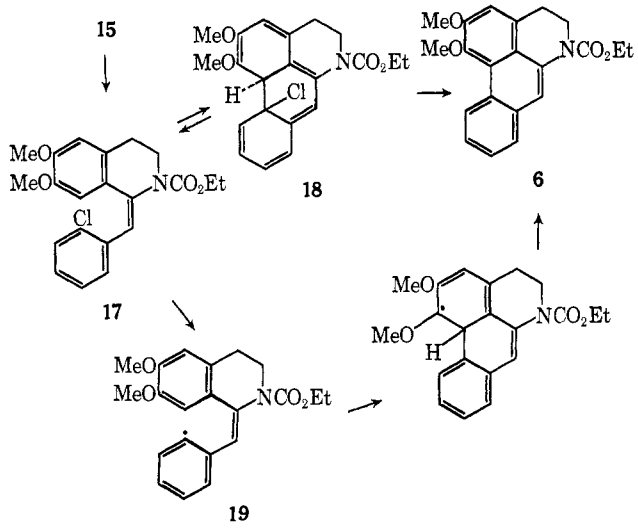
On the other hand, photolysis of 1-benzylidene-2-methylisoquinoline (**8**), either in the presence or in the absence of oxidizing agents, afforded no cyclized product (**9**). The same reaction on its *N*-ethoxycarbonyl analog (**10**) gave the expected aporphine (**11**).[8] This fact is interpreted as follows: the absorption spectrum of **8** revealed only a transition assigned to the styrylamine system which was absent in the stilbene chromophore. Therefore, the energy absorbed by the compound causes **8** to undergo rapid internal conversion to the low-lying excited state of the styrylamine system which is then deactivated to the ground state, leaving the stilbene system unreacted. On the other hand, an interception of the conjugation between the nonbonding π electron on the nitrogen and the styrene system by N-acylation reveals the stilbene chromophore in its untraviolet spectrum, and leads to the aporphine system.[8] Moreover, the *N*-ethoxycarbonylstilbene derivative (**12**) gave the dehydroaporphine **13**[7,8] which was converted to glaucine (**14**).[7]

T. Kametani was born in Tokyo in 1917 and was graduated from the Pharmaceutical Institute, Tokyo Imperial University, in 1943. He obtained his Ph.D. from Tokyo University in 1951. He has been Professor of Organic Chemistry at the Pharmaceutical Institute, Tohoku University, since 1959. He is working on the synthesis of heterocyclics, especially the total synthesis of isoquinoline alkaloids. In 1956–1957, he worked at the Israel Institute of Technology in Haifa. He has lectured at universities in Europe and in the United States. In 1969, he received the Academic Prize of the Pharmaceutical Society of Japan.

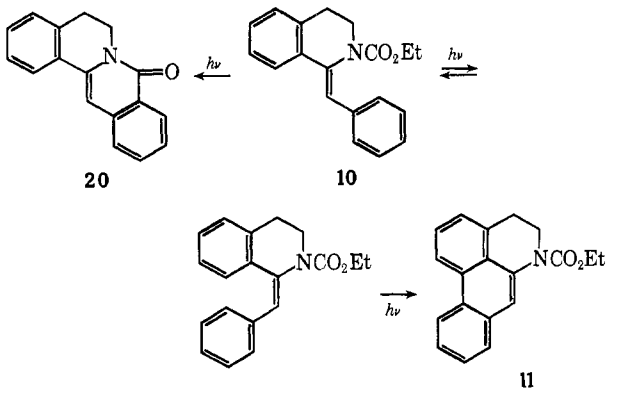
K. Fukumoto is an Assistant Professor at the Pharmaceutical Institute, Tohoku University. He received his Ph.D. from Osaka University in 1964.

(1) P. de Mayo, *Advan. Org. Chem.*, 1, 357 (1960).
(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(3) P. G. Sammes, *Quart. Rev., Chem. Soc.*, 24, 37 (1970).
(4) G. B. Gill, *ibid.*, 22, 338 (1968).
(5) R. F. Stermitz, "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, 1967, p 247.
(6) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).
(7) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 35, 175 (1970).
(8) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).

Although the above cyclizations were carried out in the presence of an oxidizing agent, Cava recently reported the nonoxidative photocyclization of halogenated stilbenes to the dehydroaporphine ring system.[7] Halogenated stilbene derivatives **15** and **16** were photolyzed in the presence of calcium carbonate as an acid scavenger, but in the absence of any added oxidant, to give dehydroaporphines **6** and **13**. The mechanism of this cyclization was suggested to be as follows: the primary photochemical conversion of the *trans*-stilbene **15** to its cis isomer **17** was followed by reversible isomerization of the latter to the dihydrophenanthrene intermediate **18**, and the irreversible loss of hydrogen halide from **18** yielded the dehydroaporphine **16**. However, the initial formation of the cis radical **19** from the *cis*-stilbene **17** by photochemical homolysis of the carbon–halogen bond, followed by ring closure and loss of a hydrogen atom to the aporphine ring, was also at least partially operative in this reaction.

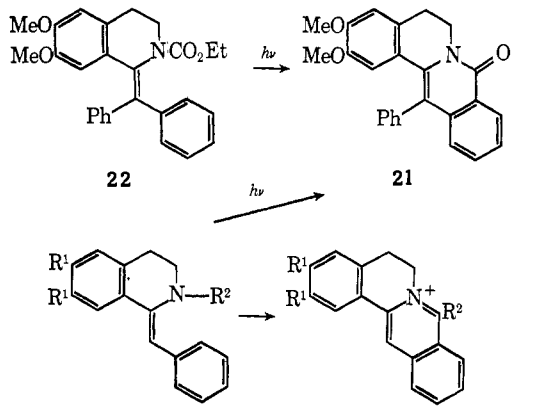


Protoberberine Alkaloids. Molecular orbital calculations on 1-benzylidene-2-ethoxycarbonylisoquinoline call for localization of electron density at the ortho position of stilbene in the excited state. The aromatic system is thus activated in the excited state, and intramolecular acylation occurs. In fact, the irradiation of *cis*-benzylidene-2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**10**) gave the dehydroprotoberberine **20**



