Registry No.—**1a**, 21182-09-2; **1b**, 21182-15-0; **1c**, 1053-39-0; **1d**, 57637-71-5; **1e**, 57637-72-6; **1f**, 57637-73-7; **1g**, 57637-74-8; **1h**, 57637-75-9; **1i**, 57637-76-0; **1j**, 57637-77-1; **1k**, 57637-78-2; **1l**, 57637-79-3; **1m**, 21182-11-6; **2**, 57637-80-6; **3**, 57637-81-7; **4**, 57637-82-8; **5**, 57637-83-9; **7a**, 1099-94-1; **7a** 2HCl, 57637-84-0; **9**, 57637-85-1; indole, 120-72-9; 4-pyridinecarboxaldehyde, 872-85-5; 5-cyanoindole, 15861-24-2; 1-methylindole, 603-76-9; benzyl chloride, 25168-05-2; methyl iodide, 74-88-4.

References and Notes

(1) E. Sawicki and C. R. Sawicki, *Ann. N.Y. Acad. Sci.*, **163**, 895 (1969).
(2) E. Sawicki, D. F. Bender, T. R. Hauser, R. M. Wilson, Jr., and J. E. Meeker, *Anal. Chem.*, **35**, 1479 (1963).
(3) J. Epstein, R. W. Rosenthal, and R. J. Ess, *Anal. Chem.*, **27**, 1435 (1955).
(4) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).
(5) A. P. Gray, *J. Org. Chem.*, **23**, 1453 (1958).
(6) J. Joule and G. F. Smith, "Heterocyclic Chemistry", Van Nostrand-Reinhold, Princeton, N.J., 1972, p 265.
(7) (a) The rapid conversion of the zwitterion **3** to **4** appears analogous to other rapid anion oxidations [G. A. Russell and A. G. Bemis, *J. Am. Chem. Soc.*, **88**, 5491 (1966)]. The slow autoxidation of alkylindoles reviewed in R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, N.Y., 1970, seems less relevant. (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, pp 779–781.
(8) In another preparation of **5** there was obtained by quantitative column chromatography a 12 mol % yield of methyl anthranilate based on the weight of starting material.
(9) H. Krauch and W. Kunz, "Organic Name Reactions", Wiley, New York, N.Y., 1962, p 283.
(10) D. N. Kramer, L. P. Bisauta, R. Bato, and B. L. Murr, Jr., *J. Org. Chem.*, **39**, 3132 (1974).
(11) A. H. Corwin, R. R. Arellano, and A. B. Chivvis, *Biochim. Biophys. Acta*, **162**, 533 (1968).
(12) N. V. Sidgwick, "The Organic Chemistry of Nitrogen", Oxford University Press, London, 1966, p 650.
(13) T. A. Scott, *Nature (London)*, **204**, 77 (1964).

A Synthetic Approach to the Cephalotaxine Skeleton

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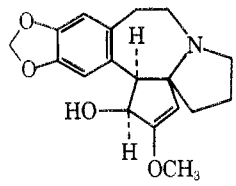
Several possible routes to the synthesis of the alkaloid cephalotaxine have been explored. Friedel–Crafts cyclization of 1-[2-(3,4-methylenedioxyphenyl)ethyl]pyrrole-2-carboxylic acid, followed by reduction with hydrogen over rhodium on charcoal, gave 8,9-methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine.

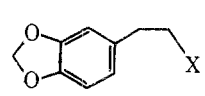
The alkaloid cephalotaxine (I), found in the plum yew, has been assigned an absolute structure based on a combination of chemical, spectral, and x-ray diffraction data.[1–6]



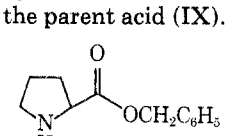
I

Esters of cephalotaxine derived from substituted malic and tartaric acids are known as harringtonines,[7–10] and are of interest because of their antitumor properties.[11] With a view to potential medicinal applications, work was begun in the fall of 1971 on the synthesis of the parent ring system, which, if successful, could be extended to other alkaloids in this series.

