bath for 2 hr. The yellow nitrotartranilate of X, 0.8 g, mp 165°, separated on cooling and was recrystallized from ethanol.

Anal. Calcd for $C_{31}H_{35}N_3O_{11}$: C, 59.52; H, 5.6; N, 6.72. Found: C, 59.07; H, 5.68; N, 6.47.

Treatment of the nitrotartranilate salt with base liberated the amine (X), identical in R_f, infrared spectrum ($CHCl_3$), and nmr spectrum ($CDCl_3$) with caseadine methyl ether prepared from natural (−)-caseadine.[2]

Registry No.—IV 20122-04-7; IV hydrochloride, 20122-05-8; VI, 20122-06-9; VII, 20122-48-9; VII picrate, 20122-49-0; VIII (N-acetyl derivative), 20122-07-0; IX, 20122-08-1; IX hydrochloride, 20122-09-2; X, 20122-10-5; X nitrotartranilate, 20122-11-6.

Acknowledgment.—We are grateful to Dr. D. B. MacLean and Dr. R. H. F. Manske for a small comparison sample of caseadine methyl ether, and for direct infrared and nmr comparisons of the synthetic and naturally derived bases. We also thank the Smith Kline and French Co., Philadelphia, for financial support of this investigation.

Some Approaches to the Total Synthesis of Lycorine

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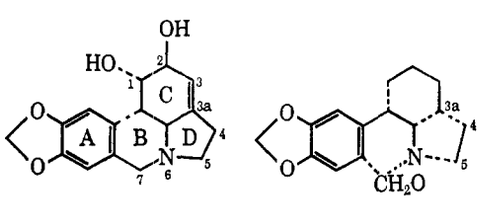
The problem of the synthesis of the lycorine family of *Amaryllidaceae* alkaloids is analyzed and two separate kinds of synthetic routes are examined experimentally. The first route, based on a Diels–Alder formation of ring C, leads to a product containing the lycorine skeleton with a nonaromatic ring C reasonably functionalized to complete the synthesis. The second approach, involving several variations on a roughly biosynthetic analogy, was frustrated on each occasion by reactions, usually internal conjugate additions, which took an undesirable course.

Lycorine (**1**) is the principal member of a family of *Amaryllidaceae* alkaloids[2] which have not been synthesized to date and which present an interesting synthetic challenge. In the present work we present an analysis of the synthetic problem and experimental work directed to several of the routes developed from this analysis, over a number of years.

The problem chiefly centers around ring C, which bears all four asymmetric centers and is in the same oxidation state as an aromatic ring, to which it readily reverts by double dehydration, destroying all asymmetric centers. The glycol is *trans* diaxial, hence in an unstable configuration on the rigid, *trans* decalin ring system. This situation argues for *trans* hydroxylation of a $\Delta^{1,2}$ double bond, while a $\Delta^{3,3a}$ double bond, presumably more susceptible to oxidation, must be retained in lycorine.



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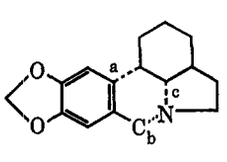


3

Starting material for the synthesis will presumably be piperonal (3,4-methylenedioxybenzaldehyde), which is readily available. Hence a second C–C bond must be formed to the aromatic ring. The piperonal aldehyde carbon can either be used as the carbon at the B/C-ring junction or as the aromatic link to the nitrogen atom. Two dissections of the skeleton into reasonable "synthons"[3] are shown in **2** and **3**, using piperonal in these two possible ways. The first dissection, **2**, is built on a Diels–Alder creation of ring C so as to assure *trans*-ring-fusion stereochemistry; the requisite diene can be four or six carbons and ring B would finally be cyclized using formaldehyde. The second dissection, **3**, is that which is utilized in biosynthesis of the *Amaryllidaceae* alkaloids,[4] oxidative coupling of phenols creating bond "a", followed by conjugate addition of nitrogen for bond "c"; this conjugate addition destroys the aromaticity of ring C which arises biosynthetically from tyrosine. We considered the Pschorr cyclization on a diazonium site to substitute for the biosynthetic oxidative coupling in linking rings A and C (bond "a").

The Diels–Alder Approach.[5]—The dienophile implicit in dissection **2** is 3,4-methylenedioxy-ω-nitrostyrene, bearing the correct skeleton and *trans* geometry and easily prepared from piperonal and nitromethane.[6] Unfortunately, this is a weakly activated dienophile, so that, while it reacted acceptably with butadiene to form **4a**, only polymers (and unchanged nitrostyrene) resulted from dienes with more than four carbons, like hexatriene or vinylacrylic acid. With vinylfuran, the nitrostyrene was consumed, but the reaction yielded a host of products (with saturated $-NO_2$ in the ir spectra) inseparable by chromatography. The expected product, **5**, should yield a bromo ketone

(1) Abstracted in part from the doctoral dissertation of D. R. D., UCLA, 1961.

(2) (a) W. C. Wildman, "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 289; (b) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960, "Akademie–Verlag, Berlin, 1961.

(3) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

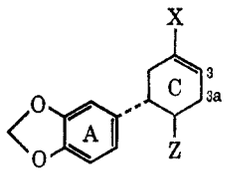
(4) (a) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, 1957, p 117; (b) A. R. Battersby, *Quart. Rev.*, **15**, 278 (1961); (c) D. A. Archer, S. W. Breuer, R. Binks, A. R. Battersby, and W. C. Wildman, *Chem. Comm.*, 168 (1963).

(5) A similar Diels–Alder construction was later used to synthesize the lycoranes by R. K. Hill, J. A. Joule, and L. J. Loeffler, *J. Amer. Chem. Soc.*, **84**, 4951 (1962).

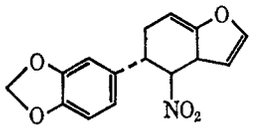
(6) L. Bouveault and A. Wahl, *Compt. Rend.*, **135**, 42 (1902). We used a modification of the procedure of D. E. Worrall, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941.

on bromination/hydrolysis, but, while bromine was consumed, no spectral indication of ketone resulted. The six-carbon diene **6** was also used under a variety of thermolysis conditions, none of which short of charring led to consumption of the nitrostyrene.

If a four-carbon diene is used, the final two carbons (4 and 5 in **2**) may conveniently be attached as an amide and cyclized to ring C later. As this later cyclization requires activating groups in ring C, we examined alternate dienes to provide other functionality there. Both 2-ethoxy-[7] and 2,3-diethoxybutadienes[8] were examined, but neither provided significant rate or yield enhancement in the cycloaddition, and both adducts were contaminated with ketonic hydrolysis products despite strenuous efforts to maintain anhydrous conditions. The pure adduct **4c**[9] from the former diene was cleanly converted to a bromo ketone on bromination, but bromination of the total cycloaddition product yielded an unacceptable mixture. Hence the choice was made to develop the simple butadiene adduct **4a** on grounds of economical logistics, since the substituted dienes themselves cost two synthetic steps to prepare. The adduct **4a** is formed in 72% yield in 48 hr at 125° and requires two successive oxidations from the ring C olefin to afford a ketone at C-3 for activating cyclization of a two-carbon amide to C-3a.



4a, X = H; Z = NO_2
b, X = H; Z = NH_2
c, X = OEt; Z = NO_2



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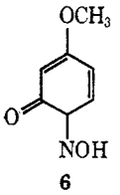
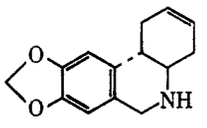
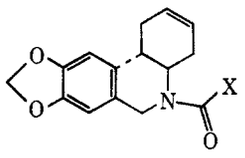


6

Chemical reduction with zinc and hydrochloric acid smoothly transformed the nitro **4a** into amino **4b** function without affecting the double bond, and this primary amine was converted in high yield to the secondary amine **7** by Helfer's procedure[10] with formaldehyde and hydrochloric acid. Before proceeding, however, it was necessary to confirm structure **7**, first with respect to retention of the *trans* ring junction, and second as to the orientation of formaldehyde condensation onto the aromatic ring. It was accepted that the diene addition produced the *trans* isomer, **4a**, and that catalytic reduction of **4a** in neutral solvent produced the dihydro derivative of **4b** without change in any configuration. We found that, when **4b** produced by zinc reduction was hydrogenated, the same dihydro derivative resulted. On the other hand, lithium aluminum hydride reduction of **4a** yielded a roughly 1:1 mixture of amino-olefins (**4b** and the epimerized *cis* isomer) which were separated as crystalline hydrochlorides and identified.[11] **4b** gave the same dihydro derivative as before when subjected to catalytic reduction, while the other gave an isomeric saturated amine. Thus, we concluded that zinc reduction in fact yields the *trans* isomer **4b**. Proof of the orientation of the formaldehyde cyclization as indicated in **4** was obtained by permanganate oxidation of **7** to 3,4-methylenedioxyphthalic (hydrastic) acid, identical with an authentic sample similarly prepared from lycorine.



7



8a, X = $CHCl_2$
b, X = $COOC_2H_5$
c, X = $CH(OCH_3)_2$

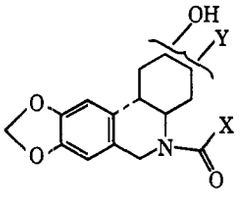
Two series of amides, **8a** and **8b**, were prepared from amine **7** with the appropriate acid chlorides and examined in detail, based on a plan of cyclization to the enol of a C-3 ketone; **8c** proved unstable to acidic conditions for olefin oxidation. To create the C-3 ketone requires unsymmetrical oxidative functionalization of the double bond, which has no strong asymmetry to influence directionality of attack. However, conversion of olefin to acyloin (α-hydroxy ketone) will allow tautomeric equilibration of the two isomers, and this equilibrium mixture can provide activation for cyclization and so be driven completely to the correct product.

