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Studies on the Bischler-Napieralski Reaction with Unsaturated Lactams. Syntheses of 5,6,9,10,11,12-Hexahydro-2,3-dimethoxybenzo[4,5-*a*]-benzo[*f*]quinolizinium and Dihydrosempervirine Salts

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The Bischler–Napieralski cyclizations of 2–(3,4–dimethoxyphenethyl)hexahydro–$\Delta^{4,5}$–3(2*H*)–isoquinolone (V) and a mixture of V and the $\Delta^{5,10}$–isomer, yielded 1,2,3,4,4a,5,7,8–octahydro–benzo[*g*]10,11–dimethoxybenzo[4,5–*a*]pyridocolinium chloride (VI) and the corresponding isomeric mixture (XI), respectively, both of which were dehydrogenated to yield the same product, 1,2,3,4–tetrahydrobenzo[*g*]10,11–dimethoxybenzo[4,5–*a*]pyridocolinium iodide (VII). Dihydrosempervirine (XVII) was easily synthesized in the similar manner.

In connection with other problems including studies on the structure of (+)–rubremetinium cation (I) reported in the previous papers,[2] the Bischler–Napieralski cyclization of 2–(3,4–dimethoxyphenethyl)hexahydro–$\Delta^{4,5}$–3(2*H*)–isoquinolone (V) was investigated, where the starting compound was prepared by the condensation of 3,4–dimethoxyphenethylamine (III) with α,β–unsaturated–δ–lactone (IV). This condensation was effected in a boiling tetralin in the presence of anhydrous magnesium sulfate, in which reaction the yields rarely fell below 60% and were usually about 70%.

Although it had been demonstrated in an earlier work by the present authors that N–(3,4–dimethoxyphenethyl)pyridone (II) and a series of these compounds do not undergo the Bischler–Napieralski cyclization,[3] the above α,β–unsaturated–δ–lactam (V) was cyclized with phosphorus oxychloride to the quaternary chloride (VI) which was rather unstable and was not isolated in a pure state. Thus, an aqueous solution of the chloride (VI) was treated with solid potassium iodide in the usual manner to separate the resinous iodide. The crude iodide was purified as yellow needles, mp 265.5—266°, after recrystallizations from acetone.

It was found that the UV spectrum of the iodide thus obtained did not agree with that of the chloride (VI), but was in good accordance with that of 9,10–dimethoxy–6,7–dihydrobenzo[*a*]quinolizinium iodide (VIII), which was described by Akaboshi, *et al.*[4] who prepared it by way of the Pschorr cyclization.

The iodide (VII) in ethanol showed light absorption maxima at 285 mμ (log ε, 4.24) and 363 mμ (log ε, 4.19), in marked contrast to that of the parent compound (VI), which has the maxima at 309 mμ and 245 mμ in an acidic medium and at 304 mμ and 273 mμ in a basic medium (Fig. 1). The analytical data of the iodide (VII) also agreed with the calculated values. Therefore, it may be understood that when the chloride (VI) was converted into the corresponding iodide, dehydrogenation took place by the liberated iodine produced from decomposition of the potassium iodide to afford the compound (VII).

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2) Y. Ban and M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **13**, 775 (1965); *Tetrahedron Letters*, No. 22, 796 (1961); A. Brossi, M. Gereke, A.R. Battersby, R.S. Kapil, Y. Ban, and M. Terashima, *Experientia*, **22**, 134 (1966).
3) Y. Ban, O. Yonemitsu, T. Oishi, S. Yokoyama, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **7**, 609 (1959).
4) S. Akaboshi, T. Kato, and A. Saiga, *Chem. Pharm. Bull.* (Tokyo), **11**, 1446 (1963).