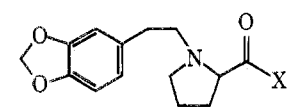
Treatment of 1,2-methylenedioxybenzene (II) with bromine gave 3,4-methylenedioxybromobenzene (III), as well as a small amount of 4,5-methylenedioxy-1,2-dibromobenzene (IV).[12] Generation of the Grignard reagent from the bromide III, followed by the addition of ethylene oxide, formed 3,4-methylenedioxyphenethyl alcohol (V). Refluxing alcohol V with phosphorus tribromide then produced 4-(2-bromoethyl)-1,2-methylenedioxybenzene (VI). Alkylation of benzyl prolinate (VII) by the bromide VI went smoothly; the intermediate benzyl ester (VIII) was not isolated, but was hydrogenated to the parent acid (IX).



V, X = OH
VI, X = Br



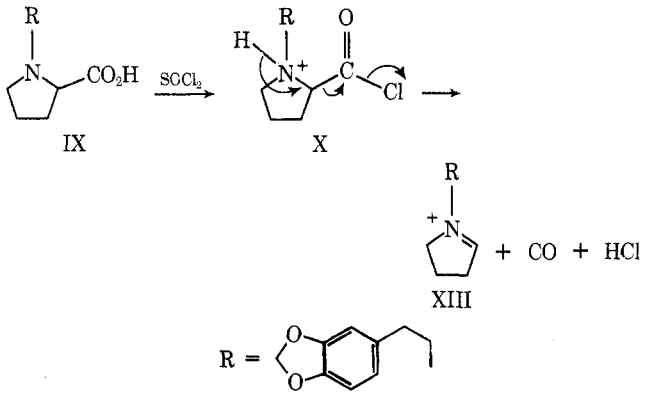
VII



VIII, X = $OCH_2C_6H_5$
IX, X = OH
X, X = Cl

The next step, Friedel–Crafts cyclization of compound IX, rather surprisingly failed because decarbonylation of the proline carboxyl group occurred with remarkable ease when attempts were made to prepare the acid chloride X. Interestingly, the treatment of proline (XI) with thionyl chloride has been said to give prolyl chloride hydrochloride (XII); unfortunately, no analytical or spectral data were provided to support the assigned structure.[13] By contrast, two other reports on the preparation of amino acid acyl chloride hydrochlorides are known and appear to be correct.[14,15] Treatment of acid IX with thionyl chloride, phosphorus trichloride, or oxalyl chloride yielded in all cases a new compound (XIII). The structure assigned to XIII was supported by the absence of a carbonyl group in the infrared and a correct proton count in the nuclear magnetic resonance spectrum for both the methylenedioxyphenylethyl and prolyl groups. These results can be explained by postulating the existence of a "reverse-Koch" reaction (Scheme I). Here, we assume the initial conversion of the acid IX to the desired acyl chloride X, which then undergoes decomposition either by nucleophilic attack or by internal rearrangement to yield the iminium chloride XII. Some support for this idea was found when it was observed that a solution of IX in methylene dichloride at −70 °C on treatment with trifluoroacetic acid evolved carbon monoxide. The same result was obtained when other modes of ring cyclization were tried with IX, for example, treatment

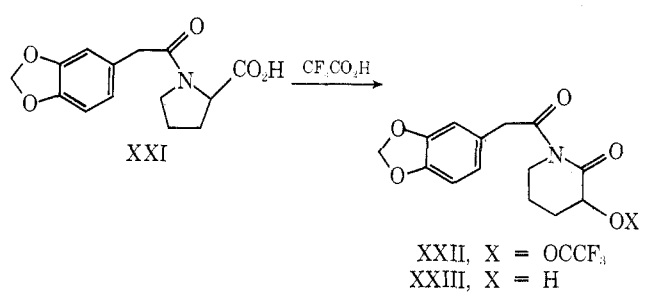
Scheme I. The Reverse-Koch Mechanism



with polyphosphoric acid or a dimethylformamide–sulfur trioxide complex.

