Method of Analysis of Products.—All product analyses were carried out using an F & M Model 720 dual-column temperature-programming vapor phase chromatograph. Columns packed with Carbowax 20M were found to be suitable for product analyses from reductions involving both β-diisobutylene oxide and styrene oxide. The products were identified by comparison of retention times with those of authentic samples. Product ratios were calculated from the areas under the corresponding peaks and the relative responses of the products with respect to 1-octanol, the internal standard. Over-all product yields and material balances were also determined in this manner. The relative responses of the products with respect to 1-octanol were determined by analysis of mixtures of carefully weighed amounts of the products and 1-octanol. All areas were determined by tracing the peaks with a planimeter.

Products from Reductions of β-Diisobutylene Oxide.—2,2,4-Trimethylpentanol-3 for comparison purposes was synthesized from isobutyraldehyde and *t*-butylmagnesium chloride.[16] 2,2,4-Trimethylpenten-1-ol for comparison purposes was synthesized according to the procedure for Rerick and Eliel.[6b]

Products from Reductions of Styrene Oxide.—1-Phenylethanol and 2-phenylethanol for comparison purposes were obtained from Aldrich Chemical Co., and were purified by distillation through a packed column under reduced pressure.

(16) B. J. Cooke, M.S. Thesis, Georgia Institute of Technology, Atlanta, Ga., 1967.

Registry No.—I, 96-06-0; VIII, 96-09-3; H_2AlO-*t*-Bu, 15649-64-6; $HAl(O\text{-}t\text{-}Bu)_2$, 15649-65-7; H_2AlO-*i*-Pr, 15649-66-8; $HAl(O\text{-}i\text{-}Pr)_2$, 15649-67-9; $HAl(OMe)_2$, 15649-68-0.

Acknowledgment.—The authors are indebted to Professor E. L. Eliel for samples of 2,2,4-trimethylpentanol-3, 2,2,3,3-tetramethylbutanol, and β-diisobutylene oxide. The authors are also indebted to the National Aeronautics and Space Administration for partial financial support of this work.

Imine Photoalkylations. Papaverine, Phenanthridine, and a General Mechanism[1]

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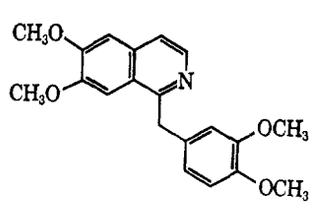
Received September 13, 1967

Irradiation of papaverine (or its hydrochloride) in methanol and ethanol produced 1-methyl-6,7-dimethoxyisoquinoline and 1-ethyl-6,7-dimethoxyisoquinoline, respectively. Irradiation of phenanthridine in ethanol yielded 6-ethylphenanthridine. A mechanism is described which serves to correlate the present results with a number of alcohol incorporations in imine photochemistry.

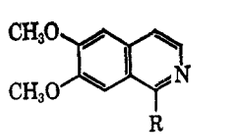
A recent report[2] on the photoalkylation of some pyrimidines and pyrazolopyrimidines prompts us to describe the details of our results[3,4] on alcohol incorporation in the photolysis of papaverine and the photoalkylation of phenanthridine. On the surface, our results and those of Ochiai[2] might appear to involve novel photochemistry. However, closer inspection and consideration of a number of seemingly unrelated literature reports on other imine photochemistry suggested to us that a general mechanism could be written which would correlate a considerable body of C=N photoreactivity. Such a correlation seems valuable at the present time since recent books on photochemistry (with one exception) have largely ignored this topic. This is in spite of the fact that sufficient data is already present in the literature to indicate a versatility of C=N photoreactivity unsurpassed by that of C=O.

