Photocyclizations of Pharmacodynamic Amines. V. Unusual Rearrangements of the Mescaline Skeleton

Osamu Yonemitsu,[1] Hideo Nakai,[1] Yuichi Kanaoka,[1] Isabella L. Karle,[2] and Bernhard Witkop[3]

Contribution from the Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan, U. S. Naval Research Laboratory, Washington, D. C. 20390, and National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014. Received December 30, 1969

Abstract: Irradiation of N-chloroacetylmescaline (I) in aqueous solution or in water–ethanol gave 7,8,9-trimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (II, 10% yield) and 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo-[5.2.2]undeca-8,10-dien-3-one (III) in 35% yield in addition to starting material (10–20%) and N-acetylmescaline (IV, >1%). Photocyclization in anhydrous methanol gave more recovered starting material (20%) and, in addition to III (11%), a new compound, 11,12-dimethoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (V) in >2% yield. The racemic photoproduct III, which crystallizes in the orthorhombic space group Aba2, was elucidated by the *symbolic addition procedure* which was applied to this space group for the first time. The nonplanar spatial orientation of the three methoxy groups of III in the crystal, and probably also in solution, resembles that of the trimethoxyphenyl moiety of reserpine. On refluxing in glacial acetic acid, III underwent a novel fragmentation reaction and aromatized to a mixture of N-acetoxymethyl-2,6-dimethoxy-4-acetoxymethylphenylacetamide (35% yield) and 2,6-dimethoxy-4-acetoxymethylphenylacetamide (34% yield), whose structures were clarified by degradation and interconversion reactions. In methanolic HCl at 20° photoproduct III underwent a new type of transannular aldol condensation to yield 1,8,8-trimethoxy-2,6-dioxo-4-(2′-aminoethyl)bicyclo[3.2.1]oct-3-ene, which was elucidated as the perchlorate by the symbolic addition procedure. The mechanism of this unusual rearrangement was studied by the use of HCl in ethanol and CD_3OD.

The multiple photocyclizations and photorearrangements of N-chloroacetylphenethylamines[4] are remarkable in the way in which the number and location of nuclear substituents determine the type and ratio of photoproducts. In this respect these N-chloroacetyl derivatives must be considered as nonconjugated donor–acceptor pairs[5] or loosely bound exciplexes in which the energy absorbed by the aromatic chromophore is transferred to the side chain and there aids in the n,π^*-activation of the carbonyl group. Such a presumably *intramolecular* triplet energy transfer should depend on the nature of the chromophore, the overall geometry of the molecule, and on the solvent.[6]

We have now extended our systematic studies to the mescaline series in which the presence of three methoxy groups again provides for novel pathways of photocyclizations. During photolysis of these N-chloroacetyl derivatives hydrogen chloride is liberated and can be continuously titrated in a pH-Stat.[7]

In this way it was determined that the half-life of N-chloroacetyl-*m*-tyramine, $t_{1/2} = 1.2$ min, is ten times shorter than that of N-chloroacetylmescaline, $t_{1/2} = 11.6$ min.[7] This was interpreted as intramolecular assistance in the breakage of the carbon–chlorine bond from the photoexcited state of a suitable phenol. The assistance is most effective when the phenolic hydroxyl is in *para* position to the location of formation of the benzazepinone system. However, this is a simplification which may hold for phenols or catechols, but not for N-chloroacetylnormescaline which liberates chloride ion at the same slow rate as mescaline.[7] Titration data alone are not sufficient to understand these differences. Studies on fluorescent quenching and quantum yield measurements are now in progress to learn more about the mode of intramolecular energy transfer.[8]

Previous attempts at photocyclization of N-haloacetylmescalines resulted only in hydrogenolysis to N-acetylmescaline.[7] Table I summarizes our new results of photolysis in three different solvent systems.

The main photoproduct in water or aqueous ethanol is 7-hydroxy-1,9,10-trimethoxy-4-azabiocyclo[5.2.2]-undeca-8,10-dien-3-one (III), mp 230–232°, whose structure was established by Roentgen analysis and application of the symbolic addition procedure.[9]

Photoproduct III crystallizes in the *orthorhombic space group Aba2* which does not have a center of symmetry and to which *symbolic addition procedure was applied for the first time.* Among the symmetry elements of the crystal there is a glide plane which acts as a mirror. Therefore, the photoproduct which has two asymmetric carbon atoms exists as a racemate, of which structure III represents one possible antipode. This is in contrast to the photoproduct from N-chloro-

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(1) Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.

(2) U. S. Naval Research Laboratory, Washington, D. C. 20390.

(3) National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014.

(4) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.*, in press.

(5) E. F. Ullman, *Accounts Chem. Res.*, 1, 353 (1968). Related photocyclizations and -isomerizations: J. Kagan, *J. Amer Chem. Soc.*, **88**, 2617 (1966); P. G. Cleveland and O. L. Chapman, *Chem. Commun.*, 1064 (1967); M. P. Cava and S. C. Havlicek, *Tetrahedron Lett.*, 2625 (1967); M. Fischer, *ibid.*, 4295 (1968); 2281 (1969); H. Morrison and R. Peiffer, *J. Amer. Chem. Soc.* **90**, 3428 (1968).

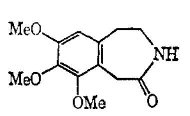
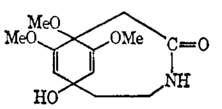
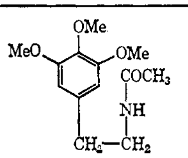
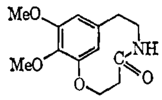
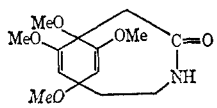
(6) *Cf.* G. A. Russell, *ibid.*, **80**, 4987, 4997 (1958).

(7) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *ibid.*, **90**, 776 (1968).

(8) We are indebted to Dr. George S. Hammond, California Institute of Technology, for advice and discussions and for communicating unpublished results in the fluorescence quenching of mixtures of aromatic substrates with chloroacetamide and methyl chloroacetate (with Thomas McCall); *cf.* M. T. McCall, G. S. Hammond, B. Witkop, and O. Yonemitsu, *ibid.*, in press.

(9) O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle, and B. Witkop, *ibid.*, **91**, 4591 (1969); the melting point of V, 176–169°, given there is erroneous; I. L. Karle and J. Karle, *Acta Cryst.*, B in press.

Table I. Dependence of Nature and Yield (in Per Cent) of Photoproducts on the Solvents Used in Photolysis

Solvent	 II	 III	 IV	Starting material I	 V	 VI
Water	9	34		19		
Aqueous ethanol	7	32.2	<1	11		
Anhydrous methanol			7.8	21	1.5	11

acetyl-3,4-dimethoxyphenethylamine[4,10] which was a conglomerate from which a single optically active crystal of 1,2-5a,7bβ-tetrahydro-5aβ,5bα-dimethoxy-5bH-cyclobuta[1,4]cyclobuta[1,2,3-*gh*]pyrrolizin-4(5H)-one, one arbitrarily chosen antipode, was picked. Cell dimensions are: $a = 25.74 \pm 0.03$ Å, $b = 13.88 \pm 0.02$ Å, $c = 7.49 \pm 0.02$ Å, $\alpha = \beta = \gamma = 90°$; there are eight molecules in the unit cell. The X-ray data were collected photographically using the Weissenberg and precession cameras. A total of 1290 independent reflections were recorded with Cu Kα radiation. Phases for the reflections were determined directly from the structure factor magnitudes by the symbolic addition procedure[11] for noncentrosymmetric crystals, and the positions of the heavy atoms were found in *E* maps. All but one hydrogen atom were found in a difference map. The final *R* factor was 6.8%. In the crystal there is one molecule of water of hydration for two organic molecules. Hydrogen bonds are formed between the water molecule and the –OH and –NH groups. In addition, the organic molecules are linked into infinite chains by hydrogen bonding between the –OH and C=O groups. Bond distances and angles are shown in Figure 1.

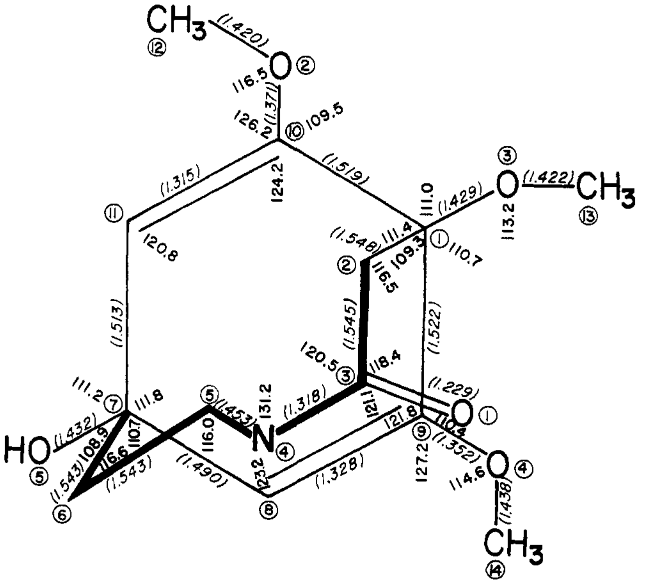


Figure 1. Bond lengths and angles of the photoproduct III from N-chloroacetylmescaline. Additional angles are C(2)C(1)O(3), 103.9°; C(9)C(1)C(10), 110.4°; C(6)C(7)C(11), 107.6°; C(8)C(7)-C(5), 106.6°.

