[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Synthetic Approaches to Ipecac Alkaloids. III. Studies on the Synthesis and Partial Reduction of Pyridones[1,2]

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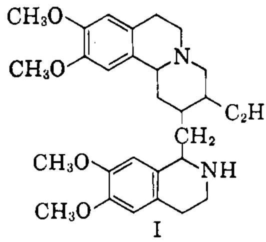
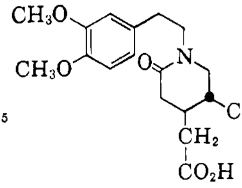
The double salt obtained from the reaction of iodine and pyridine with *N*-β-(3,4-dimethoxyphenylethyl)-4-carboxy-5-ethyl-2-methylpyridine is hydrolyzed by dilute alkali to pyridine and not to a pyridone. *N*-β(3,4-dimethoxyphenylethyl)-5-ethyl-2-pyridone and *N*-β(3,4-dimethoxyphenylethyl)-2-pyridone are, however, readily prepared by this method. The former pyridone is reduced by lithium aluminum hydride to a mixture of a (de-oxygenated) dihydropyridine and the γ,δ-unsaturated lactam, and by lithium, sodium or calcium in liquid ammonia to the γ,δ-unsaturated lactam and its phenolic, monodemethylated analog. Other transformation products of these substances are described.

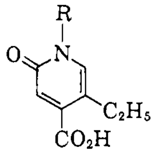
The present paper reports an extension of a previously outlined[2] experimental approach to the synthesis of emetine(I) and other alkaloids of the ipecac group. The immediate objective of this work was the stereospecific synthesis of the *trans*-piperidoneacetic acid II, which has[3,4] the "natural" stereochemistry, and which, after having been prepared by non-stereospecific means,[3,5,6] had been converted to emetine. We envisioned two means of control of the stereochemistry: (i) hydrogenation of the pyridonecarboxylic acid III to the next lower homologue of II— which would place the carboxyl group next to an epimerizable asymmetric center—followed by homologation, and (ii) attachment of a two-carbon chain to the dihydropyridone IV by Michael addition, a process that, being reversible, would be expected to afford the thermodynamically favored *trans*-stereochemistry. After this work was under way, Battersby and Turner[7] reported a successful synthesis of IV by a method other than the one we were attempting; Michael addition of malonic ester to IV, hydrolysis, and decarboxylation gave II which was converted to emetine.[7] These developments prompt us to record our observations now.



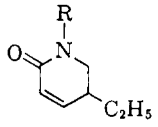
I



II



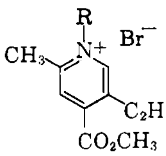
III



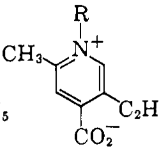
IV

R = β-(3,4-dimethoxyphenylethyl)

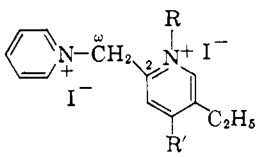
Approach (*i*) Homoveratryl bromide reacted with methyl 5-ethyl-2-methylpyridine-4-carboxylate[2b] to give the extremely hygroscopic quaternary bromide V. Reaction of V with moist silver oxide gave the hygroscopic, glassy betaine VI. Both V and VI reacted with iodine and pyridine[2a] to give the corresponding double salts VIIa and VIIb, which were also hygroscopic and were not obtained in the pure state.



V



VI



VIIa. R′ = CO_2CH_3
b. R′ = CO_2H

R = β-(3,4-dimethoxyphenylethyl)

That VIIa and VIIb were actually in hand, however, was evident from the characteristic[2a] transient blood-red color that both crude preparations gave with aqueous alkali. Although other double salts of this type are smoothly hydrolyzed by aqueous alkali to pyridones,[2a] VIIa and VIIb gave no pyridone under these conditions. The only identifiable product was pyridine, characterized as the picrate and as the hydroiodide. Apparently,

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[1] (a) This work was supported in part by a grant from Abbott Laboratories, Inc. (b) From a dissertation to be submitted by J. S. Walia in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] For previous papers in this series see (a) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956); (b) J. A. Berson and T. Cohen, *J. Org. Chem.*, **20**, 1461 (1955).

[3] E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, *J. Am. Chem. Soc.*, **79**, 4817 (1957).