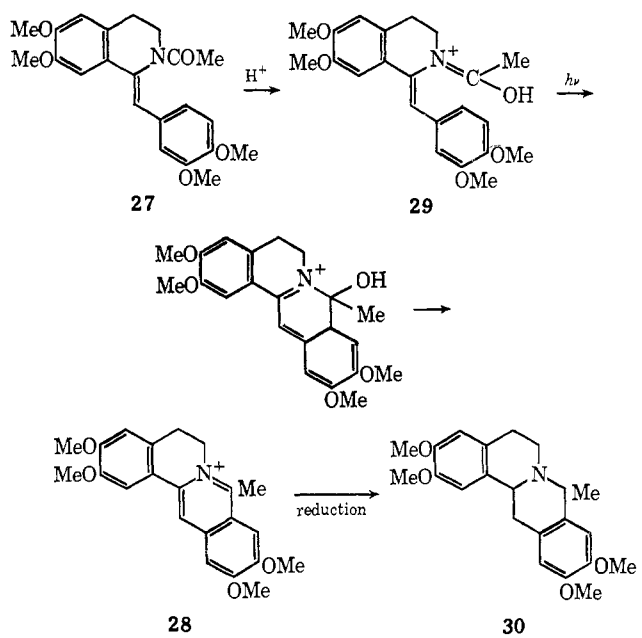
in 10–21% yield in addition to the dehydroaporphine **11**.[9]

A similar compound (**21**) was obtained in 50% yield by photoacylation of **22** with irradiation in the presence of iodine and cupric acetate. Interestingly, 2-benzoyl-1-benzylideneisoquinoline (**23**) also afforded **21**, but not the 8-phenyl analog **24**.[10] On the other



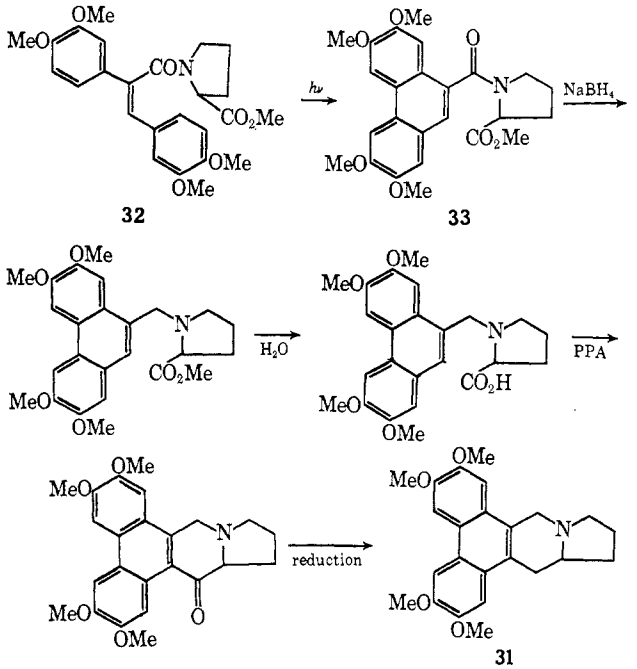
23, R^1 = OMe; R^2 = COPh **24**, R^1 = OMe; R^2 = Ph
25, R^1 = H; R^2 = COMe **26**, R^1 = H; R^2 = Me

hand, 2-acetyl-1-benzylideneisoquinoline (**25**) could be cyclized to **26** by irradiation in the presence of iodine.[11] This reaction was extended to a tetramethoxy derivative (**27**), which was irradiated in the presence of iodine and hydriodic acid to give dehydro-β-coralydine (**28**) in 75% yield. Presumably the acid protonated the amide group to give the immonium alcohol **29**, which increased the carbon to nitrogen double bond character, so that it reacted as a hexatriene system. Reduction of **28** with sodium borohydride afforded the protoberberine alkaloid, β-coralydine (**30**).[11]

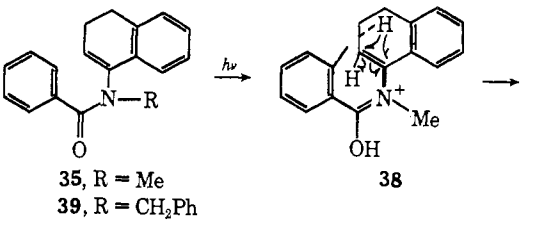


(9) N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, **88**, 5369 (1966).
(10) M. P. Cava and S. C. Havlicek, *Tetrahedron Lett.*, 2625 (1967).
(11) G. R. Lenz and N. C. Yang, *Chem. Commun.*, 1136 (1967).

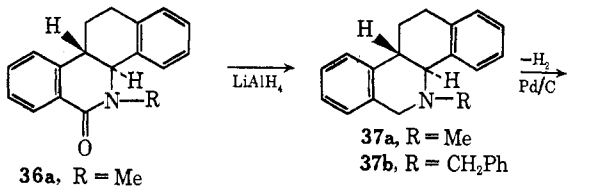
Tylophorine. The total synthesis of tylophorine (**31**) by photocyclization of a stilbene derivative to a phenanthrene has been reported. Irradiation of 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)cinnamide (**32**) in the presence of iodine gave a phenanthrene derivative (**33**), which was converted into tylophorine (**31**) by usual methods.[12]