There are two features of interest. (i) The nine-membered ring formed from four atoms of the six-membered ring, C(7), C(8), C(9), and C(1), and five atoms from the chain of the original molecule assumes a boat conformation (Figure 2). Atoms C(1), C(7), C(8), and C(9) are coplanar to within ±0.015 Å, while atoms C(2), C(3), N(4), and C(5) are coplanar to within ±0.008 Å. Dihedral angles between planes 1 and 2 and between planes 2 and 3 are 118 and 105°, respectively. Intraring distances between atoms separated by two other atoms are fairly short, *e.g.*, C(3)···(C9) is 2.78 Å and C(1)···C(7) is 2.95 Å. There is another nine-membered ring containing C(10) and C(11) instead of C(8) and C(9) which has a chair conformation.

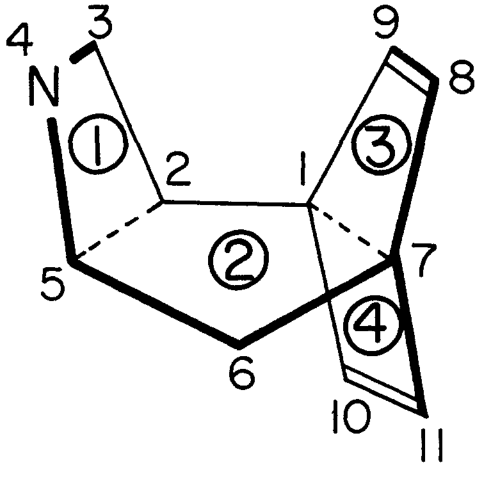


Figure 2. Conformation of the bicyclic photoproduct III.

(ii) The orientation of the methoxy groups reveals a new principle. The two OCH_3 groups adjacent to the double bonds of the six-membered rings lie so that each set of four heavy atoms in the grouping $C{=}COCH_3$ are coplanar to within ±0.02 Å. The CH_3 groups are *cis* with respect to the double bonds resulting in the short C(11)···C(12) and C(8)···C(14) separations which are only 2.79 and 2.77 Å, respectively. The hydrogen atoms on the CH_3 groups are oriented so that one H atom is in the plane of the heavy atoms and directed away from the double bond. As a consequence, the other two H atoms are symmetrically disposed above and below the plane, maximizing the distance of closest approach of a hydrogen atom to the carbon atoms in the double bond. The middle OCH_3 group lies in the

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(10) O. Yonemltsu, Y. Okuno, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 6522 (1968).

(11) I. L. Karle and J. Karle, *Acta Cryst.*, **17**, 835 (1964); J. Karle and I. L. Karle, *ibid.*, **21**, 849 (1966); J. Karle, *ibid.*, **B24**, 182 (1968).

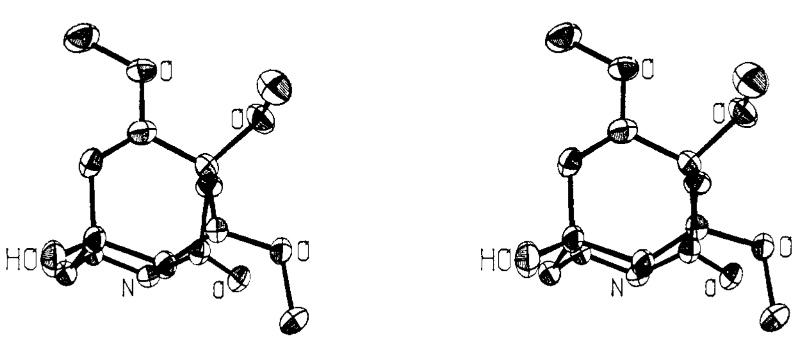
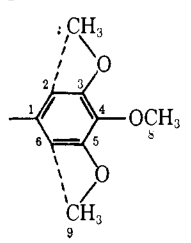


Figure 3. Three-dimensional structure of 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5.2.2]undeca-8,10-dien-3-one from mescaline as determined by X-ray analysis. The stereodrawing was made by a computer from a program prepared by C. Johnson, Oak Ridge National Laboratory. The picture should be seen with a three-dimensional viewer for printed stereophotographs (commercially available, *e.g.*, from Hubbard Scientific Company, Northbrook, Ill.).

approximate mirror plane (except for atoms N(4), C(3), and O(1)) of the molecule. The stereodrawing (Figure 3) permits an easy inspection of these interesting features.



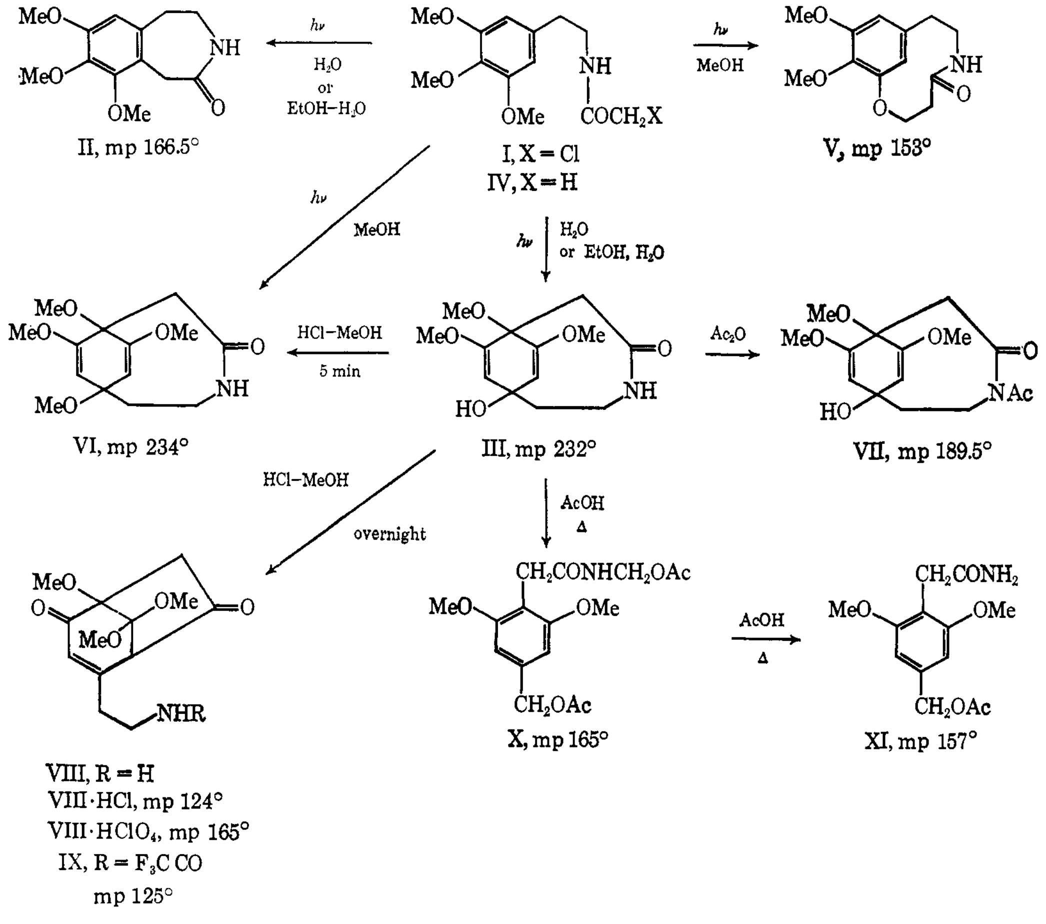
A

All oxygen atoms and the amide bond of photoproduct III are arranged on the outside of the carbon skeleton, a fact which explains the high solubility of III in water.

In the reserpine molecule, the OCH_3 groups in the trimethoxybenzene moiety (A) are disposed in a similar fashion as in the present molecule; that is, the middle OCH_3 group is approximately perpendicular to the ring, while the other two OCH_3 groups are nearly coplanar with the ring, although the ring in reserpine is a planar aromatic ring while the ring in the present molecule has a fold of 156° at C(1)···C(7). In reserpine the values for the C(2)···C(7) and C(6)···C(9) separations are similarly very low, 2.80 and 2.82 Å.[12]

This preferred conformation of the O-methyl groups is the first direct evidence which extends and confirms the observation on similar enol or phenol ethers in

Chart I. Photocyclizations of N-Chloroacetylmescaline



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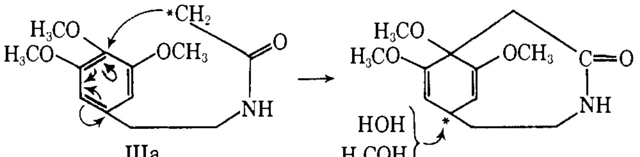
[12] I. L. Karle and J. Karle, *Acta Cryst.*, **B24**, 81 (1968); *cf.* C. Chothia and P. Pauling, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1063 (1969).

solution, that the O-methyl and vinyl protons *cis* to the ethylenic bond show long-range coupling which can be studied by the nuclear Overhauser effect (NOE).[13,14] Our present knowledge of NOE does not permit us to conclude that the two methoxy groups are fixed in this particular conformation all the time. The groups may be vibrating so that a conformation favorable for NOE is only adopted for a certain length of time which still may suffice to result in a NOE.