Results

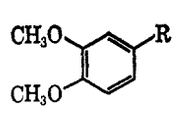
Irradiation of 10^{-3} *M* solutions of papaverine (I) or its hydrochloride in methanol or ethanol for 5–11 days caused 40–60% photolysis and formation of essentially a single basic product (II) in each case, isolated in corresponding yields. With methanol solvent, the product was 1-methyl-6,7-dimethoxyisoquinoline (IIa) and with ethanol solvent, the product was 1-ethyl-6,7-dimethoxyisoquinoline (IIb). Photolysis proceeded only slightly faster in quartz than when a Pyrex filter was used and photolysis did not occur in the same length of time with benzene as solvent. With isopropyl alcohol as solvent, photolysis was relatively rapid (I decreased significantly in hours rather than days) and a mixture of as yet unknown basic products was formed. These products appeared to undergo further photoreactions. In the case of photolysis in methanol and ethanol, the nonbasic products were separated and analyzed. Typical results are given in Table I. The relative yields of methyl and ethyl veratryl ethers (IIIa and IIIb) as compared to veratraldehyde (IIIc) were considerably variable since the former are autoxidizable to the latter. The yields



I



IIIa, R = CH_2OCH_3
b, R = $CH_2OCH_2CH_3$
c, R = CHO
d, R = CH_3
e, R = $COOCH_3$
f, R = $COOCH_2CH_3$
g, R = OCH_3
h, R = H



IIa, R = CH_3
b, R = CH_2CH_3

(1) This work was supported by Grants GM 12407 and GM 15425 from the National Institute of General Medical Sciences (U. S. Public Health Service). The major part of the work was conducted at Utah State University, Logan, Utah, and represented a portion of the Ph.D. thesis submitted to that institution by R.P.S.

(2) M. Ochiai and K. Morita, *Tetrahedron Lett.*, 2349 (1967).

(3) Preliminary results on papaverine photolysis have been reported: Abstracts, the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 40C; see also ref 4.

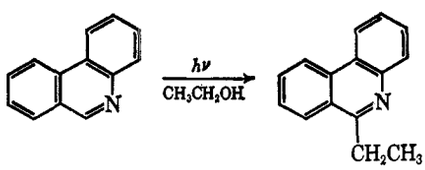
(4) F. R. Stermitz, R. Pua, and H. Vyas, *Chem. Commun.*, 326 (1967).

TABLE I
NONBASIC PRODUCTS FROM PAPAVERINE IRRADIATIONS

Reactants	Products, % yield IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	Unknown
I in CH_3OH	45		Trace	45	Trace		Trace	Trace	Trace
I·HCl in CH_3OH			90		10				
I in CH_3CH_2OH		75		15		Trace		Trace	Trace
I·HCl in CH_3CH_2OH		22	64	7				7	

of IIIa and IIIb are therefore minimum yields and those of IIIc are maximum.

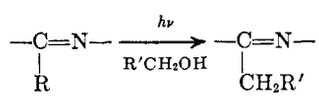
A 5×10^{-2} M solution of phenanthridine (IV) in acidified ethanol was irradiated for 14 days (Colorado sunlight) or for 41 hours in a 5-l. immersion reactor with a Hanovia 450-W L lamp, and essentially complete conversion of IV into 6-ethylphenanthridine (V) was achieved.



IV V

Discussion

The reaction we have discovered can be generalized as in eq 1. In our above cases, R = H or veratryl and

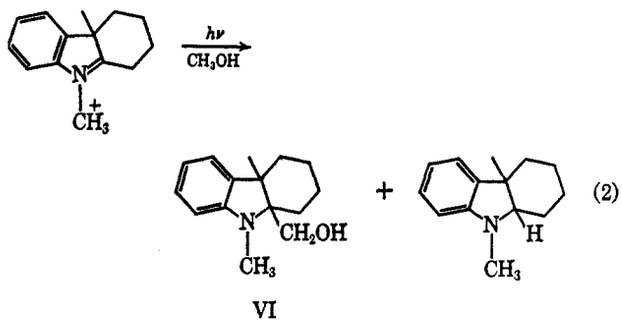


(1)

in the simultaneously discovered[2] photoalkylation of pyrimidines, R = H. A case where R = Cl is also known.[5] In view of the disparity of these R groups, it seems likely that the reaction will prove to be independent of R and therefore of some general applicability. Our results and those of Ochiai[2] indicate that limitations will, however, reside in the alcohol and in the electronic character[2] of the imine.