It is noteworthy at this point that (+)–rubremetinium cation which is represented by the correct formula (I)[2,5] containing an 2,3–dihydropyridine as the ring–C, is stable towards the similar oxidation with mild oxidizing agents such as iodine, bromine and mercuric acetate, *etc.* The difference of stabilities between (+)–rubremetinium cation (I) and the present compound (VI) might be due to the facts that ring–C of the former is fused to a pyrrole ring and the whole molecule (I) is stabilized by its resonance hybrid character, as pointed out by Openshaw, Battersby and Wood.[6]

It is also interesting to recollect that the compound (XII) of the same chromophore as VI was attempted by the same authors to prepare as a reference for interpretation of the ultra-

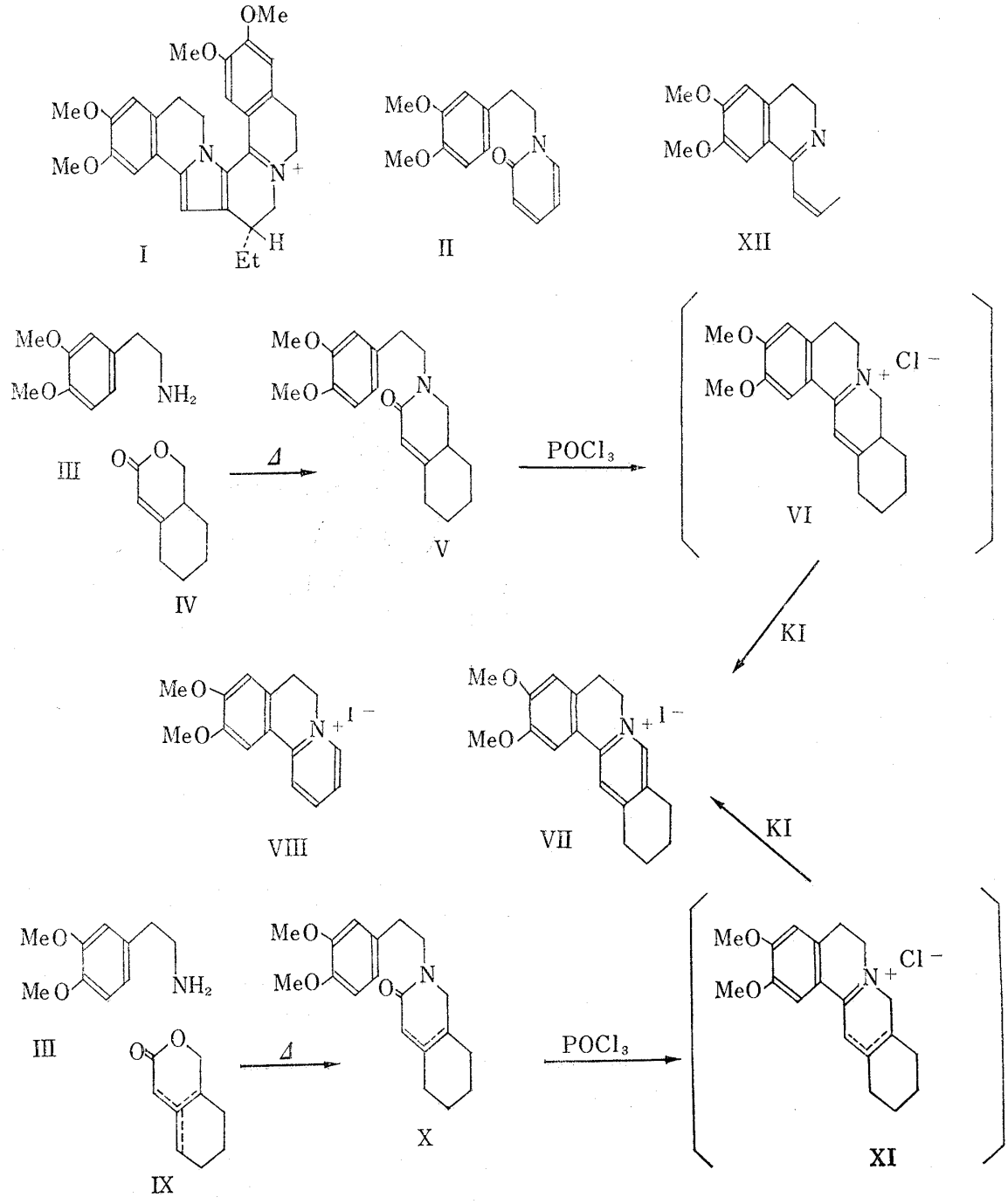


Chart 1

5) A.R. Battersby, H.T. Openshaw, and H.C.S. Wood, *Experientia*, **5**, 114 (1949).
6) H.T. Openshaw and H.C.S. Wood, *J. Chem. Soc.*, 391 (1952).