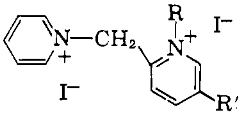
[4] A. R. Battersby and S. Cox, *Chem. & Ind.* (*London*), 983 (1957). A. R. Battersby, R. Binks, D. Davidson, G. C. Davidson, and T. P. Edwards, *Chem. & Ind.* (*London*), 982 (1957). A. R. Battersby, G. C. Davidson, and B. J. T. Harper, *Chem. & Ind.* (*London*), 983 (1957).

[5] R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskii, *J. Gen. Chem.*, **22**, 1467 (1952).

[6] M. Barash and J. M. Osbond, *Chem. & Ind.* (*London*), 490 (1958).

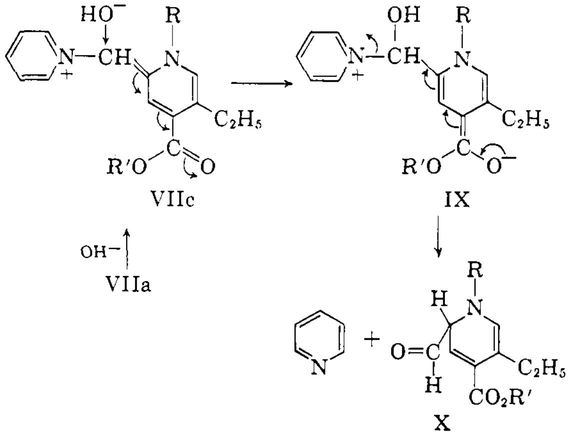
[7] A. R. Battersby and J. C. Turner, *Chem. & Ind.* (*London*), 1324 (1958).

hydroxyl ion attacked VIIa and VIIb not at the desired position, C.2, which would have given pyridone, but at C.ω, which resulted in displacement of pyridine. The previous pyridone syntheses[2a] had been carried out on double salts with the *N*-alkyl groups methyl or β-phenylethyl and without a substituent at C.4 of the pyridine nucleus. That the failures in the present cases were not caused by the use of a 3,4-dimethoxyphenylethyl group as the *N*-alkyl residue was established by the fact that the double salts (VIIIa and VIIIb) derived from *N*-β-(3,4-dimethoxyphenylethyl)-2-methylpyridinium bromide and *N*-β-(3,4-dimethoxyphenylethyl)-5-ethyl-2-methylpyridinium bromide, respectively, both gave pyridones in high yield.

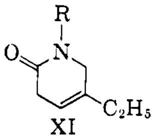


R = β-(3,4-dimethoxyphenylethyl)
VIIIa. R′ = H
b. R′ = C_2H_5

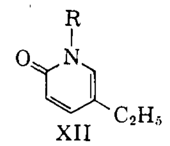
The difference in behavior of VIIa and VIIb compared to VIIIa and VIIIb is therefore presumably attributable to the ester or carboxyl function in the former salts. This is reasonable on the following grounds. In alkaline solution, the double salt is partially converted to the red anhydrobase. Attack of hydroxyl ion at C.2, leading to pyridone, most probably occurs on the double salt itself. An electron-withdrawing substituent like carbomethoxy at C.4 would increase the acidity of the methylene hydrogens, thus decreasing the amount of substrate in the double salt form, and also, would facilitate attack of hydroxyl ion at C.ω (see VIIa→VIIc→IX→X), leading to the undesirable side reaction that releases pyridine. The other product of such processes (X) would be expected to be unstable, and its transformation products may be the origin of the intractable tars observed.



Approach (*ii*). Either the dihydropyridone IV or its β,γ-unsaturated isomer XI were the objectives of these experiments. Accordingly, we investigated the partial reduction of the readily available pyridone XII, obtained in 90% yield from the nicely crystalline double salt VIIIb.



