Synthetic Studies on the Lycopodium Alkaloids. II.\(^1\) A Synthesis of a Key Intermediate, 2,3,5,6,7,8-Hexahydro-7β-methyl-3-oxo-1H-5,8a-propenooquinoline, for the Lycopodium Alkaloids

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The introduction of an amino function on the bridgehead position of the bicyclo(3,3,1)nonane ring system has been smoothly achieved by the modified Curtius reaction on some bridgehead carboxylic acids. This method has been applied on 3β-methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carboxylic acid (XIV) to afford the unsaturated aminoketone (XVI) as its hydrobromide via the carbamate. XVI was transformed into the tricyclic lactam (XVIII), via the pyruvamide (XVII) followed by cyclization. XVIII was then reduced via its lactim-ether followed by oxidation to afford 2,3,5,6,7,8-hexahydro-7β-methyl-3-oxo-1H-5,8a-propenooquinoline (XXI) in good yield, which would provide useful intermediate for syntheses of the lycopodium alkaloids.

Previously,\(^1\) the authors have reported some basic studies on the bicyclo(3,3,1)nonane ring system in connection with the synthetic study of the lycopodium alkaloids.\(^3\) The present paper describes the preparation of 2,3,5,6,7,8-hexahydro-7β-methyl-3-oxo-1H-5,8a-propenooquinoline (XXI), capable of serving as the important intermediate for total syntheses of the lycopodium alkaloids which have been attracted by many groups of organic chemists.\(^4\)

During the course of elucidation of structures of these alkaloids, interconversions\(^5\) of these alkaloids, i.e., lycopodine from α-obscureine and lycodine from α-obscureine via β-obscureine, have been already achieved and this might afford a great advantage for the syntheses of these alkaloids.

![Chemical structures](image)

There exists the common structural moiety of 5,8a-propenoperhydroquinoline, in lycopodine,\(^6\) α-obscureine,\(^5\) sauroxine\(^7\) and other alkaloids. Therefore, we have intended

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to synthesizing these alkaloids by the route via the 5,8a-propanoperhydroquinoline derivative. So far, this approach has been attempted only as the pilot experiment by Raphael and his coworkers.\(^8\)

As a preliminary study, the method for introducing a nitrogen function into the bridgehead position was investigated, employing 9-oxobicyclo(3,3,1)nonane-1-carboxylic acid derivatives (I), (II) and (III), which were prepared according to the method by Cope and his coworkers.\(^9\) The saturated keto–amide (I) was converted by the Hofmann rearrangement\(^9\) to the saturated carbamate (IV), which was identified as 2,4-dinitrophenylhydrazone. And then the unsaturated keto–acid (II) was also treated by the modified Curtius reaction,\(^10\) via the mixed anhydride with ethyl chloroformate, the acid azide and the isocyanate, to convert into the corresponding carbamate (V) in 64% yield. But, conversion of the unsaturated amide (III) into the carbamate (V) by oxidative rearrangement with lead tetaacetate\(^11\) was attempted without success.

Then, in order to introduce an oxygen function into C-3 or C-4 position, the unsaturated carbamate (V) was treated with perbenzoic acid to give the 3,4-epoxide (VI) in 86% yield, which, however, failed to lead to the diketo–ester (VIIa) or (VIIb). The Wittig reaction\(^12\) of the unsaturated keto–carbamate (IV) with 2-(carboxyethyl)triphenylphosphonium chloride\(^13\) in the presence of sodium hydride in dimethyl sulfoxide to introduce an alkyl side chain was likewise fruitless.

From these preliminary studies, which established the method of introducing a nitrogen function into the bridgehead position, we now have focused our effort onto the synthetic work toward the lycopodium alkaloids themselves, starting with the compound having necessary substituents.

First, we employed ethyl 5-benzylxoy-2-oxocyclohexanecarboxylate as the starting compound, which was subjected to the Michael condensation with methacrolein in order to prepare the bicyclo(3,3,1)nonane derivative with methyl and oxygen functions at the required positions. However, the reaction failed to lead to the bicyclo(3,3,1)nonane ring system.

