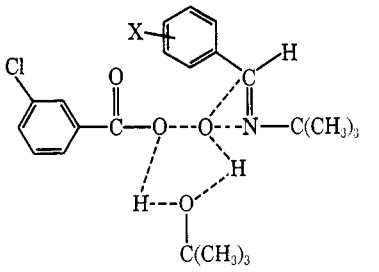
has been observed in compounds in which the nucleophilic site is directly linked to another electronegative atom (HOOH and H_2NOH examples). Electrostatic repulsions between the electron pairs of the nucleophilic site and adjacent atom increases the ground-state energy of the substrate, hence lowers the activation energy. Electrostatic repulsions are minimized in the transition state because one electron pair is engaged in forming the incipient new bond. In the present case, the low activation energy may be attributed to a "pseudo α effect" (the electron pair on nitrogen adjacent to the nucleophilic double bond, C=N).

A highly negative entropy of activation may be attributed to additional restrictions on the transition state (Va and b) imposed by the intramolecular hydrogen bonding.

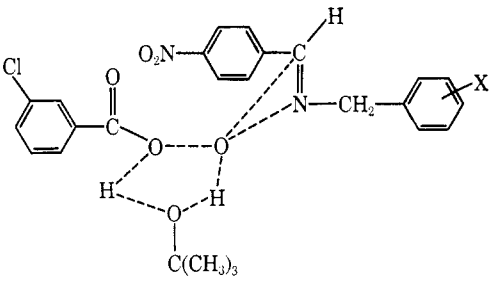
A solvent isotope effect of $k_H/k_D = 1.15$ for the oxidation of *p*-nitroaniline with peroxyacetic acid has been reported by Edwards and Ibne-Rasa.[23] The solvent isotope effect of $k_H/k_D = 1.10$ for the oxidation of Schiff bases with MCPBA is only slightly smaller (~5%). This small difference may be a specific steric requirement to solvation of the bulky MCPBA compared to peroxyacetic acid rather than to a difference in bond breaking in the O–O bonds in two cases.

In the case of oxidation of C=C with peroxy acids it has been observed that electronic effects cannot be interpreted clearly in aromatic olefins.[24] Similarly in using aromatic Schiff bases we have not found a linear relationship between log *k* against Taft σ^* values. Lack of a linear relationship may be due to the considerable steric effect in the transition state.

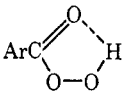
The rate of oxidation increases linearly with the increase in dielectric constant of the aprotic nonbasic solvents, indicating that the transition state is slightly more polar than the reactants. The lower values of rate constants in a protic solvent or in a solvent capable of hydrogen bonding (dioxane and *t*-butyl alcohol) are consistent with a peroxy acid structure VI. This ring is presumably present in aprotic solvents, but configurations such as VII stabilize the ground state in protic solvents, which in turn adds to the energy of activation.



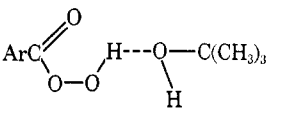
Va



Vb



VI



VII

(23) K. M. Ibne-Rasa and J. O. Edwards, *J. Am. Chem. Soc.*, **84**, 763 (1962).
(24) D. Swern, *ibid.*, **69**, 1692 (1947).

Mechanism of the Transformation of Cyclopenin to Viridicatin[1]

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Contribution from the Department of Chemistry, University of California, Berkeley, California. *Received June 2, 1969*

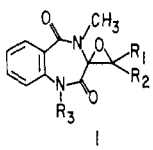
Abstract: The transformation of cyclopenin to viridicatin, which had previously been shown to occur in acid, has now been found to take place thermally and in alkali as well. Similar changes occur for isocyclopenin and methylcyclopenin, but the latter fails to rearrange in alkali. A mechanism for this decarboxylation–rearrangement, involving a tricyclic diene intermediate, is proposed based on these observations and the fact that methylisocyanate is an accompanying product in the thermal reaction. Ring-opened derivatives fail to give this reaction, demonstrating that the intact benzodiazepinedione ring is a structural requirement. The epoxide is not necessary, since a derived bromohydrin rearranges; also, the corresponding glycol gives viridicatin but requires more drastic conditions. A dihydro analog, 3-mesyloxybenzyl-4-methyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione, is transformed to the corresponding rearranged but not decarboxylated carbamoyldihydrocarbostyril. The same type of tricyclic diene intermediate resulting from benzylic carbon attack at the carbonyl-bearing aromatic site accommodates this observation.

Cyclopenin and cyclopenol, metabolites of *Penicillium cyclopium* and *P. viridicatum*, react in dilute acid solution with loss of optical activity and concomitant appearance, respectively, of viridicatin and viridicatol,

(1) Supported in part by the U. S. Army Research Office, Durham, N. C.

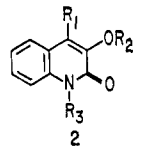
methylamine, and carbon dioxide.[2-4] Biosynthetically, cyclopenin and cyclopenol are the respective precursors of viridicatin and viridicatol,[5,6] phenylalanine and anthranilic acid are precursors to cyclopenin, and the carbon dioxide evolved in the cyclopenin–viridicatin transformation derived from the anthranilic acid carboxyl.

The structure of cyclopenin as **1a**, inferred from bio-



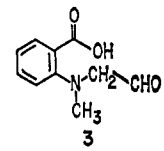
1

a. $R_1 = C_6H_5$; $R_2, R_3 = H$
b. $R_1, R_3 = H$; $R_2 = C_6H_5$
c. $R_1 = C_6H_4OH$; $R_2, R_3 = H$
d. $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
e. $R_1 = C_6H_4OCH_3$; $R_2 = H$; $R_3 = CH_3$

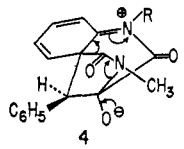


2

a. $R_1 = C_6H_5$; $R_2, R_3 = H$
b. $R_1 = C_6H_4OH$; $R_2, R_3 = H$
c. $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
d. $R_1 = C_6H_5$; $R_2 = Ac$; $R_3 = H$

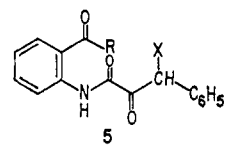


3



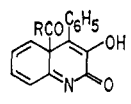
4

a. R = H
b. R = CH_3



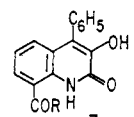
5

a. R = CH_3NH; X = OH
b. R = X = OH
c. R = CH_3NH; X = H
d. R = CH_3NH; X = Br
e. R = CH_3NH; X = Cl
f. R = CH_3NH; X = OAc
g. R = OH; X = Br
h. R = OCH_3; X = Br



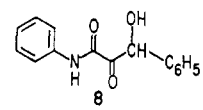
6

a. R = CH_3NH
b. R = OH



7

a. R = CH_3NH
b. R = OH



8

synthetic and other data,[4] has been confirmed and its relative stereochemistry established by synthesis.[7] The conversion of **1a** to viridicatin[2] (**2a**) could proceed *via* a hydrolysis mechanism with accompanying rearrangement and decarboxylation. However, the acid-catalyzed decarboxylation of cyclopenin, a cyclic dipeptide of anthranilic acid and phenylalanine, is particularly facile in comparison to the acid-catalyzed decarboxylation[8] of anthranilic acid itself. This marked propensity to decarboxylate–rearrange without any structural feature obviously anchimeric to either is reminiscent of the *in vivo* conversions of phosphoribosylanthranilic acid to indole glycerophosphate[9-11] and of the *in vitro* conversion of the anthranilic acid derivative **3** to N-methylindole.[12]

Our objective was to investigate the chemistry of cyclopenin in order to determine the structural and stereochemical parameters requisite to its facile rearrangement and decarboxylation to viridicatin.