A practical consequence of this nonplanarity of the central methoxy group in 3,4,5-trimethoxyphenyl derivatives is the preparatively useful preferential cleavage of this group by 20% hydrochloric acid. This has permitted a convenient synthesis of 1-demethylmescaline,[15] as well as the preferential demethylation of various alkaloidal systems.[16–18]

Both in water and in aqueous ethanol the benzazepinone II (Chart I), an analog of anhalonidine, is obtained on photolysis in comparable yields. Photolysis in anhydrous methanol (Table I, Chart I) takes a different course. While neither the benzazepinone II nor the bicyclic diene III are found, two new photoproducts are isolated, the O-methyl ether VI of III and the ten-membered lactam V. The yield of this O-methyl ether VI, which is also obtained from III by short (5 min) exposure to 1.0 *N* methanolic HCl or *via* the chloro derivative (see Experimental Section), is not improved by the addition of sodium methoxide[19] to the methanolic photocyclization mixture. Aprotic solvents, such as tetrahydrofuran, acetone, or benzene increase the amount of recovered starting material, N-acetylmescaline, or of tarry products.

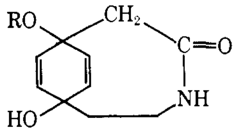
The introduction of a hydroxy in III or a methoxy in VI by the solvent points to the excited intermediates IIIa → IIIb which, despite the failure of methoxide ions to increase the yield of VI, might be formulated ionically or radically. The fact that in the mescaline series cyclization occurs *para* to the side chain, and not *meta*, as with N-chloroacetyl-3,4-dimethoxyphenethylamine,[4] may be the result of the nonplanarity of the central methoxy which in turn would influence the absorption and transfer of light energy by the excited aromatic chromophore.



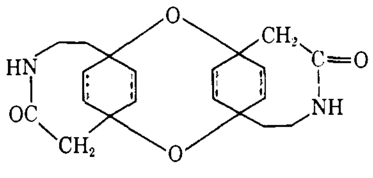
IIIa

IIIb

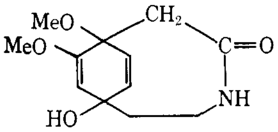
meta cyclization to the side chain has been reported for O-methyltyrosine,[7] but inspection of the water-soluble photocyclization products has now led to the isolation of the dimeric *para*-cyclization products from tyramine *via* XVII, O-methyltyramine (XVI), and O,O-dimethyldopamine (XVIII);[20] especially the dimerization process (XVII) leaves room for radical intermediates of type IIIb.



XVI

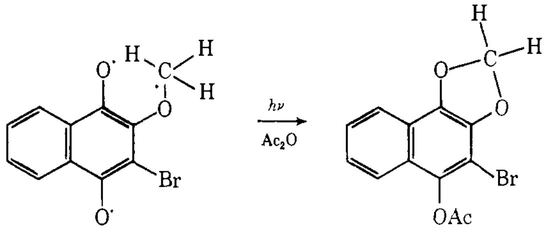


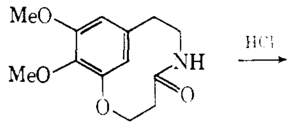
XVII



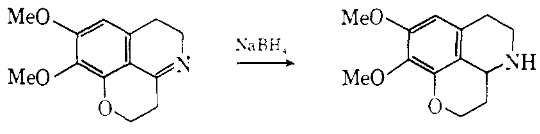
XVIII

Participation of Methoxy Substituent. The other new product obtained by irradiation in anhydrous methanol is the ten-membered lactam V. This kind of participation of an aromatic methoxy substituent has been observed in the photocyclization of quercetin pentamethyl ether[21] and with N-chloroacetyl-3,4-dimethoxyphenethylamine (in methanol *or* tetrahydrofuran), which led to the demethoxy analog of V. A similar intramolecular abstraction of hydrogen in the light-induced transformation of a methoxy into a methylenedioxy group has been formulated as proceeding by a radical mechanism.[22] The n,π* activation of the carbonyl group of I may lead to elimination of the α substituents as Cl$^-$ and a positive fragment which is capable of electrophilic aromatic substitution to give photoproducts II and possibly III and VI. In anhydrous methanol, and to some degree in tetrahydrofuran, the ten-membered lactam V may be formed by a radical mechanism. Such a dualism of photolysis is known for α-sulfonyloxy ketones.[23]





V, λ$_{max}$282 nm
(ε 700)



XIX, λ$_{max}$328 nm (18,800),
247 (10,500)

XX, λ$_{max}$ 276 nm

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(13) Professor K. Nakanishi and Dr. M. C. Woods, Department of Chemistry, Tohoku University, Sendai, Japan, personal communication.

(14) M. C. Woods, I. Miura, A. Ogiso, M. Kurabayashi, and H. Mishima, *Tetrahedron Lett.*, 2009 (1968).

(15) A. Brossi and S. Teitel, *Org. Prep. Proced.*, 1(3), 171 (1969).

(16) A. Brossi, J. Van Burik, and S. Teitel, *Helv. Chim. Acta*, 51, 1965 (1968).

(17) A. Brossi, J. O'Brien, and S. Teitel, *ibid.*, 52, 678 (1969).

(18) A. Brossi and S. Teitel, *ibid.*, 52, 1229 (1969).

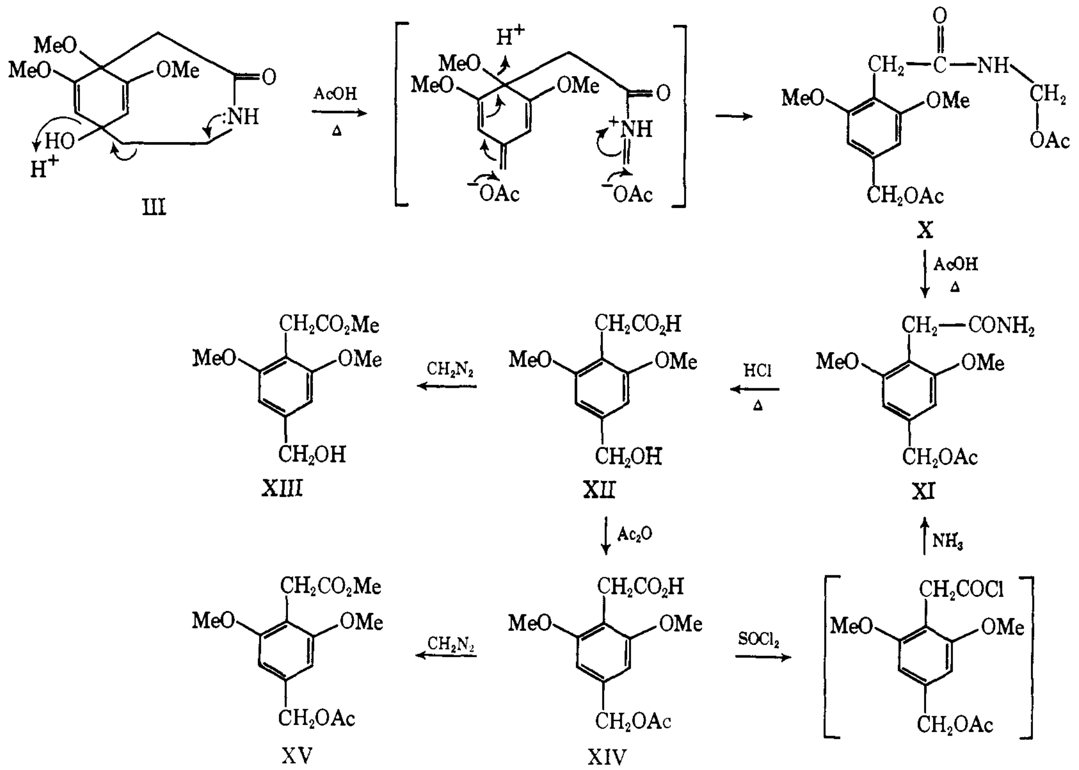
(19) *Cf.* N. C. Yang, L. C. Lin, A. Shani, and S. S. Yang, *J. Org. Chem.*, 34, 1845 (1969).

(20) O. Yonemitsu, *et al.*, unpublished observations.

(21) A. C. Waiss, Jr , R. E. Lundin, A. Lee, and J. Corse, *J. Amer. Chem. Soc.*, 89, 6213 (1967).

(22) J. E. Baldwin and J. E. Brown, *Chem. Commun.*, 167 (1969).