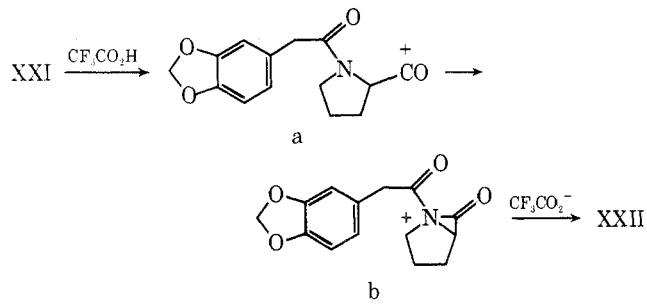
In an alternative approach, piperonal (XIV) was reduced in a Parr shaker to 3,4-methylenedioxybenzyl alcohol (XV), which on treatment with hydrogen bromide–hydrobromic acid produced the corresponding bromide (XVI). Heating XVI with sodium cyanide in dimethyl sulfoxide afforded 3,4-methylenedioxyphenylacetonitrile (XVII); subsequent hydrolysis in ethanol–water containing sodium methoxide gave 3,4-methylenedioxyphenylacetic acid (XVIII). This route from aldehyde XIV to acid XVIII is essentially the same as one already described in the literature;[16] however, our modification has the advantage that a low-pressure hydrogenation step is used on XIV, neither compounds XVI and XVII are isolated, and the overall yield of acid XVIII is quite high.

The coupling of acid XVIII to proline or proline esters was carried out by a variety of standard peptide techniques. It was found that optimum yields were obtained using an in situ formation of 2,4,5-trichlorophenyl 3,4-methylenedioxyphenylacetate (XIX), followed by the addition of thallium prolinate (XX) to form *N*-(3,4-methylenedioxyphenylacetyl)proline (XXI). An attempt to cyclize XXI with trifluoroacetic acid afforded two new products (XXII and XXIII). Compound XXII gave a negative ferric

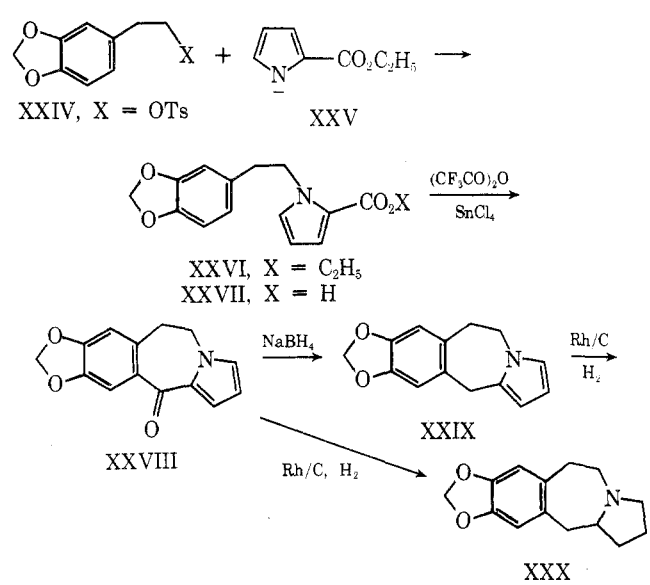


chloride test, and possessed absorptions at 1795, 1657, and 1638 cm^{-1} in the infrared. The very high carbonyl stretch at 1795 cm^{-1} in potassium bromide is characteristic of a trifluoroacetic ester, which is consistent with the unstable nature of this compound. Indeed, on recrystallization from moist solvents, or on preparative thin layer chromatography, XXII readily changed into XXIII. The latter product showed a broad band at 3300 cm^{-1}, as well as the disappearance of the 1795-cm^{-1} absorption. Other carbonyl absorptions were noted at 1760 (weak and sharp) and 1680 cm^{-1} (broad and very strong). The former can be attributed to an imide,[17] while the latter is probably due to two superimposed peaks, which, to be consistent with the rather long wavelength, are amide or hydrogen bonded carbonyls. This suggestion was confirmed by a shift to 3500, 1755, and 1715 cm^{-1}, respectively, when the spectrum was redetermined in chloroform. Further, in the nuclear magnetic resonance spectrum of XXIII, a single, exchangeable proton was detected at δ 6.4, which suggested a chelated hydroxyl proton such as –COCHOH–. Compound XXIII still contains the methylenedioxy group, seen at δ 6.0, as well as three aromatic protons at δ 6.6; so cyclization to a seven-membered ketone can be disregarded. These results can be rationalized by postulating the formation of a carbonium ion a that cyclizes to b; nucleophilic attack by trifluoroacetate ion then forms the observed product XXII (and, on hydrolysis, XXIII) (Scheme II). This type of ring expansion has been noted before, i.e., the acid-catalyzed conversion of 2-chloromethyl-*N*-methylproline to 3-chloro-*N*-methylpiperidine.[18,19]