Results and Discussion

Although the previous transformations of cyclopenin to viridicatin had been effected in solution, an early observation in our work that the melting point of isocyclopenin[13] was often that of viridicatin prompted an investigation of the thermal lability of cyclopenin, isocyclopenin, and methylcyclopenin. The former two benzodiazepines reacted at 190–200° to yield quantitatively viridicatin and methylisocyanate, identified by mass spectroscopy.[14] However, methylviridicatin (**2c**)[15,16] was not found from similar or more vigorous reaction of methylcyclopenin, indicating that the N-1 secondary amide was implicated in the thermal rearrangement–decarboxylation sequence.[17]

The thermal rearrangement of cyclopenin and isocyclopenin is best described as a concerted migration of the benzylic carbon followed by elimination of methylisocyanate *via* the diene intermediate **4**. Attempts to intercept this diene intermediate by Diels–Alder reaction in the melt with tetracyanoethylene,[18] maleic anhydride, or N-phenylmaleimide failed.

With these observations on the thermal rearrangement as suggestive, we next turned to the solution decarboxylative rearrangement. Initial data suggested that this reaction proceeded *via* a concerted mechanism, with no evidence for any appreciable concentration of an intermediate. Thus (a) the decrease in optical activity observed[2] during rearrangement of cyclopenin in acid solution paralleled the appearance of viridicatin; (b) chromatographic analysis during reaction of cyclopenin (**1a**), isocyclopenin (**1b**), or cyclopenol (**1c**) revealed the presence of reactant benzodiazepine and product carbostyril only, and (c) the nmr spectrum of cyclopenin in aqueous trifluoroacetic acid exhibited features only associated with cyclopenin, viridicatin, and methylamine.

The assumption that benzylic carbon migration occurred to the carboxyl seat of cyclopenin is a necessary consequence of concerted rearrangement and decarboxylation; candidate acyclic intermediates (*e.g.*, **5a**[4]) have two available sites for ring closure, *i.e.*, at the carboxyl-bearing carbon (**6**) or at the other carbon *ortho* to the nitrogen function (**7**). A test of the gross rearrangement features was obtained by reaction of cyclopenin in deuterium oxide 1 *N* in dideuteriosulfuric acid. Viridicatin was isolated and the nonlabile deuterium content determined by mass spectroscopy. The ratios of relative abundances of *m/e* 236 to *m/e* 238 and *m/e* 237 to

(2) A. Bracken, A. Pocker, and H. Raistrick, *Biochem. J.*, **57**, 587 (1954).
(3) J. H. Birkinshaw, M. Luckner, Y. S. Mohammed, K. Mothes, and C. E. Stickings, *ibid.*, **89**, 196 (1963).
(4) M. Luckner and Y. S. Mohammed, *Tetrahedron Letters*, 1953 (1963).
(5) M. Luckner and K. Mothes, *ibid.*, 1035 (1962).
(6) (a) M. Luckner, *Eur. J. Biochem.*, **2**, 74 (1967); (b) see also M. Luckner and K. Winter, *ibid.*, **7**, 380 (1969).
(7) H. Smith, P. Wegfahrt, and H. Rapoport, *J. Am. Chem. Soc.*, **90**, 1668 (1968).
(8) W. H. Stevens, J. M. Pepper, and M. Lounsbury, *Can. J. Chem.*, **30**, 529 (1952).
(9) P. de Mayo, "Molecular Rearrangements," Interscience Publishers, New York, N. Y., 1964, p 972.
(10) T. E. Creighton, *J. Biol. Chem.*, **243**, 5605 (1968).
(11) O. H. Smith and C. Tanofsky, *ibid.*, **235**, 2051 (1960).
(12) J. Harley-Mason, *Chem. Ind.* (London), 355 (1955).
(13) P. K. Martin, H. Rapoport, H. W. Smith, J. L. Wong, *J. Org. Chem.*, **34**, 1359 (1969).
(14) J. M. Ruth and R. J. Philippe, *Anal. Chem.*, **38**, 720 (1966).
(15) D. J. Austin and M. B. Meyers, *J. Chem. Soc.*, 1197 (1964).
(16) K. G. Cunningham and G. G. Freeman, *Biochem. J.*, **53**, 328 (1953).
(17) The facile thermal rearrangement of cyclopenin suggested the possibility that photochemical reaction might also accomplish its transformation to viridicatin. Irradiation of cyclopenin under reaction conditions for which viridicatin was stable gave two products but no evidence for viridicatin. Also, the low resolution mass spectra of cyclopenin and isocyclopenin (*m/e* 294, M^+) exhibited base peaks at *m/e* 237 corresponding to loss of C_2H_3NO, *m/e* 57. However, high-resolution measurements suggested that this was not the major fragmentation mode.
(18) C. A. Stewart, *J. Org. Chem.*, **28**, 3320 (1963).

m/e 238 were identical[6b] with those found in viridicatin prepared in the absence of deuterium. As decarboxylation of the carbostyrils (**7a** and **b**) to yield viridicatin must proceed with incorporation of solvent deuterium, the rearrangement of cyclopenin to viridicatin must proceed by benzylic carbon ring closure to the carboxyl seat, hence the carboxy- and carboxamidocarbostyrils are not intermediates. Also excluded by this test were any acyclic intermediates (*e.g.*, **8**) which result from decarboxylation prior to ring closure.

Hypothetically, a concerted rearrangement and decarboxylation is applicable to both alkaline and acid-catalyzed reactions. Concerted rearrangement in acidic media is depicted as proceeding *via* an incipient benzylic carbonium ion (**9**), bond formation being achieved by nucleophilic participation of the secondary amide moiety and subsequent collapse of the tricyclic diene intermediate (or transition state) (**4**), in analogy with the thermal process, by elimination of methylisocyanate.[6b,19] Alkaline reaction in a similar sequence (**10**) requires that the secondary amidate anion act as nucleophile to epoxide opening, or induce a conformational proximity to the rearrangement seat, or both. These solution processes can also entertain the glycol (**11a**) as precursor to rearrangement and decarboxylation.

This scheme predicts that alkylation of the secondary amide blocks the formation of amidate ion in alkaline reaction and therefore blocks rearrangement. In agreement with the latter prediction, cyclopenin (**1a**), isocyclopenin (**1b**), and cyclopenol (**1c**) react in dilute alkaline solution to yield viridicatin and viridicatol, respectively. the rearrangements being accompanied by the appearance of anthranilic acid. In reaction conditions for which 28% viridicatin was formed from cyclopenin (0.04 *M* sodium hydroxide at 25°), N-methylcyclopenin yielded only methylanthranilic acid. Viridicatin and methylviridicatin were unchanged under identical reaction conditions.