Chart II



The ten-membered lactam V with great ease undergoes an unusually facile transannular Bischler–Napieralski cyclization to the tricyclic isoquinoline derivative XIX whose azomethine group is easily reduced to the tetrahydroisoquinoline XX.

Aromatization of Photoproduct III. When a solution of III was refluxed in glacial acetic acid for 1 hr, it aromatized to a mixture of N-acetoxymethyl-2,6-dimethoxy-4-acetoxymethylphenylacetamide (X, 35%) and, by loss of acetoxymethyl from nitrogen, the phenylacetamide XI (34%) (Chart II).

This novel type of aromatization must have been initiated by the acid-catalyzed elimination of the enolic hydroxy group of III, which in a twofold allylic position is further activated by methoxy residues. The aromatization III → X → XI provides an analogy to the fragmentation reactions reported by Grob, *et al.*[24] The intermediate III probably aromatizes to X in a concerted process with the kind of push–pull mechanism that is characteristic of acetic acid and operative, *e.g.*, in the quinine quinotoxine conversion.[25]

The analogous quinol XVI obtained by photolysis of N-chloroacetyl-O-methyltyramine was recovered both on treatment with hydrochloric acid in methanol and after refluxing in glacial acetic acid. The lack of activation by methoxy groups must account for the stability of XVI to acid-catalyzed aromatization.

When photoproduct III was heated in acetic anhydride, it did not aromatize, but formed the N-acetyl derivative VII.

Transannular Effects in Photoproduct III. In analogy to the unprecedented, easy transannular cyclization of the ten-membered lactam V to the dihydroisoquinoline XIX, the nine-membered lactam III might be expected to show similar transannular effects.

While hydrogen chloride in methanol for 5 min converts the doubly allylic hydroxy of III to the O-methyl ether VI, a new product was obtained as the hydrochloride in >40% yield when the time of reaction was extended to 12 hr. Whereas III has no uv absorption, the acid-rearrangement product possesses a chromophore, λ_{max} 294 nm (ϵ 880), 245 (5580), indicative of a conjugated ketone. The new product was further characterized by a crystalline perchlorate.

The structural formula VIII of this rearrangement product was obtained by Roentgen analysis of a single crystal of the perchlorate salt. The intensities of 1637 independent reflections were measured with an automatic diffractometer using the θ–2θ scan technique and Cu Kα radiation. The material crystallizes in the noncentrosymmetric space group $P2_12_12_1$ with cell dimensions $a = 11.574$, $b = 8.184$, and $c = 17.362$ Å and four molecular units in the unit cell. This space group is enantiomorphous and requires that all molecules be of the same chirality. Since the precursor III crystallized as a racemate,[9] the salt VIII must exist as a conglomerate.

An *E* map based on phases obtained directly from the measured X-ray intensities by means of the symbolic addition procedure[11] revealed the positions of the atoms. Identification of the N and O atoms was possible by examination of the behavior of the apparent thermal parameters in the least-squares refinement and was confirmed by the interatomic distances, Figure 4. Inclusion of constant parameters for the hydrogen atoms, which were located in a difference map, in a least-squares refinement with anisotropic thermal parameters resulted in an *R* factor of 5.9%. The frac-

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[23] S. Iwasaki and K. Schaffner, *Helv. Chim. Acta*, 51, 557 (1968). Excited states with supposed diradical character are readily attacked by nucleophiles: D. G. Whitten, J. W. Happ, G. L. B. Carlson, and M. T. McCall, *J. Amer. Chem. Soc.*, 92, 3499 (1970).

[24] C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, 6, 1 (1967); C. A. Grob and F. Ostermayer, *Helv. Chim. Acta*, 45, 1119 (1962); C. A. Grob, F. Ostermayer, and W. Raudenbusch, *ibid.*, 45, 1672 (1962).

[25] *Cf.* P. Rabe and W. Schuler, *Ber.*, 81, 139 (1948).

Table II. Fractional Coordinates and Thermal Parameters[a] with Standard Deviations

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	0.2207 (5)	0.5586 (7)	0.2112 (3)	46 (4)	105 (8)	15 (4)	2 (6)	−1 (2)	10 (3)
C(2)	0.3499 (5)	0.5958 (7)	0.2228 (3)	47 (4)	110 (8)	16 (2)	9 (5)	−1 (2)	−2 (3)
C(3)	0.3999 (5)	0.7295 (7)	0.1810 (3)	45 (4)	115 (8)	21 (2)	−7 (5)	−5 (2)	−2 (3)
C(4)	0.3386 (5)	0.8123 (7)	0.1270 (3)	48 (4)	115 (9)	20 (2)	0 (6)	3 (2)	−9 (3)
C(5)	0.2126 (5)	0.7654 (7)	0.1162 (3)	47 (4)	118 (9)	22 (2)	8 (6)	−5 (2)	8 (4)
C(6)	0.1490 (5)	0.8290 (8)	0.1888 (3)	41 (4)	126 (10)	35 (2)	7 (6)	1 (3)	−12 (4)
C(7)	0.1478 (5)	0.6931 (7)	0.2482 (3)	58 (4)	147 (9)	24 (2)	14 (6)	6 (3)	−3 (4)
C(8)	0.1955 (5)	0.5801 (7)	0.1240 (3)	50 (4)	104 (9)	16 (2)	−4 (6)	−6 (2)	0 (3)
C(9)	0.3881 (6)	0.9424 (8)	0.0795 (3)	72 (5)	109 (8)	23 (2)	−6 (6)	1 (3)	5 (4)
C(10)	0.3352 (6)	1.1093 (7)	0.0960 (3)	78 (6)	106 (8)	23 (2)	9 (6)	−12 (3)	−1 (4)
N(11)	0.3682 (5)	1.1686 (7)	0.1755 (3)	75 (5)	137 (8)	25 (2)	1 (6)	−5 (2)	−7 (3)
C(12)	0.1771 (6)	0.3675 (9)	0.3151 (4)	84 (6)	184 (12)	24 (2)	−12 (7)	6 (3)	25 (4)
C(13)	0.0393 (6)	0.3900 (10)	0.0982 (5)	75 (6)	180 (12)	50 (3)	−55 (7)	−25 (4)	25 (6)
C(14)	0.2803 (7)	0.5163 (9)	0.0031 (3)	129 (7)	187 (12)	14 (2)	12 (9)	9 (3)	−5 (4)
O(1)	0.4079 (4)	0.5114 (6)	0.2672 (3)	49 (3)	189 (8)	33 (2)	9 (5)	−8 (2)	27 (3)
O(2)	0.1091 (4)	0.9632 (6)	0.1947 (3)	84 (4)	162 (8)	54 (2)	56 (6)	14 (3)	0 (4)
O(3)	0.1961 (4)	0.3936 (5)	0.2336 (2)	66 (3)	105 (6)	16 (1)	−9 (4)	−1 (2)	8 (2)
O(4)	0.0789 (3)	0.5568 (6)	0.1048 (3)	46 (3)	172 (7)	30 (1)	−20 (4)	−13 (2)	11 (3)
O(5)	0.2701 (4)	0.4786 (5)	0.0846 (2)	69 (3)	114 (6)	12 (1)	1 (4)	1 (2)	−1 (2)
Cl	0.3577 (1)	0.9450 (2)	0.3972 (1)	56 (1)	156 (2)	21 (0)	2 (2)	9 (1)	−2 (1)
O(6)	0.3395 (7)	0.9976 (10)	0.3226 (3)	196 (8)	468 (18)	32 (2)	−37 (11)	10 (3)	61 (5)
O(7)	0.2568 (5)	0.8753 (10)	0.4275 (4)	92 (5)	422 (16)	61 (3)	−64 (8)	32 (3)	32 (6)
O(8)	0.3788 (11)	1.0880 (13)	0.4397 (5)	382 (17)	416 (23)	68 (4)	−154 (19)	51 (7)	−67 (9)
O(9)	0.4515 (7)	0.8480 (13)	0.3986 (7)	160 (8)	621 (25)	137 (7)	238 (12)	36 (6)	58 (12)

[a] Each β_{ij} is multiplied by 10^4. The thermal parameters are expressed in the form $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

tional coordinates for the atoms and their thermal parameters are listed in Table II.

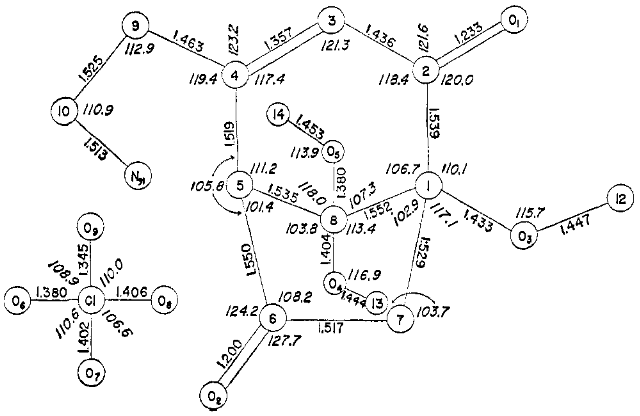

Figure 4. Bond lengths and angles for the rearrangement product VIII arising from III by HCl in methanol. Additional angles are C(2)C(1)C(7) = 109.8°, C(8)C(1)O(3) = 109.5°, O(4)C(8)O(5) = 113.7°, C(1)C(8)C(5) = 100.1°, O(6)ClO(8) = 105.0°, and O(7)-ClO(9) = 115.1°. Standard deviations for bond lengths are 0.009 Å except for the Cl–O distances where they are 0.012 Å. Standard deviations for bond angles are of the order of 0.6° except for the OClO angles where they are ~0.8°.