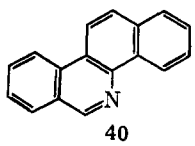
32 **33** **31**



35, R = Me
39, R = CH_2Ph **38**



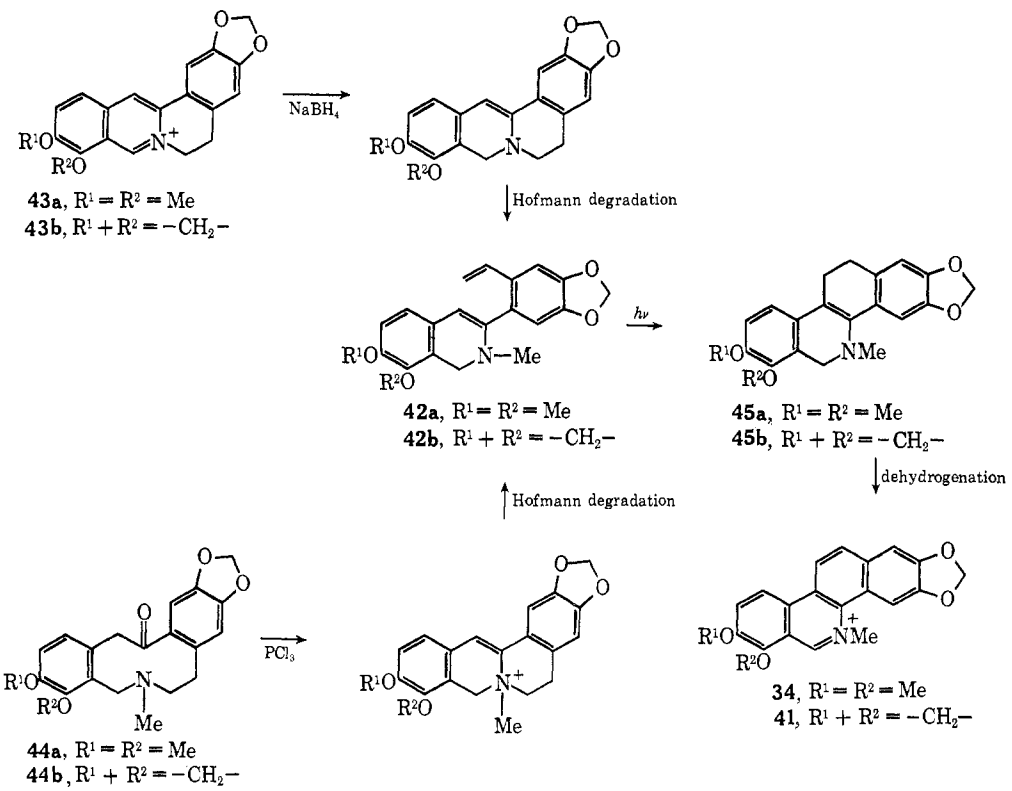
36a, R = Me
36b, R = CH_2Ph **37a**, R = Me
37b, R = CH_2Ph



40

a hexatriene system. A methanolic solution of α-tetralone *N*-benzoylmethylenamine (**35**) was irradiated to give, in 55% yield, the *trans*-benzophenanthridone **36a**, which was reduced to benzophenanthridine (**37a**). This stereoselective photocyclization to the trans-fused ring system could be considered to proceed through an intermediate (**38**).[13] The analogous transformation of **39** to **40** was also carried out, *via* **37b**.

Moreover, Onda synthesized chelerythrine (**34**) and sanguinarine (**41**) by a photolytic electrocyclic reac-



43a, $R^1 = R^2 = Me$
43b, $R^1 + R^2 = -CH_2-$

42a, $R^1 = R^2 = Me$
42b, $R^1 + R^2 = -CH_2-$

45a, $R^1 = R^2 = Me$
45b, $R^1 + R^2 = -CH_2-$

44a, $R^1 = R^2 = Me$
44b, $R^1 + R^2 = -CH_2-$

34, $R^1 = R^2 = Me$
41, $R^1 + R^2 = -CH_2-$

Benzophenanthridine Alkaloids. Benzophenanthridine, a basic skeleton of alkaloids such as chelerythrine (**34**), has been synthesized by photocyclization of the *N*-benzoyl enamine of a cyclic ketone which reacts as tion from the methine bases (**42**) derived from the protoberberine (**43**) and protopine alkaloids (**44**).[14] Ir-

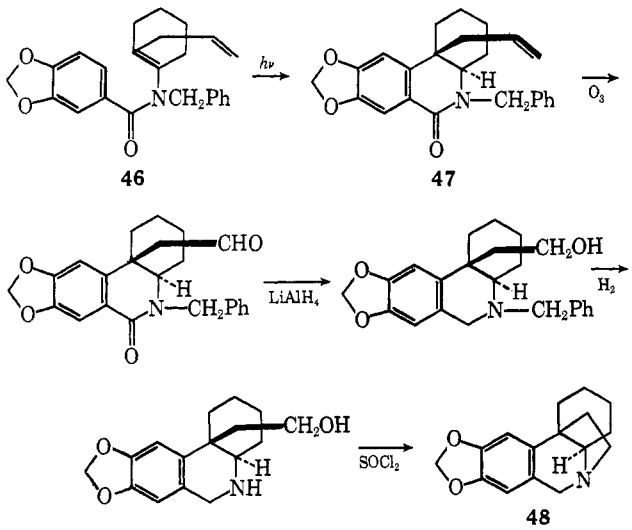
(12) R. B. Herbert and C. J. Moody, *Chem. Commun.*, 121 (1970).

(13) I. Ninomiya, T. Naito, and T. Mori, *Tetrahedron Lett.*, 3643 (1969).

(14) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.*, **17**, 404 (1969); **19**, 31 (1971).

radiation of **42a** and **42b** gave the cyclized products **45a** and **45b**, respectively, which were converted into chelerythrine (**34**) and sanguinarine (**41**).