Several routes can convert olefin to acyloin. The first oxidation step can create two possible bromohydrins or epoxides but only one *trans*-diol. The epoxide(s) from **8a**, *via* perbenzoic acid, yielded only diol **9b** on attempted oxidation to acyloins **11c** with dimethyl sulfoxide–boron trifluoride.[12] *trans*-Diol **10b** was created with performic acid. It was hoped that Oppenauer oxidation conditions using *t*-butoxide and benzophenone (or fluorenone) would convert this diol to acyloins **12c**, equilibrate these, and further catalyze Dieckmann cyclization to **14a**, but no enolic products were detected, nor indeed any oxidation of diol at all.

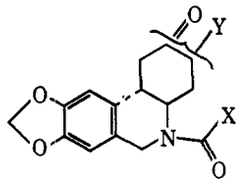
Bromohydrins **9a** and **10a** were formed in very high yield with N-bromosuccinimide in wet dimethyl sulfoxide.[13] The approximately 1:1 mixture **9a** was separable by crystallization, while **10a** was not. In each case, the mixture was smoothly oxidized to a noncrystalline bromo ketone mixture, **11a** or **11b**, respectively. Each bromo ketone mixture yielded an acetoxy ketone mixture (**11b** and **12b**, respectively) with potassium acetate in dimethylformamide; mass spectra later supported these formulations. A variety of hydrolysis and methanolysis experiments to convert **11b** to **11c**, even under stringent oxygen-free conditions, yielded only an acid product, tentatively formulated as **13** from ir spectrum, analysis, and neutralization equivalent.[14] This curious and unexpected oxidation

(7) H. L. Holmes and K. M. Mann, *J. Amer. Chem. Soc.*, **69**, 2000 (1947).
(8) J. R. Johnson, W. H. Jobling, and G. W. Bodamer, *ibid.*, **63**, 131 (1941).
(9) The structure of the adduct is based on analogy to the case reported by W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *ibid.*, **75**, 1912 (1953).
(10) L. Helfer, *Helv. Chim. Acta*, **7**, 945 (1924).
(11) Similar differences in configuration on aliphatic nitro reduction are reported by N. Kornblum and L. Fishbein, *J. Amer. Chem. Soc.*, **77**, 6266 (1955).
(12) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).
(13) Subsequently investigated further: D. R. Dalton, J. B. Hendrickson, and D. Jones, *Chem. Commun.*, 591 (1966).
(14) Later attempts to characterize this product by nmr and mass spectra were foiled by its insolubility and lack of volatility, although a mass spectrum of the precursor **11b** was consistent with that formulation.

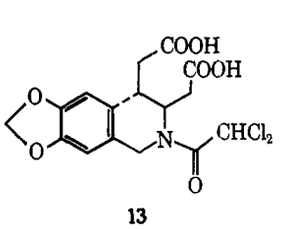
terminated the **8a** → **11c** route but showed in passing no cyclization under the basic conditions used in hydrolysis of **11b**.



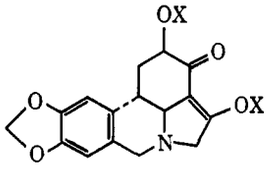
9 (X = $CHCl_2$) **10** (X = $COOC_2H_5$)
a, Y = Br **a**, Y = Br
b, Y = OH **b**, Y = OH



11 (X = $CHCl_2$) **12** (X = $COOC_2H_5$)
a, Y = Br **a**, Y = Br
b, Y = OAc **b**, Y = OAc
c, Y = OH **c**, Y = OH



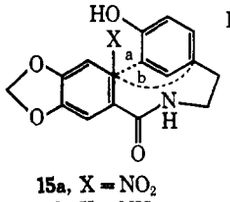
13



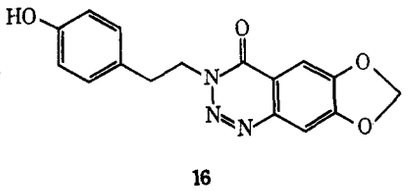
14a, X = H
b, X = Ac

In the oxalamide series **8b** → **12b** a small amount of crystalline keto acetate **12b** was obtained on extensive chromatography. Treatment of this product with methoxide in methanol yielded an enolic product, **14a**,[15] which could be acetylated to a crystalline diacetate **14b**. However, similar methoxide treatment of the noncrystalline mixture **12b** yielded no crystalline products. Accordingly, we turned our attention to other synthetic avenues.

The Biosynthetic Model Approach.—The direct analog of the biosynthetic coupling is a Pschorr coupling of two aromatic rings as in **15**, either through a nine-membered ring ("a") to the lycorine skeleton or a seven-membered ring ("b") to the crinine system, the other major *Amaryllidaceas* skeleton.[2] Conjugate addition of the nitrogen to the intermediate ring C diene would complete either reaction, just as in the natural biosynthesis. Models imply little steric strain in such cyclizations, but the statistical improbability of attaining the correct transition geometry is a grave disadvantage. However, the reaction has the advantage of being easy to try.



15a, X = NO_2
b, X = NH_2
c, X = $N_2^+BF_4^-$



16

The *p*-hydroxyphenethyl amide of 6-nitropiperonylic acid (**15a**) was readily prepared by allowing 6-nitropiperonylic acid chloride to react with *p*-hydroxyphenethylamine.[16] Hydrogenation then afforded the amine, **15b**, which was diazotized in fluoroboric acid to the crystalline diazonium fluoroborate, **15c**, which melts at 140° and bubbles at about 170°. On heating in water, this is converted to the benztriazinone, **16**, which does not bubble on heating to 300°. Pyrolysis of the diazonium salt causes extensive decomposition at atmospheric pressure under nitrogen and slow sublimation of benztriazinone *in vacuo*. This stable product is also unchanged on heating in nitrobenzene, polyphosphoric acid, or alkali, and unaffected by photoylsis.[17] Although it is in principle in equilibrium with the diazonium salt in strong acid, the benztriazinone was unaffected by anhydrous fluoroboric acid[18] or refluxing boron trifluoride in diglyme.

Thus it was apparent that, without the amide nitrogen fully substituted, we could not proceed beyond its internal attack on the diazonium grouping to form a triazinone.

The foregoing experiments were aimed not only at coupling the aromatic rings but also at destroying the aromaticity of ring C. In the subsequent experiments, we undertook to do this operation first and separately. One procedure for breaking into the aromaticity of a phenol in a way which provides useful product functionality for our purpose is the Wessely lead tetraacetate oxidation of phenols, which affords a quaternary site bearing acetoxy on a dienone.[19] Oxidation of the *o*-hydroxyphenethyl amide of 6-nitropiperonylic acid (analogous to the *para* derivative **15a**) with lead tetraacetate gave a poor yield of a neutral substance which, after chromatography, exhibited only one spot on a thin-layer plate and an ultraviolet absorption maximum of 300 mμ, like the model product from *o*-cresol, but could not be induced to crystallize. The evidence points to its formulation as **17**. It was clear, however, that the amide nitrogen had not spontaneously cyclized as desired by conjugate addition, and several different attempts to effect this by treatment with acid led only to alkali-soluble substances with no evidence either of ketone by ir or of the initial uv absorption remaining at 300 mμ. In these cases acid-catalyzed dienone–phenol rearrangement presumably intervened as the fastest reaction. Conversely, treatment with sodium hydride in tetrahydrofuran to generate the amide anion caused no change whatever in the dienone absorption at 300 mμ.

In a variation on this approach, we sought to provide

(15) This structure of **14a** is written for convenience in only one of the two tautomeric forms possible for the 1,3-diketone system.

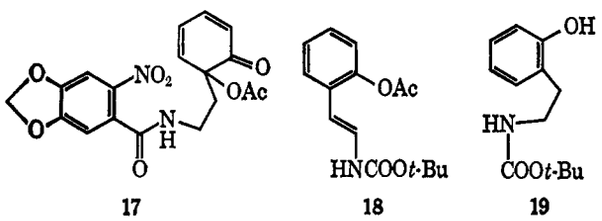
(16) The phenethylamines used in this work were synthesized from the appropriately methoxylated benzaldehyde, *via* nitromethane condensation to the β-nitrostyrene and reduction with lithium aluminum hydride to the methoxyphenethylamine; the methyl ethers were cleaved with hydriodic acid.

(17) Photolysis of benztriazines has been reported; *e.g.*, E. M. Burgess and L. McCullagh, *J. Amer. Chem. Soc.*, **88**, 1580 (1966).

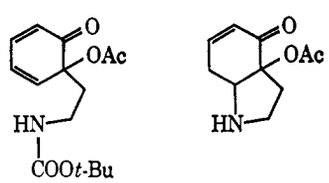
(18) A convenient source of a strong anhydrous acid containing poor nucleophiles is the solution made from commercial aqueous fluoroboric acid (50%) and trifluoroacetic anhydride. This solution, at about 1 *M* concentration in HBF_4, protonates anthraquinone completely and nitro- and 2,4-dinitrobenzene detectably by visual color change.

(19) Reviewed by J. D. Loudon in "Progress in Organic Chemistry," Vol. 5, Butterworths and Co. Ltd., London, 1961, p 51.

the nitrogen for the internal conjugate addition in the more nucleophilic form of a free amine rather than the deactivated amide which did not cyclize in **17**. However, the amine must be protected during the lead tetraacetate oxidation and subsequently released under very mild conditions after the dienone is prepared. For this purpose, we selected the *t*-butyloxycarbonyl group and synthesized compound **19** by the expedient of carrying out a Curtius rearrangement on *o*-acetoxycinnamoyl azide in boiling *t*-butanol to yield the *t*-butylurethan, **18**,[20,21] which was then hydrogenated and subjected to mild methanolysis of the phenolic *o*-acetyl, yielding **19**.