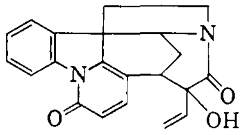
XI



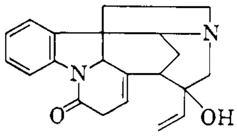
XII

R = β-(3,4-dimethoxyphenylethyl)

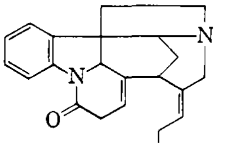
An attractive precedent for the reduction XII→XI existed in the reported[8] reduction of the pyridone XIII to the β-γ-unsaturated dihydropyridone XIV with lithium aluminum hydride. Further precedent was also available for the required isomerization XI→IV in the cyclization of isostrychnine I (XV) to strychnine (XVI) under *alkaline* conditions.[8,9] However, lithium aluminum hydride reduction of XII gave undesirable results. In ether, the reaction was slow; starting material was recovered even after prolonged reaction periods. Even in refluxing tetrahydrofuran, complete reduction of XII required several hours. From this reaction, a new base was isolated in 27% yield as the crystalline, hygroscopic, chloroform-soluble hydrochloride XIX. The infrared spectra of the new base and of its hydrochloride showed no absorption in the lactam carbonyl region. The ultraviolet spectrum clearly demonstrated that the pyridone chromophore (λ_{max} 312 mμ) had been destroyed, since only the absorption (λ_{max} 282 mμ) associated with the 3,4-dimethoxyphenylethyl nucleus remained. The hydrochloride absorbed two moles of hydrogen over platinum to give a new hydrochloride (XVII), which was identical with the hydrochloride of a base obtained by catalytic hydrogenation (two moles) of the pyridone XII to the piperidone XVIII and lithium aluminum hydride reduction of the latter.



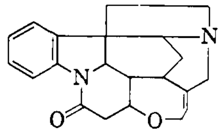
XIII



XIV



XV



XVI

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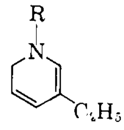
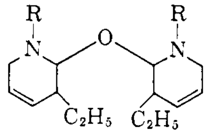
[8] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954). *Cf.*, R. B. Woodward, XIVth International Congress of Pure and Applied Chemistry, *Experientia Supplementum II*, Birkhauser Verlag, Basel, 1955, p. 213.

[9] V. Prelog, J. Battegay, and W. I. Taylor, *Helv. Chim. Acta*, **31**, 2244 (1948).

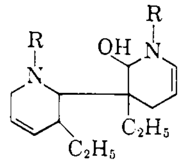
The elemental composition of the hydride reduction product XIX agreed best with the empirical formula $C_{17}H_{24}O_2NCl.{}^1/_2\ H_2O$, although a formula with C_3H_8O (from the isopropyl alcohol solvent) instead of $^1/_2\ H_2O$ was not completely excluded by the data. The former formula is consistent with structure XIXa for the free base,[10] and the dimeric formula, $C_{34}H_{50}O_5N_2Cl_2$, is consistent with that of the dihydrochlorides of the ether XIXb or the octahydrobipyridyl[10] XIXc. Regardless of which of these is correct, it is clear that the 1,6-addition observed in the change XIII→XIV did not occur, XIX being formed by formal 1,2-addition instead. The remainder of the reduction product was a mixture, a major component of which was probably the γ,δ-unsaturated lactam XX.



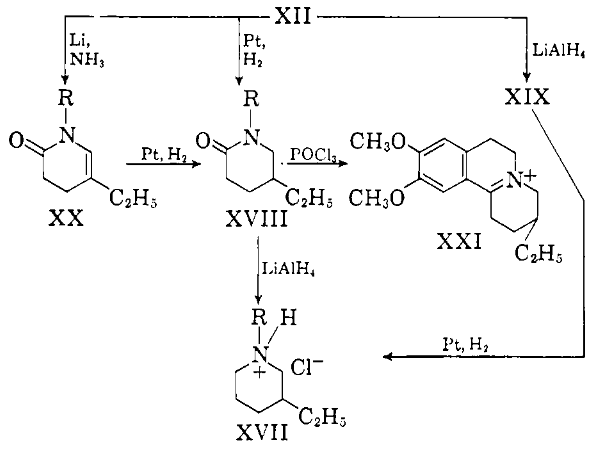
XIXa



XIXb



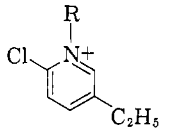
XIXc



R = β-(3,4-dimethoxyphenylethyl)

With lithium, calcium, or sodium in liquid ammonia, XII was reduced to a mixture of the γ,δ-unsaturated lactam XX and a crystalline phenolic unsaturated lactam. The empirical composition of the phenol corresponded to the next lower homologue of XX; this type of product is not unexpected, since monodemethylation of homoveratrylamine has been previously reported in a metal-ammonia reduction.[11] The phenol and the undemethylated product both consumed one mole of hydrogen over platinum. The ultraviolet (λ_{max} 282 mμ) and infrared (λ_{max} 6.13 μ) spectra of these substances demonstrated the destruction of the pyridone nucleus (λ_{max} 282, 312 mμ, 6.03 μ) with retention of the homoveratryl nucleus and lactam function. The non-phenolic lactam XX gave upon catalytic hydrogenation the same piperidone (XVIII) that was obtained by catalytic hydrogenation of the pyridone XII.