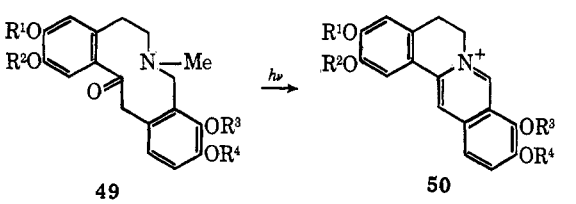
Crinan Ring System. The basic ring system of crinine, which is representative of the widely occurring *Amaryllidaceae* alkaloids, has been synthesized through stereoselective photocyclization. In this reaction, *N*-acyl enamine **46** was irradiated to afford, in 5% yield, the cyclized product **47**, having a trans ring junction, which was transformed to crinan (**48**) by familiar methods.[15]



46 47 48

Photochemical Transannular Reaction

The conversion of the protopine alkaloids into the berberine alkaloids has been accomplished by the photochemical transannular reaction of a carbonyl with a tertiary amine function in a ten-membered ring. Irradiation of cryptopine (**49a**) in 95% ethanol afforded epiberberine (**50a**) in moderate yield. The same reaction with protopine (**49b**) and α-allocryptopine (**49c**) gave coptisine (**50b**) and berberine (**50c**), respectively.[16]



49 50

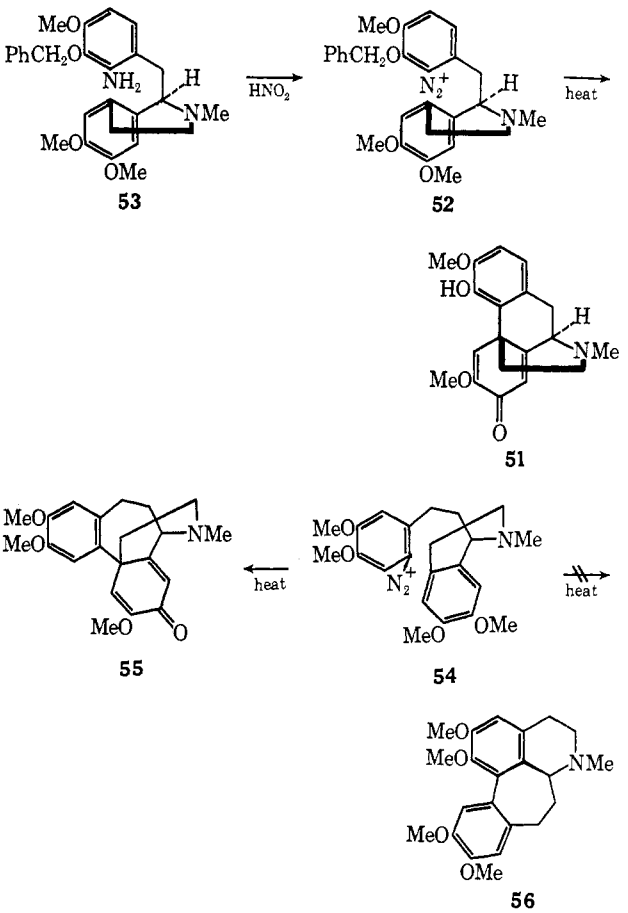
a, $R^1 = R^2 = Me$; $R^3 + R^4 = -CH_2-$
b, $R^1 = R^2 = -CH_2-$; $R^3 + R^4 = -CH_2-$
c, $R^1 + R^2 = -CH_2-$; $R^3 = R^4 = Me$

Interestingly, the use of chloroform in place of ethanol as the irradiation solvent gave the same products, but more rapidly and in higher yield. This could be due to the operation of a different mechanism in the halogenated solvent, which is known to be a good radical source under conditions of ultraviolet irradiation.[16]

(15) I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Commun.*, 1669 (1970).
(16) X. A. Dominguez, J. G. Delgado, W. P. Reeves, and P. D. Gardner, *Tetrahedron Lett.*, 2493 (1967).

Photo-Pschorr Reaction

Since its discovery in 1896 the Pschorr reaction[17] has been widely applied to the synthesis of aporphine-type compounds. Recently, we[18] extended this reaction to a general synthesis of the morphinandienone-type alkaloids, such as salutaridine (**51**), by thermal decomposition of the diazonium salt **52** from 1-(2-aminobenzyl)isoquinoline (**53**).[19] The same reaction of the diazotized phenethylisoquinoline (**54**) gave the homomorphinandienone **55**, but not the homoaporphine **56**.[20,21]

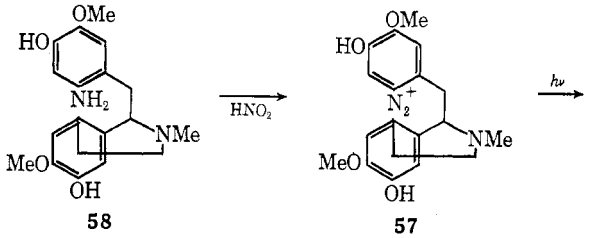


53 52 51 55 54 56

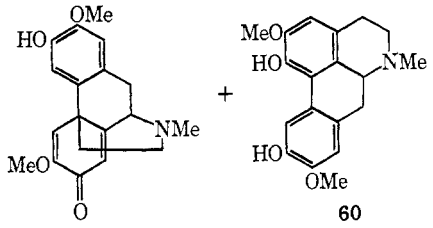
If this type of reaction proceeded through a radical intermediate formed by homolysis of the carbon–nitrogen bond, photolysis of the diazonium salt would be a more efficient way of effecting a homolysis. On the basis of the above assumption, five types of alkaloids were synthesized, as now discussed.

Benzylisoquinoline Series. Irradiation of the diazonium salt **57**, prepared from 6′-aminoorientaline (**58**) by diazotization, gave flavinantine (**59**) and bracteoline (**60**).[22] The same reaction with the diazotized iso-

(17) D. F. DeTar, *Org. React.*, **9**, 409 (1957).
(18) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1398 (1968); *J. Chem. Soc. C*, 520 (1969).
(19) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *ibid.*, 2030 (1969).
(20) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1001 (1968); *J. Chem. Soc. C*, 3084 (1968).
(21) A review of the morphinandienone and homomorphinandienone synthesis by the Pschorr reaction is found in T. Kametani and K. Fukumoto, *J. Heterocycl. Chem.*, **8**, 341 (1971).
(22) T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Pharm. Bull.*, **19**, 1513 (1971).