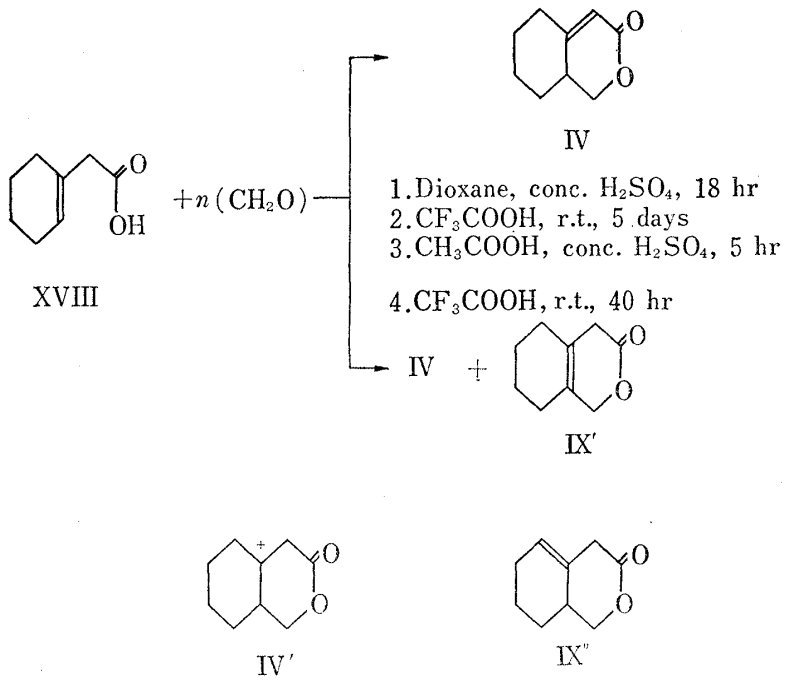


Chart 2

violet spectrum of (+)-rubremetinium cation (I), but it was too unstable to isolate or characterize.

Subsequently, an attempt was made to synthesize 6,7-dihydrosempervirine iodide (XVIIb) by the similar procedure for further confirmation of this type of cyclization. This compound (XVIIb) was synthesized by Swan in 1958,[7] and Ban and Seo in 1961,[8] independently. The condensation of tryptamine (XIII) with the α,β-unsaturated-δ-lactone (IV) provided a fairly good yield of the α,β-unsaturated lactam (XV), which on cyclization with phosphorus oxychloride gave the quaternary chloride (XVI) as yellow crystals.

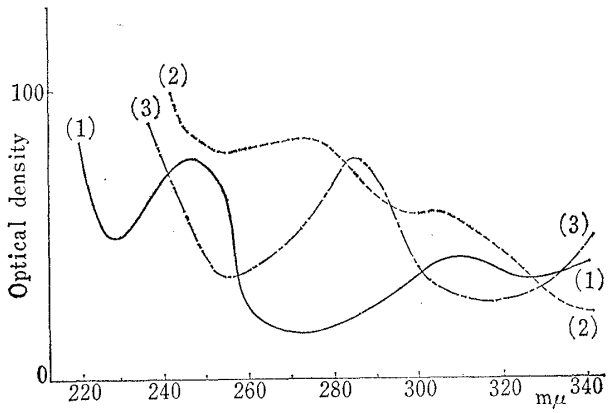


Fig. 1. Ultraviolet Absorption Spectra
(1) ——— VI in EtOH (H^+)
(2) ..... VI in EtOH (OH^-)
(3) —•—•— VII in EtOH

Dehydrogenation of XVI effected with mercuric acetate in an aqueous ethanol–acetic acid, afforded 6,7-dihydrosempervirine chloride (XVIIa) in 84% yield, which was identified with the authentic sample.[8]

Meanwhile, it seems worth while to comment on preparation of the above starting lactone which was obtained by an application of the Prins reaction according to the Belleau's procedure.[9]

The condensation of cyclohexenylacetic acid with formaldehyde catalyzed with conc. sulfuric acid in dioxane gave the α,β-unsaturated-δ-lactone (IV) as was reported by Belleau.[9]

With the purpose of synthesizing β,γ-unsaturated-δ-lactone (IX'),[9] however, cyclohexenylacetic acid (XVIII) was condensed with paraformaldehyde in boiling acetic acid

7) G.A. Swan, *J. Chem. Soc.*, 391 (1952).
8) Y. Ban and M. Seo, *Tetrahedron*, **16**, 11 (1961).
9) B. Belleau, *Canadian J. Chem.*, **35**, 673 (1958).