Scheme II. The Carbonium Ion Mechanism



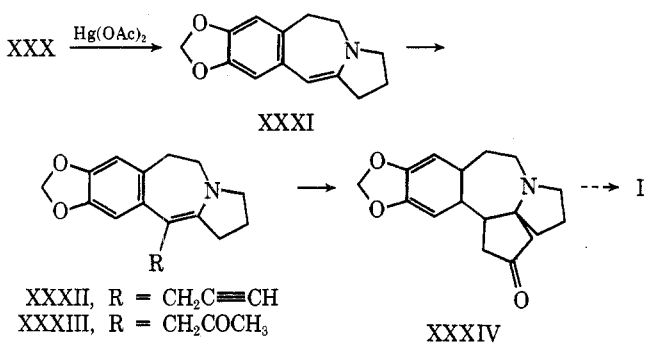
On the principle that the basicity of the proline nitrogen is the cause of the above undesired sequences, an alternative solution could be formulated in terms of a pyrrole intermediate. Thus, the alcohol V was converted into the tosylate XXIV and on addition of sodium 2-carbethoxypyrrole (XXV) there was obtained the pyrrole ester XXVI, which, without isolation, was hydrolyzed to the parent acid XXVII. Cyclization of the acid XXVII to the benzazepine



XXVIII was smoothly effected with trifluoroacetic anhydride–stannic chloride. A variety of reaction conditions were tried in order to either selectively reduce the pyrrole ring or the keto group in compound XXVIII, but only limited success was achieved. For example, sodium borohydride treatment of XXVIII gave the hydrogenolyzed benzazepine XXIX. The intermediate alcohol was easily detected by thin layer chromatography, as the spot attributed to it turned red on exposure to air. Similar deoxygenations have been seen previously in this heterocyclic system.[22] By contrast, the pyrrole ring in compounds XXVII or XXIX was rapidly reduced by a rhodium on charcoal

catalyst and the crystalline pyrrolidine (XXX) was produced in nearly quantitative yield. After the completion of this work, the same compound was obtained by another group in the form of a labile oil.[23] The reported spectral properties for this latter material were essentially identical with those measured on crystalline XXX.

The last stage in the synthesis called for the conversion of the tetracyclic base XXX via mercuric acetate oxidation to the enamine XXXI. After isolation, the desired intermediate XXXI was found to be unstable in chlorinated solvents and decomposed on standing. The same product has now been made by an alternative synthesis and a comparison of samples showed their mutual identity.[24] Reaction of XXXI with propargyl bromide formed the acetylene XXXII, which on mercury(II)-catalyzed hydration gave ketone XXXIII. Treatment of XXXIII with several acid catalysts neither produced pentacyclic ketone (XXXIV) nor any other cyclopentanone-containing product. These results are in complete agreement with a recent synthetic venture in this area,[24] but are in contrast with an earlier report.[23] Assuming that alternative modes of cyclization exist, the resulting ketone XXXIV would be converted by two or more steps into the desired alkaloid I.



At this point the work terminated, as we were unable to secure any support necessary to complete the synthesis or to begin analog studies. Note that within the past year two independent preparations of cephalotaxine have been published.[24,25] One of these is parallel to our route and intersects it at the enamine stage. Subsequently, no further effort is planned in this area.

Experimental Section[26]

3,4-Methylenedioxybromobenzene (III). Bromine vapor (187 g, 1.17 mol) was drawn through methylenedioxybenzene (143 g, 1.17 mol) in chloroform (600 ml) by an aspirator over a 4-h period. The original procedure calls for cooling the reaction mixture with an ice bath, but this gives a slow reaction rate.[12] Distillation afforded a small forerun of starting material, bp 57–68 °C (10 mm), followed by the product (216 g, 91%), bp 103–107 °C (10 mm). The residue in the still pot crystallized on cooling, and a recrystallization from methanol yielded a small quantity of 4,5-methylenedioxy-1,2-dibromobenzene, mp 86 °C.