Stereodrawings in Figure 5 illustrate the configuration of one of the antipodes of the organic ion. There are several structural features of interest.

(i) The seven-membered ring is composed of two planes, one plane (*a*) containing atoms C(1), C(2), C(3), C(4), and C(5) (all within ±0.03 Å of the plane) and the other plane (*b*) containing atoms C(5), C(6), C(7), and C(1) (all within ±0.03 Å of the plane). The two planes form a dihedral angle of 107°. The bridgehead atom C(8) is 0.86 Å below plane *a* and 0.68 Å below plane *b*.

(ii) In the ketal moiety, the CH_3 groups in the two OCH_3 groups are disposed in opposite directions about the O(4)C(8)O(5) plane in order to avoid steric hindrance between the methyl hydrogen atoms. Atom C(13) is 0.89 Å to one side of the plane and C(14) is 1.25 Å to the other side, thus separating C(13) and C(14) by 3.40 Å.

(iii) *A priori* the ethyl amine chain would be expected to be fully extended from the ring in a *trans* conformation. In fact, it is bent back toward the ring so that the N atom is in a *gauche* configuration with respect to C(4). At first glance one might postulate an internal hydrogen bond between the $-NH_3^+$ group and the carbonyl oxygen O(2); however, the N(11)···O(2) intramolecular separation is 3.45 Å, a value much too large for hydrogen bonding.

The molecular packing and possible hydrogen bonding are illustrated in Figures 6 and 7. The four possible hydrogen bonds involve the $-NH_3^+$ group. Table III lists the bond lengths and the symmetry operations for the primed atom (with respect to the coordinates listed in Table II). Linkage *A* is a conventional NH···O bond with one of the three hydrogen atoms on N(1) directed toward O(9) of the ClO_4^- ion. Linkages *B* and *C* appear to share one hydrogen atom which is oriented in a direction between O(6) of the ClO_4^- ion and O(1)′, a carbonyl oxygen. The situation is analogous to the one found for α-glycine[26] where the bifurcated NH···O bonds had lengths of 2.93 and 3.05 Å, almost identical

Table III. Possible Hydrogen Bonds

	Bond	Symmetry operation for primed atom	Length, Å
(*A*)	N(11)···O(9)′	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$	2.858
(*B*)	N(11)···O(1)′	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$	3.059
(*C*)	N(11)···O(6)	x, y, z	2.931
(*D*)	N(11)···O(3)′	$x, 1 + y, z$	2.893

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(26) G. Albrecht and R. B. Corey, *J. Amer. Chem. Soc.*, 61, 1087 (1939); R. E. Marsh, *Acta Cryst.*, 11, 654 (1958).

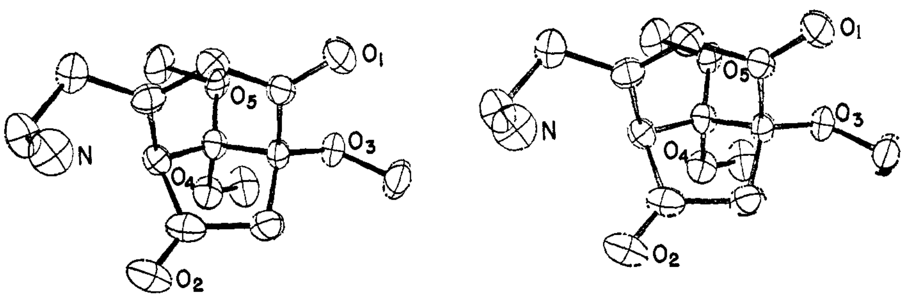

Figure 5. Stereodrawing of the configuration of 1,8,8-trimethoxy2,6-dioxo-4-(2′-aminoethyl)bicyclo[3.2.1]oct-3-ene (VIII) as determined by X-ray analysis. The ellipsoids represent the thermal motions of each atom at the 50% probability level. The drawing was made by a computer program prepared by C. K. Johnson, Oak Ridge National Laboratory, and should be viewed with a three-dimensional viewer for printed stereophotographs.

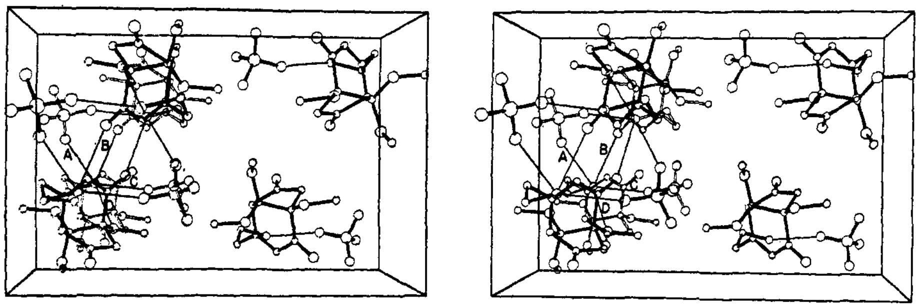

Figure 6. The contents of a unit cell of VIII plus two neighboring molecules. One set of the four possible hydrogen bonds is labeled A, B, C, and D. The axes are a ↑, c→, and b directed out of the plane of the paper.

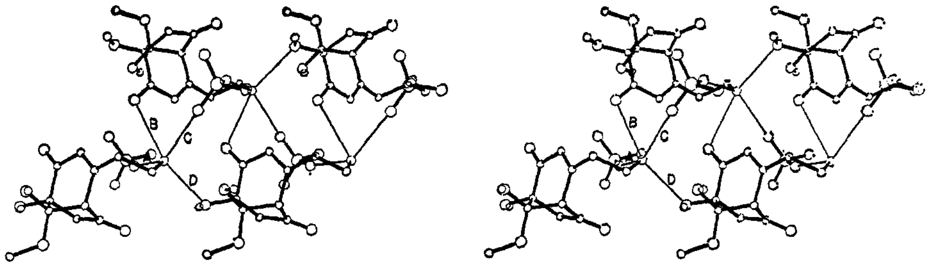

Figure 7. Four molecules of VIII from an infinite ribbon held together by hydrogen bonding. The view is perpendicular to that in Figure 3. The axial directions are a ↑ and b→.

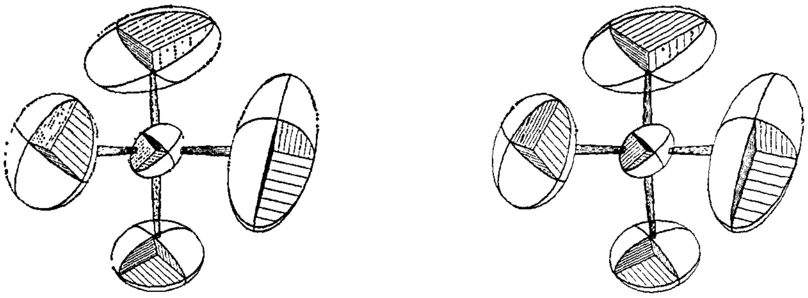

Figure 8. The perchlorate ion of VIII with thermal ellipsoids at the 50% probability level.

with the N(11)···O(1)′ and N(11)···O(6) separations found in this investigation. Other examples of bifurcated hydrogen bonds are reviewed by Donohue.[27]

Linkage D is between N(11) and O(3)′, an oxygen atom in a methoxy group. One does not ordinarily associate hydrogen bond formation with an ether oxygen. However, the NH···O(3)′ distance is 2.893 Å and, furthermore, the distance between a hydrogen atom on N(11) and O(3)′ is only 1.95 Å. Both of these values are consistent with hydrogen bond formation,[28] especially since the H···O separation is ~0.65 Å smaller than a van der Waals contact between H and O.

The hydrogen bonds tie the organic ions and the ClO_4^- ions into infinite ribbons perpendicular to the c axis.