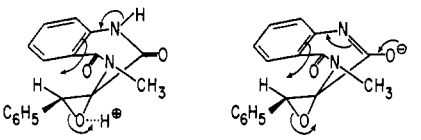
In acid solution cyclopenin (**1a**), isocyclopenin (**1b**), cyclopenol (**1c**), and methylcyclopenin (**1d**) gave excellent yields of the corresponding viridicatin derivative. These observations are best explained by attack on an incipient benzylic carbonium ion (**9**) with amide participation in the rearrangement. Invoking a similar mechanism, alkaline reaction requires a nucleophilic role for the secondary amidate ion of cyclopenin, isocyclopenin, and cyclopenol. This latter condition is not met by methylcyclopenin in which the N-1 amide is alkylated, hence rearrangement does not occur.

Although all the rearrangements observed could be explained by direct attack on the epoxide, as in **9** and **10**, leading to an intermediate of type **4**, rearrangement *via* an intermediate in which the epoxide had been previously opened was still tenable. In considering this possibility it appeared that systematic evaluation of candidate intermediates was inescapable in arriving at the structural and steric features of cyclopenin responsible for its facile rearrangement and decarboxylation. Our objective was to prepare the glycol **11a**, the hydroxypyruvamides **5a**, cited[4] as a probable intermediate in the transformation, and **5b**; subject them to conditions of cyclopenin rearrangement; and determine whether viridicatin was their reaction product.

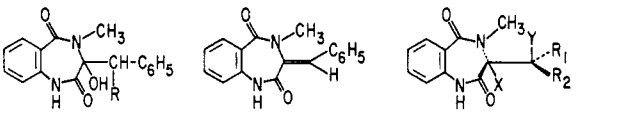
(19) A mechanism *via* acyclic intermediates has been suggested[6b] to accommodate the observation that cyclopenin reacted with Lewis acids to yield viridicatin and methylisocyanate.

The benzylidine compound **12**[7,13] provided an adequate intermediate for synthesis of the desired glycol **11a**. Reaction of **12** with hypobromous acid gave isomeric bromohydrins, isolated in 49 and 21% yields. The major product exhibited N-methyl and benzylic hydrogen resonances at δ 2.58 and 5.05, respectively; the minor product gave the same resonances at δ 3.30 and 5.12. The products were inert to oxidation, suggesting a diastereoisomeric relationship between tertiary alcohols rather than positional isomerization. Hydrogenolysis of either product gave the 3-hydroxy-3-benzylbenzodiazepine (**11b**) and the phenylpyruvamide[20] (**5c**), the latter apparently derived by ketonization of the precursor cyclol.

Solvolysis of either bromohydrin gave the bromophenylpyruvamide (**5d**), identical in all respects with a synthetic sample, and not the desired glycol (**11a**). These data confirmed that the bromohydrins are diastereomers but their failure to yield isolable quantities of cyclopenin or isocyclopenin precluded assignment of their relative stereochemistry. A tentative assignment from nmr data is that the major product is represented as structure **13a** and the minor product as **13b**, reflecting



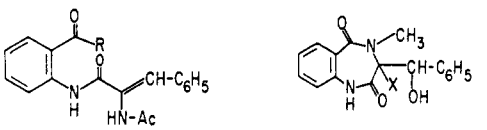
9 10



11 12 13

a. R = OH
b. R = H

a. X = OH, Y = Br, $R_1 = C_6H_5$, $R_2 = H$
b. X = OH, Y = Br, $R_1 = H$, $R_2 = C_6H_5$



14 15

a. $R = CH_3NH$
b. $R = OCH_3$
c. R = OH

a. X = Br
b. X = Cl

the expected anisotropic shifts associated with interactions of N-methyl aromatic and carbonyl-benzylic hydrogen substituents. The synthesis of the bromophenylpyruvamide (**5d**) was achieved by bromination of the acetamidocinnamamide **14a**, available from reaction[21] of the 2-methyl-4-benzylidene-5-oxazolinone[22] with methylanthranilamide.

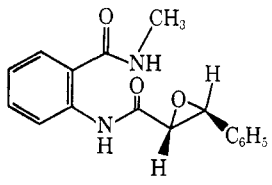
Acid hydrolysis of the minor bromohydrin yielded viridicatin as one of several products; the major bromohydrin failed to yield viridicatin under identical conditions. That the bromopyruvamide (**5d**) did not yield viridicatin was taken as evidence that a cyclol equilib-

(20) P. Wegfahrt and H. Rapoport, *J. Org. Chem.*, **34**, 3035 (1969).
(21) S. I. Lerye, S. M. Mamiofe, and K. M. Ravikovick, *J. Gen. Chem.*, **21**, 1431 (1951).
(22) R. M. Herbst and D. Shemin, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 1.

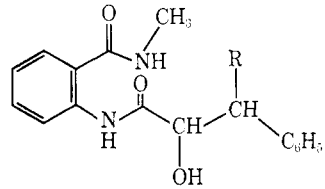
rium[20,23] does not exist between the ring-opened (**5d**) and ring-closed (**13b**) forms. The conversion of cyclopenin to viridicatin in dilute hydrobromic acid was more rapid than the conversion of the bromohydrin to viridicatin and augmented the assumption that in dilute acid solution halohydrins are not intermediates in the rearrangement of cyclopenin.

The glycol (**11a**) was obtained from reaction of cyclopenin with hydrogen chloride or bromide in moist benzene solution. The glycol was probably formed *via* the halohydrin (**15a,b**) since the bromohydrins **13** failed to yield **11a**. The suggestion of greater cationic character at the benzodiazepine 3 position than at the benzylic carbon also is consistent with the observed mode of hypobromous acid addition to the benzylidine compound **12**. The glycol (**11a**) was unreactive in 2 *N* hydrochloric acid, conditions which converted cyclopenin to viridicatin, but reacted in concentrated sulfuric acid to yield viridicatin quantitatively.

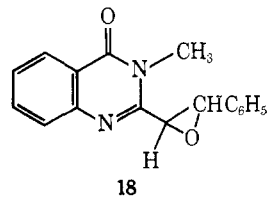
Preparation of the desired 3-hydroxypyruvamide **5a** from the corresponding chloro- or bromopyruvamide was unsatisfactory under alkaline conditions; quinazoline formation appeared to be the favored reaction. The chloropyruvamide **5e** was available in two steps from glycidamide **16**[7] *via* the chlorohydrin **17a**. Alternatively, synthesis of **5a** was accomplished from the glycidamide **16** by acetolysis to the diolmonoacetate **17b**, oxidation to the ketol acetate **5f**, and transesterification to the alcohol. Reaction of the glycidamide in ethanolic sodium acetate furnished a good yield of the quinazoline **18**. That the structure of the diolmonoacetate was as indicated is evident from its hydrogenolysis to **17c** and subsequent oxidation to the pyruvamide **5c**. The hydroxypyruvamide **5a**, previously suggested as an intermediate in the rearrangement of cyclopenin, failed to yield viridicatin by acid or alkaline hydrolysis.