Mechanistically, the problem presents itself as to how to incorporate this new reaction into our present knowledge of photochemistry. Formally, we seem to be observing alkyl–oxygen cleavage of the alcohols, a manner of photoreactivity for alcohols completely unknown (except in the case of direct irradiation with short wavelength light). Normally, alcohols have been observed to react with photoexcited molecules in only two ways: (1) *via* α-hydrogen abstraction such as in pinacol formation with ketones and (2) *via* O–H bond cleavage such as in the photoaddition to olefins. We believe that our results can best be explained by an initial hydrogen abstraction process, followed by coupling and elimination and that there is, therefore, no need to postulate a new form of alcohol reactivity. Scheme I (path A) presents our suggested mechanism, using the photolysis of papaverine in ethanol as an example.

The first stages in Scheme I (path A) are the same as those which must apply in the reaction observed[6a] by Cerutti and Schmid (see eq 2). Since the non-



(2)

VI

bonded pair on nitrogen is not available in their case or ours in acid, initial excitation must be π–π^*. The papaverine photolysis products are quite similar to those from the hydrochloride photolysis and it seems likely that π–π^* excitation is operable in the case of the free base also. Hydrogen abstraction from the alcohol provides the intermediates necessary for coupling and this is supported by the large rate increase of papaverine photolysis in isopropyl alcohol and the failure in benzene. A similar process must also precede the dimerization of 1-methyl-3,4-dihydroisoquinoline.[6b]

Because of the presence of the good veratryl leaving group, we have not been able to isolate the suspected intermediate VII. However, occurrence of VI, which cannot react further, lends support to the intermediacy of VII. The effectiveness of acid in the alkylations reported[2] by Ochiai is also explained by VII since in his cases (and ours on phenanthridine) the veratryl group is replaced by a hydrogen and acid is necessary to provide facile elimination to an intermediate such as VIII.

Additional evidence for Scheme I (path A) is suggested by the finding of products such as IIIa and IIIb, which are those expected of ionic-type reactions. Postulation of the formation of the veratryl cation X, which is rapidly converted into IIIa or IIIb, provides a logical explanation for many of the III products. Thus, the photolysis[7] of 3-methoxybenzyl acetate in 50% ethanol–water yielded ethyl 3-methoxybenzyl ether (corresponding to IIIb formation) and a mechanism involving an intermediate such as X was suggested. The photochemical autoxidation of ethers (*e.g.*, IIIb to IIIc) is well known[8] and the oxidation is also a dark reaction. The formation of ester products IIIe and IIIf from IIIc irradiation also has ample literature precedence.[9]

One nonbasic product (IIId) was found in relatively high yield only in the case of I photolysis in methanol (see Table I). This product, as well as trace products IIIg and IIIh, did not seem to be explicable in terms

(5) M. Ochiai (Takeda Chemical Industries), private communication (1967).