Phosphorus oxychloride converted XVIII to the crystalline hexahydroquinolizinium salt XXI. It is of ancillary interest that the pyridone XII was converted by phosphorus oxychloride not to a quinolizinium salt but rather to the 2-chloropyridinium salt XXII. The latter was smoothly hydrolyzed to the pyridone XII by aqueous alkali. The failure of the Bischler-Napieralski cyclization has been noted previously with the analogue XII, R = β-phenylethyl.[2a] Apparently, even a nucleus as reactive as β-(3,4-dimethoxyphenylethyl) can escape electrophilic attack under these conditions.



XXII
R = β-(3,4-dimethoxyphenylethyl)

The assignment of the double bond of XX to the γ,δ-position follows from the failure of the substance to react with sodiodiethylmalonate, potassium cyanide, or sodium bisulfite, reagents that would have been expected to add to the α,β-unsaturated lactam IV. The remaining possible isomer, the β,γ-unsaturated lactam XI, would have been expected, under the basic conditions of the Michael addition, to isomerize to IV which would undergo condensation. Even treatment with lithium amide failed to produce any discernible change in the infrared spectrum of XX. Further, crude hydride and metal-ammonia reduction mixtures were subjected to vigorous Michael condensation conditions, using large excesses of malonic ester, and the products were scrutinized by chromatography and infrared analysis. In no case was there any evidence of adduct formation. Since IV has already been shown to give a Michael adduct with malonic ester in high yield,[7] it seems unlikely that our reduction mixtures contained appreciable amounts of IV. Metal-ammonia reduction, therefore, proceeded almost exclusively by formal 1,4-addition to give XX.

The results reported here demonstrate that partial reduction of pyridones can be achieved with lithium aluminum hydride or with metal-ammonia systems. The course of these reductions appears to be unpredictable at present.

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[10] A referee has pointed out to us that A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958), have obtained a dihydropyridine from hydride reduction of a pyridone similar to XII. These authors also observed a dimeric product from acid treatment of 1-benzyl-3-acetyl-1,4-dihydropyridine.

[11] K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **75**, 5119 (1953).

EXPERIMENTAL[12]

Preparation and hydrolysis of the double salts VIIa and VIIb. A mixture of 4.80 g. of homoveratryl bromide and 3.58 g. of methyl 5-ethyl-2-methylpyridine-4-carboxylate[2b] (b.p. 95–96°/3 mm., picrate m.p. 115–116°, reported,[2b] picrate m.p. 114.2–115.5°) was heated on the steam bath for 2 days. The resulting viscous mass was dissolved in water and washed with ether to remove unreacted starting materials. Evaporation of the water left a thick glass, from which colorless crystalline material could be obtained by allowing an ethanol-ethyl acetate or pyridine solution to stand. The crystals (V) m.p. 253–256°, were extremely hygroscopic, and they liquified on exposure to moist air.

A mixture of 2.00 g. of the above salt and 1.41 g. of iodine in 25 ml. of pyridine was heated on the steam bath for 7 hr. After having been kept overnight at room temperature, the pyridine was removed *in vacuo*, and the residue was leached with several portions of warm water. The aqueous extract was washed with ether and evaporated leaving a thick glass which could not be induced to crystallize (VIIa).

The betaine VI was prepared by shaking a mixture of 1.00 g. of V in 10 ml. of water with freshly precipitated and washed moist silver oxide (from 2.38 g. of silver nitrate) until the supernatant liquor gave a negative test for bromide ion. The mixture was filtered through diatomaceous earth, the filtrate was treated with hydrogen sulfide (which gave no precipitate of silver sulfide), filtered again, and evaporated to dryness *in vacuo*. The resulting hygroscopic glass was readily soluble in water. The conjugate acid of VI, also a hygroscopic glass, was prepared by direct alkylation of 5-ethyl-2-methylpyridine-4-carboxylic acid with β-(3,4-dimethoxyphenylethyl)bromide.