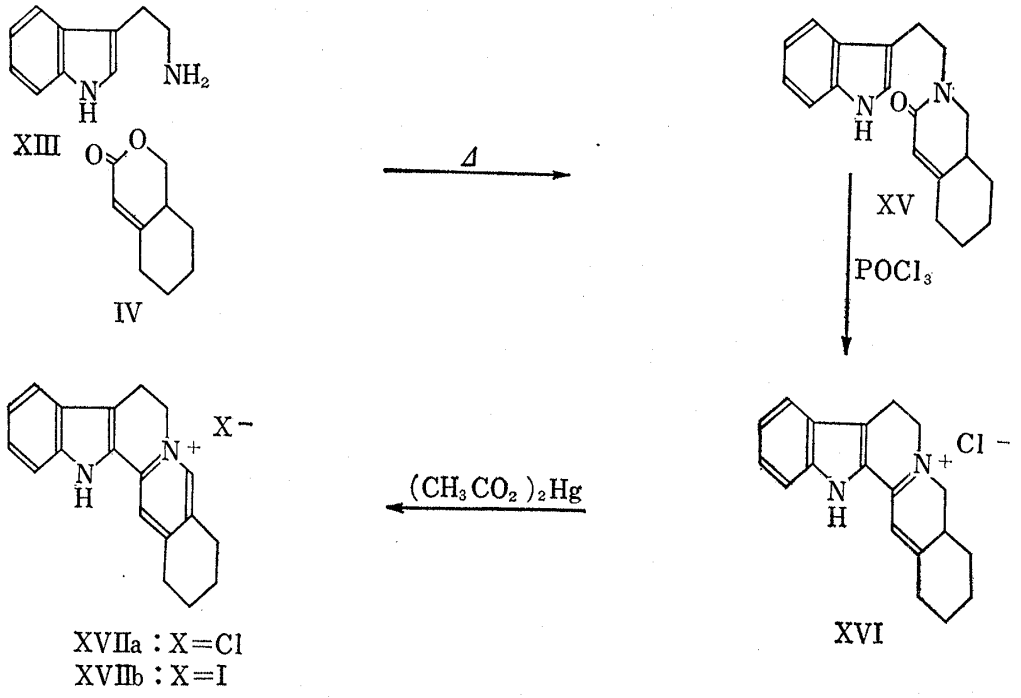
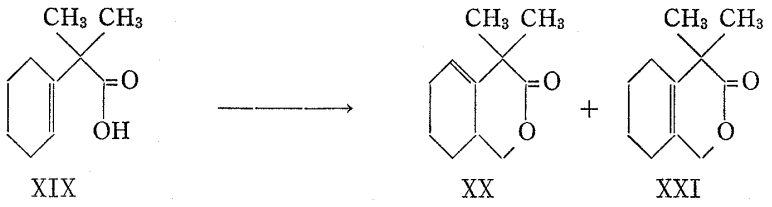


Chart 3

containing a small amount of sulfuric acid to afford only the α,β–unsaturated–δ–lactone (IV) in stead of the β,γ–unsaturated isomer, the result of which was against the Belleau's description[9] and consistent with that reported by Korte.[10,11] The product was identified with the foregoing sample (IV) by comparison of the ultraviolet spectra (λ_{max} 223 mμ) and the superimposable infrared spectra which involved a characteristic band at 1730—1733 cm^{-1} (CS_2) corresponding to the α,β–unsaturated–δ–lactone. Furthermore, it should be noticed that the NMR spectrum of this lactone (IV) in $CDCl_3$ indicates a signal of the vinyl proton at 4.27 τ (broad singlet). Meanwhile, Korte reported that the similar reaction with the β,γ–unsaturated alicyclic carboxylic acid (XIX) afforded a mixture of XX and XXI.[11] Therefore, it should be considered that there could be produced the third isomer (IX″) in the present