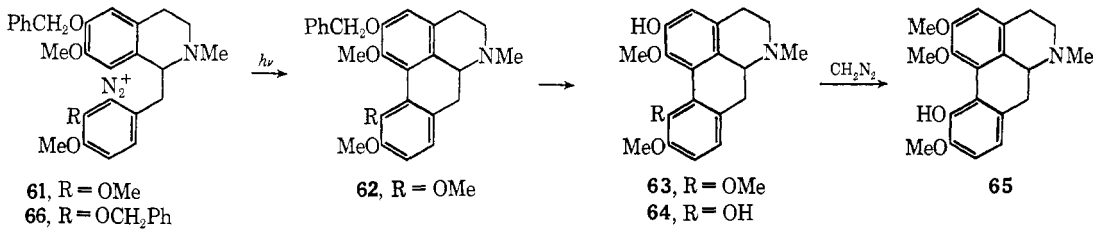


58 57



59 60

quinoline **61** afforded the aporphine **62** in 17% yield; this was converted into *N*,*O*[10]-dimethylhernovine (**63**) as shown.[23,24]

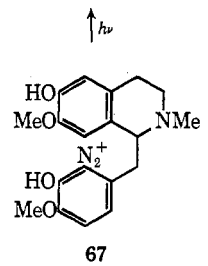


61, R = OMe
66, R = OCH_2Ph

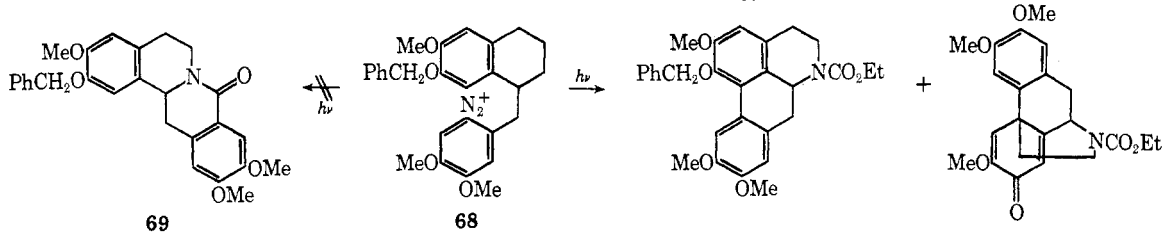
62, R = OMe

63, R = OMe
64, R = OH

65



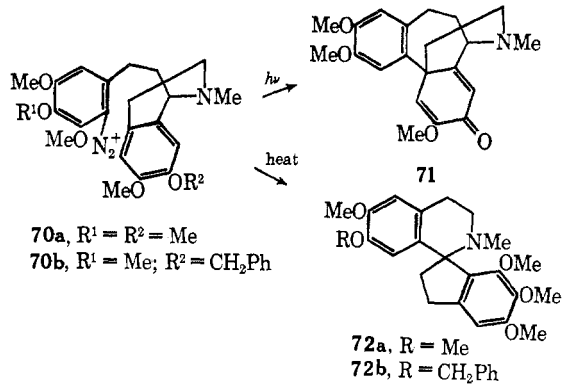
67



69 **68**

The usual Pschorr reaction of **61** gave the aporphine **62**, in only 3% yield; thus, the photo-Pschorr reaction is an improved method for the synthesis of the aporphine.[24] The same phenomenon was observed in the synthesis of *N*-methyllindecarpine (**64**) and isocorydine (**65**) from the diazotized isoquinoline **66**. The former alkaloid (**64**) was obtained directly by irradiation of the phenolic diazotized isoquinoline **67**.[25] Moreover, the side reactions, diazo coupling in the phenolic isoquinoline and loss of a protecting group, which were observed in the Pschorr reaction, did not occur in the photo-Pschorr reaction.[25] In the latter reaction, the presence of an *N*-ethoxycarbonyl group (**68**) did not lead to the protoberberine formation (**69**), which was found in the photolytic electrocyclic reaction described above.[26]

Phenethylisoquinoline Series. The photo-Pschorr reaction was also applied in the phenethylisoquinoline series under the same conditions as in the benzylisoquinoline series. Photolysis of the diazonium salts **70a** and **70b** gave *O*-methylandrocymbine (**71**),[27] but thermal decomposition of **70a** and **70b** afforded the abnormal compounds **72a** and **72b**, respectively.[27] Moreover, irradiation of **73** afforded *O*-methylandrocymbine (**71**) and kreysigine (**74**).[24] Homoaporphine (**76**), which could not be obtained by Pschorr reaction, was also synthesized from **75** by a photo-Pschorr reaction.[28]

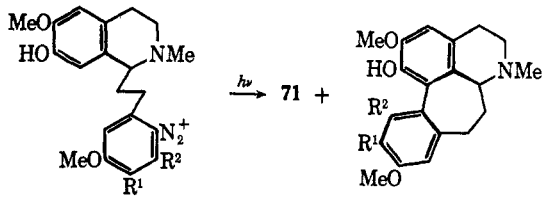


70a, $R^1 = R^2 = Me$
70b, $R^1 = Me$; $R^2 = CH_2Ph$

71

72a, R = Me
72b, R = CH_2Ph

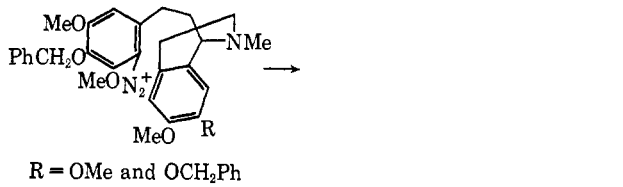
(23) T. Kametani, K. Fukumoto, and K. Shishido, *Chem. Ind. (London)*, 1566 (1970).
(24) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. C*, 1923 (1971).
(25) T. Kametani, T. Sugahara, and K. Fukumoto, *Tetrahedron*, **27**, 5367 (1971).
(26) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi, and K. Fukumoto, *Chem. Commun.*, 289 (1971).
(27) T. Kametani, M. Koizumi, and K. Fukumoto, *ibid.*, 1157 (1970); *J. Chem. Soc. C*, 1792 (1971).
(28) T. Kametani, T. Nakano, C. Seino, S. Shibuya, K. Fukumoto, T. R. Govindachari, K. Nagarajan, B. R. Pai, and P. S. Subramaniani, *Chem. Pharm. Bull.*, in press.



