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Acid-catalyzed Cyclization of 3-Acetyl-3-(3,4-dimethoxyphenyl)adiponitrile[1]

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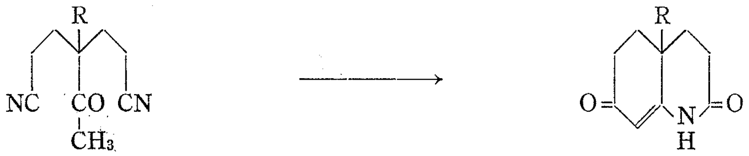
Hydrolytic cyclization of 3-acetyl-3-(3,4-dimethoxyphenyl)adiponitrile (V) in 65% sulfuric acid at 140° was found to yield 3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydroindol-2,6-dione (VI), whose structure was confirmed by spectral properties and transformation into *dl*-mesembrane (=3a-(3,4-dimethoxyphenyl)-1-methylperhydroindol) (XI). Reactions of V in 65% sulfuric acid at room temperature yielded five products, XIII, XIV, XV, XVI and XVII as intermediates of this cyclization reaction, all of which were converted to the final cyclization product (VI) by heating to 140° in the acid. Possible reaction mechanisms of the formation of VI and the intermediates were proposed. An alternate synthesis of VI from 3,4-dimethoxyphenyl acetone *via* methyl 3-(2-cyanoethyl)-3-(3,4-dimethoxyphenyl)levulinate (XIX) was also described.

The hydrolytic cyclization of γ-acetylpimelonitriles (I) has been reported by several groups. Koelsch, *et al.*[3] studied the cyclization of I (R=C_6H_5, CH_3, *etc.*) using 65—80% sulfuric acid and obtained the corresponding octahydroquinoline derivatives (II). Ban, *et al.*,[4] in the course of their synthesis of natural products related to aspidosperma alkaloids, reported the synthesis of 4a-phenoxyethyl-1,2,3,4,4a,5,6,7-octahydroquinoline-2,7-dione (II: R=$CH_2CH_2OC_6H_5$) by the reaction of I (R=$CH_2CH_2OC_6H_5$) with hydrochloric acid in dioxane.



I II

Chart 1

We studied a similar cyclization of an unsymmetrical dinitrile, 3-acetyl-3-(3,4-dimethoxyphenyl)adiponitrile (V), expecting to obtain 3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydroindol-2,6-dione (VI), which could be converted to mesembrine (XII)[5] by successive reactions including saturation of the double bond and reduction of the lactam carbonyl.

Condensation of 3,4-dimethoxyphenyl acetone (III) with chloroacetonitrile in dimethylsulfoxide (DMSO) in the presence of its anion gave 3-(3,4-dimethoxyphenyl)-4-oxo-valeronitrile (IV) in 19.4% yield, which was then subjected to Michael reaction with acrylonitrile to give V in 89.2% yield.

Hydrolytic cyclization of V in 65% sulfuric acid at 140° for 5 min gave VI in 60% yield as a single crystalline product. Its infrared absorption (IR) spectrum exhibited absorption

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[1] A part of this work was communicated: T. Oh-ishi and H. Kugita, *Tetrahedron Letters*, **1968**, 5445.

[2] Location: *No. 2-50, Kawagishi 2-Chome, Toda, Saitama.*

[3] *a*) C.F. Koelsch and H.M. Walker, *J. Am. Chem. Soc.*, **72**, 346 (1950); *b*) C.F. Koelsch and D.L. Ostercamp, *J. Org. Chem.*, **26**, 1104 (1961).

[4] *a*) Y. Ban, Y. Sato, M. Seo, I. Inoue, Y. Kanaoka and O. Yonemitsu, Abstracts of Papers, The 8th Symposium on the Chemistry of Natural Products, Nagoya, 1964, p. 123; *b*) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu and Y. Kanaoka, *Tetrahedron Letters*, **1965**, 2261.

[5] A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York and London, 1967, Chapter 11.

bands at 1740 and 1715 cm^{-1} assignable to a five membered lactam carbonyl group[6] and a strong absorption peak at 1640 cm^{-1} due to an enone.

N-Methylation of VI with dimethyl sulfate gave 3a-(3,4-dimethoxyphenyl)-1-methyl-2,3,3a,4,5,6-hexahydroindol-2,6-dione (VIII), whose IR spectrum showed a peak at 1745 cm^{-1} assignable to a five membered lactam carbonyl group[6] and a strong peak at 1625 cm^{-1} due to an enone.

These spectral data of VI and VIII excluded another possible structure VII as the cyclization product. The ultraviolet (UV) spectrum of VI was likewise in accordance with the vinylogous imide structure,[4] showing an absorption maximum at 273 mμ (ε 26200) in ethanol which shifted to 325 mμ (ε 39020) in alkaline ethanol.