17 **18** **19**

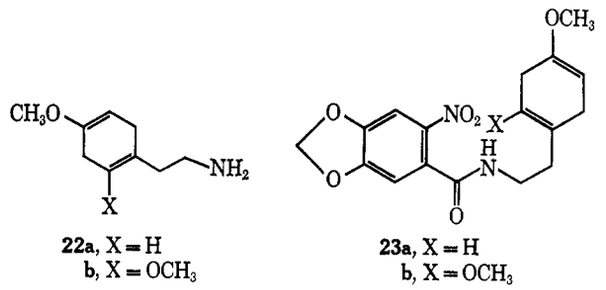


20 **21**

When the phenol **19** was subjected to lead tetraacetate treatment, the dienone **20** was obtained pure only after extensive chromatography and in very low yield; this dienone again exhibited a 301-mμ ultraviolet absorption maximum, indicating that the urethan nitrogen had not cyclized. When the urethan was dissolved in trifluoroacetic acid, it bubbled immediately and retained its dienone chromophore at 301 mμ for over an hour, but, when the solution was made basic after 3 min and worked up, only traces of nonacidic material were found. Thus it appeared that the free amine did not cyclize to **21** rapidly enough to prevent base-catalyzed rearrangement of the dienone, or that its cyclization, being reversible, did not inhibit the irreversible rearrangement.[22]

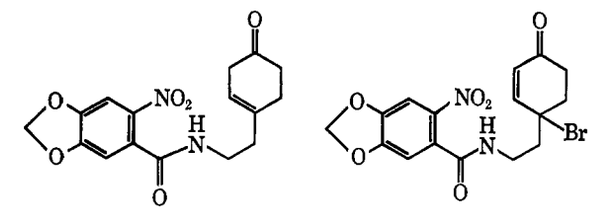
Following dissection (**3**) the expected compound **21** was to have been acylated with an appropriate piperonylic acid derivative with a view to cyclization of a ring C enol to a diazonium grouping on the piperonylic ring A. In an alternative also involving destruction of ring C aromaticity, we undertook initial Birch reduction of the phenethylamine components[16] with *p*-methoxy- or *o*,*p*-dimethoxy groups, so that on hydrolysis the nitrogen would have a basis for cyclization. With each of these phenethylamines, Birch reduction led to **22** and acylation afforded **23**.

Hydrolysis of neither free amine **22** produced characterizable secondary amino bicyclic ketones, but hydrolysis of **23a** produced a crystalline saturated ketone, characterized as **24** by analysis and spectral evidence (ir 5.8 μ, one vinyl proton at τ 4.5 in the nmr) as well as by rapid bromination to **25** which exhibited λ_{max} 227 mμ (after substraction of the 6-nitropiperonylamide chromophore) and two vinyl protons in the nmr. The salient feature here is that the amide nitrogen did not cyclize in a Michael addition, either by acid equilibration of the double bond in **24**[23] or directly in **25**.



22a, X = H
b, X = OCH_3

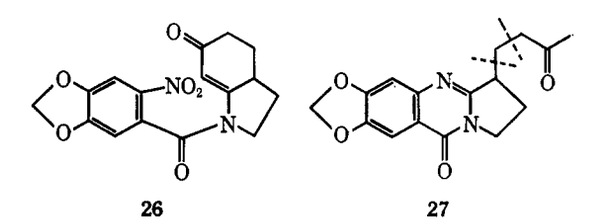
23a, X = H
b, X = OCH_3



24 **25**

The cyclization of the amide nitrogen was assured in the oxidized derivative **23b**, which on hydrolysis afforded the crystalline amide **26** of a bicyclic amino ketone, characterized by λ_{max} 289 mμ, strong ir bands at 5.94, 6.05, 6.20, 6.55, and 7.50 μ, and a single vinylic hydrogen singlet at τ 3.85. Ordinary procedures for nitro group reduction led also to destruction of the 289-mμ chromophore, but hydrogen transfer using α-phellandrene with palladium on charcoal[24] produced a crystalline product with the correct analysis and mass for the product of nitro reduction to amine in **26**.

We had anticipated that the amino group formed might add in a conjugate addition to the unsaturated ketone, but assumed that the subsequent diazotization would reverse this process; however, diazotization had no effect on this new product. The ultraviolet spectrum of this reduction product (λ_{max} 238 mμ, 320 mμ) was very reminiscent of that of the several benztriazinones (λ_{max} 242 mμ, 320 mμ), and the nmr showed no vinylic or exchangeable hydrogens, but a total of twelve protons above τ 6, three of them in a sharp singlet at τ 7.8. Since the ir showed a saturated ketone (5.84 μ) and bands at 6.02, 6.13, and 6.28 μ, we recognized the molecule as the stable 4-quinazolone derivative **27**, consistent with a formation *via* conjugate addition of the



26 **27**

(20) *t*-Butylurethans are not only conveniently prepared by the Curtius rearrangement, usually carried out directly in refluxing *t*-butanol, but serve to improve enormously the classical use of the Curtius procedure for conversion of acids to amines, since the traditional hydrolysis of isocyanates and urethans is usually plagued by intractable urea formation, while treatment of *t*-butylurethans in trifluoroacetic acid at room temperature affords the amine salt instantly and quantitatively.

(21) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957).

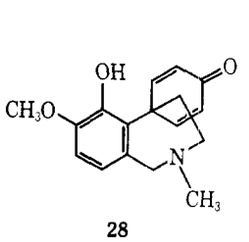
(22) A comparable base-catalyzed dienone rearrangement may be found in S. Goodwin and B. Witkop, *ibid.*, **79**, 179 (1957).

(23) For a study of α,β- $\rightleftarrows$ β,γ-cyclohexenone equilibria, see K. G. Lewis and G. J. Williams, *Tetrahedron Lett.*, 4573 (1965).

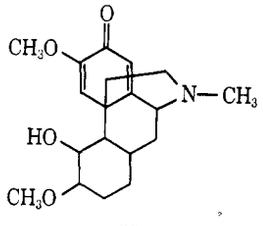
(24) R. Pallaud and H. Anh-Hoa, *Comp. Rend.*, **250**, 2730 (1960); **252**, 2896 (1961).

aromatic amino group followed by an irreversible retro-aldol reaction. In the mass spectrum, besides the parent peak (M = 300), compound **27** showed major peaks at 243 (M − 57) and 229 (M − 71) corresponding to fragmentations at the dotted lines in **27** by McLafferty rearrangements.

This results clearly puts an end to this synthetic approach to lycorine; in fact, all of the latter approaches may be said to have been frustrated by internal conjugate additions, both those which did not go as anticipated and those which went irreversibly when not desired. Previous experience in polycyclic alkaloid syntheses also implies that internal conjugate additions of heteroatoms are not always equilibrium favored, even when forming five- and six-membered rings. The steric and conformational factors which control these equilibria appear to be too complex to assess in these molecules, for the phenolic hydroxyl in **28** cyclized spontaneously[25] whereas in **29** it did not.[26]



28



29

Experimental Section[27]

Diels–Alder Reactions with β-Nitro-3,4-methylenedioxystyrene.[6]—These were carried out in sealed Pyrex Carius tubes, with small amounts of hydroquinone added for polymerization inhibition; the dienes in most cases were kept over molecular sieve and distilled from this directly into the flame-dried Carius tube. Dried solvent was added as necessary, and the tube was flushed with nitrogen, sealed, and heated in a Wood's metal bath. The following experimental conditions were examined.

These reactions were worked up by adding chloroform to the opened tube and examining the ir for the presence of the 7.45 μ band of the starting nitrostyrene and of the 6.45 μ band shown by adducts. If some of the latter was present, the mixture was chromatographed on alumina and fractions examined by ir. In the first two cases above, the nitrostyrene was always recovered in over 90% yield; much insoluble matter remained in most cases. In the third case, both starting materials were isolated in high yields. With 2-vinylfuran, disappearance of the 7.45 μ band occurred only in the nonsolvent cases. In such cases extensive column chromatography of the dark reaction residue afforded no crystalline products and thin-layer chromatography was not at that time in use. Both unreacted starting materials were recovered in low yield.

(25) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).

(26) D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *ibid.*, 2423 (1965).

(27) Melting points were determined with a Fisher–Johns block and are corrected. Infrared spectra were recorded in chloroform or methylene chloride solution unless indicated by (KBr) for solid state spectra, and were taken on a Perkin-Elmer Model 137 Infracord. All methylenedioxy compounds showed a diagnostic infrared peak at 9.6 μ, which is not separately recorded in the experiments. Ultraviolet spectra were observed in 95% ethanol solution on a Cary 14 recording spectrophotometer or a Perkin-Elmer Model 202 recording spectrophotometer and are recorded as λ_{max} in mμ (log ε). Proton magnetic resonance spectra were obtained with a Varian A-60A instrument purchased with funds from the National Science Foundation; they were recorded in $CDCl_3$ unless otherwise noted. Microanalyses were performed by Miss Heather King at UCLA, where the early work was performed, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., for later work. The described experimental work was begun in 1958 at UCLA by D. R. Dalton, and part of the present study is incorporated in his doctoral thesis in 1961 at that institution. Nmr and mass spectra were not available to use for those early studies and are therefore absent from the experimental descriptions except in a few key cases for which samples were run recently for confirmation.

TABLE I

Diene (g, mmol)	Dienophile, g, mmol	Time, hr	Temp, °C	Solvent
Vinylacrylic acid	3.18,	20	25–30	Toluene
(14.7, 150)	16	20	25–30	None
		8	100–105	Toluene
		8	100–105	None
		48	200–210	Toluene
1,3,5-Hexatriene	2.51,	48	32	Ether
(2.4, 29)	13	5	90–100	Toluene
		12	190–200	Toluene
		48	180–190	Xylene
		96	180–190	Xylene
2-Nitroso-5-methoxy-	1.0,	9	220–230	Toluene
phenol (1.0, 6.5)	5.0	48	220–230	Toluene
		48	220–230	None
2-Vinylfuran	5.0,	20	100–105	Toluene
(5.0, 53)	25	20	200–210	Toluene
		10	100–105	None
		20	100–105	None
		9	140–145	None
		6	155–160	None

Bromination of the vinylfuran products in carbon tetrachloride led to bromine uptake, and addition of water afterwards gave an acidic reaction. The solution was then shaken with aqueous thiosulfate and the organic layer evaporated to a red gum and chromatographed. This procedure again produced neither a crystalline residue nor an ir absorption from 5.5–6.1 μ.