3,4-Methylenedioxyphenethyl Alcohol (V). 3,4-Methylenedioxybromobenzene (80 g, 0.40 mol) was added dropwise with stirring to magnesium (10 g, 0.44 mol) in anhydrous tetrahydrofuran (300 ml) under dry nitrogen. The mixture was then refluxed for 0.5 h and cooled to 0 °C, and ethylene oxide (21.8 ml, 19.3 g, 0.44 mol) was distilled into the reaction flask at such a rate that the temperature never rose above 5 °C. When the addition was complete, the mixture was refluxed for 1 h and then worked up by acidification and extraction. Distillation gave a small forerun of methylenedioxybenzene (6 g), followed by the product (49.4 g, 75%), bp 115–125 °C (0.2 mm), mp 21–22 °C [lit. bp 120–122 °C (2.5 mm)].[27]

4-(2-Bromoethyl)-1,2-methylenedioxybenzene (VI). To a solution of the aforementioned alcohol (45 g, 0.3 mol) in ethyl ether (300 ml) cooled to 10 °C, phosphorus tribromide (35 g, 0.13 mol) was added dripwise while maintaining the temperature below 10 °C. The reaction mixture was then refluxed for 1 h, followed by work-up and distillation to yield the product (44.4 g, 80%), bp 142–144 °C (6 mm) [lit. bp 144 °C (6 mm)].[28]

Benzyl *N*-2-(3,4-Methylenedioxyphenyl)ethylprolinate (VIII). A solution of 4-(2-bromoethyl)-1,2-methylenedioxybenzene (22.9 g, 0.10 mol), benzyl prolinate hydrochloride (41 g, 0.20 mol),[29] potassium carbonate (20 g, 0.20 mol), and potassium iodide (23 g, 0.20 mol) in dimethylformamide (40 ml) was heated to 100 °C until the evolution of carbon dioxide ceased. Work-up by extraction gave the product (25.4 g, 75%) as a nearly colorless yellow oil.

***N*-2-(3,4-Methylenedioxyphenyl)ethylproline (IX).** The benzyl ester (6.15 g, 0.0175 mol) was hydrogenated at atmospheric pressure using 10% palladium on charcoal catalyst (1 g) in methanol (200 ml). After the uptake of hydrogen had ceased, the catalyst was removed, the solvent evaporated, and the residue recrystallized from ethyl acetate–methanol to yield the product (3.8 g, 84%): mp 195–197 °C; ir (KBr) 3010, 2840, 1625, 1490, and 1250 cm^{-1}; NMR (D_2O + NaOD) δ 6.5 (m, 3), 5.7 (s, 2), and 3.9–1.7 (11).

Anal. Calcd for $C_{14}H_{17}NO_4$ (263.17): C, 63.87; H, 6.51; N, 5.32. Found: C, 64.38; H, 6.60; N, 5.04.

3,4-Methylenedioxybenzyl Bromide (XVI). Piperonal (100 g, 0.667 mol) was dissolved in methanol (200 ml) and hydrogenated for 12 h in a Parr shaker using platinum oxide (300 mg) activated with ferric sulfate (150 mg, 1.00 mmol) and sodium methoxide (108 mg, 2.00 mmol). On removal of the solvent in vacuo, the crystalline residue, mp 57 °C, was treated with fuming hydrobromic acid prepared by saturating concentrated hydrobromic acid with gaseous hydrogen bromide at 0 °C. After about 1 min, the oil that formed resolidified into a mass of needles, which were filtered and dried in vacuo (140 g, 98%), mp 49–50 °C.

3,4-Methylenedioxyacetonitrile (XVI). 3,4-Methylenedioxybenzyl bromide (21.6 g, 0.1 mol) was added in portions to a stirred suspension of sodium cyanide (10 g, 0.2 mol) in dimethyl sulfoxide (20 ml)–water (5 ml) at such a rate that the temperature did not rise above 40 °C. When the last portion of bromide was added, the colorless slurry turned into a thick paste. Dilution with water (100 ml) and work-up by extraction yielded the product as a partially crystalline, pale yellow oil, which was used without further purification in the next step. A small portion was distilled for spectral purposes, bp 135–140 °C (5 mm).

3,4-Methylenedioxyphenylacetic Acid (XVIII). The aforementioned nitrile was refluxed overnight in ethanol (50 ml) containing water (5 ml) and sodium methoxide (10 g, ca. 0.2 mol). Work-up by extraction followed by crystallization from water and recrystallization from benzene yielded colorless needles (14.7 g, 82%), mp 128–129 °C (lit. mp 128–129 °C[16]).

Thallium Prolinate (XX). Proline (11.5 g, 0.100 mol) was suspended in refluxing ethanol (50 ml) and treated with thallium ethoxide (7.2 ml, 0.10 mol) and the resulting solution was cooled to 6 °C and diluted with ether (75 ml). The resulting mass of colorless crystals was collected and dried in vacuo (29.9 g, 94%).