The structure VI for the cyclization product was finally proved by a sequence of reactions leading to *dl*-mesembrane (XI).[7] Catalytic hydrogenation of VI on palladium in an acidic medium gave 3a-(3,4-dimethoxyphenyl)octahydroindol-2-one (IX). This compound showed a carbonyl absorption peak at 1690 cm^{-1} due to the five membered lactam in the IR spectrum and a quartet (AB type) attributable to C-3 methylene at 2.52 ppm in the nuclear magnetic resonance (NMR). The lactam (IX) was methylated with sodium hydride and methyl iodide to give 3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindol-2-one (X), which in turn was reduced with lithium aluminum hydride to give *dl*-mesembrane (XI) as a colourless oil. Its hydrochloride and picrate were identical with the corresponding authentic samples.[8]

The successful transformation of VI to *dl*-mesembrane (XI) in high yield confirms not only the structure of VI but also the *cis* ring-fusion of IX and X.

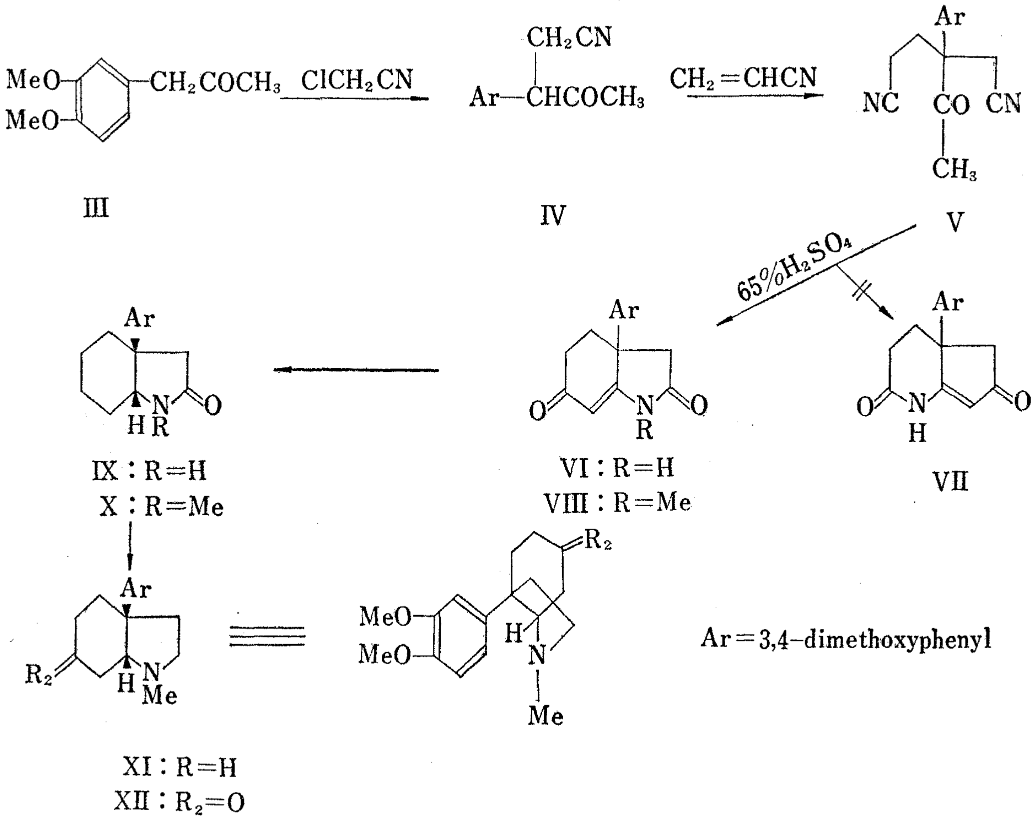

Chart 2

Now that the hydrolytic cyclization of V was proved to yield exclusively the desired ring system, the scope and mechanism of this reaction have been investigated. Reaction of V in

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[6] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden–Day, Inc., San Francisco, 1962, p. 46.

[7] A. Popelak, G. Lettenbauer, E. Haack and H. Spingler, *Naturwissenschaften*, 47, 231 (1960).

[8] We are indebted to Dr. A. Popelak for providing us with the authentic sample of *dl*-mesembrane.

65% sulfuric acid at room temperature gave five products: 4-(2-cyanoethyl)-5-hydroxy-4-(3,4-dimethoxyphenyl)-5-methyl-2-pyrrolidinone (XIII), 4-(2-cyanoethyl)-4-(3,4-dimethoxyphenyl)-5-methylene-2-pyrrolidinone (XIV), 3-(2-cyanoethyl)-3-(3,4-dimethoxyphenyl)levulinic acid (XV), 3a-(3,4-dimethoxyphenyl)-7a-methyl-2,6-dioxooctahydrofuro[2,3-*b*]pyridine (XVI) and 2-amino-3-(2-cyanoethyl)-3-(3,4-dimethoxyphenyl)-2-methyl-5-oxotetrahydrofuran (XVII). The proportion of these products varied depending on the reaction time as shown in Table 1. All these compounds, on heating in the acid at 140° for 5 min, gave the final cyclization product (VI).

The structure of the first intermediate (XIII), which was obtained as an uncrystalline substance, was not conclusively determined becasue of its instability during purificantion. When kept at room temperature, it lost one molecule of water and turned to a crystalline substance (XIV), whose structure was confirmed by spectral properties and elemental analysis. This transformation became fast when XIII was heated either *in vacuo* or in an inert solvent containing a trace of acid.[9] When XIV was kept at room temperature in dilute acid, an equilibrium was attained resulting in an almost 1:1 mixture of XIII and XIV. On treatment with a small amount of methanol, XIII was converted to relatively stable crystals containing methanol as crystalline solvent. The crystalline product showed a broad absorption band (ν_{OH}) at 3500—3000 cm^{-1}, a band at 1670 cm^{-1} due to a lactam carbonyl group and a band at 2270 cm^{-1} due to a nitrile group in its IR spectrum. Its NMR spectrum in acetone-d_6 showed a singlet at 1.03 ppm due to the tertiary methyl group and a singlet at 2.68 ppm due to the C-3 methylene protons.