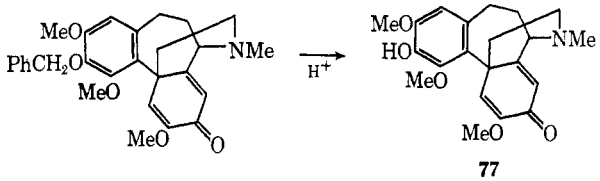
73, $R^1 = R^2 = OMe$
75, $R^1 = OH$; $R^2 = H$

74, $R^1 = R^2 = OMe$
76, $R^1 = OH$; $R^2 = H$

The total synthesis of androcymbine (**77**) has been accomplished by an application of the photo-Pschorr reaction, as follows.

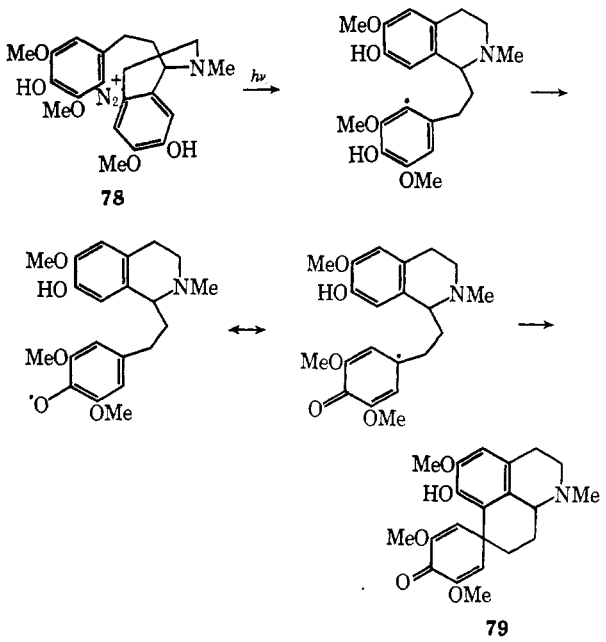


R = OMe and OCH_2Ph



77

However, direct conversion of **78** to androcymbine did not occur; instead this reaction produced the homoproaporphine **79**, probably *via* radical intermediates as illustrated.[29]

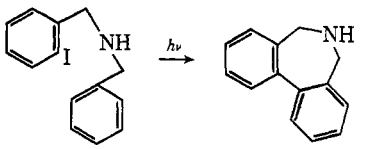


78

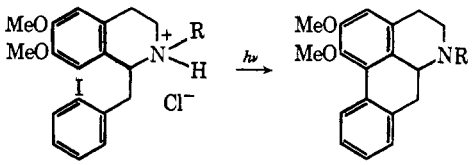
79

Photolytic Cyclodehydrohalogenation

It is well known that photolysis of aromatic halides in benzene results in the formation of biphenyl derivatives by the reaction of the aryl radicals produced by homolytic cleavage of the carbon–halogen bond.[30] Intramolecular reactions of this type also give cyclization products. Intramolecular cyclization by photolysis is utilized in the total synthesis of the isoquinoline alkaloids.



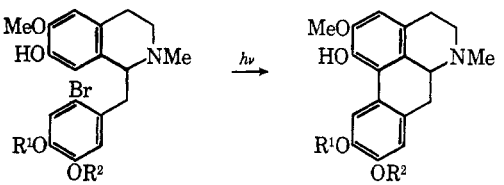
Aporphine Alkaloids. Kupchan synthesized nornuciferine (**80**) and nuciferine (**7**) from the corresponding 1,2,3,4-tetrahydro-1-(2-iodobenzyl)isoquinoline hydrochlorides by photolytic intramolecular cyclization. Although the same reaction of *N*-acyl derivatives produced the corresponding aporphines, the free base of the above 1-benzylisoquinolines gave no aporphines. Apparently, the presence of the free electron lone pair on nitrogen was detrimental to the desired photocyclization. *N*-Acyl derivatives or isoquinoline hydrochlorides, which circumvented the detrimental effect of the basic nitrogen, showed smooth cyclization.[31]



R = H and Me

80, R = H
7, R = Me

Moreover, synthesis of the aporphine alkaloids from the phenolic bromoisoquinolines has been reported by the present authors. In these reactions irradiation of 6′-bromoorientaline (**81a**), 6′-bromoreticuline (**81b**), and its methylenedioxy analog (**81c**) gave bracteoline (**60**), isoboldine (**82**), and domesticine (**83**), respectively, in moderate yields, in addition to the morphinandienone alkaloids described later.[32,33]



81a, $R^1 = H$; $R^2 = Me$
81b, $R^1 = Me$; $R^2 = H$
81c, $R^1 + R^2 = -CH_2-$

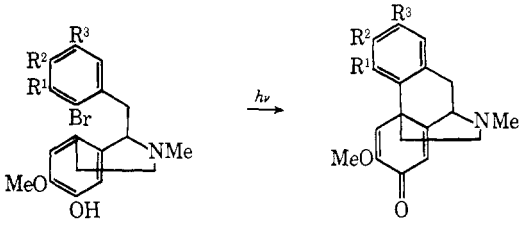
60, $R^1 = H$; $R^2 = Me$
82, $R^1 = Me$; $R^2 = H$
83, $R^1 + R^2 = -CH_2-$

Morphinandienone Alkaloids. In the photolytic cyclization of the phenolic bromoisoquinolines, coupling is possible at the position ortho as well as para to the phenolic hydroxy group, and a coupling reaction at the latter position could lead to the morphinandienone

(29) T. Kametani, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3729 (1971).