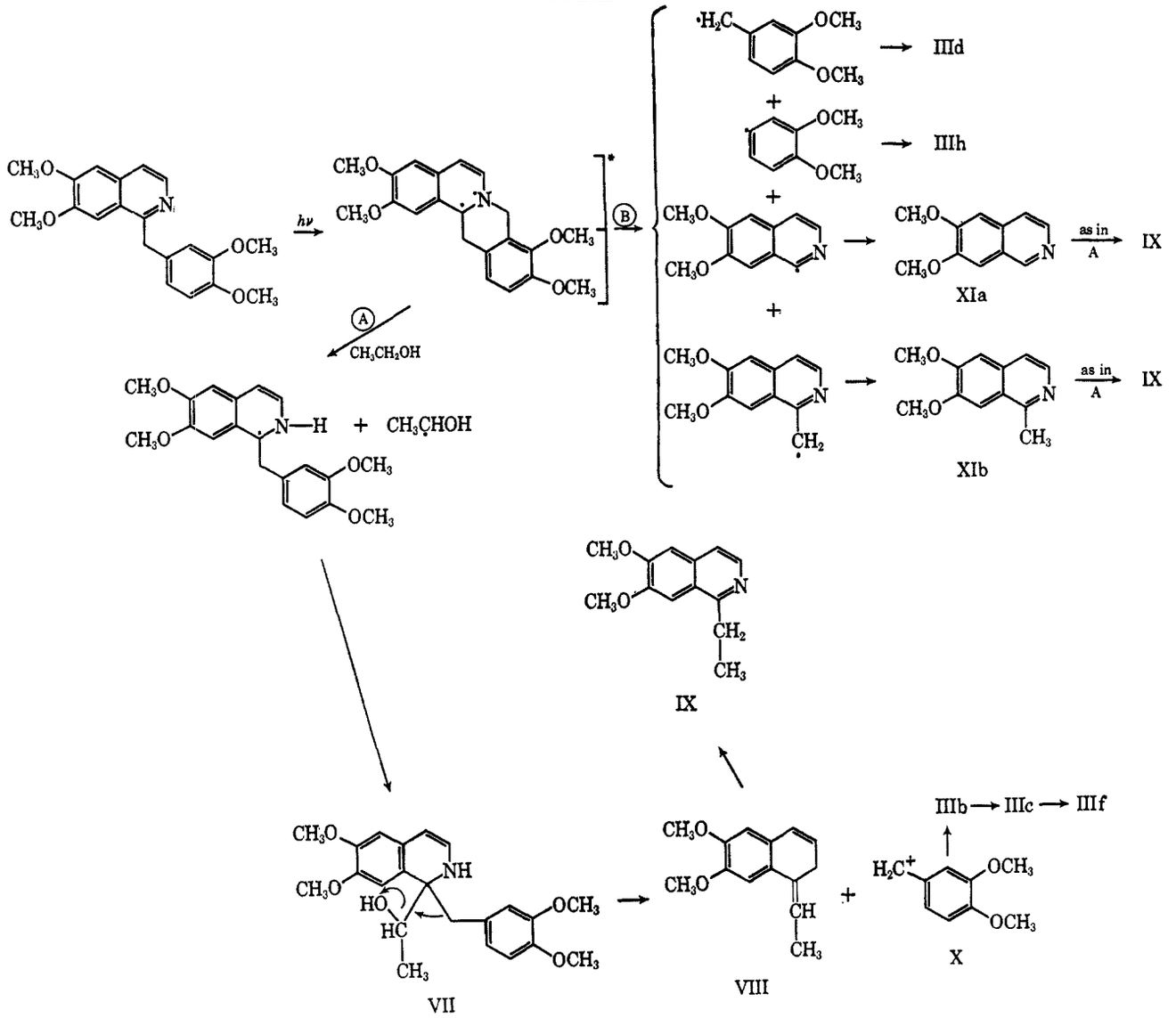
(6) (a) P. Cerutti and H. Schmid, *Helv. Chim. Acta*, **45**, 1992 (1962); (b) *ibid.*, **47**, 203 (1964).

(7) H. E. Zimmerman and V. R. Sandel, *J. Amer. Chem. Soc.*, **85**, 915 (1963).

(8) A. M. Clover, *ibid.*, **46**, 419 (1924); N. A. Milas, *ibid.*, **53**, 221 (1931); D. B. Sharp and T. M. Patrick, Jr., *J. Org. Chem.*, **26**, 1389 (1961).

(9) P. de Mayo, *Advan. Org. Chem.*, **2**, 413 (1960).

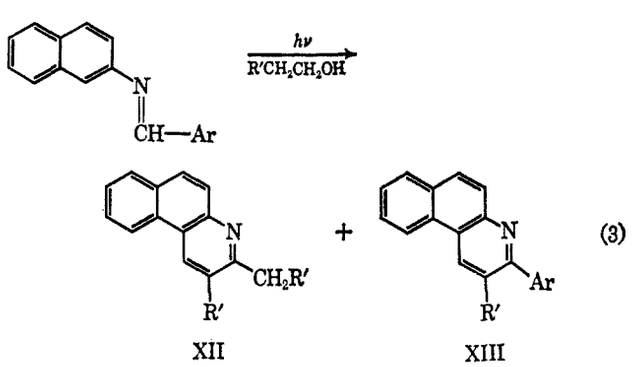
SCHEME I



of path A and, therefore, path B is proposed as a (usually) secondary mode of papaverine photolysis. The isoquinolines XIa and XIb would be readily converted *via* path A into IX and this would explain our failure to find XIa and XIb. Experiments are presently underway to provide further evidence for path B.