The reaction mechanism of the formation of XIII from V and conversion to XIV could be outlined as shown in Chart 3: hydrolysis of one of the nitrile groups with the neighboring

Table I. The Yields (%) of the Isolated Products in Reactions of V in 65% Sulfuric Acid at Room Temperature

Reaction time (hr)	XIII XIV	XV	XVI	XVII[a]
1.5—2	*ca.* 65	21.6	0	22.6
5	*ca.* 29	65.5	0.9	—
22	*ca.* 18	49.8	2.0	54.3

[a] XVII was obtained in a differenrt run. See experimental section.

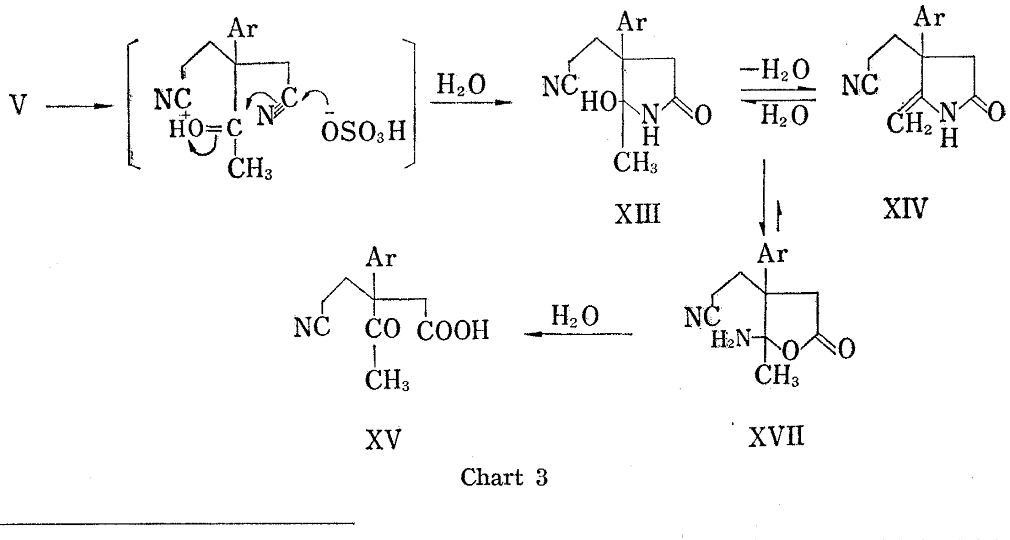

Chart 3

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[9] This was observed even when XIII was dissolved in CDCl$_3$ containing a few drops of CF$_3$COOH for NMR measurement.

acetyl group participation[10] proceeds fast to yield exclusively the five membered lactam XIII. Although the existence of XIV in the reaction mixture could not be proved, it is reasonable to assume that XIII and XIV exist as an equilibrium mixture in 65% sulfuric acid.

The carboxylic acid (XV) was obtained after the reaction mixture was diluted with water and allowed to stand one to two days at room temperature, and its structure was confirmed by the identification of its methyl ester (XIX) with an authentic sample prepared by an unambiguous route shown in Chart 6. But XV could not be obtained byext raction of the reaction mixture immediately after the dilution of the reaction mixture with water. The reaction of XV in 65% sulfuric acid at room temperature for 21.5 hours yielded XVI in 73% yield. However, V gave XVI in only 2% yield together with XV in 49.8% yield after 22 hours' reaction in 65% sulfuric acid at room temperature as shown in Table 1. These results suggest the presence of another basic intermediate between XIII (and/or XIV) and XV, and this intermediate should be relatively stable in 65% sulfuric acid, while it could be readily hydrolyzed to XV on dilution with water. To prove this hypothesis, the reaction mixture of V and 65% sulfuric acid was neutralized with potassium carbonate immediately after dilution with water. There was obtained a crystalline amine (XVII), the structure of which was confirmed by inspection of physical properties of the acetate (XVIII). This amine (XVII), as expected, was recovered unchanged almost quantitatively when kept in 65% sulfuric acid for 6 hours and readily hydrolyzed to XV in 10% sulfuric acid. The relation between XIII and XVII resembles the tautomeric relation for leavulinoamides.[11] Hydrolysis of XVII to XV which proceeds extremely slowly in 65% sulfuric acid at room temperature may be the first rate-limiting step of the cyclization of V to VI. Heating the reaction mixture should facilitate this hydrolysis.