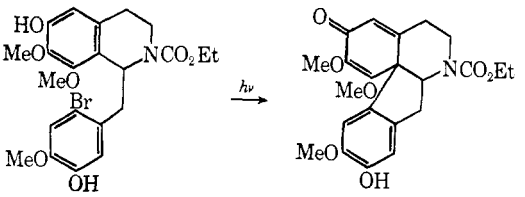
(30) R. K. Sharma and N. Kharasch, *Angew. Chem.*, **80**, 69 (1968).
(31) S. M. Kupchan and R. M. Kanojia, *Tetrahedron Lett.*, 5353 (1966).
(32) T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc. C*, 2446 (1971).
(33) T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Ind. (London)*, 818 (1971).

alkaloids. Irradiation of **81a**, **81b**, and **81c** produced flavinantine (**59**), pallidine (**84**), and amurine (**85**), respectively.[32,33] Moreover, photolysis of 2′-bromoreticuline (**81d**) in the presence of sodium iodide gave salutaridine (**86**), which had been converted into morphine.[34] Furthermore, the proerythrinadienone-type



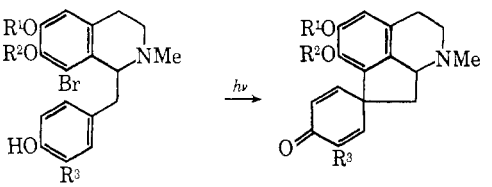
81a, $R^1 = H$; $R^2 = OH$; $R^3 = OMe$ **59**, $R^1 = H$; $R^2 = OH$; $R^3 = OMe$
81b, $R^1 = H$; $R^2 = OMe$; $R^3 = OH$ **84**, $R^1 = H$; $R^2 = OMe$; $R^3 = OH$
81c, $R^1 = H$; $R^2 + R^3 = -OCH_2-$ **85**, $R^1 = H$; $R^2 + R^3 = -OCH_2O-$
81d, $R^1 = OH$; $R^2 = OMe$; $R^3 = H$ **86**, $R^1 = OH$; $R^2 = OMe$; $R^3 = H$

compound **87** was synthesized from its 6-hydroxy analog (**88**) under similar conditions.[35]



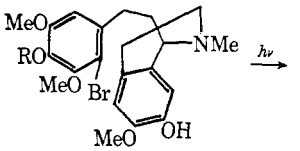
88 **87**

Proaporphine Alkaloids. Because of the information that the morphinandienone alkaloids have been synthesized by photocyclization, the synthesis of proaporphine alkaloids from 8-bromo-1-(4-hydroxybenzyl)isoquinoline by photolysis was examined. The phenolic bromoisoquinolines **89a**, **89b**, and **89c** were irradiated to give mecambrine (**90a**), pronuciferine (**90b**), and glaziovine (**90***c*).[33,36,37] Alkaloid **90b** was also obtained by irradiation of **89b** in the presence of sodium borohydride and sodium hydroxide, followed by oxidation of the resulting dienol.[38] *O*-Methylorientalinone (**91**) was obtained from **89d** in addition to *O*-methylisoorientalinone, a spiro isomer of **91**.

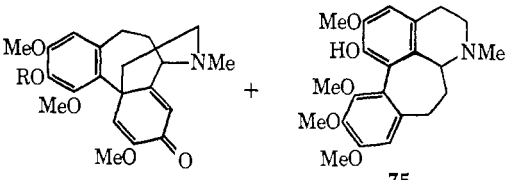


89a, $R^1 + R^2 = -CH_2-$; $R^3 = H$ **90a**, $R^1 + R^2 = -CH_2-$; $R^3 = H$
89b, $R^1 = R^2 = Me$; $R^3 = H$ **90b**, $R^1 = R^2 = Me$; $R^3 = H$
89c, $R^1 = Me$; $R^2 = R^3 = H$ **90c**, $R^1 = Me$; $R^2 = R^3 = H$
89d, $R^1 = R^2 = Me$; $R^3 = OMe$ **91**, $R^1 = R^2 = Me$; $R^3 = OMe$

Phenethylisoquinoline Series. Photolytic cyclization of the phenolic bromobenzylisoquinolines to the aporphine, morphinandienone, and proaporphine alkaloids was extended, as follows, to the synthesis of the corresponding alkaloids in the phenethylisoquinoline group. 1-(2-Bromophenethyl)-7-hydroxyisoquinoline (**92**) was irradiated to afford *O*-methylandrocymbine (**71**) and kreysigine (**75**).[39] Androcymbine (**77**) was also obtained by the same reaction from **93**.[40] The

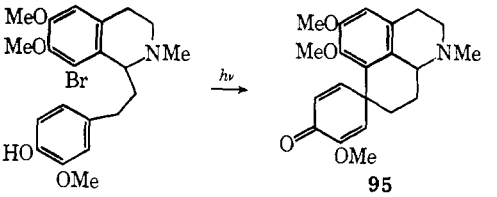


92, R = Me
93, R = H



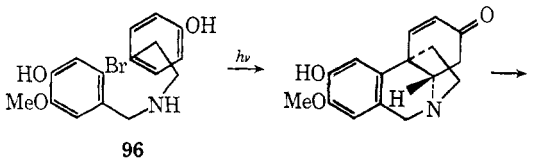
71, R = Me
77, R = H

same reaction of 8-bromo-1-(4-hydroxyphenethyl)-isoquinoline (**94**) gave *O*-methylkreysiginone (**95**).[36]

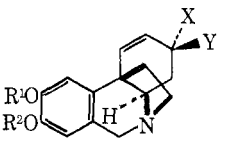


94 **95**

Amaryllidaceae Alkaloids. The spirodienone synthesis by photolytic cyclization of the phenolic bromo compound was applied to the total synthesis of some *Amaryllidaceae* alkaloids. In this reaction, irradiation of the phenolic bromo amine **96**, as usual, gave the enone, which has already been converted into maritidine (**97**).[41] In a similar way (±)-epicrinine (**98**) was synthesized by photolysis of the corresponding amine, followed by reduction.[42] Moreover, the phenolic

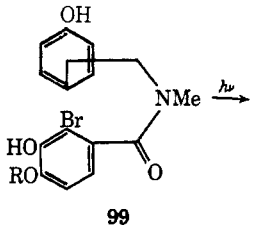


96



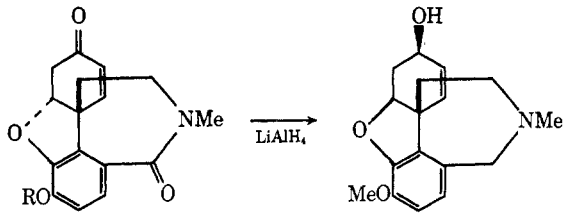
97, $R^1 = R^2 = Me$; X = OH, Y = H
98, $R^1 + R^2 = -CH_2-$; X = H; Y = OH