1-Ethoxy-4-nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (4c).—To 5.0 g (25 mmol) of β-nitro-3,4-methylenedioxystyrene, powdered and dried *in vacuo* at 80°, was added 2-ethoxy-1,3-butadiene[7] (5.0 g, 51 mmol) by direct distillation from a molecular sieve into a dry Carius tube. Several crystals of hydroquinone were added, and the tube was flushed with dry nitrogen, sealed, and heated for 24 hr at 120°. On opening the tube, rinsing out the chloroform, evaporation, and chromatography on alumina in benzene, there was obtained the adduct **4c**: 2.3 g (31%); mp 105–106°; ir 6.00, 6.45 μ.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.82; H, 5.89; N, 5.02.

A second material from the chromatography was the nitro ketone corresponding to **4c**: 3.10 g (46%); mp 197–198°; ir 5.82, 6.44 μ. 100 mg of **4c** was refluxed for 10 hr in 5 ml of 95% ethanol containing 1 drop of 5% sulfuric acid. The solution was cooled, water was added, and an ether extraction was performed. The extract on washing, drying, and evaporation yielded an oil which crystallized from methanol: 82 mg (91%), mp and mmp 197–198° with the ketone above.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.07; H, 5.17; N, 5.27.

Bromination of the enol ether **4c** in chloroform afforded the expected bromo ketone, crystallized from methanol: mp 121–130°; ir 5.82, 6.04 μ.

Anal. Calcd for $C_{13}H_{12}NO_5Br$: C, 45.62; H, 3.78; N, 4.07. Found: C, 45.51; H, 3.77; N, 3.88.

***trans*-4-Nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (4a).**—3.5 g of β-nitro-3,4-methylenedioxystyrene and a few crystals of hydroquinone were added to 8.0 g of liquefied butadiene and 15 ml of toluene in a cooled steel-clad pyrex bomb. The bomb was sealed and heated for 3 days at 120–125°, then cooled in Dry Ice and opened. The contents were dissolved in a minimum of ether and passed through 40 g of alumina with about a liter of ether. Evaporation yielded 2.98 g (72%) of adduct **4a**, mp 99.8–100.2°.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.92; H, 5.21; N, 5.87.

***trans*-4-Amino-5-(3,4-methylenedioxyphenyl)cyclohexane (4b).**—The nitro olefin **4a** (10 g, 40.5 mmol) was placed in a 1-l. three-neck flask with stirrer, condenser, addition funnel, and heating mantle. To the nitro olefin was added purified zinc dust (50 g, 0.766 g-atom), water (50 ml), and *t*-butyl alcohol (3 ml). Heating and stirring was begun, and, when the water started to reflux, 1:1 aqueous hydrochloric acid (150 ml) was added slowly over about 2 hr, then refluxed for 4 hr and filtered through glass wool. The solution was cooled, made strongly basic with 20% sodium hydroxide, and continuously extracted with ether.

The ether extract (about 300 ml) was dried, 5 ml of anhydrous methyl alcohol followed by anhydrous hydrogen chloride, added, and the solution left to crystallize in the refrigerator. The crystals of amine hydrochloride (9.9 g, 97%) were filtered and recrystallized from methyl alcohol: mp 208–209°.

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.53; H, 6.35; Cl, 13.98. Found: C, 61.52; H, 6.51; Cl, 13.89.

trans-**2-(3,4-Methylenedioxyphenyl)cyclohexylamine. A.**—The amine **4b** was generated as an oil by making an aqueous solution of the above hydrochloride basic and extracting with methylene chloride. To 447 mg (2.06 mmol) in 10 ml of 95% ethanol was added 25 mg of platinum oxide and hydrogenation at atmospheric pressure was carried to an uptake of one equivalent of hydrogen. On filtration, evaporation to small volume, and treatment with 1:1 hydrochloric acid, 354 mg (79%) of crystalline hydrochloride was obtained, mp 260–261°.

Anal. Calcd for $C_{13}H_{18}NO_2Cl$: C, 61.10; H, 7.10; Cl, 13.88. Found: C, 61.19; H, 7.32; Cl, 13.61.

B.—The nitro olefin **4a** (322 mg, 1.47 mmol) in 40 ml of 95% ethyl alcohol was hydrogenated at 40-lb pressure with W-5 Raney nickel. After filtration of the solution through a mat of Celite, it was evaporated to a colorless oil which yielded a tan solid (89%) on treatment with 1:1 aqueous hydrochloric acid (4 ml). This solid, mp 247–255°, recrystallized from chloroform–ethanol to mp 260–261°, mmp with the hydrochloride from A above, 260–261°.

cis-**4-Amino-5-(3,4-methylenedioxyphenyl)cyclohexane.**—To lithium aluminum hydride (9 g, 0.237 mol), suspended in anhydrous ether (300 ml) in a 1-l. three-neck flask with condenser, stirrer, and addition funnel, was added 4-nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (10 g, 0.40 mol) in anhydrous ether (200 ml). The nitro olefin was added slowly with stirring, maintaining a slow reflux throughout the addition. After 1 hr for the addition, the solution was refluxed with stirring for an additional 3.5 hr, then cooled, and the excess hydride decomposed by careful addition of 5% aqueous potassium hydroxide. On sudden precipitation of solids, the addition of base was halted and the ether decanted. The precipitate was washed with ether and the solution and washings were combined, washed with water, and dried. After filtration, the ether was evaporated to a small volume (about 50 ml), methyl alcohol (5 ml) added, and the solution cooled in an ice bath while anhydrous hydrogen chloride was passed in.

On cooling overnight in the refrigerator, 4.2 g (41%) of a white crystalline solid, mp 231–233°, were deposited.

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.53; H, 6.36; Cl, 13.98. Found: C, 61.48; H, 6.22; Cl, 13.98.

After filtration, the mother liquors were evaporated and the residue taken up in hot 4:1 chloroform–methanol. On cooling, 4.05 g (40%) of colorless crystals were collected, mp and mmp with the *trans*-amino olefin **4b** above, 208–210°. Hydrogenation yielded the same dihydro compound as above, mp and mmp 260–261°.

cis-**2-(3,4-Methylenedioxyphenyl)cyclohexylamine.**—Hydrogenation of the *cis*-amino olefin as described above yielded a dihydro compound as the hydrochloride (91%), mp 227–228°.

Anal. Calcd for $C_{13}H_{18}NO_2Cl$: C, 61.10; H, 7.10; Cl, 13.88. Found: C, 60.92; H, 6.85; Cl, 13.59.

sec-**Amino Olefin 7.**—The *trans*-4-amino-5-(3,4-methylenedioxyphenyl)cyclohexene (**4b**) hydrochloride (5.22 g, 2.06 mmol) was converted to the free amine with aqueous hydroxide. This was extracted into ether, dried, and evaporated to an oil. The oil was treated, dropwise, with stirring and steam bath warming, with 10 g of 20% formaldehyde solution, then stirred and heated for 1 hr. To the gum and solution, hot benzene was added and the benzene extracts were dried and evaporated to a colorless oil, which was treated with warm 1:1 hydrochloric acid to yield a white crystalline solid, 5.0 g (91%), mp 270.5–271°.

Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.77; H, 6.07; N, 5.27. Found: C, 63.28; H, 6.03; N, 5.30.

1.0 g was dissolved in water and heated during dropwise addition of 4 g of potassium permanganate (in 100 ml of water) for 1 hr, treated with sulfur dioxide, and the clear acidic solution concentrated, washed with ethyl acetate, then continuously extracted with ether to yield 137 g of a gum, sublimation of which afforded 27 mg of white crystals, mp 174–175°, mmp 173–175° with a sample of hydrastic acid comparably produced from permanganate oxidation of natural lycorine.

N-Dichloroacetyl Amino Olefin (8a).—The amine hydrochloride (839 mg, 3.15 mmol) was converted to free amine **7** as above; its ether solution (80 ml) was treated with 5 ml of triethylamine and a solution of 1.0 g (6.85 mmol) of dichloroacetyl chloride in ether (20 ml); the ether solution was added dropwise over a period of 15 min; and the solution was allowed to stir at room temperature overnight. This was poured into ice (100 g) and sulfuric acid (1 *N*, 20 ml) extracted with methylene chloride; the extracts were combined and washed with aqueous potassium hydroxide (5%) until the wash was clear, then with 1 *N* sulfuric acid and water. The methylene chloride was dried, filtered, and evaporated to yield 957.2 mg (89%) of offwhite crystals. Recrystallization from 1:1 methyl alcohol–chloroform gave 946 mg of white needles, mp 223–224°, ir 6.02 μ.

Anal. Calcd for $C_{16}H_{15}NO_3Cl_2$: C, 56.49; H, 4.44; Cl, 20.85. Found: C, 56.29; H, 4.75; Cl, 20.50.

The dibromide was prepared by bromination of the olefin in chloroform solution: mp 193.5–194.0°.

Anal. Calcd for $C_{16}H_{15}NO_3Cl_2Br_2$: C, 38.43; H, 3.02; N, 2.80. Found: C, 38.61; H, 3.26; N, 2.80.

Epoxidation of the Dichloroacetamide 8a.—The amido olefin **8a** (914 mg, 2.68 mmol) was dissolved in chloroform (50 ml) and perbenzoic acid (6.5 ml of 0.44 *M* or 2.86 mmol) in chloroform was added. The mixture was allowed to stand overnight. Saturated sodium bicarbonate solution (20 ml) was added, stirred for half an hour, and the chloroform washed with water, dried, filtered, and passed through a plug of alumina (neutral). The eluent yielded a white crystalline epoxide (836 mg), mp 251–252°.