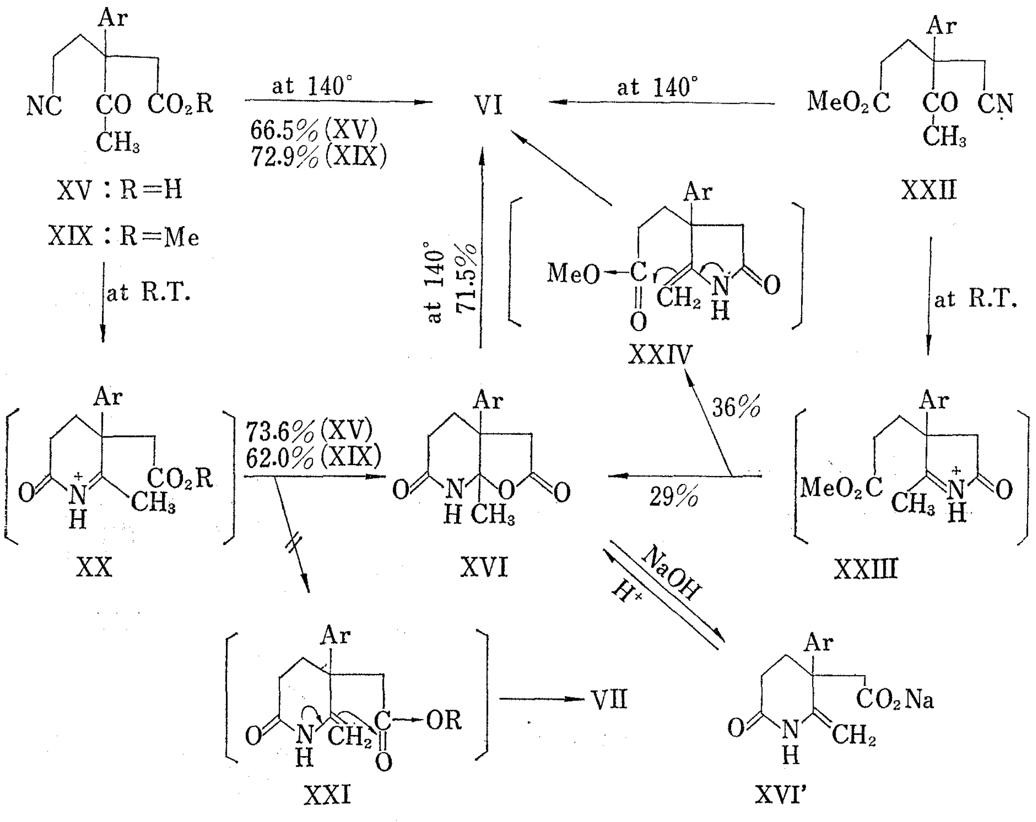

Chart 4

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[10] F. Johnson and R. Madronero, "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York and London, 1966, p. 95.

[11] "Beilsteins Handbuch der Organischen Chemie," 4th ed., III, 1921, p. 676; N.H. Cromwell and K.E. Cook, *J. Am. Chem. Soc.*, **80**, 4573 (1958).

The cyanocarboxylic acid (XV) could not be regarded as the intermediate of the reaction product (VI) because XV would give VII *via* the intermediates XX and XXI as shown in Chart 4.[12] However, as was already stated, the reaction of XV in 65% sulfuric acid at room temperature gives XVI in a good yield: formation of XX by the hydrolytic cyclization between the acetyl group and the cyanoethyl group should be the intermediary step of this reaction. The lactone formation to give XVI should probably be faster than the enamine type cyclization to give VII *via* XXI and this may be the reason of the failure to yield another product (VII) in the hydrolytic cyclization of V.

Reaction of the methyl ester (XIX) in 65% sulfuric acid at room temperature likewise gave XVI in 62% yield. However, it is noteworthy that the reaction of the reversed ester (XXII) in 65% sulfuric acid at room temperature for 21.5 hours also gave XVI in 29% yield together with VI in 36% yield. The latter product (VI) could be produced from the hypothetical intermediate (XXIII) through XXIV, but the formation of XVI was unexpected. This indicates another mechanism operating competitively with the one which directly yields VI.

The transformation of XVI into the final product (VI), occuring only by heating the reaction mixture, may proceed by the mechanism shown in Chart 5. Although the intermediates were not isolated, it is probable that the hydrolysis of XVI followed by recyclization gives XXV, which in turn gives the final product (VI) *via* XXVI. This transformation may be the second rate-limiting step in the hydrolytic cyclization of V.

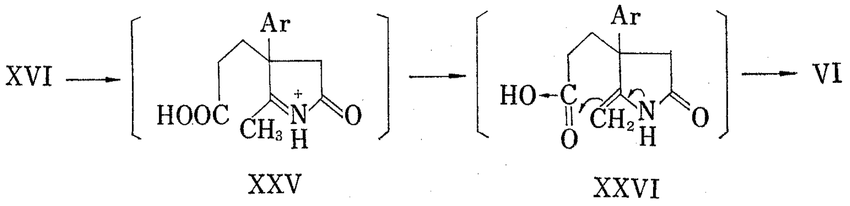

Chart 5

The methyl ester (XIX) described previoulsy gave VI in 72.9% yield on heating with 65% sulfuric acid. This provides another course for preparation of VI (Chart 6). Monoalkylation of III with allyl bromide and sodium *iso*-propoxide gave 4-(3,4-dimethoxyphenyl)-1-hexen-5-one (XXVII), which was submitted to ketalization giving an oil (XXVIII). Oxidative cleavage of the ketal (XXVIII) with potassium permanganate followed by esterification gave methyl 3-(3,4-dimethoxyphenyl)-4-oxovalerate (XXIX). Michael reaction of XXIX with acrylonitrile gave XIX. Synthesis of VI *via* XIX appeared more workable than *via* V because of the low yield and a tedious purification of IV encountered in the latter.