In turn, the Michael condensation of 4-methylcyclohexanone with acrolein, followed by acid-catalyzed cyclization proceeded smoothly to afford the epimeric keto–alcohols (VIII) in good yield, which gave the diketo–ester (IX) on oxidation and the unsaturated keto–ester (X) on dehydration and the orientation of methyl group in these products has the favorable $\beta$-equatorial, identical with that in natural products, as described in the previous paper.\(^{14}\)

Now, we have intended to prepare the diketo–acid (XII), which seemed suitable for introducing amino group on the bridgehead position and oxygen function at C–7 position. First, hydrolysis of the diketo–ester (IX) under the acidic and alkaline media were examined but spontaneous ring cleavage was taken place to give, upon the following esterification, possibly either XIa or XIb, having the infrared absorption different from that of the starting ester (IX), but the structure was not determined yet. Thus, to avoid unfavorable ring cleavage possibly due to the presence of the carbonyl groups, the keto–alcohols (VIII) were first reduced with sodium borohydride to give the dihydroxy–ester, which was hydrolyzed and then oxidized with Jones reagent\(^{14}\) to the diketo–acid (XII) in 62% yield from VIII. However, the modified Curtius reaction on XII as described in II to obtain the diketo–carbamate (XIII) was likewise unsuccessful.

Finally, we chose the unsaturated keto-ester (X) for further syntheses. 3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carboxylic acid (XIV), which was obtained by mild hydrolysis in alkaline medium of X, was converted smoothly by the modified Curtius reaction into the benzyl carbamate (XVa) or tert-buty carbamate (XVb), upon treatment with the respective alcohols, structures being assured by the infrared maxima at 3380—3390 and 1710—1720 cm⁻¹ for NH and carbamate carbonyl groupings. Epoxidation of the unsaturated benzyl carbamate (XVa) with perbenzoic acid gave the α-epoxide (XXII) as a sole product, having the α-configuration of the epoxide ring assumed from the consideration of steric requirements. The epoxide (XXII) was likewise unaffected to various treatments for ring opening of the epoxide, as in the case of VI. Both carbamates (XVa) and (XVb) underwent hydrolytic decarboxylation with anhydrous hydrogen bromide in glacial acetic acid¹⁹ to afford the aminoketone (XVI), isolated as its hydrobromide in order to avoid dimerization.

Direct alkylation of the amine hydrobromide (XVI) with monobromoaacetone ethylene-ketal¹⁶ in the presence of base, i.e., triethylamine or potassium carbonate, failed to afford the desired monoalkylated secondary amine but in situ the dimeric product (XXIII) was isolated. Thus, the construction of the third ring was performed following the manner reported briefly by Raphael and his coworkers.⁴⁶

The oily pyruamide (XVII), obtained from the amine hydrobromide (XVI) by acylation⁴⁷ with a mixture of pyruvic acid and phosphorous oxychloride in the presence of triethylamine, was cyclized in excellent yield by means of sodium hidride in refluxing tetrahydrofuran to give the tricyclic lactam (XVIII), which exhibited the infrared absorptions at 1681 and 1639 cm⁻¹ and a singlet signal at 3.65 τ in NMR spectrum both due to the α,β-unsaturated carbonyl grouping.

Upon treatment with the Meerwein’s reagent,¹⁸ the lactam (XVIII) was converted to the lactim–ether (XIX) quantitatively, which was then reduced with lithium aluminum hydride in refluxing tetrahydrofuran to the amino–alcohol (XX) as a sole product. Oxidation of XX with Jones reagent afforded the α,β-unsaturated keto–amine (XXI), which was characterized as its hydrochloride.

This product (XXI) would serve as the important intermediate for the syntheses of both lycopodine and suroxine types of the alkaloids. Further work with XXI toward the lycopodium alkaloids are now extensively in progress.

**Experimental**

Melting points and boiling points are uncorrected. NMR spectra were taken on Hitachi Perkin–Elmer H-60 type Spectrometer at 60 Mc in deuterochloroform with tetramethylsilane as an internal standard.

**Ethyl 9-Oxobicyclo(3,3,1)nonane-1-carbamate (IV)—** To an alcoholic solution of NaOEt prepared from Na (119 mg) and abs. EtOH (10 ml) was added the acid amide⁹ (I; 448 mg) followed by a solution of Br₂ (271 mg) in EtOH (3 ml).