Anal. Calcd for $C_{16}H_{15}NO_4Cl_2$: C, 53.95; H, 4.25; N, 3.93. Found: C, 54.06; H, 4.31; N, 3.78.

Attempted Oxidation of the Epoxide to the Acyloin (11c).—The epoxide (732 mg, 2.05 mmol) was dissolved in anhydrous dimethyl sulfoxide (60 ml), the solution treated with anhydrous boron trifluoride etherate (0.2 ml), and the mixture warmed on the steam bath with a drying tube. After 5 hr, an additional 0.2 ml of boron trifluoride was added, and after 10 hr an additional 0.2 ml. After 22 hr the dark mixture was removed, poured into ice–water (1 l.), and the aqueous solution extracted with ether. The ether extract was washed with 5% aqueous potassium hydroxide, 1:1 aqueous hydrochloric acid, and water, dried, filtered, and evaporated to 397 mg of light yellow oil, which crystallized on standing in chloroform, depositing 74 mg of crystals, mp 216–218°; like the total oil, these showed no ir absorption at 5.8–6.0 μ but did have bands around 3 μ, suggestive of the diol **9b**.

Bromohydrins 9a.—The amido olefin **8a** (993 mg, 2.91 mmol) was dissolved in 5:1 diglyme–water (100 ml), heated in a water bath (80–90°), and stirred while 8 drops of perchloric acid was added. The solution was then treated, over a 45-min period, with N-bromosuccinimide (1.0 g, 5.62 mmol). The color of the solution following the addition of a portion of the N-bromosuccinimide was allowed to fade before the next portion was added. After the addition was complete, the solution still retained a slight yellow color and was allowed to remain at 80–90° for an additional 30 min. Afterward, a few crystals of sodium bisulfite were added to destroy the excess N-bromosuccinimide.

The colorless solution was partitioned between ether and water and the ether dried and evaporated to an oil; treatment with several drops of methyl alcohol resulted in the deposition of 1.18 g (93%) of crystalline material, mp 170–177°.

Several recrystallizations from benzene gave one isomer, mp 223–224°, in 44% yield.

Anal. Calcd for $C_{16}H_{16}NO_4BrCl_2$: C, 43.96; H, 3.69; N, 3.20. Found: C, 44.05; H, 3.94; N, 3.42.

Combination and evaporation of the mother liquors yielded 490 mg (41%) of the other isomer, mp 211–212°.

Anal. Calcd for $C_{16}H_{16}NO_4BrCl_2$: C, 43.96; H, 3.69; N, 3.20. Found: C, 43.61; H, 3.51; N, 3.47.

An admixture of these isomers possessed a melting point of 174–183°.

Bromo Ketones (11a).—The crystalline bromohydrin mixture (5.04 g, 11.5 mmol) was dissolved in acetone (250 ml) with warming, the solution was cooled to −5°, and 2.86 ml (7.67 mmol) of chromic anhydride solution (made from 26.7 g of anhydride in 23 ml concentrated sulfuric acid and diluted to 100 ml with water) was added dropwise over 1.25 hr below 0°. The solution was allowed to warm to room temperature over a period of 1.5 hr and poured into 1 l. of cold water; the resulting suspension was filtered and the precipitate dissolved in warm chloroform, which was dried and evaporated to yield 5.07 g of slightly yellow oil, which crystallized on treatment with methanol.

Recrystallization from 1:1 methanol–chloroform yielded 2.6 g, mp 219–220°, ir 5.80, 6.06 μ.

Anal. Calcd for $C_{16}H_{14}NO_4BrCl_2$: C, 44.17; H, 3.24; N, 3.22. Found: C, 43.94; H, 3.39; N, 3.36.

Evaporation of the mother liquors yielded 2.4 g of material with ir identical with that of the crystalline sample and presumed to consist of a mixture of the two bromo ketones, **11a**.

Treatment of the Bromo Ketone 11a with Alkali.—The crystalline bromo ketone (254 mg, 0.582 mmol) was suspended in a cup above a solution of 2.0 mmol of potassium hydroxide in absolute ethanol (20 ml). After the system had been flushed with helium, the cup was inverted and the bromo ketone allowed to fall into the solution. An immediate yellow color and a white precipitate developed. After stirring at room temperature overnight, the solution was treated with water (25 ml) and 1 *N* sulfuric acid until it was acidic to litmus, and then continuously extracted with ether. The ether extract was washed once with water, dried, filtered, and evaporated to yield 103 mg of the crystalline acid, mp 221–223°, recrystallized from chloroform to 97 mg: mp 225–226°; ir (KBr) 3–3.5, 5.80, 5.91, 6.10 μ.

Anal. Calcd for $C_{16}H_{15}NO_7Cl_2$: C, 47.53; H, 3.74; Cl, 17.54. Found: C, 46.48, 49.00; H, 3.90, 4.13; Cl, 16.76. Neutralization equivalent: 197.2, 198.2.

When only one equivalent of base was used under comparable conditions, only starting material was isolated in 91% yield.

Keto Acetate 11b.—The bromo ketone **11a** (52.5 mg, 0.12 mmol) was dissolved with stirring in dimethylformamide (5 ml), and potassium acetate (48.2 mg, 0.492 mmol) was added. The solution was stoppered and allowed to stir at room temperature overnight, then diluted with water (50 ml) and extracted with ether; the ether extracts were washed once with water, dried, filtered, and evaporated; and the residue was treated with several drops of methanol. The crystals which formed weighed 30.2 mg (61%), mp 250–252°. Recrystallization from chloroform yielded white microcubes: mp 256–257°; ir 5.64, 5.70, 6.02 μ; mass spectrum, see keto acetate **12b** below.

Anal. Calcd for $C_{18}H_{17}NO_6Cl_2$: C, 52.19; H, 4.14; Cl, 17.12. Found: C, 52.47; H, 4.51; Cl, 16.99.

Treatment of 68 mg of this material with excess alkali, as with bromo ketone, afforded 51 mg of the same acid **13**, mp 222–223°.

N-Ethoxalyl Amino Olefin 8b.—20 g (7.5 mmol) of the amine hydrochloride was converted as before to the free amine **7** in 100 ml of chloroform, and 10 g of ethoxalyl chloride (7.5 mmol) in 50 ml of chloroform was added and stirred for 15 min. 100 ml of 5% aqueous potassium hydroxide was then stirred with this slurry for 20 min and the phases were separated. The chloroform was washed with 2 *N* hydrochloric acid and water, dried, and evaporated to an oil which was crystallized from a small amount of methanol to 16.4 g (70%) of colorless crystals which melted in two polymorphic modifications in different preparations, 130° and 160–161°, both giving the higher melting point when seeded with 160° material and both showing the same ir spectrum in solution: 5.74, 6.07 μ.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.38; H, 5.65; N, 4.45.

Hydroxylation of Olefin 8b.—To 861 mg (2.62 mmol) of olefin **8b** in 5 ml of trifluoroacetic acid and 0.5 ml of water was added 13 drops (350 mg, 1.2 equiv) of 30% hydrogen peroxide at 0°. The temperature was raised to 40°, and in 45 min 5 more drops of peroxide was added. After 2 hr, excess peroxide was destroyed with aqueous sodium bisulfite and the solution was made alkaline and continuously extracted with chloroform. The 500 mg residue was dissolved in 25 ml of 1 *N* hydrochloric acid in ethanol and refluxed for 4 hr to remove trifluoroacetate esters. The hydrochloric acid–ethanol was then evaporated and the residue was chromatographed on silica in chloroform–acetone mixtures. 300 mg of oil was obtained from the 1:1 solvent eluents. The oil crystallized from chloroform to yield 229 mg (33%) of **10b**: mp 159–160°, recrystallized to 161–162°; ir 3.0, 5.75, 6.12 μ; uv λ_{max} 290 mμ (log ε 3.72).

Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.82; N, 3.85. Found: C, 59.78; H, 5.91; N, 3.70.

Oppenauer Oxidations of the Diol 10b.—35 mg of diol **10b** and 23 mg of benzophenone were dissolved in 2 ml of dimethyl sulfoxide (previously dried with molecular sieve) under dry nitrogen, and 18 mg of sublimed potassium *t*-butoxide was added, causing a clear orange color. After several hours, the color had deepened somewhat and water was added to the mixture, which was extracted (with difficulty owing to emulsions) with chloroform. Drying of the extracts afforded 13 mg of an oil, which was shown by ir comparison to be largely benzophenone. Acidification of the aqueous layer and extraction with chloroform led to 22 mg of a yellow oil with a negative ferric chloride test and an ir and uv spectrum virtually identical with the starting ester diol, and with a sample of the presumed oxamic acid separately obtained from it, as an impure powder, by saponification.

The use of fluorenone under the same conditions overnight led to nearly quantitative recovery of fluorenone (96%) and a base-soluble residue similarly showing the spectral characteristics only of the oxamic acid diol. Overnight refluxing of toluene, fluorenone, and the diol led only to intractable gums and some recovered fluorenone. The Oppenauer oxidation using aluminum *t*-butoxide in refluxing toluene with quinone or fluorenone likewise returned those ketones largely unchanged along with a residue, a nonmelting and largely insoluble solid which left a residue on combustion. The nonmelting solid contained the ir absorptions only of the ethoxamide carbonyls.

Bromohydrins 10a.—To 3.36 g (10.2 mmol) of olefin **8b** in 100 ml of dimethyl sulfoxide was added 12 drops of perchloric acid. 1.89 g (10.6 mmol) of N-bromsuccinimide was added over 45 min, and the solution was stirred overnight and poured into water. The precipitate was filtered, dissolved in chloroform, washed with 5% potassium hydroxide and water, dried, and evaporated to 3.82 g of a gum with an ir (2.80, 5.75, 6.09 μ) consistent with the expected product, **10a**. The gum would not crystallize and was used directly.