Prins reaction as well.[12] At the present experiments where trifluoroacetic acid was used as both solvent and catalyst following the Belleau's procedure which had been reported to afford the pure β,γ–unsaturated–δ–lactone (IX′),[9] there was obtained the α,β–unsaturated–δ–lactone (IV) accompanied by a mixture of the β,γ–unsaturated lactones (IX′ and IX″), the presence of the latters was qualitatively deduced by the NMR spectrum in $CDCl_3$ involving signals at τ, 4.24 (broad singlet) and τ, 4.40 (multiplet) in addition to absorptions at 1750 and 1733 cm^{-1} in its infrared spectrum, which should be due to a mixture of a non–conjugated

10) F. Korte, J. Falbe, and A. Zschocke, *Tetrahedron*, **6**, 201 (1959).
11) J. Falbe, H. Wetkamp, and F. Korte, *Tetrahedron*, **19**, 1479 (1963).
12) We appreciate the advice of the referee suggesting us to check the presence of this isomer (IX″).

and conjugated lactones.[13] Prolonged treatment of the above reaction mixture to isolate the β,γ–unsaturated isomer resulted in an increased proportion of the α,β–unsaturated lactone (IV). Moreover, when the reaction mixture in trifluoroacetic acid was left for 5 days at room temperature, the pure α,β–unsaturated–δ–lactone (IV) was isolated and identified with an authentic specimen. It may be assumed that under these conditions, β,γ–unsaturated–δ–lactones (IX′ and IX″)[13] could be readily isomerized to the corresponding α,β–unsaturated isomer(IV).

Thus, the foregoing mixture (IX) of the α,β– (IV) and β,γ–unsaturated–δ–lactones, (IX′ and IX″) was condensed with 3,4–dimethoxyphenethylamine (III) to afford possibly the corresponding amide (X),[14] mp 82—83°, (compared with mp 87—88° of the pure α,β–unsaturated compound (V)), which in turn was cyclized to the quaternary chloride (XI), followed by the iodine oxidation to yield the same compound (VII) as the one obtained by the foregoing procedure from the pure α,β–unsaturated lactone (IV).

The Prins reaction followed by the Bischler–Napieralski cyclization is being extended to the syntheses of various indolo– and benzoquinolizine derivatives.

Experimental[15]

2-Hydroxymethylcyclohexlideneacetic Acid Lactone (IV)——a) This compound was prepared by the condensation of cyclohexeneacetic acid (NMR in CCl_4 τ: 4.42 (>C=CH–), broad singlet) with paraformaldehyde in dioxane containing a small amount of sulfuric acid according to the procedure of Belleau.[9] Colorless needles, mp 59—60° (bp 150—152°) (7 mmHg). UV: λ_{max}^{EtOH} 223 mμ (log ε, 3.94). IR: $\nu_{max}^{CS_2}$ cm^{-1}: 1733, 1700. NMR τ: 4.27 (in $CDCl_3$); 4.40 (in CCl_4); broad singlet.

b) The pure material (IV) was obtained by the procedure of Belleau[9] for preparation of 2–hydroxymethyl–1–cyclohexeneacetic acid lactone (IX′).

A solution of 8 g (0.057 mole) of cyclohexeneacetic acid and 2 g of paraformaldehyde in 25 ml of glacial acetic acid containing 0.3 ml of conc. H_2SO_4 was refluxed for 5 hr.

On cooling, 2 g of fused sodium acetate was added to the reaction mixture. The acetic acid was removed *in vacuo* and the crude product was distilled to give 5 g of colorless liquid bp 125—138° (5—7 mmHg), which was taken up in ether, washed with aq. $NaHCO_3$, water, and dried. The oil obtained on evaporation of the solvent was distilled *in vacuo* to give 3.5 g of viscous oil, which solidified on standing.