(34) T. Kametani, H. Nemoto, T. Nakano, S. Shibuya, and K. Fukumoto, *Chem. Ind. (London)*, 788 (1971).
(35) T. Kametani, *et al.*, Symposium Papers of the 15th Symposium on the Chemistry of Natural Products, Nagoya, Japan, 1971, p 123.
(36) T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Commun.*, 724 (1971).
(37) T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5993 (1971).
(38) Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Lett.*, 1167 (1971).
(39) T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3733 (1971).
(40) T. Kanetani and M. Koizumi, *J. Chem. Soc. C*, 3976 (1971).
(41) T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Chem. Commun.*, 774 (1971).
(42) T. Kametani and T. Kohno, *Tetrahedron Lett.*, 3155 (1971).



99

R = Me and CH_2Ph



100 101

R = Me and CH_2Ph

bromo amide **99** was cyclized to the narwedine-type compound **100**, which was a key intermediate to galanthamine (**101**).[35]

In this Account, we have shown simple syntheses of several types of isoquinoline alkaloids. Photolysis provides novel methods for the total synthesis of natural products. The improvements of yield and the availability of stereospecificity or stereoselectivity by appropriate modifications of the reaction provide methods of synthesis which are simpler and more elegant than classical methods which require many steps and much time.

It is a great pleasure to acknowledge the aid of my able coworkers, especially Dr. S. Shibuya and Dr. M. Koizumi. We are indebted to the Department of Education, Japanese Government, and the Japan Society for the Promotion of Science under the Japan–U. S. Cooperative Science Program, for their financial support.

Carboxypeptidase A: a Mechanistic Analysis

EMIL THOMAS KAISER*[1] AND BONNIE LU KAISER[2]

Departments of Chemistry and Biochemistry, University of Chicago, Chicago, Illinois 60637

Received March 12, 1971

The research to be discussed in this Account was directed toward the mechanistic elucidation of the esterase and peptidase action of the proteolytic enzyme, carboxypeptidase A. This enzyme was chosen for study for a number of reasons, among which are its moderate molecular weight (approximately 34,000), its ready availability in a highly pure crystalline form, and the inherently interesting fact that it is a metalloenzyme requiring the presence of one Zn^{2+} ion per molecule at its active site for catalytic activity. Carboxypeptidase A catalyzes the hydrolysis of the peptide or ester bonds of *N*-acyl α-amino acids and *O*-acyl α-hydroxy acids adjacent to the terminal free carboxyl groups.[3-5]

Our investigation has concentrated on the kinetic analysis of the hydrolysis of selected synthetic substrates because we feel that only by kinetic studies can one measure directly the dynamics of reaction, the principal aspect of enzyme action which any postulated mechanism must explain. When we began our studies, in 1962, the prospects of interpreting the results of kinetic investigations in terms of the structure of carboxypeptidase A were rather limited. No definite information was available concerning the nature of the Zn^{2+} binding ligands in the enzyme and only partial peptide sequence data were in hand. Before the completion of our kinetic studies not only were electron density maps at 2.0-Å resolution obtained for carboxypeptidase A and a complex of the enzyme with the dipeptide glycyl-L-tyrosine[6-8] but also the determination of the entire primary amino acid sequence was reported.[9] Carboxypeptidase A became thus the first metalloenzyme for which the high-resolution structure and sequence were known.

From the X-ray and chemical sequence studies, it is known that there are three amino acid ligands from

Emil Thomas Kaiser was born in Budapest, Hungary, in 1938, and emigrated to the United States shortly before World War II. After receiving the B.S. degree at the University of Chicago in 1956, he took his Ph.D. at Harvard University under Professor F. H. Westheimer. After postdoctoral work at Harvard with E. J. Corey and at Northwestern with Myron Bender, he served two years on the faculty of Washington University in St. Louis. In 1963 he moved to the University of Chicago, where he became Professor of Chemistry and Biochemistry in 1970. His research interests are primarily in bioorganic chemistry with strong emphasis on the roles of metal ions in enzymatic action, the effects of the introduction of new intramolecular nucleophiles at enzyme active sites, and the modes of action of cyclic AMP and peptide hormones.

Bonnie Lu Kaiser did both undergraduate and graduate work at the University of Chicago, receiving her Ph.D. degree in 1970 under the joint direction of Professor F. J. Kézdy and her husband, E. T. Kaiser. The Kaisers have one child, Elizabeth Ann, born on March 11, 1971.

(1) Fellow of the Alfred P. Sloan Foundation, 1968–1970.
(2) Predoctoral Trainee of the National Institutes of Health, 1965–1970.
(3) E. Waldschmidt-Leitz, *Physiol. Rev.*, 11, 358 (1934).
(4) K. Hoffman and M. Bergmann, *J. Biol. Chem.*, **134**, 225 (1940).
(5) J. E. Snoke, G. W. Schwert, and H. Neurath, *ibid.*, **175**, 7 (1948).
(6) W. N. Lipscomb, J. A. Hartsuck, G. N. Reeke, Jr., F. A. Quiocho, P. H. Bethge, M. L. Ludwig, T. A. Steitz, H. Muirhead, and J. C. Coppola, *Brookhaven Symp. Biol.*, **21**, 24 (1968).
(7) W. N. Lipscomb, G. N. Reeke, Jr., F. A. Quiocho, and P. H. Bethge, *Phil. Trans. Roy. Soc. London, Ser. B*, **251**, 177 (1970).
(8) W. N. Lipscomb, *Accounts Chem. Res.*, **3**, 81 (1970).
(9) R. A. Bradshaw, L. H. Ericsson, K. A. Walsh, and H. Neurath, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1389 (1969).