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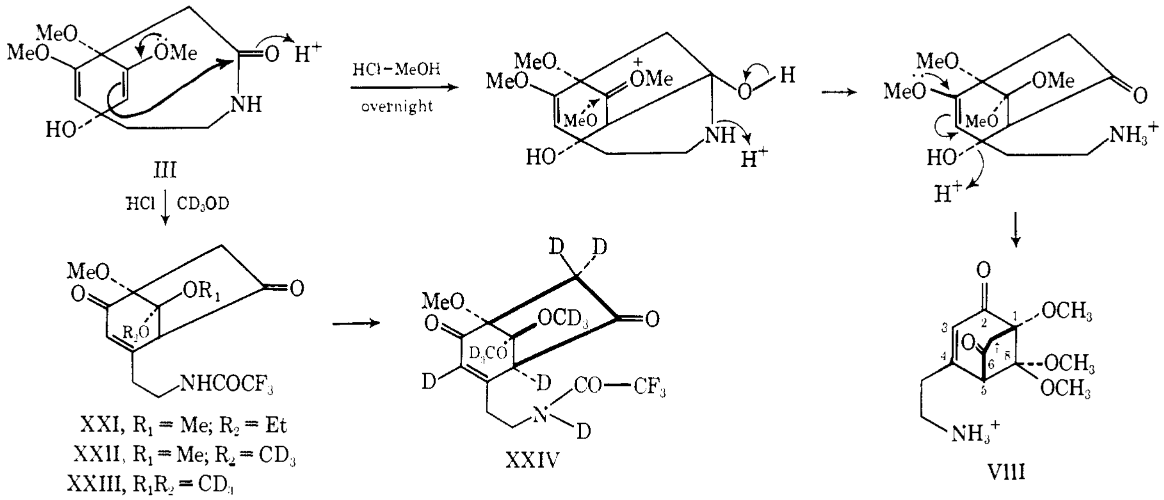
(27) J. Donohue in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman and Co., San Francisco, Calif., 1968, pp 450–456.

(28) See, *e.g.*, W. Hamilton and J. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, Inc., New York, N. Y., 1968, pp 12–17.

Chart III. Transannular Interactions and Solvent Participation in the Rearrangement of III to VIII



Four molecules from such a ribbon are illustrated in Figure 7. Each ClO_4^- ion participates in only two hydrogen bonds. The nearest approaches between atoms of different molecules, aside from those involved in hydrogen bonding, are between C(10) and O(5)′, O(7)′ and O(9)′ ranging from 3.11 to 3.15 Å. The closest intermolecular C···C approach is 3.44 Å between C(12) and C(14)′.

The oxygen atoms in the ClO_4^- ion, Figure 8, are somewhat disordered, a phenomenon fairly characteristic of crystalline perchlorates;[29] consequently the determination of the Cl–O bond lengths and the OClO angles is less reliable than that of the bond lengths and angles in the organic ion.

Mechanism of Acid Rearrangement and Participation of Solvent. We feel tempted to consider the rearrangement of III to VIII as a type of acid-catalyzed aldol condensation[30] facilitated by transannular interaction across the nine-membered ring (Chart III). The ketalization of the (8)-carbonyl requires participation of the solvent, either in a concerted fashion with retention of the original OCH_3 (positions 9 or 10) or by preferred *de novo* ketalization of the (8)-CO of VIII which must be more reactive than the conjugated (2)-CO. The results of rearrangements conducted with hydrogen chloride in ethanol or CD_3OD leave room for both interpretations, the former being favored.

Thus, in ethanol, 1,8-dimethoxy-8-ethoxy-2,6-dioxo-4-(2′-aminoethyl)bicyclo[3.2.1]oct-3-ene (XXI) was obtained and characterized as the N-trifluoroacetyl derivative, mp 106.5° (N-trifluoroacetyl derivative of VIII, mp 125°). The mass spectrum of this ketal shows a strong peak for the molecular ion at 379 and a negligible peak at 393, M^+ for the diethyl ketal.

The rearrangement in CD_3OD–HCl gave a product VIII (N-trifluoroacetyl derivative, mp 125°) which according to the mass spectrum consists mainly of the monotrideuteriomethyl- (M^+ 368, XXII) and bistrideuteriomethylketals (M^+ 371, XXIII). In addition, there is present a population of other deuterio compounds up to D_{11}, *i.e.*, all exchangeable hydrogens have been replaced by D (XXIV). However, such an exchange is not possible with XXII or XXIII and must occur, therefore, in the process of rearrangement from III → XXIV. These experiments would be simplified by avoiding labile deuterium or by using DCl and CD_3OD.

This investigation shows the preparative usefulness of intramolecular energy transfer from excited aromatic chromophores to suitable acceptors located in side chains. New classes of heterocycles of potential pharmacological interest have become available, the evaluation of which will focus especially on possible CNS effects.

Experimental Section

Photocyclizations of N-Chloroacetylmescaline. A. In Water. 7,8,9-Trimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (II). A solution of 863 mg (3 mmol) of N-chloroacetylmescaline (I) in 300 ml of water was irradiated with a 100-W mercury lamp (Eiko-Sha) under nitrogen for 4 hr. Two batches were combined and stirred with excess silver carbonate in order to remove chloride ion, and the silver salts were then removed by filtration through a Büchner funnel containing a matting of Celite filter aid. The filtrate was concentrated *in vacuo* at 35° to a volume of 30 ml and extracted with ethyl acetate. The ethyl acetate extract on evaporation left 830 mg of a brown oil which was chromatographed on a column (1.7 × 20 cm) of silica gel. Elution with ethyl acetate–dichloromethane (1:1) afforded 326 mg (19%) of recovered starting material (I) and 133 mg (8.8%) of 7,8,9-trimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (II) which was recrystallized from ethyl acetate to give colorless small prisms: mp 164.5–166.5°; uv λ_{max}^{EtOH} nm (ϵ) 281 (1200); ir ν^{Nujol} cm^{-1} 1676; mass *m/e* 251 (M^+), 195, 194, 179; nmr δ^{DCCl_3} 6.38 (s, 1 H), 3.84 (s, 9 H), 3.82 (s, 2 H), 3.50 (2 H), 3.08 (2 H).

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.95; H, 6.88; N, 5.75.

7-Hydroxy-1,9,10-trimethoxy-4-azabicyclo[5.2.1]undeca-8,10-dien-3-one (III). The above-mentioned aqueous layer was filtered and evaporated to dryness *in vacuo* to leave 980 mg of a black tar which was taken up in 50 ml of ethanol and treated with active charcoal. Filtration and evaporation left 860 mg of an orange powder which was recrystallized from 15 ml of ethanol to give 550 mg (34%) of a pale yellow crystalline powder of 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5.2.2]undeca-8,10-dien-3-one (III), mp 225–228°. Two more recrystallizations from a small amount of water gave 304 mg (19%) of colorless prisms: mp 230–232°; uv no λ_{max} above 205 nm; ir ν^{Nujol} cm^{-1} 3460, 3320, 1697, 1630; mass *m/e* 269 (M^+, $C_{13}H_{19}NO_5$*), 238 (M^+ − MeO, $C_{12}H_{16}NO_4$*), 198, 197 ($C_{10}H_{13}O_4$*, base peak), 184, 183, 169, 167; nmr δ^{D_2O} 5.17 (s, 2 H), 3.85 (s, 3 H), 3.66 (s, 3 H), 3.47 (d, 1 H, J = 14 Hz), 3.5–3.2 (2 H), 3.21 (s, 3 H), 2.57 (d, 1 H, J = 14 Hz), 2.15–1.85 (2 H).

Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.05; H, 7.04; N, 4.84.

B. **In Ethanol–Water.** A solution of 914 mg (3.18 mmol) of I in 30 ml of ethanol and 270 ml of water was irradiated as described above. The reaction mixture was stirred with 1 g of silver carbonate for 15 min, and the silver salts were then removed by filtration with the aid of active charcoal. The filtrate was concentrated *in vacuo* to a volume of 30 ml and extracted with ethyl acetate.

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[29] See, *e.g.*, I. L. Karle and J. Karle, *Acta Cryst.*, 21, 860 (1966).

[30] *Cf. Org. Reactions*, 16, 9 (1968).

The extract was dried over anhydrous sodium sulfate and evaporated *in vacuo* to leave 174 mg of a pale yellow solid which was chromatographed on a column of 10 g of silica gel. Elution with ethyl acetate–dichloromethane (1:1) gave three fractions. The first fraction was 83 mg (10.4%) of starting material (I) which was recrystallized from ethyl acetate–*n*-hexane to give colorless needles, mp 75–77.5°. The second fraction was 58 mg (6.8%) of II which was recrystallized from ethyl acetate to give colorless small prisms, mp 164–166°. The third fraction was recrystallized from ethyl acetate–*n*-hexane to give 2 mg (0.25%) of **N-acetylmescaline (IV)** as colorless needles, mp 87–89° (lit.[31] mp 93–94°), identical with an authentic sample by mixture melting point and tlc.

The aqueous layer was filtered and evaporated *in vacuo* to dryness to leave 484 mg of crude III as dark brown crystals which were dissolved in ethanol and stirred with 1 g of silica gel GF254. After filtration of the silica gel and evaporation of ethanol, a colorless solid was obtained which was recrystallized from ethanol to give 275 mg (32.2%) of III as colorless prisms, mp 228–230°. One more recrystallization from ethanol–ether raised the mp to 230–232°.