***N*-(3,4-Methylenedioxyphenylacetyl)proline (XXI).** To a stirred solution of 3,4-methylenedioxyphenylacetic acid (1.8 g, 10 mmol) dissolved in ethyl acetate (50 ml), *N,N'*-dicyclohexylcarbodiimide (2.1 g, 10 mmol) was added, followed by 2,4,5-trichlorophenol (2.6 g, 10 mmol). A white precipitate of *N,N'*-dicyclohexylurea immediately formed, after which thallium prolinate (3.18 g, 10.0 mmol) was added and the mixture allowed to stand for 20 h. A solution of sodium iodide was added to precipitate thallium ion; then the mixture was filtered and extracted with saturated sodium bicarbonate. The aqueous phase was neutralized, and the resulting crude product was collected, recrystallized from benzene, and sublimed (1.8 g, 65.5%): mp 165–168 °C dec; ir (KBr) 2700, 2570 (broad), 1735, 1595, and 1200 cm^{-1}; NMR ($CDCl_3$) δ 9.7 (s, 1), 6.6 (s, 3), 6.0 (s, 2), 4.6 (b, 1), 3.7 (s, 2), 3.6 (b, 2), and 2.1 (b, 4).

Anal. Calcd for $C_{14}H_{15}NO_5$ (277.16): C, 60.63; H, 5.45; N, 5.05. Found: C, 60.32; H, 5.39; N, 4.81.

Reaction of *N*-(3,4-Methylenedioxyphenylacetyl)proline with Trifluoroacetic Anhydride. The aforementioned acid (1.35 g, 5.00 mmol) was dissolved in tetrahydrofuran (40 ml) containing trifluoroacetic anhydride (2 g, ca. 10 mmol). After 15 min, the solvent was removed and the residue was recrystallized from tetrahydrofuran–ether to yield an unstable, minor component (XXII). On exposure to air or on heating the product rearranged into compound XXIII: ir (KBr) 1795, 1657, and 1638 cm^{-1}; negative ferric chloride test.

The mother liquors were evaporated and the residue was recrystallized from chloroform to yield the second component (XXIII): mp 165–168 °C dec; ir (KBr) 3300 (broad), 1760 (sharp, weak), and 1680 cm^{-1} (broad, very strong); ir ($CHCl_3$) 3500, 1755, and 1715

cm^{-1}; NMR ($CDCl_3$) δ 6.85 (s, 3), 6.41 (broad, exchangeable with D_2O, 1), 6.02 (s, 2), 4.55 (s, 1), 3.6–4.2 (m, 1), 2.15–3.5 (m, 4), and 1.9–2.15 (pentet, 3). No satisfactory analysis could be obtained owing to the labile nature of this product.

2-(3,4-Methylenedioxyphenyl)ethyl Tosylate (XXIV). Pyridine (8.0 g, 0.1 mol) and 3,4-methylenedioxyphenethyl alcohol (16.5 g, 0.10 mol) were dissolved in dichloromethane (50 ml) and the solution was dried by distilling the solvent until the vapor temperature reached 40 °C. After cooling to 0 °C, *p*-toluenesulfonyl chloride (20 g, 0.105 mol) was dissolved in dichloromethane (30 ml), filtered, and then added to the other reactants. After standing for 1 day at room temperature, the reaction mixture was cooled to −6 °C and filtered to remove the pyridine hydrochloride (ca. 10 g, very hydroscopic). Work-up by extraction with dilute hydrochloric acid, followed by crystallization from ether at −70 °C, gave the product (29.2 g, 94%): mp 59–60 °C; ir (KBr) 2900, 1360, 1165, and 770 cm^{-1}; NMR ($CDCl_3$) δ 7.7 (d, 2), 6.6 (m, 3), 5.9 (s, 2), 4.2 (t, 2), 2.8 (t, 2), and 2.4 (s, 3).

Anal. Calcd. for $C_{16}H_{16}O_5S$ (320.23): C, 60.00; H, 5.00; S, 10.00. Found: C, 59.77; H, 5.18; S, 9.80.