Crystallization of the crude material from ether–petroleum ether gave 3.0 g (34%) of IV as colorless needles, mp 60—61°, UV λ_{max}^{EtOH} mμ (log ε): 223 (3.94), which was undepressed on admixture of the product obtained as described under (a). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.78; H, 8.11.

c) A solution of 8 g (0.057 mole) of cyclohexeneacetic acid and 2 g paraformaldehyde in 10 ml of CF_3CO_2H was kept for 5 days at room temperature, and the solvent was removed. The residue was distilled *in vacuo* to give the colorless liquid, bp 60—120°(7 mmHg), 0.7 g and bp 120—140° (6—7 mmHg), 7.0 g. Both of the fractions solidified upon standing and showed the similar IR spectra (1733, 1700 cm^{-1} in CS_2).

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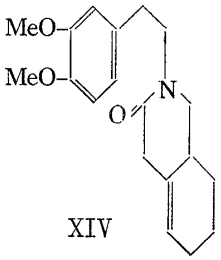
13) These results are aslo different from the description by Korte, *et al.*,[10] who stated that only the α,β–unsaturated lactone (IV) was obtained in the Prins reaction with XVIII having no substituent at α–carbon of the carboxyl group. But the formation of a mixture of IV, IX′ and IX″ from a possible intermediate (IV′) under this condition is reasonable and seems to be compatible with the mechanism of the Prins reaction recently proposed by L.J. Dolby, *et al.* (*J. Am. Chem. Soc.*, **85**, 47 (1963); *J. Org. Chem.*, **30**, 3581 (1965)).

14) Inspection of the NMR spectrum of X which indicated no signal around τ 4.40, confirmed that this product did not contain the lactam (XIV) which should have been obtained from the corresponding lactone (IX″).



XIV

15) The NMR spectra were measured on Model H–60 Hitachi High Resolution Nuclear Magnetic Resonance Spectrometer using tetramethylsilane (10 τ) as an internal reference. We are grateful to Miss Y. Kishio of this Faculty for measurements of these spectra.

The main fraction (7 g) was dissolved in ether and washed with aq. $NaHCO_3$ solution, water, and dried. Redistillation gave 5 g (42%) of colorless liquid, bp 135—138° (5 mmHg), which was crystallized from ether–*n*-hexane to give colorless needles of (IV), mp 61—62°. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.15; H, 7.96.

It did not show the depression of the melting point on admixture with a sample of the α,β-unsaturated lactone obtained as described under (a) and (b).

A mixture of 2-Hydroxymethyl-cyclohexylidene Acetic Acid Lactone (IV) and 2-Hydroxymethyl-1-cyclohexeneacetic Acid Lactone (IX′) and 2-Hydroxymethyl-6-cyclohexene Acetic Acid Lactone (IX″)——A solution of 2 g of cyclohexeneacetic acid and 0.5 g of paraformaldehyde in 6 ml of CF_3CO_2H was allowed to stand for 40 hr at room temperature, and worked up in a similar fashion to the procedure of (c). Distillation gave 1.4 g (70%) of colorless liquid, bp_{4-5} 127—128°. The infrared spectrum had absorptions at 1750 and 1733 cm^{-1} (CS_2), indicating that the product was a mixture of the α,β- (IV) and β,γ-unsaturated lactones (IX′ and IX″), which was also supported by NMR spectrum in $CDCl_3$ having two signals at 4.24 τ and 4.40 τ for the vinyl proton. Efforts to isolate the β,γ-unsaturated-δ-lactone resulted in failure, inducing the increase in intensity of the band at 1733 cm^{-1} and the decrease at 1750 cm^{-1}, which indicated that β,γ-unsaturated lactone isomerized into the α,β-unsaturated isomer.

2-(3,4-Dimethoxyphenethyl)hexahydro-$\Delta^{4,5}$-3(2*H*)-isoquinolone (V)——A mixture of 1.8 g (0.01 mole) of 3,4-dimethoxyphenethylamine (III), 1.5 g (0.01 mole) of the lactone (IV), 2 g of anhyd. $MgSO_4$ in 15 ml of tetralin was refluxed for 5 hr under a stream of nitrogen and allowed to stand overnight.