C. Photocyclization in Methanol. A stirred solution of 230 mg (0.8 mmol) of I in 80 ml of anhydrous methanol containing 126 mg (0.46 mmol) of powdered silver carbonate was cooled in an ice bath and irradiated with a 10-W low-pressure mercury lamp (Osawa Co.) for 10.5 hr. Four batches with a total volume of 320 ml were combined and filtered. The filtrate was taken up in 30 ml of water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated *in vacuo* to leave 468 mg of a pale yellow oil which was chromatographed on a column containing 40 g of alumina. Elution with ethyl acetate gave three fractions. The first fraction was recovered starting material (I, 187 mg, 20.1%); the second fraction was 51 mg (6.2%) of N-acetylmescaline (IV) which was recrystallized from ethyl acetate–*n*-hexane to give colorless needles, mp 87–89°, identical with an authentic sample by the criteria of tlc, ir spectra and mixture melting point. The third fraction was 11.8 mg (1.5%) of **11,12-dimethoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one** (V) which was recrystallized from ethyl acetate to give colorless prisms: mp 150–153°; uv $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ϵ) 282 (700); ir ν^{Nujol} cm^{-1} 3450, 1660; mass *m/e* 251 (M^+, base peak), 222, 184, 179, 167, 163, 138. The structure of this ten-membered lactam was proven by the ease with which it formed the isoquinoline derivative XIX.

8,9-Dimethoxy-2,3,5,6-tetrahydropyrano[2,3,4-*ij*]isoquinoline (XIX). A solution of 1.126 mg (0.0045 mmol) of V in 2 ml of ethanol containing 1 drop of concentrated hydrochloric acid was heated on a water bath under gentle reflux. Evaporation gave 1.2 mg (100%) of a hydrochloride as colorless crystals which were dissolved in 10 ml of ethanol. The ethanol solution displayed the characteristic uv spectrum: $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ϵ) 247 (10,500), 328 (18,800), in accordance with the transformation V → XIX. When 1 mg of the hydrochloride was dissolved in water and neutralized with sodium bicarbonate, extraction with ethyl acetate and evaporation gave the free base as an oil which was rather unstable: mass *m/e* 233 (M^+, base peak), 218 (calcd $C_{13}H_{15}NO_3$, 233).

8,9-Dimethoxy-2,3,3a,4,5,6-hexahydropyrano[2,3,4-*ij*]isoquinoline (XX). To the solution of 1 mg of the hydrochloride in methanol was added 1 mg of sodium borohydride at room temperature. After 5 min methanol was removed *in vacuo*. The residue dissolved in ethanol showed $\lambda_{\max}^{\mathrm{EtOH}}$ 276 nm.

1,7,9,10-Tetramethoxy-4-azabicyclo[5.2.2]undeca-8,10-dien-3-one (VI). Method A. The aqueous layer from the photocyclization in methanol (C) was evaporated *in vacuo* to leave 495 mg of yellow oil, which was chromatographed on a column containing 45 g of alumina. Elution with ethyl acetate gave 10 mg (1.1%) of recovered starting material (I), mp 74–77° (ethyl acetate–*n*-hexane), 13 mg (1.6%) of N-acetylmescaline (IV), mp 85–88° (ethyl acetate–*n*-hexane), and 103 mg (11.1%) of 1,7,9,10-tetramethoxy-4-azabicyclo[5.2.2]undeca-8,10-dien-3-one (VI), which was recrystallized from acetone to give colorless prisms: mp 232–234°; uv no $\lambda_{\max}$ above 210 nm; ir ν^{Nujol} cm^{-1} 3410, 3305, 3185, 1695, 1670; mass *m/e* 283 (M^+), 252, 240, 212, 211 (base peak), 183, 181; nmr δ^{D_2O} 5.05 (s, 2 H), 3.80 (s, 3 H), 3.63 (s, 3 H), 3.31 (s, 3 H), 3.14 (s, 3 H), 3.7–3.2 (3 H), 2.52 (d, 1 H, J = 14 Hz), 2.0–1.7 (2 H).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.32; H, 7.40; N, 4.92.

Method B. To 100 mg (0.372 mmol) of III in 10 ml of anhydrous methanol was added 10 ml of 2.0 *N* hydrochloric acid in methanol. The solution was allowed to stand at room temperature for 5 min and concentrated *in vacuo* to leave a colorless oil. In order to remove hydrochloric acid the oil was dissolved in 3 ml of methanol, and the solvent was removed again *in vacuo*. The residual oil was chromatographed on a column containing 25 g of alumina, from which elution with acetone gave 44 mg (41.9%) of VI. Recrystallization from acetone gave 27.5 mg (26.1%) of colorless prisms, which was identical with the photoproduct (VI) from I in methanol, with regard to tlc, mixture melting point, ir, uv, and mass spectra.

Method C. A solution of 10.7 mg of III in 1 ml of anhydrous pyridine was cooled in an ice bath, and one drop of thionyl chloride was added. The mixture was allowed to stand in a refrigerator overnight. The orange solution was concentrated to dryness *in vacuo* at 25°. The residual oil was dissolved in 1 ml of methanol, and the solvent was removed *in vacuo* to leave a yellow oil which was chromatographed on a column of 4 g of alumina. Elution with ethyl acetate gave 5.2 mg (46.2%) of crude VI as a colorless powder which was recrystallized from acetone to give colorless prisms, mp 228–230°.

Photocyclization of I in Methanol Containing Sodium Methoxide. A solution of 15 mg of I in 5 ml of methanol containing 12 mg of sodium was irradiated with a 10-W low-pressure mercury lamp at room temperature for 6.5 hr. As monitored by gas chromatography mostly starting material (I), some N-acetylmescaline (IV), and a small amount of the O-methyl ether VI were detected. The yield of VI compared with photocyclization in methanol alone was not improved.

Irradiation of I in Tetrahydrofuran. A solution of 14 mg of I in 10 ml of tetrahydrofuran containing 7 mg of silver carbonate was cooled in an ice bath and irradiated with a 10-W low-pressure mercury lamp under nitrogen for 5.5 hr. By checking with the gas chromatography and tlc, N-acetylmescaline (IV) was mainly observed, accompanied by a small amount of the ten-membered lactam V.

Attempts Photocyclizations of I. Photolysis was conducted with a 100-W high-pressure mercury lamp under nitrogen in both *absolute acetone* and in *absolute benzene* solution containing silver carbonate for 2–3 hr. In all cases almost all the starting material (I) was recovered with the exception of a very small amount of dark brown photoproducts.

N-Acetyl-7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5.2.2]undeca-8,10-dien-3-one (VII). Fifty mg (0.186 mmol) of III in 0.5 ml of acetic anhydride was heated at 130° (bath temperature) for 10 min. After evaporation of acetic anhydride *in vacuo*, a colorless solid was kept in an alkaline desiccator overnight and recrystallized from ethyl acetate to give 37 mg (66%) of colorless needles of VII: mp 188–189.5°; ir ν^{Nujol} cm^{-1} 3510, 1700, 1650; mass *m/e* 311 (M^+), 280, 268, 197 (base peak), 184; nmr $\delta^{\mathrm{DCCl_3}}$ 4.95 (s, 2 H), 3.65 (s, 6 H), *ca.* 3.6 (m, 2 H?), 3.31 (s, 2 H), 3.11 (s, 3 H), 2.70 (s, 1 H, OH), 2.22 (s, 3 H), 1.85–2.3 (2 H).

Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.85; H, 6.81; N, 4.50. Found: C, 57.92; H, 6.80; N, 4.24.

1,8,8-Trimethoxy-2,6-dioxo-4-(2′-aminoethyl)bicyclo[3.2.1]oct-3 ene (VIII) Hydrochloride. III (54 mg) was dissolved in 3 ml of 1.2 *N* hydrochloric acid in methanol and allowed to stand overnight at room temperature. Evaporation and recrystallization from methanol–ether afforded 27 mg (41.5%) of colorless needles, mp 108–111°, which were dried over phosphorus pentoxide at 50° overnight, and then melted at 118–124°: uv $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ϵ) 245 (5580), 294 (880); ir ν^{Nujol} cm^{-1} 3560, 3250, 1772, 1690; nmr δ^{D_2O} 6.27 (s, 1 H), 3.92 (s, 1 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.41 (s, 3 H), 2.9–3.5 (m, 6 H).

Anal. Calcd for $C_{13}H_{19}NO_5 \cdot HCl \cdot H_2O$: C, 48.22; H, 6.85; N, 4.33. Found: C, 48.40; H, 6.74; N, 4.93.

Perchlorate. To a solution of 40 mg of the hydrochloride in 0.3 ml of water was added 0.2 ml of 60% perchloric acid. The precipitated colorless powder was collected by filtration and recrystallized from 1 ml of water to yield 21 mg (43.8%) of colorless fine needles, mp 163–165°, of which one single crystal was used for X-ray analysis: ir ν^{Nujol} cm^{-1} 3200, 1769, 1683, 1085; uv $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ϵ) 245 (3370), 294 (770).

Anal. Calcd for $C_{13}H_{19}NO_5 \cdot HClO_4$: C, 42.23; H, 5.45; N, 3.79. Found: C, 42.51; H, 5.64; N, 4.32.