A number of attempts to prepare crystalline double salts of the ester V, betaine VI and conjugate acid were carried out. Double salts were obtained in each case, as was indicated by the color reaction with alkali, but none could be induced to crystalline. The following experiment is typical.

A solution of 0.7764 g. of the conjugate acid of VI in 25 ml. of ice-cold pyridine was treated dropwise with a solution of 0.548 g. of iodine in pyridine during 20 min. The mixture was kept at room temperature for 1 hr., then heated briefly (3–4 min.) on the steam bath. At this point, the solution gave a negative test with starch-iodide paper. The pyridine was removed *in vacuo*, the residue was taken up in water, the aqueous solution was washed with ether (two 10-ml. portions) and the aqueous layer cooled and treated dropwise with cold 2*N* sodium hydroxide. Each drop of alkali produced a blood-red color which gradually faded. When further addition of alkali produced no more color, the solution was kept at room temperature for 2 hr. and then acidified with dilute hydrochloric acid. Evaporation of the solution left a salt residue which was leached with hot absolute ethanol. The ethanol solution was evaporated and the residue crystallized from isopropyl alcohol-hexane to give 0.247 g. of material of m.p. *ca.* 250–268° (dec.). A mixed m.p. with an authentic sample of pyridine hydroiodide (m.p. 255° dec.) was not depressed. The ultraviolet spectra of the two samples were identical. The *picrate* had m.p. 166–167° after recrystallization from ethanol. A mixed m.p. with an authentic sample of pyridine picrate, m.p. 165–166°, was undepressed. A mixed m.p. with β-(3,4-dimethoxyphenylethylamine) picrate, m.p. 165–166°, was depressed to 139–150°.

Anal. Calcd. for $C_{11}H_8N_4O_7$: C, 42.85; H, 2.60; N, 18.18. Found: C, 43.04; H, 2.60; N, 18.32.

The yield of pyridine hydroiodide was not decreased by repeated evaporation of the original pyridine reaction mixture with water or by exhaustive extraction of the aqueous solution with ether and chloroform before addition of alkali. This indicated that the pyridine isolated subsequent to the addition of alkali was a product of the hydrolysis of the double salt and not an artifact carried through from the original pyridine solvent. Similar results were obtained in experiments with VIIa. The crude reaction mixtures from several hydrolyses were free of absorption in the 6μ region.

Preparation and hydrolysis of VIIIa and VIIIb. A suspension of 1.69 g. of *N*-β-(3,4-dimethoxyphenylethyl)-2-methylpyridinium bromide (m.p. 179–181°, prepared in 85% yield from α-picoline and homoveratryl bromide) in 20 ml. of pyridine was treated dropwise with a solution of 1.29 g. of iodine in 20 ml. of pyridine while the reaction mixture was heated on the steam bath. After about 30 min., 2.40 g. of the double salt VIIIa had separated as pale pink crystals. This material was filtered off and hydrolyzed without further purification. A solution of the salt in 10 ml. of water was treated with dilute sodium hydroxide. A transient blood-red color was observed. When further addition of alkali produced no more color, the mixture was extracted with chloroform, the extract was dried, filtered, and evaporated. The residue was taken up in ether and washed with dilute hydrochloric acid to remove a little pyridine, dried, and evaporated. The residue, a black, viscous oil, was fractionally distilled in a Vigreux column to give 0.81 g. (69% based on VIIIa) of a pale yellow oil, b.p. 218–220°/3.5 mm., which crystallized upon standing at room temperature. After recrystallization from benzene-hexane, *N-β-(3,4-dimethoxyphenylethyl)-2-pyridone* was obtained as colorless needles m.p. 82–83°; the ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 286,303 mμ, log ε 3.84, 3.80, infrared maximum in chloroform at 6.02 μ.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.36; H, 6.44; N, 5.32.

The *picrate*, m.p. 126–127°, was prepared in ether-ethanol and recrystallized from ethanol.

Anal. Calcd. for $C_{21}H_{20}O_{10}N_4$: C, 51.64; H, 4.10. Found: C, 51.50; H, 4.35.