***N*-[2-(3,4-Methylenedioxyphenyl)]ethylpyrrole-2-carboxylic Acid (XXVII).** A solution of 2-carbethoxypyrrole (39 g, 0.36 mol) in diethylene glycol dimethyl ether (diglyme) was added dropwise to a stirred suspension of sodium hydride (50% suspension in mineral oil, 16 g, 0.36 mol) in diglyme (200 ml) under a nitrogen blanket. When all of the sodium hydride has reacted, the aforementioned tosylate (11.5 g, 0.358 mol) was added and the mixture was heated for 3 days at 70 °C. After removal of most of the solvent in vacuo, the residue was saponified by refluxing in 2 M ethanolic potassium hydroxide (250 ml) overnight. Work-up by extraction as before and recrystallization from benzene gave the product (59.0 g, 63.5%): mp 127–130 °C; ir (KBr) 2700, 2630, 2560, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 11.1 (broad, 1), 7.3 (pair of doublets, 1), 6.7 (m, 4), 6.2 (pair of doublets, 1), 6.0 (s, 2), 4.55 (m, 2), and 3.05 (m, 2).

Anal. Calcd for $C_1H_{13}NO_4 \cdot \frac{1}{2}H_2O$ (248.16): C, 62.90; H, 5.24; N, 5.20. Found: C, 62.70; H, 4.77; N, 5.16.

11-Oxo-8,9-methylenedioxy-6-hydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXVIII). Trifluoroacetic anhydride (25 ml, ca. 0.2 mol) was added with stirring to a suspension of *N*-[2-(3,methylenedioxyphenyl)]ethylpyrrole-2-carboxylic acid (25.9 g, 0.100 mol) in ethanol-free chloroform (500 ml) under nitrogen. The mixture turned deep red within 5 min, at which time thin layer chromatography indicated that the starting acid was absent in the reaction. After the mixture was cooled to 0 °, stannic chloride (32.7 ml, 0.300 mol) was added dropwise, and the mixture allowed to come to room temperature and stand for 4 h. After destruction of the stannic chloride–product complex by the addition of aqueous ammonia, the organic layer was separated and the solvent was removed in vacuo. The residue was recrystallized from ethyl acetate to give the product (21.1 g, 88%): mp 121–123 °C; uv (acetonitrile) 236 nm (ϵ 32 000), 277 (16 000), and 240 (38 000); ir (KBr) 3070, 2960, 2910, 2780, 1640 (weak), 1595 (strong), and 1475 cm^{-1}; NMR ($CDCl_3$) δ 5.78 (s, 1), 7.4 (m, 1), 6.9 (m, 1), 6.7 (s, 1), 6.3 (m, 1), 6.1 (s, 2), 4.4 (d, 1), 4.3 (d, 1), and 3.2 (m, 2).

Anal. Calcd. for $C_{14}H_{11}NO_3$ (241.16): C, 69.70; H, 4.60; N, 5.81. Found: C, 70.50; H, 4.61; N, 5.71.

8,9-Methylenedioxy-1,6-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXIX). The aforementioned benzazepine (1.2 g, 0.05 mol) was refluxed overnight in diglyme (200 ml) containing sodium borohydride (12 g, large excess). At this time the intermediate alcohol, which was easily detectable by thin layer chromatography as a spot that rapidly turned dark red, was virtually absent. The mixture was then poured into water (500 ml), filtered, and recrystallized from methanol to yield the pale yellow product (11 g, 97%). Recrystallization from benzene–petroleum ether and sublimation (95 °C, 0.02 mm) gave a pure sample: mp 120–122 °C; ir (KBr) 3130 (sharp), 2960, 2890, 2780, and 15 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (d, 2), 6.4 (t, 1), 5.9 (m, 2), 5.8 (s, 2), 4.1 (pair of doublets), 3.8 (s, 2), and 3.0 (pair of doublets).

Anal. Calcd for $C_{14}H_{13}NO_2$ (203.23): C, 70.91; H, 6.45; N, 6.89. Found: C, 70.61; H, 6.44; N, 6.82.