The whole mixture was filtered, and the filtrate was distilled *in vacuo* to leave the residue, which was warmed with 15 ml of 10% NaOH on a steam bath for 15 min. After cooling, the separated oil was taken up in ether. The ethereal solution was washed with 5% HCl, 5% $NaHCO_3$, and with water. Removal of the dried ethereal solution left 2.1 g (67%) of the residue, which solidified upon standing. The IR spectrum showed the expected lactam band at 1650 cm^{-1}, and it absorbed at λ_{max}^{EtOH} 280 mμ in the spectrum as expected for 3,4-dimethoxyphenethylamine. The solid residue was chromatographed on 60 g of neutral alumina prepared in benzene–ether (1:1) to give 1.9 g of the lactam (V), which was crystallized from ether–petroleum ether to give colorless needles, mp 87—88°. *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.25; H, 7.99; N, 4.44. Found: C, 71.99; H, 8.30; N, 4.70. UV λ_{max}^{EtOH} mμ (log ε): 280 (3.50), 230 (4.02).

A mixture of 2-(3,4-Dimethoxyphenethyl)hexahydro-$\Delta^{4,5}$- and $\Delta^{5,10}$-3(2*H*)-isoquinolone (X)——To a solution of 3.6 g (0.02 mole) of 3,4-dimethoxyphenethylamine (III) in 30 ml of tetralin was added 3 g (0.02 mole) of a mixture of the unsaturated-δ-lactones (IV, IX′ and IX″) and anhyd. $MgSO_4$, and the whole mixture was refluxed for 18 hr under an atmosphere of nitrogen. On treatment in the same fashion as the preparation of the compound (V), 4.6 g (73%) of X was obtained as an oil, which was then chromatographed over neutral alumina. Elution with ether–benzene (1:1) provided 3.1 g of the lactam (X) which solidified upon standing. Recrystallizations from ether gave colorless needles, mp 82—83°. *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.20; H, 8.23; N, 4.69. UV λ_{max}^{EtOH} mμ (log ε): 280 (3.49), 230 (4.02).

1,2,3,4,4a,5,7,8-Octahydrobenzo[*g*]-10,11-dimethoxybenzo[4,5-*a*]pyridocolinium Chloride (VI) and 1,2,3,4,7,8-hexahydrobenzo[*g*]10,11-dimethoxybenzo[4,5-*a*]pyridocolinium Iodide (VII)——a) A mixture of 2.1 g of the lactam (V), 10 ml of $POCl_3$ and 10 ml of toluene was refluxed for 4 hr. After removal of the solvent *in vacuo*, 20 ml of water was added to the residue. The mixture was warmed, the aqueous layer was separated and washed with benzene. The chloride (VI) in water absorbs at 309 mμ, 245 mμ in an acidic medium and 304 mμ, 273 mμ in a basic medium. The aqueous solution of the chloride was saturated with KI, and the iodide separated as an oil was taken up in $CHCl_3$, then the extract was dried.

The residue (1.9 g, 67%) obtained on distillation of $CHCl_3$ was crystallized from acetone to give 190 mg of VII. Recrystallizations from EtOH gave yellow needles, mp 265.5—266°. There was not observed any significant difference between an acidic and a basic medium on the determination of UV spectra of the iodide (VI). UV λ_{max}^{EtOH} mμ (log ε): 285 (4.24), 363 (4.19). This iodide was shown to be identical with the one prepared from IX *via* X and XI by the procedure (b) through the mixed melting point, IR, UV absorptions and elemental analysis. *Anal.* Calcd. for $C_{19}H_{22}O_2NI$: C, 53.64; H, 5.64; N, 3.31. Found: C, 53.63; H, 5.40; N, 3.65.

b) A solution of 2 g of X and 10 ml of $POCl_3$ in 10 ml of toluene was refluxed for 4 hr. The solvent and the excess of $POCl_3$ were evaporated to leave the residue, to which was addded warm water. The mixture was extracted with benzene and the aqueous layer was treated with charcoal. The UV spectrum of the chloride (XI) showed 310 mμ, 283 mμ, 245 mμ in an acidic medium and 280 mμ in a basic medium.