Bromo Ketones 12a.—2.88 g of crude bromohydrin **10a** was treated as above for **9a** with 2 ml (5.3 mmol) of chromic anhydride solution. The resultant 2.50 g of oil exhibited ir bands at 5.78 and 6.08 μ, similar to the previous bromo ketones, but could not be induced to crystallize despite several attempts at chromatographic purification.

Keto Acetate 12b.—1.65 g of the crude bromo ketones **12a** was dissolved in 30 ml of dimethylformamide, and 1.46 g of dry potassium acetate was added. Allowed to stand overnight, the solution turned very dark and was poured into water and extracted with ether, which was dried and evaporated to a weight-constant residue. This was dissolved in chloroform and washed with 5% potassium hydroxide, 1:1 hydrochloric acid, and water, dried, and evaporated to 0.70 g of a gum which was chromatographed on alumina. The first chloroform fractions contained a major band which partially crystallized, yielding 0.40 g, mp 145–155°, recrystallized from methanol to mp 204–205°, ir (no OH band) 5.76, 6.04, 8.1 μ.

Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.55; H, 5.25; N, 3.47. Found: C, 58.69; 58.74; H, 5.36, 5.53.

Mass spectra of the two keto acetates, **11b** and **12b**, have subsequently been measured and confirm the assignments. Both show correct parent peaks, a major peak at *m/e* 187 ($C_{11}H_9NO_2$), and a methylenedioxy–isoquinoline fragment with an added methyl as well as a hydroxypenanthridine from ring C aromatization and loss of amide at *m/e* 242 ($C_{14}H_{12}NO_3$); both show peaks at P − 60 for loss of acetic acid and peaks for loss of the acyl unit from nitrogen. Below *m/e* 242 the spectra are very similar. The dichloroacetamide exhibits three parent peaks (*m/e* 413, 415, 417) in the expected intensities for two chlorines, and also peaks arising from loss of one or both of these chlorines.

Dieckmann Cyclization of 12b to 14a.—47 mg of crystalline keto acetate **12b** was dissolved in 5 ml of methanol containing 122 mg of sodium methoxide and stirred for 19 hr to a clear yellow solution. This was brought to about pH 3 with five drops of concentrated hydrochloric acid and evaporated almost to dryness, then partitioned between water and chloroform. The chloroform yielded 23 mg of yellow foam with a green ferric chloride color (in pyridine): uv λ_{max} 291 mμ (log ε 3.6); ir 5.65, 5.80, 6.05 μ.

The product was acetylated in 2 ml each of pyridine and acetic anhydride overnight at room temperature. After evaporation and chromatography on alumina, the main fraction (22 mg) afforded crystals from benzene (10 mg): mp 139–140°; ir 5.62, 5.72, 5.82, 6.08 μ.

N-(6-Nitro-3,4-methylenedioxybenzoyl)tyramide (15a).—2.11 g (10.0 mmol) of 6-nitropiperonylic acid[28] and 2.2 g of phosphorus pentachloride were covered with 10 ml of carbon tetrachloride, refluxed for 20 min, and the carbon tetrachloride evaporated off. 20 ml more carbon tetrachloride was added and boiled off, and the residue was dissolved in ether (50 ml) and washed with water.

(28) J. B. Ekely and M. S. Klemme, *J. Amer. Chem. Soc.*, **50**, 2711 (1928).

A solution of 1.74 g (10.0 mmol) of tyramine hydrochloride in 20 ml of water and 20 ml of triethylamine was mixed in and shaken for 10 min. The precipitated solid was separated by centrifugation, dissolved in 1 *N* sodium hydroxide, and washed with ether. After acidification and filtration, the collected solid was crystallized from methanol, yielding a first crop of 0.59 g, mp 218–220°, and a second crop of 0.42 g, mp 210–215° (total yield 33%), with ir (KBr) 3.1, 6.08, 6.45, 6.55 μ; uv λ_{max} 225 (log ϵ 4.47), 250 (4.68), 340 (3.70) mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.96; H, 4.31; N, 8.27.

Diazonium Fluoroborate 15c.—1.00 g of nitro amide **15a** and 42 mg of platinum oxide were hydrogenated in 75 ml of absolute ethanol at atmospheric pressure; hydrogenation became very slow after an uptake of 232 ml (theoretical uptake is 243 ml for nitro reduction). The catalyst was filtered and the solvent was evaporated to a gum (1.0 g) which showed ir bands at 2.88, 2.98, and 6.04 μ, but none at 6.5 μ. The gum was treated with 1.20 ml of 50% fluoroboric acid and 25 ml of water and warmed to effect solution. It was then cooled to −5°, and a solution of 2.70 g of sodium nitrite was added. A precipitate formed immediately, and more came out on addition of 15 ml of fluoroboric acid. The yellow crystalline solid was washed with fluoroboric acid, methanol, and ether and dried over P_2O_5: mp 140–145°, bubbled at 160–170°; ir (KBr) 3.0, 4.44, 6.01 μ and a large BF_4^- absorption at 9.0–9.7 μ.

Decompositions of Diazonium Salt 15c.[29]—7 mg of the diazonium salt **15c** was added to a solution of 100 mg of potassium hydroxide in 15 ml of water and heated on the steam bath for 8 hr. The salt dissolved only slowly, and was replaced by a new crystalline solid which, after cooling, was extracted with methylene chloride and obtained, after drying and solvent evaporation, as colorless crystals, mp 206–208° (6 mg), no bubbling below 300°.

20.7 mg of salt **15c** heated at 250° under nitrogen gave only intractable tars; 10 mg heated at 220° at 20-μ pressure for 1 hr exhibited some bubbling and sublimation of a major fraction, mp 210–211°, the remaining material being negligible or charred.

13.3 mg of salt **15c** was dissolved in 5 ml of nitrobenzene and heated at reflux for 1 hr, then poured into 130 ml of water and 100 ml boiled off to remove the nitrobenzene. Extraction with methylene chloride, drying, and evaporation afforded 7.8 mg of orange solid, mp 201–205°.

20.0 mg of salt **15c** was added to freshly prepared polyphosphoric acid (1 ml) and heated for 1 hr at 185°, then poured into water when cool and extracted with methylene chloride, which yielded no organic product; continuous extraction of the aqueous phase with ether afforded 3 mg of black tar, which was discarded.

The solids obtained in each case were shown to be the benztriazinone **16**, which was recrystallized from methanol to mp 210–211° and ir 2.80, 6.00, 6.80 (s) μ; uv showed 243 (log ϵ 4.24), 248 (4.27), 254 (4.26), 260 (4.16). 318 (3.47) mμ.

Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.78; H, 4.31; N, 13.35.

Reactions of the Benztriazinone 16.[30]—Anhydrous fluoroboric acid was made by adding 1.0 g of 50% aqueous fluoroboric acid to 5.9 g of redistilled trifluoroacetic anhydride at 0° with stirring; the phases become homogeneous in 10 min. The resulting solution is 7.1% or 0.81 *M* in fluoroboric acid. 35.2 mg of benztriazinone **16** in 2 ml of this acid was slowly heated to reflux. In the cold, the solution was clear yellow with most of the salt undissolved, and became orange-brown and all dissolved at reflux temperature. The solution was refluxed for 27 hr, cooled, poured into ice and ether, and extracted with ether. The ether extracts were washed with bicarbonate solution and water, dried, and evaporated to a partly crystalline residue, identified as substantially pure starting material from ir and tlc comparisons.

103 mg (0.33 mmol) of benztriazonone **16** was dissolved in 8 ml of diglyme (distilled from hydride), and 57 mg (0.4 mmol) of distilled boron trifluoride etherate was added. The solution was refluxed for 3 hr and allowed to stand overnight. The solution and black gummy deposits were washed out with benzene and 1 *N* NaOH and partitioned. The benzene layer on filtration and evaporation yielded 4 mg of a gum exhibiting the ir and uv spectra of starting material, while acidification and extraction of the alkali yielded a similar crude product.

77 mg of benztriazinone **16** was dissolved in 6 ml of dioxane, saturated with argon gas, and photolyzed for 16 hr in Pyrex with an Osram lamp. Work-up by partitioning between benzene and alkali as above afforded less than 2 mg from the benzene layer, essentially only benztriazinone, and the remainder, alkali soluble, proving to be the same.

***N*-(6-Nitropiperonyl)-*o*-hydroxyphenethylamide.**—The procedure for the tyramide analog **15a** above was utilized with 1.91 (14 mmol) of *o*-hydroxyphenethylamine[16] to create 1.98 g (43%) of pale crystals, crystallized from methanol: mp 159–162°; ir 2.90, 6.00, 6.55 μ; λ_{max} 225 (log ϵ 4.41), 268 (3.69), 342 (3.66) mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.88; H, 4.02; N, 8.16.

Lead Tetraacetate Oxidation to 17.—330 mg (1.0 mmol) of N-(6-nitropiperonyl)-*o*-hydroxyphenethylamide and 800 mg of lead tetraacetate were heated on the steam bath in 15 ml of acetic acid for 10 min. Work-up of an aliquot showed starting material on tlc. Another 800 mg of lead tetraacetate was added and heating continued for 10 min. The cooled solution was poured onto excess sodium carbonate decahydrate covered with 50 ml of methylene chloride, 100 ml water was added, and the lead dioxide was filtered out with Celite. The layers were separated, and the organic layer was washed, dried, and evaporated to a small volume and passed onto a silica column. Elution with chloroform yielded no substance, and the fractions taken with 15% acetone in chloroform were monitored with uv spectra. A major fraction of 211 mg of yellow foam showed a uv maximum at 300 mμ (ϵ 5500), one major and one close minor spot on tlc, and ir bands at 2.90, 5.74, 6.00, and 6.55 μ.

The crude dienone was treated with (a) concentrated sulfuric acid in acetic acid (5% solution) for 10 min at reflux; (b) 1 equiv of *p*-toluenesulfonic acid in methylene chloride for 2 hr at room temperature; (c) excess sodium hydride in dry tetrahydrofuran for 2 hr at room temperature. In all cases, tlc and ir showed the isolated material to be essentially all starting material.