16

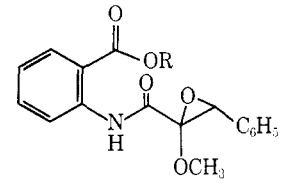


17a, R = Cl
b, R = OAc
c, R = H

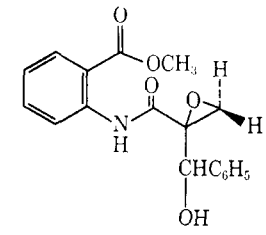


18

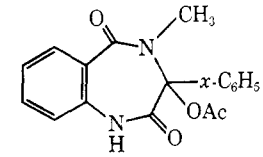
The synthesis of the final candidate intermediate **5b** was accomplished by two routes. The α-acetamidocinnamamide derivative **14c** was prepared from the corresponding methyl ester **14b** by selective hydrolysis. Bromination gave **5g**, which was solvolyzed in aqueous dimethyl sulfoxide. Alternatively, the same product mixture was obtained by reaction of the bromopyruvamide **5h** with sodium methoxide to yield the methoxy epoxide **19a**, hydrolysis to **19b**, and acid-catalyzed conversion of **19b** to crude hydroxypyruvamide **5b**, which with diazomethane yielded the glycidamide ester **20**. Treatment of the hydroxypyruvamide **5b** with acid or base yielded anthranilic acid and no viridicatin.



19a, R = CH_3
b, R = H



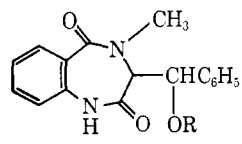
20



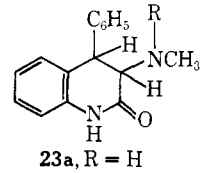
21a, X = CHOH
b, X = CO

These data exclude acyclic intermediates in the transformation of cyclopenin to viridicatin and force the conclusion that rearrangement occurs *via* an intermediate benzodiazepine. The glycol monoacetate **21a**, available by reduction of the ketone **21b**,[24] failed to yield viridicatin or acetyl viridicatin[2] **2d** on exposure to dilute acid or alkali but viridicatin was a product from its reaction with concentrated sulfuric acid.

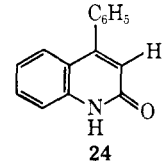
The benzodiazepine functionalities implicated in the rearrangement are the benzylic substituent and the primary amide, the latter being especially needed for alkaline rearrangement. Since these features are present in the dihydro models of cyclopenin, rearrangement could potentially occur with the 3-hydroxybenzylbenzodiazepine (**22a**).[7] Using the mesylate substituent of **22b** as the leaving group, this hypothesis was put to the test. Acid treatment of **22b** gave an alkaline product which exhibited a methyl singlet at δ 2.44, two one-proton doublets (J = 6.5 Hz) at δ 3.58 and 4.36, and nine aromatic hydrogens. Acylation gave a monoacetyl derivative which showed two methyl singlets at δ 2.13 and 2.35, and two one-proton doublets (J = 6.5 Hz) at δ 4.5 and 6.1. The mass spectrum showed a molecular ion at *m/e* 294 and base peak at *m/e* 251, the latter corresponding to the result of a typical McLafferty rearrangement.[25] Degradation of this aminodihydrocarbostyril **23a** to 4-phenylcarbostyril[26] (**24**) confirmed its structure. The rearrangement of **22b** to **23a** also was accomplished in 20% aqueous acetone without added mineral acid although rearrangement of its alcohol precursor **22a** to **23a** was observed only with concentrated sulfuric acid.



22a, R = H
b, R = Ms
c, R = Ac



23a, R = H
b, R = Ac
c, R = CO_2H
d, R = CO_2CH_3



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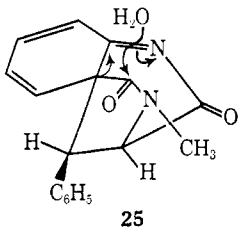
(24) H. W. Smith and H. Rapoport, to be published.
(25) J. A. Gilpin, *Anal. Chem.*, **31**, 935 (1959).
(26) E. F. M. Stephenson, *J. Chem. Soc.*, 2556 (1956).

The relative stereochemistry of **23a** obtained from **22a** and **22b** differ as evident from the coupling constants of the methine hydrogens (J = 8.5 and 6.5, respectively). While neither reaction was clearly stereospecific, cisoid geometry, implied from nmr data, was expected from **22b** if bond making is well advanced in the transition state. Confirmation that **23a** was obtained *via* **23c** was obtained by reaction of **22a** in methanol solution. The product obtained was carbamate **23d**, containing all elements of the benzodiazepine in rearranged but not decarboxylated form. The origin of the carbon dioxide evolved in aqueous solution rearrangement was therefore the carboxyl of **23c**. That reactions of **22a**, **b** did not occur *via* the benzylidine compound **12** was clear from the failure of the latter to rearrange.

Retention of the amino group in the rearrangement and decarboxylation of the mesylate derivative **22b** indicates that methylisocyanate elimination is not requisite to rearrangement. Also, **23a** was obtained by decarboxylation of the carbamic acid **23c**, which in turn must result from concerted hydrolysis, rearrangement and displacement of the mesylate moiety.

These observations can all be rationalized by invoking the same type of tricyclic-diene intermediate (**4**, **9**, **10**) proposed to explain the acid-catalyzed rearrangement–decarboxylation of cyclopenin (**1a**), isocyclopenin (**1b**), methylcyclopenin (**1d**), the glycols **5b** and **21a**, and the bromohydrin **13b**, as well as the thermal and alkaline rearrangements. For the case of the dihydro analog, mesylate **22b**, this intermediate would take the form **25** as the result of displacement at the benzylic mesylate carbon. Decomposition to products would then result from water or methanol attack at the benzodiazepine-5-carbonyl carbon, which of course could be a mode of decomposition for the other nonthermal rearrangements as well.



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Experimental Section[27]

***dl*-Methylcyclopenin (1d).** Cyclopenin (**1a**, 76 mg) in a solution of *t*-butyl alcohol (15 ml), previously treated with 50% sodium hydride (25 mg), was stirred at 25° for 30 min. Methyl iodide (2 ml) was added and the turbid mixture allowed to react for 19 hr. The mixture was diluted with methylene chloride, washed with ice-cold 0.2 *N* hydrochloric acid, dried, and evaporated. The residue was dissolved in benzene and filtered through silica gel. Elution with methylene chloride–ethyl acetate (3:1) gave **1d** (53 mg): mp 192–193° (lit.[4] mp *l*-methylcyclopenin 206°; uv 285 nm (ϵ 2000), 212 (31,200); nmr (CD_3OD) δ 7.15 (m, 8, ArH), 6.50 (m, ArH), 3.84 (s, 1, CHAr), 3.41 (s, 3, NCH_3), 3.20 (s, 3, NCH_3); mass spectrum 308 (M^+, 100), 251 (21).

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 69.9; H, 5.2; N, 9.1.