The resulting mixture was stirred at room temperature for 10 min followed by refluxing for 15 min. After cooling, the reaction mixture was poured into ice–water (50 ml) and extracted with AcOEt (3×20 ml). The combined extracts were washed with brine, dried and evaporated to give a viscous oil (350 mg), which was chromatographed on silica gel (8 g). Elutions with CCl₄ followed by CHCl₃ were performed and the CHCl₃ elute afforded the carbamate (100 mg), homogeneous on thin–layer chromatography (TLC). IR: νmax cm⁻¹: 3420 (NH), 1720 (CO). 2,4-Dinitrophenylhydrazone was recrystallized from C₆H₄-petr. benzoi to give orange leaflets, mp 148.5—149.5°C. IR νmax cm⁻¹: 3390, 3311 (NH), 1790 (CO,Et), 1621 (C=N). Anal. Calcd. for C₁₉H₂₅O₂N₅: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.36; H, 5.73; N, 17.34.

**Treatments of III with Pb(OAc)₄—** The unsaturated amide⁹ (III) was treated with excessive amount of Pb(OAc)₄ in MeOH or in DMF at the temperature ranging from room to refluxing temperatures for 2—5 hr. However, only the starting material was recovered from any of these reactions.

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Ethyl 9-Oxobicyclo[3.3.1]non-3-ene-1-carbamate (V)—To a stirred solution of the unsaturated acid\(^9\) (II; 2.05 g) in acetone (10 ml) containing \(\mathrm{H}_2\mathrm{O}\) (2 ml) was added triethylamine (1.17 g) in acetone (5 ml) dropwise while maintaining the solution below 0\(^\circ\)C with ice-salt cooling and stirring was continued for 30 min. After adding ethyl chloroformate (1.15 g) in acetone (5 ml) followed by stirring for 30 min, a solution of \(\mathrm{NaH}(900\,\text{mg})\) in \(\mathrm{H}_2\mathrm{O}\) (5 ml) was added to the reaction mixture above and stirred for another 1 hr. The reaction temperature was maintained below 15\(^\circ\)C throughout the reaction. The mixture was poured into iced-water and extracted with ether (3 x 50 ml). The combined extracts were washed with brine and dried over anhyd. MgSO\(_4\). To the dried organic layer was added dry toluene (20 ml) and ether was evaporated under reduced pressure at room temperature. The resulting organic layer was heated under reflux on an oil bath for 2 hr and upon adding \(\mathrm{EtOH}\) (10 ml), refluxing was continued for 5 hr. After removing the solvent, the residue was submitted to chromatography on silica gel (10 g). Elution with CHCl\(_3\) gave a pale yellow oil (1.60 g. 64.3\%), bp 110—115\(^\circ\)C (0.01 mm Hg). \(\varepsilon^\text{max}\) cm\(^{-1}\): 3320 (NH), 1710 (CO). NMR \(\tau\): 3.75 (IH, broad s, -NH), 4.28 (2H, m, -CH=CH-), 5.95 (2H, q, \(J=7\), \(\text{cps, -CH}_2\text{CH}_3\)), 8.76 (3H, t, \(J=7\), \text{cps, -CH}_3\text{CH}_2\)). 2,4-Dinitrophenylhydrazone was recrystallized from EtOH to give yellow leaflets, mp 174—174.5\(^\circ\)C. \(\varepsilon^\text{max}\) cm\(^{-1}\): 3367, 3279 (NH), 1718 (CO,Et), 1613 (C=N). \textit{Anal. Calcd. for C\(_8\)H\(_{12}\)O\(_8\)N\(_2\): C, 53.59; H, 5.25; N, 17.36. Found: C, 53.52; H, 5.08; N, 17.54.}

Ethyl 3,4-Epoxo-9-oxobicyclo[3.3.1]nonane-1-carbamate (VI)—To a stirred solution of the unsaturated carbamate (V; 223 mg) in CHCl\(_3\) (5 ml) was added a solution of perbenzoic acid (152 mg) in CHCl\(_3\) (1 ml) and the resultant mixture was allowed to stand in the dark at room temperature for 3 days. After adding CHCl\(_3\) (20 ml), the mixture was washed with satd. NaHCO\(_3\) brine and dried. Evaporation of the solvent gave the oily residue (205 mg; 85.8\%), which solidified on standing, mp 79—83\(^\circ\)C. Recrystallization from petr. ether to give colorless prisms, mp 84—86\(^\circ\)C. \(\varepsilon^\text{max}\) cm\(^{-1}\): 3342 (NH), 1730 (sh), 1702 (CO). NMR \(\tau\): 3.78 (1H, broad s, -NH), 5.95 (2H, q, \(J=7\), 1.5 cps, -CH\(_2\)CH\(_3\)), 8.77 (3H, t, \(J=7\), 1.5 cps, -CH\(_3\)CH\(_2\)). \textit{Anal. Calcd. for C\(_8\)H\(_{12}\)O\(_2\)N: C, 80.24; H, 7.16; N, 5.85. Found: C, 80.41; H, 7.09; N, 5.85.}