We are thus essentially suggesting that imine photochemistry is quite analogous to ketone photochemistry. The dimerization mentioned above[6b] and acridine reductive dimerization[10] are thus analogs of symmetrical pinacol formation (benzopinacol from benzophenone in isopropyl alcohol), whereas our results and others discussed here are analogs of mixed pinacol formation (1,1-diphenyl-1,2-ethanediol from benzophenone in methanol[11]).

Imine photoreduction, however, can apparently lead to one additional type of product involving rearrangement of the abstracted hydrogen prior to coupling. This is, in the first example, exemplified by a mechanism we would like to suggest (Scheme II) for the complex transformation[12] observed recently (eq 3).



(3)

XII XIII

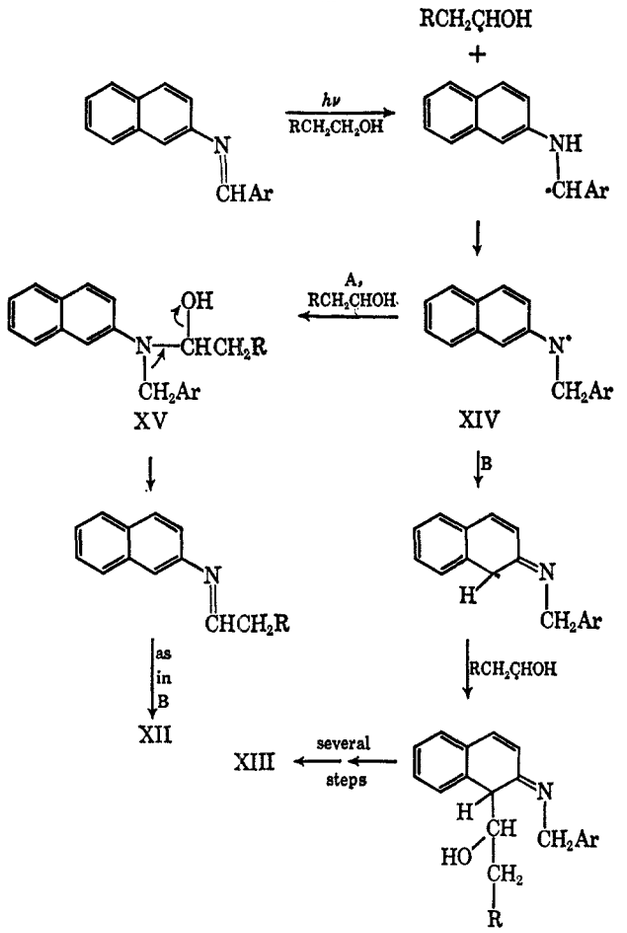
No explanation for this transformation has been given previously and it has only been suggested[10,12] that the alcohol is probably oxidized to aldehyde as a first step. Our mechanism (Scheme II) follows Scheme I with the exception that the hydrogen abstracted from the alcohol by the excited imine first migrates from nitrogen to carbon before the coupling takes place. We feel that it is less likely that intermediate XIV would be formed by direct hydrogen abstraction to the carbon

(10) See, for example, R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., New York, N. Y., 1966, p 225, and references given there.

(11) H. Göth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965).

(12) P. J. Collin, H. Silberman, S. Sternhell, and G. Sugowdz, *Tetrahedron Lett.*, 2063 (1965); J. S. Shannon, H. Silberman, and S. Sternhell, *ibid.*, 659 (1964).

SCHEME II



end of the C=N, although this remains a possibility. Finally, it should be pointed out that riboflavin photobleaching has been shown[13] to be initiated by the same process proposed here with the exception that in the case of riboflavin an *intramolecular* hydrogen abstraction takes place. In this study[13] a postulated structure for leucodeuteroflavin (a transitory intermediate) was the analog of XV and thus the three steps leading to XV in Scheme II are exactly analogous to the intramolecular ones believed to apply in riboflavin photochemistry.