2-(3-Hydroxy-3-phenylpyruvamido)-N-methylbenzamide (5a). Acetoxy ketone **5f** (490 mg) in methanol (100 ml) was treated with toluenesulfonic acid (37 mg) and the solution heated at reflux for 20 hr. The solution was concentrated, diluted with methylene chloride, and washed with sodium bicarbonate solution. Silica gel chromatography of the residue from the organic phase afforded **5a** (100 mg), mp 176–177°, after recrystallization from methanol–ethyl acetate: uv 297 nm, 255; nmr δ 7.6 (m, 9, ArH), 5.56 (d, 1, CHAr), 2.90 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.4; w, 5.2; N, 9.0. Found: C, 65.1; H, 5.0; N, 9.0.

2-(3-Hydroxy-3-phenylpyruvamido)benzoic Acid (5b). A solution of **5g** (1.25 g) in dimethyl sulfoxide 20 ml) was cooled and treated with cold water (10 ml) with intermittent cooling during 10 min then allowed to stand at 25° for 12 hr. The precipitate (200 mg) was removed and extraction of the filtrate with methylene chloride and evaporation of the methylene chloride gave 640 mg of product. The two products exhibited different R_f values on tlc but gave the same product mixture on reaction with diazomethane. Attempted purification of either acid fraction failed: uv 307 nm, 250; nmr (CD_3OD) 8.30–7.0 (m, 9, ArH), 6.23 (s, CH), 4.95 (s, CH). The collapse of low-field methine hydrogen resonance (6.23) to a higher field methine singlet (4.95) in methanolic solution was typical of the pyruvamide derivatives.[21]

A solution of **19b** (37 mg) in dioxane (6 ml) was cooled, 0.5 *M* perchloric acid (2 ml) was added, and, after 1 hr, the solution was diluted with water and extracted with methylene chloride. Drying and evaporation of the extract gave an acid residue spectroscopically and chromatographically indistinguishable from the major product from **5g**. This material was used without further treatment.

2-(3-Phenylpyruvamido)-N-methylbenzamide (5c). A. By Oxidation of 2-(2-Hydroxy-3-phenylpropionamido)-N-methylbenzamide (17c). A solution of hydroxypropionamide **17c** (140 mg) in acetone (10 ml) was cooled to 0° and chromic acid was added dropwise. The precipitate obtained on dilution with water was filtered, dried, and recrystallized from acetone–hexane to yield **5c** (48 mg), mp 191–192°, identical in all respects with an authentic sample.[20]

B. By Hydrogenolysis of 3-Hydroxy-3-bromobenzyl-4-methyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione (13). The major bromohydrin **13a** (250 mg, mp 173°) in ethyl acetate (125 ml) was treated with 10% palladium on carbon (250 mg) and hydrogen at 47 psi for 5 hr, the reaction mixture was filtered, and the filtrate was evaporated. Two crystallizations from ether afforded 70 mg of **11b**: mp 142–143°; nmr δ 6.85–8.05 (m, 10, ArH), 3.00 (s, 3, NCH_3), 2.86 (s, 2, CH_2Ar). The combined mother liquors were evaporated, dissolved in methanol, and permitted to isomerize at 4°. Evaporation to a viscous residue and crystallization of the residue from ether yielded 25 mg of **5c**, mp 188–190° (lit.[20] mp 191°).

The minor isomeric bromohydrin **13b** (200 mg, mp 166°) was hydrogenolyzed in the same manner. Crystallization led to recovery of **13b** (50 mg) from methylene chloride solution and the residue from the filtrate was chromatographed on silica gel (5 g). The product eluted with methylene chloride crystallized from ether solution to afford 30 mg of **5c**, mp 188–190°.

2-(3-Bromo-3-phenylpyruvamido)-N-methylbenzamide (5d). 2-(2-Acetamidocinnamamido)-N-methylbenzamide (**14a**, 1.01 g) in acetic acid (40 ml) was vigorously stirred during the addition of bromine (720 mg) in acetic acid (10 ml). Dissolution of suspended material occurred toward the end of the addition and stirring was continued for 15 min. The solution was diluted with ice-water and extracted with ethyl acetate. The extracts were cycled through water and sodium bicarbonate washes, dried, and evaporated to a residue which deposited 450 mg of recovered **16a** from ether. Chromatography of the filtrate on silica gel and crystallization of the methylene chloride eluate from ether–hexane gave **5b** (230 mg): mp 119–120°; uv 298 nm (ϵ 4500), 250 (12,400); nmr ($CDCl_3$) δ 6.8–7.8 (m, 9, ArH), 6.57 (s, 1, CHAr), 2.86, 2.93 (d, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.4; H, 4.0, N, 7.5. Found: C, 54.4; H, 4.2; N, 7.1.

Isomerization of 3-Hydroxy-3-bromobenzyl-4-methyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione (13) to 2-(3-Bromo-3-phenylpyruvamido)-N-methylbenzamide (5d). A solution of the major bromohydrin **13a** (50 mg), mp 173°, in acetone (10 ml) and water (10 ml), after 48 hr at 25°, was evaporated to precipitation and the precipitate extracted into methylene chloride. Drying and removal of solvent gave a residue which was dissolved in methylene chloride and filtered through silica gel. The effluent was evaporated and the residue was crystallized from ether–hexane to yield **5d** (10 mg), mp 116–117°, identical in all respects with the synthetic sample.

The minor bromohydrin **13b** (50 mg), mp 166°, was treated as above to yield 8 mg of **5d**, mp 116–117°.

(27) Nmr spectra were determined in DMSO-d_6, unless otherwise specified, with internal tetramethylsilane; ultraviolet spectra were taken in ethanol; melting points are uncorrected and were determined on a Mel-Temp apparatus.

2-(3-Chloro-3-phenylpyruvamido)-N-methylbenzamide (5e). The chlorohydrin **17a** (1.0 g) in ethyl acetate (40 ml) was treated with excess chromic acid at 0° during 3 hr. The reaction mixture was diluted with water and the solution was extracted with ethyl acetate. Drying and evaporation of the organic phase gave a viscous residue. Chromatography on silica gel (50 g) gave **5e** (300 mg), mp 134° after crystallization of the residue from methylene chloride elution: uv 298 nm (ε 3740), 250 (13,100), 216 (21,600); nmr ($CDCl_3$) 7.53 (m, 9, ArH), 6.41 (s, 1, CHAr), 2.84, 2.78 (d, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.7; H, 4.6; N, 8.5. Found: C, 61.8; H, 4.8; N, 8.6.

2-(3-Acetoxy-3-phenylpyruvamido)-N-methylbenzamide (5f). A solution of diolacetate **17b** (2.0 g) in acetone (50 ml) was cooled and excess chromic acid added. After standing at 15° for 6 hr, the mixture was diluted to 500 ml with ice–water and the precipitate extracted into ethyl acetate. Drying and evaporation of the ethyl acetate gave a residue which deposited 400 mg of recovered **17b** from ether solution. The residue from the filtrate was dissolved in benzene and chromatographed on silica gel (60 g). Elution with methylene chloride–ethyl acetate (9:1) gave **5f** (710 mg), mp 138–139°, from ether–hexane. A second crystal modification, mp 101–102°, was obtained by slow crystallization from ether–hexane: uv 300 nm (ε 4150), 252 (11,100); nmr δ 8.75, 8.65 (d, 1, CHAr), 7.40 (m, 9, ArH), 2.83 (d, 3, NCH_3), 2.16 (s, 3, CH_3CO).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.4; H, 5.1; N, 8.0. Found: C, 64.4; H, 5.4; N, 8.1.