Attempted Oxide Ring Cleavage of VI—To a stirred solution of VI (566 mg) in dry C\(_6\)H\(_6\) (10 ml) was added BF\(_3\) ether (0.6 ml) with ice-water cooling and stirring was continued at room temperature for 10 min. The mixture was washed with satd. NaHCO\(_3\), \(\mathrm{H}_2\mathrm{O}\) and dried. Evaporation of the solvent gave the oily residue (402 mg), which showed many spots on TLC and was difficult to separate any single product.

Attempted Wittig Reaction of V with 2-(Carboxyloxy)triphosphonium Chloride—To the mixture, prepared by adding NaH (100 mg) to dry DMSO (5 ml) followed by warming under N\(_2\) stream at 60\(^\circ\)C for 1 hr, was added a solution of V (223 mg) and 2-(carboxyloxy)triphosphonium chloride\(^{10}\) (445 mg) in dry DMSO (10 ml) and stirring was continued at room temperature for 5 hr. The resulting reaction mixture was poured into ice-water (50 ml) containing dil. \(\mathrm{HCl}\) (5 ml) and extracted with \(\text{AcOEt}\) (3 x 30 ml). The combined extracts were washed with brine, 5% \(\text{NaOH}\) and brine, and dried. Evaporation of the solvent gave the starting material unchanged.

Hydrolases of Ethyl 3\(\beta\)-Methyl-6,9-dioxobicyclo[3.3.1]nonane-1-carboxylate (IX)—A mixture of the diketo-ester\(^3\) (IX; 300 mg) and 5% \(\text{NaOH}\) (10 ml) containing acetone (2 ml) was stirred at room temperature for 30 hr. After stirring the mixture, with ether, the aqueous layer was acidified with conc. HCl, and extracted with AcOEt. The organic extracts were washed with brine, dried and evaporated to give a crude acid, exhibiting bands at 2250—2700, and 1700 cm\(^{-1}\) in CHCl\(_3\). (Hydrolysis of IX with 10% \(\text{H}_2\text{SO}_4\) by refluxing for 6 hr gave the identical acid.) Stabilization of the oily crude acid with \(\text{EtOH}\)–HCl gave an ester which was different from the starting ester (XI), bp 110—115\(^\circ\)C (0.01 mm Hg) (bath temp.), on TLC, IR and NMR. \(\varepsilon^\text{max}\) cm\(^{-1}\): 1725—1710 (CO). NMR \(\tau\): 5.90 (2H, q, \(J=7\), -CH\(_2\)CH\(_3\)), 8.75 (3H, t, \(J=7\), -CH\(_3\)CH\(_2\)). 2,4-Dinitrophenylhydrazone was recrystallized from EtOH to give orange fibers, mp 97.5—98.5\(^\circ\)C. \(\varepsilon^\text{max}\) cm\(^{-1}\): 3331 (NH), 1732 (CO,Et), 1621 (C=N). \textit{Anal. Calcd. for C\(_8\)H\(_{12}\)O\(_2\)N: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.11; H, 6.07; N, 14.25.}