Experimental Section[14]

General Irradiation Procedure.—Irradiations were conducted in an immersion reactor using an Hanovia Type S (200-W) lamp with a Pyrex filter. (In trial experiments using quartz the typical basic cleavage products were observed to form at only a slightly faster rate, but the total material remaining after solvent evaporation was considerably greater than starting material and there was apparently solvent decomposition during irradiation.) Prior to irradiation, the solution was flushed with nitrogen and nitrogen was bubbled through the solution constantly during irradiation. This prevented the rapid oxidation of papaverine to papaveraldine and other products which occurred when nitrogen was omitted. The solution was stirred magnetically during the entire irradiation. Reagent grade methanol, 95% ethanol, isopropyl alcohol, and benzene were redistilled (discarding initial and final distillates) prior to use.

Papaverine and Papaverine Hydrochloride Photolysis.—A typical complete procedure for papaverine in methanol will be given, followed by whatever different procedures were used in other cases.

A solution of 1.53 g (0.00452 *M*) of papaverine (λ_{max} 324 (log ϵ 3.45) and 316 (log ϵ 3.41)) in 4.5 l. of methanol was irradiated (see above) for 7 days. The progress of photolysis was checked by tlc. Papaverine gave a red-violet spot at R_f 0.60 and a blue-green spot appeared at R_f 0.56 after 24 hr of irradiation. At the end of 7 days, the two spot densities were about equal. The solvent was removed *in vacuo* at room temperature with a rotary evaporator and the residue was dissolved in 50 ml of ether. The ether solution was extracted with three 15-ml portions of 0.1 *N* hydrochloric acid and the acidic layer was brought to pH 3 by the addition of base. The ether layer was dried and evaporated to leave 0.253 g of "nonbasic fraction." The acid solution was extracted with three 50-ml portions of chloroform. The chloroform layer was dried and evaporated to leave 1.08 g of unreacted papaverine. The acidic layer was made basic and extracted with three 50-ml portions of chloroform. The chloroform layer was dried and evaporated to leave 0.249 g of light brown viscous oil which showed (on tlc) only the blue-green spot at R_f 0.56. Upon sublimation of this material, 1-methyl-6,7-dimethoxyisoquinoline (IIa), mp 104–107° (lit.[15] mp 106–107°) was obtained. It formed a hydrochloride salt of mp 224–228° (lit.[16] mp 226–228°) and had an nmr spectrum in agreement with this structure. The "nonbasic fraction" (see above) showed seven peaks on vpc. The nmr spectrum of the mixture before vpc was identical with that obtained by collecting the seven peaks after vpc. Two of the peaks were approximately equal in area and represented about 90% of the nonbasic fraction. These were shown to be homoveratrole (IIId), identified by spectral comparison with an authentic purchased sample (K & K Laboratories), and methyl veratryl ether (IIIa), identified by spectral comparison with an authentic sample prepared from veratryl chloride and sodium methoxide solution. Of the remaining five trace constituents, four could be identified. These were veratrole (IIIh), 1,3,4-trimethoxybenzene (IIIg), veratraldehyde (IIIc), all identified by spectral comparison with authentic purchased samples (Aldrich Chemicals), and methyl veratrate (IIIe), identified by spectral comparison with an authentic sample prepared by esterification of 3,4-dimethoxybenzoic acid.

Irradiation of 1.69 g (0.005 *M*) of papaverine hydrochloride in 4.5 l. of methanol for 11 days and work-up of the products as before yielded 0.663 g of unreacted papaverine, 0.432 g of IIa, and 0.343 g of "nonbasic fraction." The "nonbasic fraction" was found to be composed of 90% veratraldehyde (IIIc) and 10% methyl veratrate (IIIe) as above.