2-(3-Bromo-3-phenylpyruvamido)benzoic Acid (5g). A suspension of the cinnamamide **16c** (500 mg) in acetic acid (20 ml) was treated with a solution of bromine (280 mg) in acetic acid (10 ml) during 10 min. Dissolution occurred during the addition and after standing at 25° for 15 min, water (10 ml) was added to incipient precipitation and the mixture stirred for 15 min. Further dilution with water (30 ml) gave 280 mg of crude **5g**. Recrystallization from ethyl acetate–hexane yielded pure **5g**: mp 202° dec; nmr δ 8.0–7.0 (m, 9, ArH), 6.65 (s, 1, CHAr).

Anal. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.3; H, 3.3; Br, 22.1; N, 3.9. Found: C, 53.6; H, 3.3; Br, 22.3; N, 4.0.

Methyl 2-(3-Bromo-3-phenylpyruvamido)benzoate (5h). The cinnamamide **14b** (670 mg) was treated with bromine (351 mg) as above. The solution was diluted with methylene chloride, washed successively with water and 5% sodium bicarbonate, and the organic phase was dried and evaporated. Chromatography of the residue on silica gel (20 g) and crystallization from ethyl acetate–hexane gave pure **5h**: mp 136°; uv 308 nm (ε 5620), 250 (11,600), 218 (28,400); nmr ($CDCl_3$) δ 8.1–6.8 (m, 9, ArH), 6.55 (s, 1, CHAr), 3.92 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{41}BrNO_4$: C, 54.3; H, 3.8; Br, 21.2; N, 3.7. Found: C, 54.4; H, 3.8; Br, 21.7; N, 3.8.

3,4-Dihydro-3-hydroxy-3-hydroxybenzyl-4-methyl-1H-1,4-benzodiazepine-2,5-dione (11a). Hydrogen chloride was slowly bubbled through a solution of cyclopenin (150 mg) in benzene (50 ml) during 30 min. The suspension was diluted with methylene chloride, the methylene chloride layer was evaporated, and the residue was triturated with ether to yield 122 mg of crude **11a.** The product was recrystallized from methanol–water then ethyl acetate to yield pure **11a**: mp 206–207°; uv 295 nm; nmr δ 8.2–7.2 (m, 9, ArH), 6.35 (s, 1, OH), 4.70 (s, 1, CH), 2.60 (s, 3, NCH_3); mass spectrum *m/e* (relative intensity) 312 (1.8), 294 (9.5), 189 (100), 205 (13.6), 105 (96).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 65.3; H, 5.0; N, 8.9.

3-Hydroxy-3-bromobenzyl-4-methyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione (13). 3-Benzylidine-1,4-benzodiazepine **12**[13] (1.39 g) in dioxane (25 ml) was treated with N-bromoacetamide (1.38 g) and to the cold solution was added dropwise 0.5 *M* perchloric acid (5 ml). The solution was warmed to and kept at room temperature for 4.5 hr, treated with cold, dilute sodium sulfite, then diluted with ice–water. The precipitate was extracted into methylene chloride, the extract washed with water, dried, and evaporated to a crystalline residue which was triturated with ether to yield 926 mg (49%) of **13a**: mp 173–174°; uv 295 nm (ε 2700), 217 (28,600); nmr δ 7.30 (m, 9, ArH), 5.05 (s, 1, CHAr), 2.58 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.4; H, 4.0; N, 7.5. Found: C, 54.6; H, 4.1; N, 7.5.

The mother liquor was evaporated and the residue dissolved in methylene chloride from which **13b** (403 mg, 21%) crystallized: mp 166°; uv 295 nm (ε 2260), 227 (23,800); nmr δ 7.20 (m, 9, ArH), 5.12 (s, 1, CHAr), 3.30 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.4; H, 4.0; N, 7.5. Found: C, 54.5; H, 4.1; N, 7.6.

2-(2-Acetamidocinnamido)-N-methylbenzamide (14a). 4-Benzylidine-2-methyl-5-oxazolone[22] (3.74 g) and *o*-aminomethylbenzamide (3.0 g) in benzene (60 ml) were heated at reflux for 16 hr. Dilution of the cooled mixture with ether and filtration gave a crude product (4.3 g) which was recrystallized from methanol–ethyl acetate to yield **14a** (3.6 g): mp 246–247°; uv 310 nm sh (ε 15,800), 292 (16,700); nmr δ 9.90 (s, 1, NH), 8.75–7.2 (m, 11, ArH, CH, NH), 2.83, 2.78 (d, 3, NCH_3), 2.16 (s, 3, $COCH_3$).

Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.6; H, 5.7; N, 12.5. Found: C, 67.6; H, 5.8; N, 12.4.

Methyl 2-(2-Acetamidocinnamamido)benzoate (14b). A solution of 4-benzylidine-2-methyl-5-oxazolone[22] (3.74 g) in benzene (150 ml) was treated with methyl anthranilate (1.51 g) and the solution was heated at reflux for 36 hr. The solution was evaporated to a solid residue, and the residue was triturated with 50% ether–hexane solution and filtered to yield **14b**. Filtration through silica gel gave **14b**, mp 176° after recrystallization from ethyl acetate–hexane: uv 318 nm (ε 21,000), 292 (23,100); nmr δ 9.90 (s, 1, NH), 8.80, 8.67 (d, 1, CHAr), 8.02–7.90 (m, 9, ArH), 3.87 (s, 3, OCH_3), 2.16 (s, 3, CH_3CO).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.4; H, 5.4; N, 8.3. Found: C, 67.7; H, 5.4; N, 8.2.

2-(2-Acetamidocinnamamido)benzoic Acid (14c). A solution of cinnamamide **14b** (2.0 g) in dioxane (50 ml) was treated with 1 *N* sodium hydroxide (40 ml) at 25° for 23 hr. The solution was diluted with water and acidified, and the precipitate was filtered to yield **14c** (1.8 g): mp 221–222° dec; uv 310 nm (ε 21,200), 295 (20,200); nmr δ 9.90 (s, 1, NH), 8.9–7.4 (H, 11, ArH, CH, NH), 2.16 (s, 3, CH_3CO).

Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6. Found: C, 66.7; H, 5.2; N, 8.7.

2-(3-Chloro-2-hydroxy-3-phenylpropionamido)-N-methylbenzamide (17a). The phenylglycidamide (**16**)[7] (600 mg) in ethylene glycol dimethyl ether (20 ml) was treated dropwise with concentrated hydrochloric acid (3 ml) and the gently exothermic reaction was stirred for 2 hr. The solution was diluted with methylene chloride which was washed with water, dried, and evaporated. Chromatography of the residue on silica gel (40 g) and elution with methylene chloride–ethyl acetate (9:1) gave 217 mg of **17a**: mp 165–167°; uv 295 nm (ε 3500), 254 (16,800), 217 (27,900); nmr δ 7.40 (m, 9, ArH), 5.60 (d, 1, J = 2.5 Hz, CHCl), 4.45 (d, 1, J = 2.5 Hz, CHOH), 2.84 (d, 3, NCH_3).

Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.4; H, 5.2; Cl, 10.7; N, 8.4. Found: C, 61.5; H, 5.3; Cl, 10.5; N, 8.3.

2-(3-Acetoxy-2-hydroxy-3-phenylpropionamido)-N-methylbenzamide (17b). Phenylglycidamide **18** (500 mg) in acetic acid (10 ml) was heated at 95° for 1 hr. The solution was diluted with methylene chloride, washed with water, then with 5 wt % sodium carbonate, dried, and evaporated to a viscous residue. Crystallization of the residue from ethyl acetate–hexane solution afforded **17b**: mp 119–121°; uv 300 nm (ε 4200), 252 (11,000); nmr (CD_3OD) δ 7.3 (m, 9, ArH), 6.22 (d, 1, J = 3 Hz, CHOAc), 4.44 (d, 1, J = 3 Hz, CHOH), 2.85 (s, 3, NCH_3), 1.98 (s, 3, CH_3O).

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.0; H, 5.7; N, 7.9. Found: C, 63.8; H, 5.9; N, 7.6.

2-(2-Hydroxy-3-phenylpropionamido)-N-methylbenzamide (17c). The chlorohydrin **17a** (328 mg) in ethyl acetate (150 ml) was hydrogenolyzed over 10% Pd/C (328 mg) during 1.25 hr. The catalyst was removed and the filtrate was evaporated to residue which was crystallized from ethyl acetate–hexane, giving 170 mg of **17c**: mp 167–168°; uv 295 nm (ε 3750), 253 (16,700), 212 (28,200); nmr (CD_3OD) δ 7.20 (m, 9, ArH), 4.35 (t, 1, J = 4 Hz, CH), 3.10 (d, 2, J = 4 Hz, CH_2), 2.80 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.4; H, 6.1; N, 9.4. Found: C, 68.2; H, 6.0; N, 9.3.

2-(1,6-Epoxy-6-phenyl)ethyl-3-methyl-4-quinazolinone (18). A solution of the glycidamide **16** (1.0 g) in 95% ethanol (100 ml) was treated with sodium acetate (2.0 g) and the solution refluxed for 2.5 hr. The cooled solution was evaporated to dryness, the residue was suspended in water, and the oily precipitate was extracted into methylene chloride. The extract was dried and evaporated and the residue was crystallized from acetone–hexane to yield **18** (0.54 g): mp 107° after recrystallization from methanol–water; uv 315 nm (ε 3610), 303 (4700), 275 (10,200), 228 (32,600); nmr ($CDCl_3$) δ 7.35 (m, 9, ArH), 4.32 (d, 1, J = 2.5 Hz, CH), 3.97 (d, 1, J = 2.5 Hz, CH), 3.62 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.6; H, 5.2; N, 9.8.

Methyl 2-(2-Methoxy-3-phenylglycidamido)benzoate (19a). A solution of bromopyruvamide **5h** (1.0 g) in dry toluene (70 ml) was

treated with sodium methoxide (320 mg) in dry methanol (4 ml) in four portions. The turbid mixture was stirred at room temperature for 15 min. The reaction mixture was poured on to ice–water and extracted with methylene chloride, and the organic phase was dried and evaporated to a yellow oil which was chromatographed on silica gel (40 g); elution with benzene gave **19a** (135 mg) after recrystallization from methanol–water: uv 292 nm, 260, 221; nmr ($CDCl_3$) δ 8.2–7.3 (m, 9, ArH), 4.27 (s, 1, CHAr), 3.84 (s, 3, CO_2CH_3), 3.54 (s, 3, OCH_3).

2-(2-Methoxy-3-phenylglycidamido)benzoic Acid (19b). A solution of the ester **19a** (100 mg) in dioxane (10 ml) was treated with 1 *N* sodium hydroxide (5 ml) and the suspension agitated at 25° for 20 hr. The reaction solution was diluted with water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. Drying and evaporation of the methylene chloride gave a residue which deposited **19b** (58 mg): mp 167–168° from methanol–water; uv 305 nm, 255, 227; nmr (CD_3OD) δ 7.30 (m, 9, ArH), 4.27 (s, 1, CHAr), 3.56 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.8; N, 4.5. Found: C, 64.9; H, 4.9; N, 4.3.

Methyl 2-(2-Hydroxybenzylglycidamido)benzoate (20). A solution of 290 mg of crude **5b**, prepared from either **5g** or **19b**, in 25 ml of ether was cooled to 0° and treated with 2.28 mmoles of ethereal diazomethane for 20 min. The solution was then evaporated and the residue was chromatographed on silica gel. Elution with methylene chloride–ethyl acetate (90:10) gave 170 mg of **20**: mp 128°, after recrystallization from ethyl acetate–hexane; uv 306 nm (ϵ 5100), 255 (12,600), 224 (24,200); nmr ($CDCl_3$) 7.9 (H, 2, ArH), 7.25 (H, 7, ArH), 5.50 (s, 1, CHAr), 3.80 (s, 3, OCH_3), 3.33 (d, 1, J = 5 Hz, CH), 2.90 (d, 1, CH, J = 5 Hz).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.0; H, 5.3; N, 4.3. Found: C, 66.1; H, 5.3; N, 4.5.

3-Mesyloxybenzyl-4-methyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione (22b). A solution of **22a**[7] (2.0 g, 6.7 mmoles) in pyridine (15 ml) was treated with methanesulfonyl chloride (5 ml) and the cooled solution was stirred for 1.5 hr. The reaction mixture was poured into ice–water and the precipitate filtered, dried, and crystallized from ethyl acetate to yield 1.96 g of **22b** (5.25 mmoles, 77%): mp 168–170°; nmr δ 7.35 (m, 9, ArH), 5.22 (d, 1, J = 11 Hz, CH), 4.70 (d, 1, J = 11 Hz, CH), 2.78 (s, 3, CH_3), 2.66 (s, 3, CH_3).

Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.7; H, 4.8; N, 7.5; S, 8.5. Found: C, 57.6; H, 4.7; N, 7.6; S, 8.6.

***trans*-3,4-Dihydro-3-methylamino-4-phenylcarbostyril (23a).** To cold concentrated sulfuric acid was added **22a** (200 mg) and the solution was stirred at 25° for 15 min, poured into ice water, and extracted with ethyl acetate to yield 53 mg of the *trans*-benzylidine compound **12**. The aqueous phase was neutralized and extracted with methylene chloride. Drying and evaporation of the extract gave a residue which crystallized from methanol–water to yield *trans*-**23a**: mp 173–175°, uv 254 nm; nmr ($CDCl_3$) 7.4–6.8 (m, 9, ArH), 4.28 (d, 1, J = 8.5 Hz, CH), 3.58 (d, 1, J = 8.5 Hz, CH), 2.38 (s, 3, NCH_3).