3\(\beta\)-Methyl-6,9-dioxobicyclo[3.3.1]nonane-1-carboxylic Acid (XII)—To a stirred solution of the ketoo alcohols\(^5\) (VIII; 2.177 g) in \(\text{EtOH}\) (20 ml) was added \(\text{NaBH}_4\) (230 mg) port Wine with ice-cooling and stirring was continued at room temperature for 3 hr and then allowed to stand overnight. Upon adding \(\text{AcOH}\) and \(\text{H}_2\text{O}\), the solvent was allowed under reduced pressure. The residue was extracted with \(\text{AcOEt}\) (3 x 20 ml) and the combined extracts were washed with \(\text{H}_2\text{O}\), dried and concentrated to give the oily residue (2.2 g), \(\varepsilon^\text{max}\) cm\(^{-1}\): 3350 (OH) and 1705 (CO,Et), which was dissolved in MeOH (25 ml) containing KOH (2 g). The resulting solution was heated under reflux for 7 hr and then allowed to stand at room temperature overnight. After removing the solvent, \(\text{H}_2\text{O}\) (10 ml) was added and the mixture was extracted with ether (2 x 20 ml) and the aqueous layer was allowed with conc. HCl and extracted with \(\text{AcOEt}\) (50 ml). Evaporation of the solvent gave a semi-solid (1.17 g), \(\varepsilon^\text{max}\) cm\(^{-1}\): 3300, 2750—2300. 1700. This crude dihydroxy acid was oxidized with Jones reagent in the usual way. Evaporation of the solvent from the dried extract gave the diketo-acid (1.17 g; 92% from VIII) as a solid. An analytical sample was recrystallized from ether–petr. ether to give colorless needles, mp 194.5—196\(^\circ\)C (dried at 100\(^\circ\)C in vacuo for 24 hr). \(\varepsilon^\text{max}\) cm\(^{-1}\): 2817—2439 (OH), 1724, 1603 (CO). \textit{Anal. Calcd. for C\(_8\)H\(_7\)O\(_2\): C, 62.80; H, 6.85.}

The Modified Curtius Reaction of XII—The diketo-acid (XII; 1.81 g) was treated under the modified Curtius reaction condition as described in the preparation of V to afford a crude oil (940 mg), which was chromatographed on either silica gel or alumina, affording a semi-solid, almost homogeneous on TLC from
the latter fraction eluted by CHCl₃. IR ν/cm²⁻¹: 3320, 3200, 1755 (s), 1710 (s). This product could not be purified further by recrystallization.

3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carboxylic Acid (XIV)—A mixture of the keto-ester⁹ (X; 14.1 g), 5% NaOH (200 ml) and acetone (30 ml) was stirred at room temperature for 3 days. After washing the mixture with AcOEt (100 ml), the aqueous layer was acidified with conc. HCl. The oil thus separated was extracted with AcOEt (3 × 100 ml) and the combined extracts were washed with brine and dried over anhyd. MgSO₄. Evaporation of the solvent gave the residue which solidified on standing upon titration with n-hexane (20 ml) and the crude acid was collected (10.724 g; 87.5%). An analytical specimen was obtained by recrystallization from n-hexane or cyclohexane to give colorless needles, mp 114—116.5°. Anal. Calcd. for C₃₅H₄₃O₇: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.21. IR ν/cm²⁻¹: 2800—2330 (OH), 1718 (sh), 1706 (CO), 1653 (C=C). NMR τ: -1.17 (1H, s, -CO₂H), 4.23 (2H, m, -CH=CH₂), 9.01 (3H, d, J = 5.5 cps, -CH₂).

Benzyl 3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carbamate (XVA)—To a stirred solution of the acid (XIV; 5.82g) in aceton (40 ml) containing H₂O (3 ml) was added triethylamine (3.34g) in aceton (10 ml) dropwise while maintaining the solution below 0° with ice-salt cooling and stirring was continued for 30 min. After adding ethyl chloroformate (3.58 g) in aceton (10 ml) dropwise over a period of 30 min, a solution of NaN₃ (2.14g) in H₂O (5 ml) was added to the reaction mixture and stirring was continued for 1 hr. The reaction mixture was maintained below 0° throughout the reaction. The mixture was poured into ice-water (200 ml) and the ether (3 × 60 ml). The organic layer was washed with brine and dried over anhyd. MgSO₄. After removing MgSO₄, dry toluene (50 ml) was added to the organic solution and ether was evaporated under reduced pressure at room temperature. The resulting organic layer was heated under reflux on an oil bath for 5 hr and then, after adding benzyl alcohol (10 ml) refluxing was continued for further 20 hr. After cooling the benzyl alcohol in vacuo, the brown oily residue was chromatographed on alumina (100 g). Elution with C₄H₄ following CHCl₃, separated a brown oily carbamate (4.865 g; 54%) which was distilled to give a pale yellow oil, bp 160—165° (0.01 mmHg) (bath temp.). IR ν/cm²⁻¹: 3378 (NH), 1718 (CO), 1647 (C=C). NMR τ: 2.50 (5H, s, -C₅H₅), 3.64 (1H, broad s, -NH), 4.34 (2H, m, -CH₂), 4.97 (2H, s, -OCH₂C₅H₄), 9.06 (3H, d, J = 6 cps, -CH₂). Anal. Calcd. for C₇H₈O₃N: C, 72.21; H, 7.07; N, 4.63. Found: C, 72.07; H, 6.98; N, 4.60.