The methyl ester (XXII), prepared from IV, also gave VI in 73% yield on heating with 65% sulfuric acid.

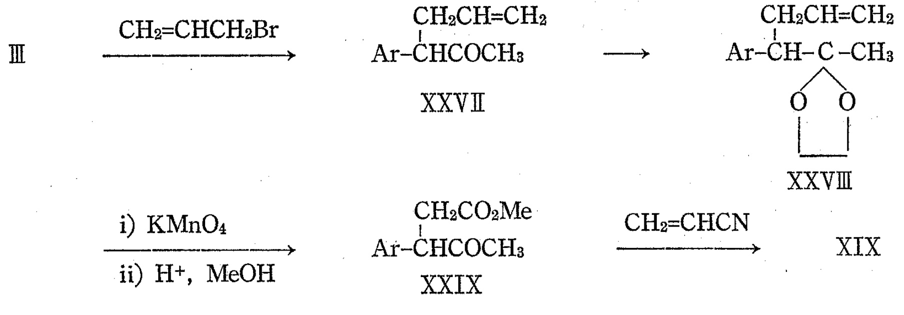

Chart 6

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[12] *a*) C.F. Koelsch and H.M. Walker, *loc. cit*; *b*) N.F. Albertson, *J. Am. Chem. Soc.*, **74**, 249 (1952); *c*) O. Cervinka, *Collection Czech. Chem. Commun.*, **25**, 1174, 1183 (1960).

Experimental[13]

3-(3,4-Dimethoxyphenyl)-4-oxovaleronitrile (IV)——A solution of dimethylsulfinyl carbanion in DMSO was prepared under nitrogen atmosphere from sodium hydride (14.8 g) and DMSO (400 ml) according to Corey, *et al.*[14] To this solution was introduced 3,4-dimethoxyphenyl acetone (III) (100 g) with stirring and ice-cooling so as to keep the temperature below 20°, and subsequently added dropwise chloroacetonitrile (40 g) at such a rate that the temperature did not exceed 30°. After stirring at room temperature for 15 min, the reaction mixture was poured into ice-water and extracted with benzene. The benzene extracts were washed with water, dried over Na_2SO_4 and evaporated to give an oily substance, which was distilled at reduced pressure. A distillate boiling above 195°/5.5 mmHg was collected (yellow viscous oil, 43.8 g), which was crystallized soon on dilution with ether. Recrystallization from EtOH gave IV (23.3 g, 19.4%), mp 88—89°, as colourless prisms. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.99; H, 6.20; N, 6.35. IR ν_{max}^{Nujol} cm^{-1}: 2280 (CN), 1705 (C=O).

3-Acetyl-3-(3,4-dimethoxyphenyl)adiponitrile (V)——To a stirred solution of IV (11.2 g) and Triton B (0.8 ml of 40% methanolic solution) in dioxane (112 ml) was added acrylonitrile (3.04 g) under cooling with tap water. The reaction mixture was stirred at room temperature for 1.5 hr and neutrallized with AcOH. The solvent was removed *in vacuo* to give a semisolid, which was crystallized from MeOH to give V (12.10 g, 89.2%), mp 119—119.5°. *Anal.* Calcd. for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.33; N, 9.79. Found: C, 67.32; H, 6.04; N, 9.61. IR ν_{max}^{Nujol} cm^{-1}: 2300 (CN), 1705 (C=O).

3a-(3,4-Dimethoxyphenyl)-2,3,3a,4,5,6-hexahydroindol-2,6-dione (VI)——A suspension of V (1.0 g) in 65% sulfuric acid (6 ml) was heated at 140° for 5 min and poured into ice–water (30 ml). The precipitates were collected by filtration and recrystallized from EtOH to give VI (0.6 g, 60%), mp 206—208°. Analytical sample melted at 210—212°. *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.97; N, 4.88. Found: C, 67.13; H, 5.96; N, 5.24. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1740 (s) and 1715 (w) (lactam), 1640 (enone). UV λ_{max}^{EtOH} mμ (ε): 273 (26200); $\lambda_{max}^{EtOH(OH^-)}$ mμ (ε): 325 (39030).

3a-(3,4-Dimethoxyphenyl)-1-methyl-2,3,3a,4,5,6-hexahydroindol-2,6-dione (VIII)——A stirred mixture of VI (17.1 g), dimethyl sulfate (45 g) and EtOH (350 ml) was heated to 70°. To this was added dropwise alcoholic KOH solution prepared from KOH (24 g) and EtOH (120 ml). The mixture was stirred at 70° for 30 min and then heated to reflux for 1 hr. After cooling, water was added to dissolve a deposited crystalline mass and the most of EtOH was evaporated. A separated oil was extracted with $CHCl_3$. The extract was washed with water dried over Na_2SO_4 and evaporated to give a crystalline residue, which was recrystallized from EtOH to give VIII (16.31 g, 91.0%) as colourless prisms, mp 178—180°. *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.34; N, 4.65. Found: C, 67.80; H, 6.43; N, 4.55. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (lactam), 1625 (enone). NMR ($CDCl_3$) δ: 2.86 (2H, singlet, C-3 methylene protons), 3.11 (3H, singlet, N–CH_3), 5.72 (1H, singlet, olefin proton).