3,4-Dihydro-3-methylacetamido-4-phenylcarbostyril (23b). A suspension of 381 mg of **22b** in 30 ml of 2 *N* hydrochloric acid was heated at 95° for 1 hr. The solution was evaporated, the residue was dissolved in water, sodium bicarbonate solution was added to pH 8 and the resulting precipitate was filtered to yield 190 mg (75%) of 3,4-dihydro-3-methylamino-4-phenylcarbostyril (**23a**), mp 149–152°. Crystallization from methanol–water did not significantly change the *cis*:*trans* ratio from 3:1: uv 253 nm (ϵ 14,800); nmr ($CDCl_3$) 7.4–6.8 (m, 9, ArH), 4.44 (d, 1, J = 6.5 Hz, CH), 3.83 (d, 1, J = 6.5 Hz, CH), 2.68 (s, 3, NCH_3); the spectrum also contained signals at 4.28 (J = 8.5 Hz), 3.58 (J = 8.5 Hz), and 2.3 (s, 1, NCH_3).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.2; H, 6.4; N, 11.1 Found: C, 76.1; H, 6.2; N, 11.1.

Crude **23a** was dissolved in 2 ml of pyridine and treated with 2 ml of acetic anhydride for 6 hr at room temperature, then poured into ice–water. The precipitate was extracted into ethyl acetate, washed with dilute hydrochloric acid followed by bicarbonate solution, dried, and evaporated to a crystalline residue. Recrystallization from ether gave 172 mg (90%) of **23b**: mp 203°; uv 252 nm (ϵ 14,850); nmr ($CDCl_3$) δ 7.30–6.95 (m, 9, ArH), 6.10 (d, 1, J = 7.5 Hz, CHN), 4.48 (d, 1, J = 7.5 Hz, CHAr), 2.35 (s, 3, NCH_3), 2.12 (s, 3, CH_3CO); mass spectrum 294 (M^+), 221 (100).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.4; H, 6.2; N, 9.5 Found: C, 73.5; H, 6.1; N, 9.3.

3-N-Carbomethoxy-N-methylamino)-3,4-dihydro-4-phenylcarbostyril (23d). A suspension of **22b** (400 mg) in methanol (60 ml) was heated at reflux for 5.5 hr. The solution was evaporated to 15 ml, water was added, and the resulting precipitate filtered to yield pure **23d** (210 mg): mp 193–194°; uv 254 nm; nmr ($CDCl_3$) δ 7.25 (m, 9, ArH), 5.78 (d, 1, J = 7.5 Hz, CH), 4.50 (d, 1, J = 7.5 Hz, CHC_6H_5), 3.80 (s, 3, OCH_3), 2.34 (s, 3, CH_3N); mass spectrum 310 (M^+, 10), 221 (100).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.7; H, 5.8; N, 9.0. Found: C, 70.0; H, 5.5; N, 8.9.

4-Phenylcarbostyril (24). Crude dihydrocarbostyril **23a** (100 mg) in methyl iodide (15 ml) was heated at reflux until precipitation ceased. The precipitate was removed and dissolved in methanol. Evaporation of the methanol gave a residue which was triturated with ethyl acetate. The crude product was dissolved in hot *t*-butyl alcohol, added to a solution of 50% sodium hydride (200 mg) in *t*-butyl alcohol (30 ml), and the mixture was stirred at room temperature for 24 hr, concentrated, diluted with water, and acidified. The precipitate was filtered, dried, and crystallized from ethanol to yield **24**, mp 261–262° (lit.[26] mp 259–261°), identical in all respects with an authentic sample prepared as described:[28] uv 331 nm (ϵ 5750), 280 (7100), 228 (33,100).

Formation of Viridicatins (2). A. By Pyrolysis of Cyclopenin (1a), Cyclopenol (1c), and Isocyclopenin (1b). Cyclopenin was dissolved in freshly distilled methylene chloride, the solvent was evaporated to yield a film on the capillary wall, the capillary tube was sealed *in vacuo* and the sample was heated at 195–202° for 5 min. The sample was introduced into the gas inlet port of the Varian M-66 mass spectrometer and the mass spectrum of the volatile components was recorded. Mass peaks at *m/e* 84, 86, 88 were assigned to residual methylene chloride and those at *m/e* 27, 28, 56 to methyl isocyanate.[14] The nonvolatile residue was chromatographed on silica gel, yielding viridicatin.

The same procedure applied to cyclopenol and isocyclopenin gave methylisocyanate and viridicatol (**2a**) and viridicatin (**2**), respectively.

B. By the Action of Deuteriosulfuric Acid on Cyclopenin (1a). A suspension of 10 mg of cyclopenin in 3 ml of 2 *N* D_2SO_4 (prepared from concentrated D_2SO_4 and 99.8 D_2O) was heated at 95° under nitrogen for 20 min. The suspension was centrifuged, the D_2SO_4 was decanted, and the precipitate was washed to neutrality with water. The product was crystallized from ethanol–water solution to yield 5.0 mg (62.5%) of viridicatin which after being dried over P_2O_5 at 80° *in vacuo* was analyzed by mass spectroscopy. The *m/e* 236:237:238 ratio was determined to be 5.35:5.67:1. The *m/e* 236:237:238 ratio determined for viridicatin obtained by conventional acid treatment of cyclopenin was 5.50:5.75:1.

C. By Acid Treatment of 3,4-Dihydro-3-hydroxy-3-hydroxybenzyl-4-methyl-1H-1,4-benzodiazepine-2,5-dione (11a). Concentrated sulfuric acid (0.5 ml) was added at 0° to **11a** and the solution was allowed to stand at 25° for 30 min. Diluting with water, filtering the precipitate, and drying yielded viridicatin.

D. By Alkali Treatment of Cyclopenin (1a), Isocyclopenin (1b), Cyclopenol (1c), and Methylcyclopenin (1d). **Cyclopenin** (25 mg) and **methylcyclopenin** (25 mg) each in ethanol (1.0 ml) were treated with 0.05 *N* sodium hydroxide (3 ml) at room temperature for 4 days. Methyl cyclopenin partially precipitated shortly after addition of base. The reaction mixtures were each diluted with water (20 ml) and extracted with ethyl acetate after which the aqueous phases were acidified and reextracted. Both basic and acidic extracts were dried and evaporated and the residues were dissolved in ethanol.

The alkaline extract from **cyclopenin** contained viridicatin as the major constituent; the acid extract, anthranilic acid. For spectrophotometric assay the long wavelength maxima was used: 330 nm (ϵ 8300) for viridicatin, 338 mμ (ϵ 4700) for anthranilic acid. The yields of viridicatin and anthranilic acid were 27.5 and 33%, respectively.

The alkaline and acidic extracts from the hydrolysis of **methylcyclopenin** contained only unreacted methylcyclopenin and methylanthranilic acid, respectively.

A solution of **isocyclopenin** (2 mg) in 1 *N* sodium hydroxide was allowed to stand at 25° for 48 hr. Neutralization to pH 8, extraction with ethyl acetate, and evaporation of the ethyl acetate yielded viridicatin.

Cyclopenol (10 mg) in 1 *N* sodium hydroxide (1.0 ml) was allowed to stand at room temperature for 11 hr. The solution was neutralized to pH 8, extracted with ethyl acetate, acidified, and extracted again. The extracts were separately dried and evaporated. Viridicatol and anthranilic acid were the major products in the alkaline and acidic extracts, respectively.

(28) C. R. Hauser, C. J. Eby, *J. Am. Chem. Soc.*, **79**, 728 (1957).