tert-Butyl 3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-carbamate (XVB)—The crude isocyanate, obtained from the ketoacid (XIV; 5.3 g), triethylamine (3.04 g) and ethyl chloroformate (3.25 g) following the procedure described above, was dissolved in tert.-BuOH (30 ml) and the mixture was heated under reflux for 35 hr. Evaporation of the solvent gave the residual oil (5 g), which was submitted to chromatography on alumina (Woelm, neutral; 100 g). Elution with C₆H₆ gave a very viscous oil (3.255 g; 45%) which was distilled to give an analytical sample as a yellow oil, bp 150—160° (0.01 mmHg) (bath temp.), solidified on standing, mp 66—67°. IR ν/cm²⁻¹: 3390 (NH), 1709 (CO), 1653 (C=C). NMR τ: 3.92 (1H, broad s, -NH), 4.32 (2H, m, -CH₂=CH₂), 8.56 (9H, s, -CH₂C₆H₅), 9.04 (3H, d, J = 6 cps, -CH₂). Anal. Calcd. for C₁₃H₁₇O₃N: C, 76.89; H, 8.74; N, 5.28. Found: C, 76.84; H, 8.82; N, 5.23.

Benzyl 6a,7a-Epoxy-3β-methyl-9-oxobicyclo(3,3,1)nonane-1-carbamate (XXII)—To a stirred solution of the unsaturated keto-carbamate (XVA; 325 mg) in CHCl₃ (5 ml) was added a solution of perbenzoic acid (154 mg) in CHCl₃ (1 ml) and the resulting mixture was allowed to stand in the dark for 4 days. Then, after adding CHCl₃ (30 ml), the reaction mixture was washed with satd. NaHCO₃ and brine and dried over anhyd. MgSO₄. Evaporation of the solvent afforded the oily residue (310 mg), which was chromatographed on silica gel (5 g) with a mixture of CHCl₃-CCI₄ (2:1) as eluent. The fore-running fraction gave the starting material (118 mg), identified from IR and TLC and the latter fraction afforded a viscous oil (180 mg), homogeneous on TLC, which solidified on standing and was recrystallized from ether-petr. ether to give the epoxide (XXII) as colorless prisms, mp 91.5—93°. IR ν/cm²⁻¹: 3390 (NH), 1709 (CO). NMR τ: 2.70 (5H, s, -C₅H₅), 3.69 (1H, broad s, -NH), 4.09 (2H, s, -CH₂C₅H₄), 9.04 (3H, d, J = 6 cps, -CH₂). Anal. Calcd. for C₁₃H₁₇O₃N: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.44; H, 6.65; N, 4.41.

Attempted Oxide Ring Cleavage of XXII—A solution of the epoxide (XXII; 630 mg) in dry C₄H₆ (10 ml) in the presence of BF₃-ether (1 ml) was stirred at room temperature for 24 hr. The reaction mixture was washed with satd. NaHCO₃ and brine, dried and evaporated. The residual oil thus obtained (550 mg) showed several spots on TLC and was unable to isolate any single product.

3β-Methyl-9-oxobicyclo(3,3,1)non-6-ene-1-amino Hydrobromide (XVI)—Dry HBr gas was introduced by bubbling into a solution of the benzyl carbamate (XVA; 1.126 g) in glacial AcOH (30 ml) for 3 hr and the mixture was allowed to stand at room temperature for 1 hr. Upon adding H₂O (100 ml), the mixture was washed with C₄H₆ and the aqueous layer was concentrated completely in vacuo to give a solid (786 mg; 85%), mp 190—200°. Recrystallization from ether-EtOH gave an analytical sample as colorless needles, mp 198—199°. IR ν/cm²⁻¹: 3390 (NH), 2740—2469 (N⁻), 1739 (CO) 1637 (C=C). Anal. Calcd. for C₁₀H₁₆BrONBr: C, 48.79; H, 6.71; N, 5.78. Found: C, 48.56; H, 6.62; N, 5.66.