3a-(3,4-Dimethoxyphenyl)octahydroindol-2-one (IX)——VI (2.5 g) was hydrogenated in EtOH (60 ml) containing 10% HCl (1 ml) over 10% Pd/C at room temperature until three moles of hydrogen was absorbed. The reaction product, after recrystallization from EtOH, gave a pure sample of IX (2.12 g, 88.4%), mp 149—151°. *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.43; N, 5.37. IR ν_{max}^{Nujol} cm^{-1}: 1690 (γ-lactam). NMR ($CDCl_3$) δ: 2.52 (2H, AB type quartet, J=15.6 cps, $\Delta\nu$=9 cps, C-3 methylene protons), 4.22 (1H, broad singlet, w/2=6/cps, C-7a methine proton), 7.5 (1H, broad singlet, CON$\underline{H}$–).

3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindol-2-one (X)——A mixture of IX (500 mg), sodium hydride (65 mg) and toluene (15 ml) was heated to reflux with stirring for 2 hr. To this was added methyl iodide (3 ml) and refluxing was continued for an hour. After evaporation of excess methyl iodide, the reaction mixture was washed with water, dried over Na_2SO_4 and evaporated to give a viscous oil, which was solidified on addition of ether. Recrystallization from ether gave X (475 mg, 90.5%), mp 85—87°. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.44; H, 8.11; N, 4.51. IR ν_{max}^{Nujol} cm^{-1}: 1670 (γ-lactam). NMR ($CDCl_3$) δ: 2.50 (2H, singlet, C-3 methylene protons), 2.86 (3H, singlet, N–C$\underline{H}_3$), 3.95 (1H, C-7a methine proton).

***dl*-Mesembrane (XI)**——A mixture of X (1.6 g), lithium alminum hydride (500 mg) and ether (50 ml) was heated to reflux for 18 hr. Excess lithium alminum hydride was destroyed with small quantity of water and inorganic substances were filtered off. The filtrate was extracted with 10% HCl. The extract was washed with ether and made alkaline with solid NaOH. A separated oil was taken to benzene, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave an oily substance, which was distilled *in vacuo* to give *dl*-mesembrane (1.1 g, 72.3%) as a colourless oil, bp 140° (0.1 mmHg). Treatment with HCl

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[13] All melting and boiling points are uncorrected. IR spectra were measured on a Nippon Bunko Model IR-S or IR-E spectrophotometer. NMR spectra were determined on a Japan Electron Optics Co. JNM C-60 spectrometer with tetramethylsilane as an internal standard.

[14] E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

in iso-PrOH gave a hygroscopic hydrochloride of XI, mp 193—194°, whose IR (Nujol) spectrum is identical with that of authentic *dl*-mesembrane hydrochloride. Its picrate, mp 172—174° (EtOH), is also identical with the authentic sample in melting point and IR spectrum. *Anal.* Calcd. for $C_{23}H_{28}O_9N_4$ (picrate): C, 54.76; H, 5.59; N, 11.11. Found: C, 54.43; H, 5.32; N, 11.26.

Reaction of V in 65% Sulfuric Acid at Room Temperature——a) Isolation of XIII, XIV, XV and XVI: i) A suspension of V (6.9 g) in 65% sulfuric acid (42 ml) was mechanically shaken for 1.5 hr at room temperature. The resultant clear solution was diluted with water (200 ml) and extracted with $CHCl_3$. The extract was washed successively with water and saturated $NaHCO_3$ solution, and evaporated *in vacuo* to give a viscous oil (3.5 g), which showed at least two spots on TLC. (Neutralization of the $NaHCO_3$ washing with 10% HCl did not give any appreciable amount of an acidic substance.) The aqueous layer was extracted again with $CHCl_3$ after being allowed to stand two days at room temperature. The $CHCl_3$ extract was washed with water and saturated $NaHCO_3$ solution, and evaporated *in vacuo* to give a viscous oil (0.66 g), whose thin–layer chromatogram was almost identical with that of the former $CHCl_3$ extract. Neutralization of the $NaHCO_3$ washing in this time gave a crystalline acid (XV), (1.59 g, 21.6%), mp 119—120°. *Anal.* Calcd. for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.92; H, 6.33; N, 4.37. IR ν_{max}^{Nujol} cm^{-1}: 2290 (CN), 1700 (C=O, COOH). NMR ($CDCl_3$) δ: 1.96 (3H, singlet, C$\underline{H}_3$CO–), 3.16 (2H, doublet, –C$\underline{H}_2$COOH), 9.04 (1H, singlet, COO$\underline{H}$).

Methylation of XV with diazomethane in AcOEt gave a methyl ester (XIX), mp 102—103°, in quantitative yield which was identical in all respects to the product prepared from XXVII *via* XXIX (Chart 6).