1,8,8-Trimethoxy-2,6-dioxo-4-(2′-trifluoroacetylaminoethyl)bicyclo-[3.2.1]oct-3-ene (IX). An 80-mg (0.25 mmol) sample of the hydrochloride of VIII was dissolved in 0.5 ml of trifluoroacetic anhydride at room temperature. After 10 min trifluoroacetic anhydride was evaporated *in vacuo* to leave a colorless solid which was kept in an alkaline desiccator overnight and recrystallized from ether–*n*-hexane to give 65 mg (72%) of colorless needles: mp 124–125°; ir ν^{Nujol} cm^{-1} 3340, 1765, 1710; mass *m/e* 365 (M^+), 350, 334, 333, 318, 205

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[31] E. Späth and J. Bruck, *Chem. Ber.*, 71B, 1275 (1938).

(base peak); nmr $\delta^{\mathrm{DCCl_3}}$ 6.06 (s, 1 H), 3.67 (s, 3 H), 3.56 (s, 3 H), *ca.* 3.65 (2 H), 3.49 (s, 1 H), 3.28 (s, 3 H), 2.95–2.6 (4 H); mass *m/e* 365 (M^+, $C_{15}H_{18}NO_6F_3$), 350 ($M^+ - CH_3$, $C_{14}H_{15}NO_6F_3$), 333 ($M^+ - CH_3OH$, $C_{14}H_{14}NO_5F_3$), 318 ($M^+ - CH_3,CH_3OH$, $C_{13}H_{11}NO_5F_3$), 205 (base peak, $C_{11}H_9O_4$).

Anal. Calcd for $C_{15}H_{18}NO_6F_3$: C, 49.32; H, 4.97; N, 3.84. Found: C, 49.42; H, 4.87; N, 3.84.

1,8-Dimethoxy-8-ethoxy-2,6-dioxo-4-(2′-trifluoroacetylaminoethyl)bicyclo[3.2.1]oct-3-ene (XXI). To a solution of 50 mg (0.186 mmol) of III in 12 ml of ethanol was added 4 ml of 6.0 *N* hydrogen chloride in ethanol cooling with ice. After 1 hr the reaction mixture was brought to room temperature and allowed to stand overnight and concentrated to dryness *in vacuo* at 20°. The residue was dissolved in 1 ml of ethanol, and the solvent was removed *in vacuo* to leave an oil which was kept in a desiccator over KOH overnight to give 53 mg of 1,8-dimethoxy-8-ethoxy-2,6-dioxo-4-(2′-aminoethyl)bicyclo[2.3.1]oct-3-ene as a pale yellow oil. This oil was dissolved in 0.5 ml of trifluoroacetic anhydride. After 15 min, evaporation *in vacuo* yielded 57 mg of yellow oil which was purified by preparative tlc on silica gel, eluting with methylene chloride, and recrystallized from a mixture of ether and *n*-hexane to give 30 mg (43%) of colorless prisms of XXI: mp 106–106.5°; ir ν^{Nujol} cm^{-1} 3400, 1763, 1733, 1696; mass *m/e* 379 (M^+), 364 ($M^+ - CH_3$), 350 ($M^+ - C_2H_5$), 347 ($M^+ - CH_3OH$), 333 ($M^+ - C_2H_5OH$), 318, 292 (base peak), 205, 179; nmr $\delta^{\mathrm{DCCl_3}}$ 6.04 (s, 1 H), 3.65 (s, 3 H), 3.53 (s, 3 H), 3.6–3.05 (5 H), 2.85–2.4 (4 H), 1.15 (t, 3 H, $J = 7$ Hz).

Anal. Calcd for $C_{16}H_{20}NO_6F_3$: C, 50.66; H, 5.31; N, 3.69. Found: C, 50.71; H, 5.36; N, 3.59.

Rearrangement of III in Methanol-*d* with Hydrogen Chloride. A stream of dry hydrogen chloride gas was passed slowly through a solution of 50 mg (0.186 mmol) of III in 1 ml of CD_3OD for 1 min with external ice cooling. After 1 hr the solution was allowed to return to room temperature and stand overnight and was then concentrated to dryness *in vacuo*. The dried residue, 52 mg of a yellow solid, was dissolved in 0.5 ml of trifluoroacetic anhydride and evaporated after 10 min. Purification by preparative tlc on silica gel, elution with methylene chloride, and recrystallization from ether–*n*-hexane yielded 35 mg (51.3%) of colorless prisms, mp 124–125°, which on the basis of mass and nmr spectra are a mixture of the trideuterio- (XXII), hexadeuterio- (XXIII), and compounds containing up to 11 deuterium atoms (XXIV).

N-Acetoxymethyl-2,6-dimethyoxy-4-acetoxymethylphenylacetamide (X). A solution of 200 mg (0.744 mmol) of III in 10 ml of glacial acetic acid was heated under gentle reflux for 1 hr. After evaporation of acetic acid the pale yellow oil was kept in a desiccator over KOH overnight and then chromatographed on a silica gel column (10 g). Elution with ethyl acetate gave two fractions. The first fraction was 89 mg (35%) of N-acetoxymethyl-2,6-dimethoxy-4-acetoxymethylphenylacetamide (X) which was recrystallized from ethyl acetate–*n*-hexane to give colorless needles: mp 164–165°; ir ν^{Nujol} cm^{-1} 1754, 1730, 1675; mass *m/e* 339 (M^+), 279, 250, 223 (base peak), 195, 186; nmr $\delta^{\mathrm{DCCl_3}}$ 7.10–6.70 (broad, 1 H), 6.56 (s, 2 H), 5.12 (d, 2 H, $J = 8$ Hz), 5.06 (s, 2 H), 3.83 (s, 6 H), 3.62 (s, 2 H), 2.10 (s, 3 H), 2.00 (s, 3 H).

Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.82; H, 6.26; N, 4.22.

Acetic Acid Treatment of X. A solution of 5 mg of X in 0.7 ml of acetic acid was heated at 130° (bath temperature) for 45 min. After evaporation of acetic acid a colorless solid (3.2 mg, 81%) was obtained by preparative tlc on silica gel, using dichloromethane–ethyl acetate (1:1), and was identified as XI (see below).

2,6-Dimethoxy-4-acetoxymethylphenylacetamide (XI). The second fraction, 68 mg (34%), was recrystallized from ethyl acetate–*n*-hexane to give colorless needles, mp 155–157°, identified as XI: ir ν^{Nujol} cm^{-1} 1744, 1658; uv $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ϵ) 282 (2000); mass *m/e* 267 (M^+, $C_{13}H_{17}NO_5$), 224, 223 (base peak, $M^+ - CONH_2$), $C_{12}H_{15}O_4$), 207, 182, 163, 153; nmr $\delta^{\mathrm{DCCl_3}}$ 6.55 (s, 2 H), 5.65 (broad, 2 H, disappeared on addition of D_2O), 3.81 (s, 6 H), 3.58 (s, 2 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 57.97; H, 6.53; N, 5.12.

2,6-Dimethoxy-4-hydroxymethylphenylacetic Acid (XII). A 21-mg (0.788 mmol) sample of XI in 10 ml of 4.0 *N* hydrochloric acid was refluxed for 1 hr. After cooling, the pale brown solid which precipitated was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to give 14 mg (80%) of a pale-yellow crystalline powder which was recrystallized from acetone–water to give colorless needles, mp 192–194°, insoluble in water, but soluble in dilute sodium bicarbonate: mass *m/e* 226 (M^+, $C_{11}H_{14}O_5$), 186, 182, 181 (base peak, $M^+ - CO_2H$, $C_{10}H_{13}O_3$), 165.

Methyl 2,6-Dimethoxy-4-hydroxymethylphenylacetate (XIII). To a solution of 4.7 mg of crude XII in 2 ml of methanol was added excess diazomethane in ether solution at room temperature. After 10 min the reaction mixture was evaporated to leave a colorless oil: mass *m/e* 240 (M^+), 223, 199, 182, 181 (base peak), 151.

2,6-Dimethoxy-4-acetoxymethylphenylacetic Acid (XIV). A solution of 4.3 mg of XII in 0.4 mg of acetic anhydride was heated at 90° for 1 hr. Evaporation of acetic anhydride gave a colorless oil: mass *m/e* 268 (M^+, $C_{13}H_{16}O_6$), 250, 226 ($M^+ - CH_2CO$, $C_{11}H_{14}O_5$), 223 ($M^+ - CO_2H$), 209, 182, 165, 151.

Methyl 2,6-Dimethoxy-4-acetoxymethylphenylacetate (XV). A methanol solution of 2.5 mg of XIV was treated with diazomethane in ether to give XV as a colorless oil: mass *m/e* 282 (M^+), 250, 240, 223 (base peak), 199.

2,6-Dimethoxy-4-acetoxymethylphenylacetamide (XI). To a solution of 11 mg of XIV in 5 ml of benzene was added 16 mg (2 drops) of thionyl chloride, and the solution was heated at 60° for 1 hr. Benzene and excess thionyl chloride were evaporated *in vacuo* to leave a colorless oil, which was dissolved in 5 ml of benzene, and the solution was saturated with ammonia gas with cooling for 1 hr. Evaporation and preparative tlc on silica gel (ethyl acetate elution) gave a colorless solid which was identical with XI, prepared from III by acetic acid treatment, with regard to tlc and mass spectra.