Reaction of XVI with Bromoacetone Ethyleneketal—A mixture of the amine hydrobromide (XVI; 460 mg), bromoacetone ethyleneketal₆ (340 mg) and anhydrous K₂CO₃ (1 g) in acetone (50 ml) was heated under reflux for 8 hr. After removing the inorganic salt and evaporating the solvent, the residue was dissolved in ether and extracted with dil. HCl (3 × 10 ml). The acidic extracts were allowed to stand at room tem-
perature for 30 hr, followed by neutralization with Na₂CO₃ and extracted with CHCl₃ (3 × 20 ml). The organic extracts were washed with brine, dried and evaporated to give the residual semi-solid (220 mg). IR ν₁₇₃₃ cm⁻¹: 1720, 1667 and 1647. Chromatography on either silica gel or alumina gave a fraction showing two absorptions at 1667 and 1647 cm⁻¹ in IR, which crystallized on standing to colorless crystals, sublimed at 100°/0.01 mm, mp 105.5−110.5°. The following physical properties and also analysis suggested its dimeric structure, most plausibly as 1,2,3,4,5,6,7,8,9a-decahydro-3,8-dimethyl-1,4a,6,9a-dipropenophene-nazine (XXIII). IR ν₁₇₃₃ cm⁻¹: 1667, 1647 (C=C, C=N). NMR r: 4.35 (4H, m, CH₃), 9.07 (6H, d, J = 6 cps, CH₃), 2.1 (2H, x, 2). Anal. Calcd. for C₉₈H₈₆N₂: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.34; H, 8.80; N, 9.45.

The reaction described above was also carried out in the presence of triethylamine in CH₃OH, resulting in the isolation of the identical dimeric product (XXIII) as above.

3β-Methyl-9-oxobicyclo[3.3.1]non-6-ene-1-pyruvamide (XVII) — To a suspension of the above hydrochloride (XVI) (930 mg in dry THF (20 ml) was added dropwise triethylamine (1.146 g) and pyruvic acid (332 mg) successively while maintaining the reaction temperature below −10°. After stirring for 30 min, a solution of POCl₃ (578 mg) in dry THF (5 ml) was added to the mixture during 2 min and stirring was continued for another 1 hr at the same temperature. Upon adding H₂O (20 ml) and saturating with NaCl, the organic layer was separated and the aqueous layer was extracted with ether thoroughly. The combined extracts were washed with brine and dried over anhyd. MgSO₄. The solvent was evaporated to give a brown oil (356 mg), which was submitted to chromatography on silica gel (10 g). Elution with CHCl₃ afforded a yellow oil (496 mg; 70.6%), boiled at 110−115° under 0.01 mm as colorless oil. IR ν₃₅₂₀ cm⁻¹: 3356 (NH), 1738 (CO), 1686 (NCOCO), 1633 (sh, C=C). NMR r: 1.62 (1H, broad, s, −NH, 4.30 (2H, m, CH₃), 7.58 (8H, s, −CO-CH₂), 9.04 (3H, d, J = 6 cps, −CH₃). Anal. Calcd. for C₁₂H₁₀O₄N₂: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.15; H, 7.26; N, 5.84.

2,3,5,6,7,8-Hexahydro-7β-methyl-2,3-dioxo-1H-5,8a-propanoquinoline (XVIII) — To a stirred suspension of NaH (550 mg of 85.5% oil dispersion, washed with dry THF before use) in dry THF (50 ml) was added the pyruvamide (XVII; 1.68 g) and the mixture was heated under reflux for 3 hr. After adding a small amount of EtOH with ice-cooling, the solvent was evaporated, extracted with CHCl₃ and dried. Evaporation of the solvent gave a viscous oily residue (1.62 g), from which a crystalline product was collected upon triturating with n-hexane (20 ml). Yield was 1.571 g (85%), mp 200−205°. Recrystallization from iso-ProOH−n-hexane gave colorless fine needles, mp 214−216°. IR ν₃₅₂₀ cm⁻¹: 3215 (NH), 1681 (NCOCO), 1639 (C=C). NMR r: 0.08 (1H, broad, s, −NH), 3.63 (1H, s, −C−CH−CO), 4.28 (2H, m, −CH₂−CH₂), 9.08 (3H, d, J = 5.5 cps, −CH₂−CH₂). Anal. Calcd. for C₁₂H₁₀O₄N₂: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.68; H, 6.85; N, 6.42.