The combined viscous oil (4.5 g, *ca.* 65%) obtained from the $CHCl_3$ extracts was chromatographed on alumina. From an early part eluted with $CHCl_3$ was recovered the starting material (V), (230 mg, 3.3%) and subsequent elution with the same solvent gave XIV (1.20 g, 17.4%),15) mp 121—124°. *Anal.* Calcd. for $C_{16}H_{18}O_3N$: C, 67.11; H, 6.34; N, 9.79. Found: C, 67.34; H, 6.12; N, 9.94. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 2270 (CN), 1710 (s) and 1680 (w) (lactam), 1640 (C=C). NMR ($CDCl_3$) δ: 2.7 (2H, doublet, $J=3$ cps, C-3 methylene protons), 4.1 (1H, doublet, $J=2$ cps, olefin proton), 4.6 (1H, doublet, $J=2$ cps, olefin proton). Finally, elution with $CHCl_3$–EtOH (95:5) gave XIII (0.83 g)15) as amorphous powder. This amorphous powder was tritulated with MeOH to give a crystalline substance, mp 102—104° (decomp.), which was found to contain MeOH as crystalline solvent on NMR spectrum and failed to prepare the sample for elemental analysis because of instability during purification. IR ν_{max}^{Nujol} cm^{-1}: 3500—3000 (OH, broad), 2270 (CN), 1670 (C=O). NMR (CD_3COCD_3) δ: 1.03 (3H, singlet, C$\underline{H}_3$), 2.68 (2H, singlet, C-3 methylene protons), 3.25 (*ca.* 3H, singlet, C$\underline{H}_3$OH).

ii) Treatment of V (10 g) in 65% sulfric acid (60 ml) for 5 hr as described above gave a mixture of XII and XIV (2.92 g, *ca.* 29%) and XV (6.98 g, 65.5%), in addition to which a small quantity of XVI (0.09 g, 0.85%) was isolated.

iii) Treatment of V (1.0 g) in 65% sulfuric acid (5 ml) for 22 hr as described above gave a mixture of XIII and XIV (0.18 g, *ca.* 18%), XV (0.53 g, 49.8%) and XVI (0.02 g, 1.97%).

b) Isolation of XVII: i) A suspension of V (1.0 g) in 65% sulfuric acid (5 ml) was shaken for 2 hr and poured into ice–water. The diluted reaction mixture was washed with $CHCl_3$ in order to remove XIII, XIV and XVI, neutralized with K_2CO_3 under cooling and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give crude amine (XVII) (0.24 g, 22.6%), mp 155° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3350 (NH_2), 2280 (CN), 1755 (C=O), 1625 (NH_2).

The amine (XVII) was dissolved in Ac_2O and kept standing at room temperature for 2 or 3 days. After excess Ac_2O was removed *in vacuo*, the residue was treated with aqueous MeOH to give the acetate (XVIII), mp 100—103° (decomp.), which was found to contain 1 mole of crystal water. *Anal.* Calcd. for acetate (XVIII), $C_{18}H_{22}O_5N_2 \cdot H_2O$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.49; H, 6.65; N, 7.64.

ii) Treatment of V (2.8 g) in 65% sulfuric acid (16.8 ml) for 20 hr and working up as described above gave XVII (1.61 g, 54.3%).

Reaction of XV in 65% Sulfuric Acid——i) A suspension of XV (157 mg) in 65% sulfuric acid (0.75 ml) was heated at 140° for 5 min and poured into water. Crystallization from EtOH gave VI (104 mg, 66.5%), mp 204—206°.

ii) A suspension of XV (3.0 g) in 65% sulfuric acid (15 ml) was shaken at room temperature for 21.5 hr. The clear reaction mixture was poured into water (60 ml), extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated *in vacuo* to give a crystalline mixture (1.09 g), which was chromatographed on alumina. Elution with $CHCl_3$ gave XVI (0.90 g, 30%), mp 205—206°. Further elution with $CHCl_3$–EtOH (9:1) gave VI (0.12 g, 4.75%), mp 208—211°. From the aqueous layer, after kept standing at room temperature for 1—2 hr, further crop of XVI (1.31 g, 43.6%), mp 206—207°, was obtained as crystalline precipitate. The total yield of XVI was 2.21 g (73.6%). *Anal.* Calcd. for XVI, $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.80; H, 6.19; N, 4.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340—3320 (NH), 1775 (γ-lactone), 1680 (lactam). NMR ($CDCl_3$) δ: 1.52 (3H, singlet, CH_3), 3.08 (2H, AB type quartet, $J=16$ cps, $\Delta\nu=15$ cps, C-3 methylene protons), 7.8 (1H, singlet, NH).

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15) These yields do not represent the actual composition of XIII and XIV in the reaction mixture.

3-(3,4-Dimethoxyphenyl)-2-methylene-6-oxopiperidin-3-acetic Acid Sodium Salt (XVI′)——To a suspension of XVI (0.15 g) in MeOH was added a little excess NaOH solution in MeOH and kept standing at room temperature. After a while, sodium salt (XVI′) began to precipitate. Recrystallization from MeOH gave the pure sample of XVI′ (110 mg), mp>250°. *Anal.* Calcd. for $C_{16}H_{18}O_5N \cdot Na$: C, 58.89; H, 5.56; N, 4.29. Found: C, 58.80; H, 5.30; N, 4.33. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3120, (NH), 1655 (lactam), 1575 (COO^-), 1635 (C=C), 855 ($C=CH_2$). NMR (D_2O) δ: 2.63 (2H, singlet, $-C\underline{H}_2COO^-$), 4.52 (1H, singlet, olefin proton). The signal of the other olefin proton is superposed to that of H_2O (5.42 ppm).