The separated iodide was extracted with $CHCl_3$ and the extract was washed with $NaHSO_3$ solution, water and dried over anhyd. Na_2SO_4. The residue obtained on evaporation of $CHCl_3$ was crystallized from acetone to give 362 mg (14%) of VII. Recrystallizations from EtOH gave yellow needles, mp 265.5—266° which are completely identical with the iodide obtained by the procedure (a) through the mp IR and UV spectra, and elemental analysis. *Anal.* Calcd. for $C_{19}H_{22}O_2NI$: C, 53.64; H, 5.64; N, 3.31. Found: C, 53.74; H, 5.27; N, 3.64.

2-[2-(3-Indolyl)ethyl]hexahydro-$\Delta^{4,5}$-3(2*H*)-isoquinolone (XV)——A mixture of 3.5 g of tryptamine (XIII), 3.0 g of α,β-unsaturated lactone (IV) and 3.5 g of anhyd. $MgSO_4$ in 35 ml of tetralin was heated at 200—230° for 10 hr under an atmosphere of nitrogen and was left overnight.

The solution was filtered and the filtrate was concentrated to a half volume, to which ether was added. The mixture was allowed to stand overnight. The precipitate was filtered and washed with ether to give 2 g of the lactam (XV), mp 179—182°. Recrystallizations from EtOH gave colorless needles, mp 187—188°. *Anal.* Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.52; H, 7.76; N, 9.19.

The residue obtained on distillation of mother liquid was mixed with 10% NaOH and the mixture was warmed for 20 min.

The oil separated was extracted with ether. The ethereal extracts were washed with 2N-HCl, with water and dried over anhyd. $MgSO_4$.

Distillation of the ether left 2.5 g of the residue, which was crystallized from EtOH to give 1.5 g of (XV) mp 165—175°. Total yield, 60%.

1,2,3,4,5,6,7,8-Octahydro-13*H*-benz[*g*]indolo[2,3-*a*]pyridocolinium Chloride (XVI)——To 1.6 g of the lactam (XV) was added 3.5 ml of $POCl_3$ in 150 ml of dry benzene. The mixture was refluxed gently for 3 hr under a stream of nitrogen and allowed to stand overnight at room temperature. The precipitate was collected, washed with ether and dried to 2.0 g of yellow powder. The product gave a positive reaction in the silver nitrate test in dil. HNO_3 and also a positive phosphate test with ammonium molybdate.

Recrystallizations from water gave yellow needles, mp above 270°. UV λ_{max}^{EtOH} mμ: 248, 358.

The Iodide of XVI——To a solution of 300 mg of chloride (XVI) in aqueous EtOH was added a saturated solution of KI. The mixture was left for 1 hr. The precipitate was collected to give 240 mg of the iodide of (XVI), which showed the UV spectrum corresponding to the chloride (XVI).

Recrystallization from EtOH gave yellow needles, mp 315—325° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}N_2I$: C, 56.44; H, 5.24; N, 6.93. Found: C, 56.29; H, 5.21; N, 7.17. IR ν_{max}^{Nujol} cm^{-1}: 1645, UV λ_{max}^{EtOH} mμ (log ε): 248 (3.89), 358 (4.13).

1,2,3,4,7,8-Hexahydro-13H-benz[*g*]indolo[2,3-*a*]pyridocolinium Chloride (XVII)——To a solution of 520 mg of XVI in 30 ml of 10% acetic acid and 30 ml of EtOH was added 1.2 g of mercuric acetate in 5 ml of 10% acetic acid, and the mixture was heated at 60—70° for 7 hr. Mercurous acetate was removed by filtration, and the filtrate was saturated with hydrogen sulfide for 1.5 hr at 60—70°. The hot solution was filtered and evaporated to dryness.

Crystallization from EtOH gave 430 mg of yellow needles (XVIIa), mp 324°(decomp.), undepressed upon admixture with an authentic specimen. Yield, 84%. Iodide (XVIIb), yellow needles, decomp. above 350°. *Anal.* Calcd. for $C_{19}H_{19}N_2I$: C, 56.72; H, 4.76; N, 6.96. Found: C, 56.70; H, 4.79; N, 7.20. IR ν_{max}^{KBr} cm^{-1} 1640. UV λ_{max}^{EtOH} mμ (log ε): 224 (4.32), 319 (4.23), 385 (4.19).

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