8,9-Methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXX). From XXIX. The aforementioned pyrrole (227 mg, 1 mmol) was hydrogenated at atmospheric pressure in acetic acid (40 ml) using 5% rhodium on charcoal catalyst (50 mg). After 1 h the hydrogen uptake dropped markedly, and the reaction mixture was worked up. The product was converted to the hydrochloride salt by addition of a few drops of concentrated hydrochloric acid to a solution of the acetate salt in an ether–ethanol solution to give white needles (250 mg, 97%), mp 260–270 °C dec (lit. mp 265–266 °C dec).[23]

From XXVIII. The ketopyrrole (480 mg, 2.00 mmol) was dissolved in hot 95% ethanol (200 ml) and the solution was added to a stirred suspension of presaturated 5% rhodium on charcoal (10 g) in 95% ethanol (20 ml) containing perchloric acid (10 drops). After approximately 1 day, 8 equiv (17.9 ml) of hydrogen had been absorbed and no starting material or intermediate alcohol could be detected by thin layer chromatography. After filtration, the solvent was removed in vacuo, and the residue was extracted into chloroform following neutralization of the salt. The chloroform was evaporated and the residue was crystallized from methanol, followed by sublimation to give the product (450 mg, 98%), mp 70–71 °C. The spectral properties of this compound were identical with those reported in the literature.[23] Addition of hydrochloric acid to a solution of the amine in 2-propanol afforded the salt, mp 260–270 °C dec.

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Registry No.—II, 274-09-9; III, 2635-13-4; IV, 5279-32-3; V, 6006-82-2; VI, 57587-02-7; VII HCl, 16652-71-4; VIII, 57587-03-8; IX, 57587-04-9; XIV, 120-57-0; XVI, 2606-51-1; XVII, 4439-02-5; XVIII, 2861-28-1; XX, 57587-05-0; XXI, 57587-06-1; XXII, 57587-07-2; XXIII, 57587-08-3; XXIV, 57587-09-4; XXVII, 57587-10-7; XXVIII, 57587-11-8; XXIX, 57587-12-9; XXX, 35667-18-6; XXX HCl, 35667-19-7; 3,4-methylenedioxyphenylacetic acid, 2861-28-1; 2,4,5-trichlorophenol, 95-95-4; trifluoroacetic anhydride, 407-25-0; *p*-toluenesulfonyl chloride, 98-59-9; carbethoxypyrrole, 2199-43-1.

References and Notes

(1) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963).
(2) W. W. Paudler and J. McKay, *J. Org. Chem.*, **38**, 2110 (1973).
(3) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969).
(4) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).
(5) S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, **39**, 1269 (1974).
(6) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).
(7) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *Tetrahedron Lett.*, 815 (1970).
(8) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972).
(9) S. Brandange, S. Josephson, and S. Vallen, *Acta Chem. Scand., Ser. B*, **28**, 153 (1974).
(10) T. Ipaktchi and S. M. Weinreb, *Tetrahedron Lett.*, 3895 (1973).
(11) R. G/ Powell, D. Weisleder, and C. R. Smith, Jr., *J. Pharm. Sci.*, **61**, 1227 (1972).
(12) F. Dallacker and H. Zegers, *Justus Liebigs Ann. Chem.*, **689**, 156 (1965).
(13) Y. Liwschitz, A. Zilka, H. Borensztain, and M. Frankel, *J. Org. Chem.*, **21**, 1531 (1956).
(14) S. Levine, *J. Am. Chem. Soc.*, **76**, 1382 (1954).
(15) E. Fischer, *Ber.*, **38**, 2914 (1905).
(16) E. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).
(17) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., pp 352–354.
(18) R. H. Reitsema, *J. Am. Chem. Soc.*, **71**, 2041 (1949).
(19) R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760 (1948).
(20) R. Huisgen and E. Laschturka, *Chem. Ber.*, **93**, 65 (1960).
(21) E. Laschturka and R. Huisgen, *Chem. Ber.*, **93**, 81 (1960).
(22) K. H. Bell, *Aust. J. Chem.*, **22**, 601 (1969).
(23) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972).
(24) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975).
(25) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975).
(26) All melting points were determined on a Reichert Thermopan apparatus, and are uncorrected; infrared spectra (ir) were determined on a Perkin-Elmer 257 spectrophotometer, nuclear magnetic resonance (NMR) on a Varian Associates A-60 instrument, and ultraviolet (uv) on a Cary 14. The following symbols are used in the presentation of NMR data: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The solvents used were reagent grade unless otherwise noted. Microanalyses were furnished by Galbraith Laboratories, Knoxville, Tenn.
(27) T. Fujii, M. Tashiro, K. Ohara, and M. Kumai, *Chem. Pharm. Bull.*, **8**, 266 (1960).
(28) S. Sugasawa and Y. Suzuta, *J. Pharm. Soc. Jpn.*, **71**, 1159 (1951).
(29) R. E. Neumann and E. L. Smith, *J. Biol. Chem.*, **93**, 97 (1951).