***N*-(*o*-Acetoxy-β-styryl)-*t*-butylurethan (18).**—*o*-Acetoxycinnamic acid was made from salicylaldehyde and converted to its acid chloride, mp 53° (lit. mp 54°), following the precedure of Houben and Pfankuch.[31] 23.44 g of the acid chloride was converted to the azide by dissolving in 100 ml of acetone, chilling to 0°, and adding, over 10 min with stirring, an iced solution of 10 g of sodium azide in 40 ml of water. Stirring was continued at 0° for 1 hr (when an aliquot removed for ir showed essentially complete conversion) and another hour at room temperature; 200 ml of ether was added and the phases were separated. The ether layer was washed with water, dried, and evaporated to the crystalline azide, mp 36–39°; ir 4.68, 5.69, 5.94 μ.

The total azide was dissolved in *t*-butyl alcohol (250 ml) and benzene (50 ml), refluxed for 4 hr, evaporated, and dissolved in CH_2Cl_2. This solution was washed with 1 *N* hydrochloric acid, aqueous sodium bicarbonate, and brine, and evaporated to 50 ml. Benzene was twice added and evaporated down to 100 ml. Addition of 40 ml of hexane and cooling yielded 10.90 g of colorless crystals, mp 137°; the mother liquors yielded a further 1.50 g, mp 127–132°, recrystallized from benzene to mp 138–139° and ir 2.90, 5.71, 5.78, 6.01, 6.65 μ.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 56.35; H, 7.10; N, 5.16.

Hydrolysis of 18 to *N*-(*o*-Hydroxy-β-styryl)-*t*-butylurethan.—347 mg of urethan **18** was suspended in 3 ml of methanol and 300 mg of potassium hydroxide, and 2 ml of water was added with stirring. After 5 min, the solution was filtered, acidified dropwise with 1 *N* hydrochloric acid to about pH 5, and extracted with chloroform; the extract was washed with bicarbonate solution, dried, and evaporated to 246 mg of slightly yellow oil, yielding 188 mg of white crystals, mp 100–102°, recrystallized from benzene–petroleum ether to ir 2.80 (w), 2.90, 3.00, 5.87, 6.04, 6.65 μ; uv λ_{max} 273 (log ϵ 4.27), 282 (4.19), 305 (4.04), 313 (4.05) mμ.

Hydrogenation to 19.—3.15 g of *N*-(*o*-hydroxy-β-styryl)-*t*-butylurethan was hydrogenated at atmospheric pressure over 33 mg of platinum oxide in 25 ml of 95% ethanol; the catalyst clumped together and hydrogen uptake stopped at 147 ml (theory, 300 ml) in 40 hr. A further 85 mg of catalyst was added, affording a further 254-ml uptake (114% of theoretical)

(29) It should be pointed out that reactions on these compounds in strong acid are often characterized by the opening of the methylenedioxy ring, which is acid labile as an acetal of formaldehyde. A classical color test for the presence of a methylenedioxy ring is its dark discoloration in sulfuric acid.

(30) F. E. King, J. A. Barltrop, and R. J. Wally, *J. Chem. Soc.*, 277 (1954).

(31) J. Houben and E. Pfankuch, *Chem. Ber.*, **59**, 1598 (1926).

in 5 hr more. Filtration and evaporation left 3.15 g of a nearly colorless oil. Preparative tlc produced crystals which seeded the oil and allowed its recrystallization from benzene–hexane to 1.53 g of **19**, mp 74–77°; the mother liquors were nearly indistinguishable on tlc or ir comparison. Analyses were variable; the compound decomposes slowly over several weeks at room temperature or on heating to 100°; ir showed 2.90, 3.05, 5.85 (sh), 5.93, 6.65 μ.

Oxidation of Phenol 19 to the Dienone 20.—To 243 mg of the phenol **19** in 2 ml of acetic acid was added 623 mg of solid lead tetraacetate (recrystallized from acetic acid and washed dry with ether); the solution was stirred in a 20° bath and went very dark. After one minute, the mixture was poured into a slurry of 6.4 g of sodium carbonate decahydrate and 25 ml of methylene chloride. The solution was stirred for 5 min and the organic layer was separated. The residual salts were washed white with more methylene chloride, and the combined organic phases washed with aqueous sodium bicarbonate, dried, and evaporated to 266 mg of dark residue, showing five spots on tlc. This was placed on three preparative tlc plates in ethyl acetate–chloroform (1:3) and four bands taken, all of roughly equal yield, and examined on analytical plates and by uv spectra. The promising fraction (λ_{max} 300 mμ) was rechromatographed and one fraction from the second plate crystallized from cold ether to 14 mg of crystals: mp 87–90°; ir 2.90, 5.75, 5.87, 5.98, 6.65 μ; uv λ_{max} 301 (log ε 3.43). In a repeat experiment, the same fraction (identical by tlc and spectra) could not be crystallized.

Decomposition of the Dienone 20.—34 mg of dienone **20**, as a colorless oil from chromatography spectrally identical with the crystalline sample, was dissolved in 1 ml of trifluoroacetic acid and bubbled vigorously. After 1 min, aqueous sodium bicarbonate was added and the mixture extracted with methylene chloride. On drying and evaporation, the extract yielded only 3 mg of an oil which darkened on standing, showed indiscriminate tailing from 215 to 400 mμ in the uv, one major carbonyl band at 5.75 μ, and a very minor band at 5.95 μ. In another experiment, 10 ml of methylene chloride and 1.5 ml of triethylamine were added after 5 min to the trifluoroacetic acid solution of 39 mg of dienone.

The solution was evaporated, taken up in benzene, and extracted with water. On evaporation of benzene, only 2 mg remained, with an ir spectrum resembling starting material's. In each case, continuous extraction of the aqueous layers, after basification with alkali, yielded negligible material.

When 1 mg of crystalline dienone **20** was dissolved in 1 drop of trifluoroacetic acid, left for five minutes, and diluted with acetonitrile, the uv showed the band at 301 mμ unchanged, and little change was seen after 22 hr. If, after dilution with acetonitrile, 2 drops of triethylamine is added, the band at 301 mμ disappeared, but only a long tailing absorption without maxima replaced it.

1-Methoxy-4-(β-aminoethyl)-cyclohexadiene-1,4 (22a).—2.0 g of *p*-methoxyphenethylamine[32] were dissolved in 10 ml of methanol, and about 150 ml of liquid ammonia was distilled into the solution, cooling it to −70°. 1.6 g of sodium metal was added with stirring over 3 min, and the blue color disappeared in about 5 min. The ammonia was evaporated, ether and water were added, and the mixture was extracted with ether, which was dried and evaporated to 1.7 g of an oil. It exhibited ir bands at 5.90 and 6.02 μ, completely lacked several strong absorptions due to starting material, and exhibited only end absorption in the uv above 215 mμ and nmr at 4.56 (~s, 1 H), 5.39 (s, 1 H), 6.50 (s, 3 H), 7.3 (m, 6 H), 7.9 (m, 4 H). Distillation at 60° (15 μ) yielded 1.0 g of an oil which did not materially differ in its spectra.

Hydrolysis of this enol ether **22a** in 2 *N* sulfuric acid at room temperature for 1 hr yielded variable amounts of ether-extractible material after basification. These oils could not be distilled without decomposition, and no crystalline hydrochloride or picrate could be prepared. Extended manipulation afforded increasing amounts of an insoluble yellow amorphous solid, and only small amounts were recoverable from silica chromatography.

6-Nitropiperonylamide (23).—A solution of 6-nitropiperonyl chloride in ether [from 5 g (24 mmol) of nitro acid and 5 g of phosphorus pentachloride as above for **15a**] was added to a solution of 3.9 g (25 mmol) of the amino enol ether, **22a**, in ether containing 10 ml of triethylamine, and stirred for 12 hr. The solution was washed with hydrochloric acid, sodium hydroxide, and water, dried, and evaporated to 4.9 g of an oil from which 2.9 g (35%) crystallized from benzene: mp 158–159°; ir 2.90, 5.98, 6.55, 7.50 μ.

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.10. Found: C, 58.61; H, 5.12; N, 7.92.

Hydrolysis of 23a to 24.—100 mg of the nitro amide, **23a**, was dissolved, with warming, in 20 ml of 95% ethanol with 1 drop of concentrated hydrochloric acid and stirred at room temperature for 2 hr. Most of the ethanol was removed *in vacuo*, and water and methylene chloride were added. The mixture was washed with more methylene chloride.

The combined organic layers were dried and were then evaporated to 75 mg of a gum from which 48 mg of crystals were obtained from benzene: mp 134–137°; ir 2.90, 5.85, 6.00, 6.52 μ; uv λ_{max} 242 (log ε 4.0), 343 (3.6); nmr 2.60 (s, 1 H), 3.30 (s, 1 H), 3.85 (s, 2 H), 4.45 (m, 1 H), 6.6 (m, 2 H), 7.2–8.4 (m, 8 H), none exchangeable with D_2O.

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.82; H, 4.85; N, 8.44. Found: C, 57.89; H, 5.01; N, 8.57.

Bromination of 24 to 25.—To 60 mg (0.18 mmol) of ketone **24** in methylene chloride was added 29 mg (0.18 mmol) of bromine in methylene chloride. The solution was left until virtually colorless, washed with water and sodium thiosulfate solution, dried, and evaporated to 64 mg of **25**, mp 151–153°, giving a precipitate with alcoholic silver nitrate: ir 2.90, 6.00, 6.55 μ; uv λ_{max} 228 (log ε 3.8), 243 (3.7), 285 (3.3), 342 (3.3), and subtraction of **24** from **25** showed a peak at 227 mμ; nmr 2.52 (s, 1 H), 2.90 (s, 1 H), 3.09 (s, 1 H), 3.25 (~ s, 1 H), 6–8 (m, 8 H).