5,6,7,8-Tetrahydro-2-ethoxy-7β-methyl-3-oxo-3H-5,8a-propanoquinoline (XIX) — To a solution of the keto-lactam (XVIII; 1.086 g) in CH₂Cl₂ (20 ml) was added a solution of freshly prepared excess Meerwein reagent(16) in CH₂Cl₂ with ice-cooling and the resulting mixture was allowed to stand at room temperature overnight. The mixture was poured into ice−water and the organic layer was separated, washed with H₂O, satd. NaHCO₃, H₂O, dried and concentrated. The residue (1.09 g), was chromatographed on silica gel (10 g) using CHCl₃ as eluent to give a yellow oil (920 mg; 80%), bp 115−120° (0.01 mmHg) (bath temp.). IR ν₃₅₂₀ cm⁻¹: 1667 (C=C-O), 1631 (C=C). NMR r: 3.76 (1H, s, −C−CH−CO), 4.27 (2H, m, −CH₂−CH₂), 5.81 (2H, q, J = 7 cps, −OCH₃CH₂), 8.64 (3H, t, J = 7 cps, −OCH₃), 9.08 (3H, d, J = 6 cps, −CH₂−CH₂). Anal. Calcd. for C₁₂H₁₀O₄N₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.27; H, 7.72; N, 5.66.

2,3,5,6,7,8-Hexahydro-3-hydroxy-7β-methyl-1H-5,8a-propanoquinoline (XX) — To a suspension of LiAlH₄ (337 mg) in dry THF (20 ml) was added a solution of the lactam−ether (XIX; 725 mg) in dry THF (10 ml) dropwise with ice-cooling and the resulting mixture was heated under reflux for 6 hr. After decomposing excess LiAlH₄ with AcOEt, the solvent was removed and extracted with hot CHCl₃ repeatedly. The combined extracts were washed with brine and dried. Evaporation of the solvent gave a solid (545 mg; 90%), which was recrystallized from AcOEt to give colorless leaflets, mp 184−185° (measured in sealed tube). IR ν₃₅₂₀ cm⁻¹: 3279 (NH, OH), 1667, 1634 (C=O). Anal. Calcd. for C₁₂H₁₄ON: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.79; H, 9.24; N, 6.82.

2,3,5,6,7,8-Hexahydro-3-methyl-5-oxo-1H-5,8a-propanoquinoline (XXI) — To a stirred solution of the amino−alcohol (XX; 320 mg) in purified acetone (5 ml) containing a few drops of conc. H₂SO₄, was added one equivalent anhyd of Jones reagent at 0° and stirring was continued for 10 min. Upon adding H₂O (20 ml), the mixture was made alkaline with 5% NaOH and extracted with CHCl₃ (3 × 15 ml). The organic layer was washed with H₂O, and dried. Evaporation of the solvent gave a brown oil (278 mg), which was chromatographed on alumina (Woelm, neutral, 5 g). Elution with CHCl₃ afforded a pale yellow oil (267 mg, 84%), bp 115−120° (0.01 mmHg) (bath temp.). IR ν₃₅₂₀ cm⁻¹: 3313 (NH), 1643 (C=C=O), 1637 (sh, −C=C), 3.44 (1H, s, −C−CH−CO), 4.32 (2H, m, −CH₂−CH₂), 6.52 (4H, s, −N−CH₂−CH₂), 9.07 (8H, d, J = 6 cps, −CH₂−CH₂).

The hydrochloride, prepared in the usual way, was recrystallized from iso-ProOH−ether, to give colorless needles, mp 212−214° (decomp.). IR ν₃₅₂₀ cm⁻¹: 2732−2364 (−N⁺), 1685 (C=C=O), 1639 (C=C). Anal. Calcd. for C₁₈H₁₄ONCl: C, 65.12; H, 5.75; N, 3.84. Found: C, 65.07; H, 5.73; N, 3.85.