Irradiation of 1.68 g (0.005 *M*) of papaverine in 4.5 l. of 95% ethanol for 11 days and work-up as before yielded 0.271 g of unreacted papaverine, 0.501 g of "nonbasic fraction," and 0.539 g of a basic product having the same R_f on tlc as papaverine. However, the nmr showed the presence of two methoxyl groups and an aromatic ethyl substituent. Sublimation yielded pure 1-ethyl-6,7-dimethoxyisoquinoline (IIb), mp 70–71° (lit.[17] mp 75–76°). Elemental analysis and detailed nmr and mass spectral analysis confirmed the identity. The "nonbasic fraction" consisted of 15% homoveratrole (IIId), 75% ethyl 3,4-dimethoxybenzyl ether (IIIb), identified by spectral comparison with an authentic sample prepared from veratryl chloride and sodium ethoxide, and three trace components. Of the trace components, one was veratrole (IIIh) and a second ethyl veratrate (IIIf). The latter was not obtained pure, but was always contaminated by the third trace component, which has remained unidentified. However, the major portion of the nmr spectrum and infrared spectrum of the mixture was identical with that of authentic ethyl veratrate (prepared by esterification of 3,4-dimethoxybenzoic acid).

Irradiation of papaverine hydrochloride in 95% ethanol in a similar manner yielded, in addition to unreacted papaverine and

(13) W. M. Moore, J. T. Spence, F. A. Raymond, and S. D. Colson, *J. Amer. Chem. Soc.*, **85**, 3367 (1963).

(14) Melting points are uncorrected and were taken on a Mel-Temp apparatus. Nmr spectra were obtained with Varian A-60 and Varian A-60A spectrometers at 60 Mc/sec using tetramethylsilane as an internal reference. Mass spectra were determined with an Hitachi Perkin-Elmer RMU 6-E, ultraviolet spectra with a Cary 15, and infrared spectra in KBr (solids) and CCl_4 (liquids) using a Beckmann IR-8 spectrophotometer. Thin layer chromatography (tlc) was performed on silica gel F254 plates (Brinkmann) with 1:4 methanol–benzene as developing solvent and iodoplatinic acid as the visualizing agent. Vapor phase chromatography (vpc) was performed at 235° using a 10-ft 20% Carbowax on Chromosorb W column in a Varian Aerograph A90P apparatus. Organic solutions were dried with sodium sulfate before evaporation.

(15) A. Ahl and T. Reichstein, *Helv. Chim. Acta*, **27**, 366 (1944).

(16) G. N. Walker, *J. Amer. Chem. Soc.*, **76**, 3999 (1954).

(17) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

IIb, a "nonbasic fraction" consisting of 64% veratraldehyde (IIIc), 22% ethyl 3,4-dimethoxybenzyl ether (IIIb), and 7% each of homoveratrole (IIId) and veratrole (IIIh).

A number of trial runs on papaverine irradiation in isopropyl alcohol were attempted using 800 ml of a 10^{-3} M solution. For example, after 3 hr of irradiation, tlc showed the presence of five new trace spots positive to iodoplatinic acid. However, upon continued irradiation these spots began to disappear as did that for the papaverine starting material. Evaporation of the solvent left residues weighing two to four times as much as that of the total starting material and preliminary attempts at isolation of any specific pure products were not successful.

Irradiations conducted in a similar manner, except using benzene as solvent, showed no photolysis products on tlc. In one case, an Hanovia Type L (450 W) lamp was used and no new product could be detected after 2 days of irradiation. The solvent was evaporated and the residue found to be only unreacted papaverine. Under these conditions, product spots could be observed using methanol solvent after 2 hr and in less than 1 hr using isopropyl alcohol as solvent.

Irradiation of Phenanthridine.—Phenanthridine (0.91 g or 0.0048 M) was dissolved in a mixture of 992 ml of 95% ethanol and 8 ml of concentrated hydrochloric acid and the resulting solution was placed in a 1000-ml Pyrex flask. This was stoppered, inverted, and placed in the sunlight. After 14 days of irradiation, the solvent was removed *in vacuo*, the residue was dissolved in methanol, the solution evaporated, and the residue triturated with benzene–ether. This left a brown oil whose nmr spectrum showed the disappearance of the downfield singlet due to the proton at the 6 position (next to nitrogen) and the appearance of a characteristic upfield triplet and quartet of an ethyl group. Essentially the same result was obtained when 5 l. of the same solution was irradiated for 41 hr in an Hanovia immersion reactor (450-W Type L lamp) under nitrogen and using a Pyrex filter. Gas chromatography showed the residue to be contaminated with about 10% phenanthridine. The gas chromatographic separation yielded a white solid which was then recrystallized from *n*-heptane to give 6-ethylphenanthridine, mp 55° (lit.[18] mp 54–55°). The mass spectrum was exactly analogous with that reported[19] for 2-ethylpyridine (as opposed to other ethylpyridines) and constituted additional proof of structure.