Anal. Calcd for $C_{16}H_{15}BrN_2O_6$: C, 46.73; H, 3.68; N, 6.82. Found: C, 46.81; H, 3.59; N, 6.71.

1,5-Dimethoxy-4-(β-aminoethyl)cyclohexadiene-1,4 (22b).—2,4-Dimethoxyphenethylamine[33] was reduced as described for its analog **22a** except that ethanol was required as the alcohol and was added in portions over 1.5 hr until the sodium color disappeared. The crude reduction product, as a colorless oil containing no starting amine (by tlc and nmr), was used without further purification.

6-Nitropiperonylamide (23b).—This amide was prepared by a completely analogous procedure to that for the amide **23a**, using the crude product from reduction of 1.0 g (5.5 mmol) of 2,4-dimethoxyphenethylamine and obtaining, after crystallization from petroleum ether, 650 mg (31%) of needles: mp 154–156°; ir 2.90, 5.88 (w), 6.00, 6.55, 6.62 μ.

Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.45; H, 5.36; N, 7.45. Found: C, 57.56; H, 5.32; N, 7.11.

Hydrolysis of (22b). Formation of 26.—In no case could crystalline material, as free amine or its salts, be isolated from hydrolyses of the bis enol ether **22b** under conditions similar to those tried for **22a**. The following procedure produced a derivative. 260 mg of enol ether **22a** was refluxed for 0.5 hr in 95% ethanol containing 0.25 ml of concentrated hydrochloric acid and evaporated to a residue which was partitioned between methylene chloride and aqueous sodium hydroxide. The organic phase was washed with water, evaporated to 90 mg of an oil, and dissolved in ether. 6-Nitropiperonylic acid (220 mg) was converted to its acid chloride in ether as described above and added to the crude amine and about 100 mg of triethylamine. After stirring overnight, the ether was washed with water, dried, and evaporated to yield a gum (170 mg) which yielded crystals on removing the major spot from a preparative tlc plate (silica, 1% methanol in chloroform). The crystals were recrystallized from ethanol: mp 215–220°; ir 5.94, 6.05, 6.20, 6.55, 7.50 μ; uv λ_{max} 246 (log ε 4.1), 289 (4.3), 340 (sh, 3.8); nmr 2.36 (s, 1 H), 3.20 (s, 1 H), 3.78 (s, 2 H), 3.85 (s, 1 H), 6.0–8.5 (m, 9 H).

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.96; H, 4.31; N, 8.32.

Hydrolysis of the Enol Ether Amide 23b.—300 mg (0.8 mmol) of the bis enol ether **23b** was dissolved in 50 ml of 95% ethanol, 0.3 ml of concentrated hydrochloric acid was added, and the system was refluxed for 2 hr, boiled down to 10 ml, and cooled. The deposited crystals were filtered (220 mg) and recrystallized from ethanol to yield 120 mg (46%) of the same product as above, **26**, by comparison of spectra and melting point (mp 217–219°, mmp 215–220°).

Reduction of 26.—160 mg (0.5 mmol) of nitro amide **26** and 160 mg of palladium–charcoal were added to α-phellandrene (20

(32) L. H. Klemm, R. Mann, and C. D. Lind, *J. Org. Chem.*, **23**, 346 (1958).

(33) The procedure of R. I. T. Crombie and J. Harley-Mason, *J. Chem. Soc.*, 2525 (1952), was used, affording the 2,4-dimethoxy-β-nitrostyrene, mp 102–103°, followed by 2,4-dimethoxy-β-phenethylamine, hydrochloride mp 158–160°.

ml) and heated with stirring on an oil bath. At about 130°, a vigorous evolution of gas occurred and the temperature rose to 150°. When this activity subsided, the suspension was cooled, filtered, and washed with 5 *N* hydrochloric acid. The aqueous layer was made basic and extracted with methylene chloride, and the organic phase was dried and evaporated to yield 110 mg (75%) of crystals, recrystallized from benzene to mp 134–135°; ir 5.84, 6.01, 6.14 μ; uv λ_{max} 238 (log ϵ 4.2), 320 (3.7); nmr 2.49 (s, 1 H), 3.03 (s, 1 H), 3.92 (s, 2 H), 4.0 (m, 2 H), 7.82 (s, 3 H), 6.5–8.3 (7 H), no protons exchanged with D_2O; mass spectrum major peaks *m/e* 300 (p), 243, 229.

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.57; H, 5.25; N, 9.66.

Diazotization in aqueous nitrous acid or with isoamyl nitrite in trifluoroacetic acid led only to unchanged starting material, identified by spectra and tlc.

Registry No.—**1**, 476-28-8; **4a**, 20286-59-3; **4b** HCl, 20302-79-8; **4c**, 20286-60-6; **4c** (nitro ketone), 20286-61-7; **4c** (bromo ketone), 20286-62-8; *trans*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20302-80-1; *cis*-4-amino-5-(3,4-methylenedioxyphenyl)cyclohexene HCl, 20286-63-9; *cis*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20286-64-0; **7**, 20286-65-1; **8a**, 20286-66-2; **8a** (dibromide), 20286-67-3; **8a** (epoxide), 20286-68-4; **8b**, 20286-69-5; **9a**, 20286-70-8; **9a**, 20286-71-9; **10b**, 20286-72-0; **11a**, 20286-73-1; **11a**, 20286-74-2; **11b**, 20286-75-3; **11b**, 20286-76-4; **12b**, 20286-77-5; **12b**, 20286-78-6; **15a**, 20286-79-7; **15c**, 20287-27-8; **16**, 20286-80-0; N-(6-nitropiperonyl)-*o*-hydroxyphenethylamide, 20286-81-1; **18**, 20286-82-2; N-(*o*-hydroxy-β-styryl)-*t*-butylurethan, 20286-83-3; **19**, 20286-84-4; **20**, 20286-85-5; **23a**, 20286-86-6; **23b**, 20286-87-7; **24**, 20286-88-8; **25**, 20286-89-9; **26**, 20286-90-2; **27**, 20286-91-3.

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Syntheses and Optical Rotatory Dispersion Studies of (*S*)-5-(2′-Pentyl)barbituric Acid Derivatives[1]

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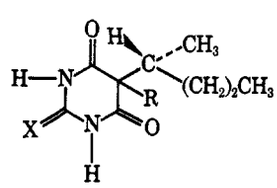
The syntheses of several (*S*)-5-(2′-pentyl)barbituric acid derivatives are reported and their optical properties have been investigated. Although the ultraviolet spectra of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) shows only one maximum under the conditions studied, optical rotatory dispersion measurements have shown two Cotton effects. Some pH dependent optical rotatory dispersion studies indicate that the lower wavelength Cotton effect is the result of a $\pi-\pi^*$ transition and the higher wavelength Cotton effect is of type $n-\pi^*$. The $\pi-\pi^*$ Cotton effect is positive and the $n-\pi^*$ Cotton effect is negative. The ultraviolet spectrum of the monosubstituted barbituric acid, (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc), in acid solution showed one maximum and the optical rotatory dispersion curve in the same solvent showed a negative $\pi-\pi^*$ low wavelength and a positive $n-\pi^*$ high wavelength Cotton effect. These results show that the biologically active IIa has optical rotatory dispersion properties greatly different from those of the biologically inactive IIc. These results are discussed in relation to the differences in the structure of these two compounds.

In a recent paper the preparation of some (*R*)-5-(2′-pentyl)barbituric acid derivatives (I) was reported.[2] In order to compare the optical properties, the pharmacological effects, and the metabolic fate, it was necessary to obtain the enantiomeric (*S*)-5-(2′-pentyl)barbituric acid derivatives (II) in high optical purity. The (*R*)-isomers I could be readily prepared in a high state of optical purity from commercially available (*R*)-(+)-pulegone.[2] However, the unavailability of the corresponding (*S*) isomer or other similar (*S*) derivative convertible to the (*S*)-barbituric acid derivatives II, made it necessary to seek a different synthesis of these enantiomers. Although there are two reports of the preparation of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) in the literature, in both cases the optical purity was very low. A method reported by Kleiderer and Shonle[3] involved a displacement reaction at the asymmetric carbon atom and proved to be unsuitable for the preparation of the (*S*) isomers II in high optical purity.[4]



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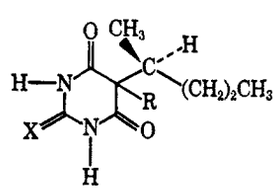

II

a, R = C_2H_5, X = O
b, R = C_2H_5, X = S
c, R = H, X = O
d, R = CH_2=$CHCH_2$—, X = O
e, R = CH_2=$CHCH_2$—, X = S

In 1966 Knabe and Philipson[5] reported the separation of racemic 5-ethyl-5-(2′-pentyl)barbituric acid (pentobarbital) into its optical antipodes *via* fractional crystallization of its diastereomeric N-methylquininium salt from a methanol and ether mixture followed by regeneration of the acid. The (*S*) isomer IIa thus obtained had $[\alpha]^{20}D$ −3.5° and was, therefore, only 28% optically pure when compared to $[\alpha]^{20}D$ 13.12° obtained for Ia.[2] Since the (*S*) isomer was reported to be the more crystalline of the two salts and easier to separate, further recrystallization of this salt should lead to optically pure IIa. Indeed, we found that IIa having $[\alpha]^{24}D$ −13.38°

(1) This research was carried out under Contract PH43-65-1057 of the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Md.

(2) C. E. Cook and C. R. Tallent, *J. Heterocycl. Chem.*, **6**, 203 (1969).

(3) E. C. Kleiderer and H. A. Shonle, *J. Amer. Chem. Soc.*, **56**, 1772 (1934).

(4) The optical purity of IIa obtained by Kleiderer and Shonle (ref 3) was 36%.

(5) J. Knabe and K. Philipson, *Arch. Pharm.* (Weinheim), **299**, 232 (1966).