The sodium salt (XVI′) was reverted to the original lactone (XVI) on acidification with 10% HCl.

Reaction of XIX in 65% Sulfuric Acid——i) A suspension of XIX (168 mg) in 65% sulfuric acid (0.84 ml) was heated to 140° for 5 min and poured into water. Recrystallization of the precipitate from EtOH gave VI (0.11 g, 72.9%), mp 205—208°.

ii) A suspension of XIX (0.50 g) in 65% sulfuric acid (3.0 ml) was shaken at room temperature for 2 hr. The clear reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. Recrystallization of the residue from EtOH gave XVI (0.13 g, 27.2%), mp 204—207°. From the aqueous layer, after kept standing at room temperature for 2 hr, further crop of XVI (165 mg, 34.4%), mp 204—207°, was obtianed as a crystalline precipitate. The total yield of XVI was 295 mg (61.6%).

Reaction of XXII in 65% Sulfuric Acid——i) A suspension of XXII (0.20 g) in 65% sulfuric acid (1.0 ml) was heated to 140° for 5 min and poured into ice-water. Recrystallization of the precipitate from EtOH gave VI (0.13 g, 73.0%).

ii) A suspension of XXII (1.0 g) in 65% sulfuric acid was shaken at room temperature for 21.5 hr. The clear reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on alumina. Elution with $CHCl_3$ gave XVI (0.04 g, 4.2%), mp 204—206°. Further elution with $CHCl_3$–EtOH (9:1) gave VI (0.32 g, 35.6%), mp 209—211°. The aqueous layer, after kept standing at room temperature for 1 hr, was extracted again with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give XVI (0.24 g, 25.2%), mp 203—207°. The total yield of XVI was 0.28 g (29.4%).

4-(3,4-Dimethoxyphenyl)-1-hexen-5-one (XXVII)——To a stirred solution of sodium isopropoxide in iso-PrOH (prepared from 12 g of Na and 400 ml of iso-PrOH) was introduced 3,4-dimethoxyphenyl acetone (III) (100 g) and subsequently added dropwise allyl bromide (62.5 g) under ice–cooling. Stirring was continued at room temperature for 2 hr and then under gentle refluxing for an hour. After the solvent was removed, the reaction mixture was extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave an oil. Distillation gave a colourless oil (XXVII) (91.5 g, 75.5%), bp 150—153° (0.1 mmHg). IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 1700 (C=O), 1632 (C=C), 995 and 915 ($CH=CH_2$). 2,4-Dinitrophenylhydrazone of XXVII, mp 130—132°. *Anal.* Calcd. for $C_{20}H_{22}O_6N_4$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.93; H, 5.51; N, 13.60.

5-Ethylenedioxy-4-(3,4-dimethoxyphenyl)-1-hexene (XXVIII)——A solution of XXVII (84.6 g), *p*-toluenesulfonic acid (0.8 g), and ethylene glycol (30 ml) in benzene (500 ml) was refluxed for 8 hr under azeotropic removal of water. After cooling, it was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated. Distillation of the residue gave XXVIII (85.7 g, 84.9%). IR $\nu_{\max}^{\text{liq.}}$ cm^{-1}: 1632 (C=C), 995 and 915 ($CH=CH_2$).

Methyl 3-(3,4-Dimethoxyphenyl)levulinate (XXIX)——Powdered $KMnO_4$ (26.8 g) was added portionwise to a cooled mixture of XXVIII (11.75 g), $NaHCO_3$ (1.4 g) and acetone (118 ml) with stirring. Stirring was continued at room temperature overnight. Water (118 ml) was added and the mixture was filtered by suction. The organic solvent was removed *in vacuo*. The resulted aqueous solution was washed with $CHCl_3$, acidified with 10% HCl and extracted with $CHCl_3$. Evaporation of the solvent gave an oily acid (11.5 g). It was dissolved in abs. MeOH (50 ml), saturated with dry HCl gas and heated to reflux for 2 hr. After evaporation of MeOH, the residue was taken to benzene, washed with water, dried over Na_2SO_4 and evaporated. Distillation of the residue gave XXIX (6.4 g, 56.7%), bp 155—160° (0.3 mmHg), as an oil, which crystallized on standing, mp 70—72°. *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.18; H, 6.82. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1715 (ester), 1695 (ketone).

Methyl 3-(2-Cyanoethyl)-3-(3,4-dimethoxyphenyl)levulinate (XIX)——To a stirred solution of XXIX (30 g), Triton B (1.0 ml of 40% MeOH solution) in dioxane (6 ml) wss added dropwise acrylonitrile (1.0 g). Stirring was continued at room temperature overnight. The reaction mixture was neutralized with AcOH and evaporated *in vacuo*. Recrystallization of the residue from EtOH gave XIX (2.40 g, 66.7%), mp 102—103°. *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.72; H, 6.65; N, 4.50. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2300 (CN), 1725 (C=O).

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