Registry No.—I, 58-74-2; I hydrochloride, 61-25-6; IV, 229-87-8.

Acknowledgment.—The authors are indebted to Drs. R. C. Anderson and W. M. Moore of Utah State University for many helpful discussions and comments.

(18) A. Pictet and A. Hubert, *Ber.*, **29**, 1186 (1896).

(19) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., New York, N. Y., 1962, p 134.

The Electron-Impact Fragmentation of Dimethylaminoacetone and 2-Dimethylaminocyclohexanone

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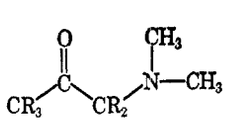
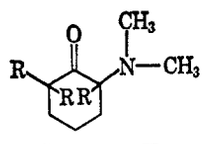
Received August 24, 1967

The mass spectra of dimethylaminoacetone and 2-dimethylaminocyclohexanone have been analyzed with the help of their deuterated analogs. Fragmentation patterns are interpreted as being virtually exclusively directed by the nitrogen function with insignificant fragmentation direction by the carbonyl group.

As a prelude to studying the photochemistry of some amino ketones, and particularly the intramolecular interactions of the amino and ketone functions, it was deemed of interest to study the electron impact fragmentation of some model compounds. It has been suggested a number of times in the literature that mass spectra, particularly of aliphatic ketones, can be correlated with photochemistry. The presence of an amino function (strongly directing in electron impact fragmentation) in the same molecule as a carbonyl (highly reactive photochemically) might be expected to test severely this correlation. This paper reports an analysis of the mass spectra of dimethylaminoacetone (Ia) and 2-dimethylaminocyclohexanone (IIa) assisted by the spectra of the deuterio analogs Ib and IIb.



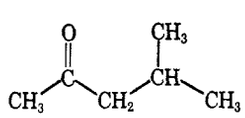
Ia, R = H
b, R = D



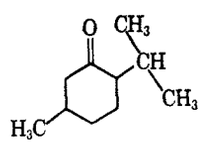
IIa, R = H
b, R = D

Figures 1–4 give the 80-eV mass spectra of Ia, Ib, IIa, and IIb, respectively.

It is perhaps most instructive to compare these spectra with those of similar structure, but in which first the nitrogen is replaced by carbon and, alternatively, the carbonyl group is replaced by CH_2. For the first comparison, mass spectra of 4-methyl-2-pentanone[2] (III) and menthone[3] (IV) are particu-

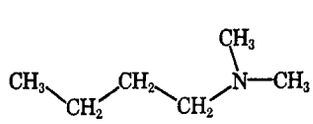


III

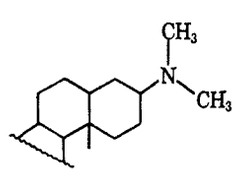


IV

larly useful. For the second comparison, spectra of dimethyl-*n*-butylamine[4] (V) and a number of dimethylamino steroids[5] (VI) are available. For the



V



VI

(1) Public Health Service Research Career Development Awardee (5-K3-GM-16,698) of the National Institute of General Medical Sciences (U.S.P.H.S.) at Utah State University (1963–1967). The experimental portion of this work was conducted at Utah State University under Grant GM-12407 from the N.I.G.M.S.

(2) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, Figure 8.5, p 124.

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc. San Francisco, Calif., 1964, Figures 1-12 and 1-13, p 23.

(4) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962).

(5) L. Dolejs, V. Hanus, V. Cerny, and F. Sorm, *Collect. Czech. Chem. Commun.*, **28**, 1584 (1963); Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 574 (1965).