Heating a mixture of homoveratryl bromide and 5-ethyl-2-methylpyridine gave the *quaternary bromide*, m.p. 153–156° (soft at 145°), after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: Br, 21.86. Found: Br, 21.80.

When 3.66 g. of the above bromide and 2.54 g. of iodine were heated in 15 ml. of pyridine for 3 hr., 4.3 g. of the double salt VIIIb were obtained. Recrystallization from aqueous ethanol gave faintly yellow plates, m.p. 210–210.5° with pre-darkening at 205°.

Anal. Calcd. for $C_{23}H_{28}O_2I_2N_2$: C, 44.64; H, 4.53; N, 4.53; I, 41.10. Found: C, 44.49; H, 4.41; N, 4.51; I, 41.26.

Hydrolysis of the double salt VIIIb was carried out as for VIIIa. Distillation gave 90% of *N-β-(3,4-dimethoxyphenylethyl)-5-ethyl-2-pyridone* (XII) as a viscous oil, b.p. 220–225°/3.5 mm., which crystallized slowly upon standing. Recrystallization from ether gave material of m.p. 57–58°; the ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 287, 313 mμ, log ε 3.77, 3.80; the infrared spectrum in chloroform showed λ_{max} 6.02 μ.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.08; H, 7.32; N, 4.88. Found: C, 70.97; H, 7.45; N, 4.85.

The *picrate*, prepared in ether-alcohol and recrystallized from ethyl acetate-hexane, had m.p. 99–100°.

Anal. Calcd. for $C_{23}H_{24}O_{10}N_4$: C, 53.52; H, 4.69; N, 10.66. Found: C, 53.57; H, 4.55; N, 10.63.

From a large scale preparation in which 106 g. of double salt gave 41 g. of XII, there was obtained as distillation fore-run 4.5 g. of a by-product, b.p. 95–97°/5 mm., which gave a picrate m.p. 161–162°.

Reaction of XII *with phosphorus oxychloride.* A solution of 2.75 g. of XII in 10 ml. of dry benzene was treated with a solution of 9 ml. of phosphorus oxychloride in 20 ml. of benzene and the mixture was boiled in a nitrogen atmosphere for 3 hr. The solvent and excess phosphorus oxy-

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[12] Melting points are corrected. The microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, 24, Calif., and by Truesdail Laboratories, Los Angeles, Calif.

chloride were removed *in vacuo* and the residue was taken up in water and treated with a saturated solution of potassium iodide. The resulting precipitate was recrystallized from aqueous alcohol to give XXII *iodide*, m.p. 194–195°; in ethanol, λ_{max} 281 mμ, log ϵ 3.87.

Anal. Calcd. for $C_{17}H_{21}O_2ClIN$: C, 47.05; H, 4.83. Found: C, 46.60; H, 4.77.

Heating this material with 10% aqueous sodium hydroxide regenerated XII.

Conversion of XII *to* XXI. Catalytic hydrogenation of XII was carried out over platinum oxide in methanol. Gas consumption ceased after 2.02 moles had been absorbed. The product, XVIII, was a colorless oil, whose infrared spectrum showed λ_{max} 6.15 μ.

Cyclization of 5.0 g. of XVIII was accomplished with phosphorus oxychloride in boiling benzene. Treatment with potassium iodide of an aqueous solution of the residue obtained by evaporation of the reaction mixture gave 6.0 g. of XXI *iodide*, m.p. 188–190°. Recrystallization from ethyl acetate-aqueous alcohol gave material of m.p. 195–196°. The ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 246, 302, 352 mμ, log ϵ 4.23, 3.94, 3.99. A mixed m.p. with XXII iodide was depressed. Fifty milligrams of uncyclized XVIII were recovered from the reaction mixture by extraction with ether.

Anal. Calcd. for $C_{17}H_{24}O_2IN$: C, 50.88; H, 5.99; N, 3.49; I, 31.67. Found: C, 50.82; H, 6.11; N, 3.54; I, 31.63.

Lithium aluminum hydride reduction of XII *to* XIX. A solution of 12.0 g. of XII in 75 ml. of dry tetrahydrofuran (distilled from calcium hydride) was treated in portions with 2.00 g. of lithium aluminum hydride in tetrahydrofuran. The reaction mixture was boiled for 11 hr. and then evaporated, cooled, and treated with cold dilute hydrochloric acid. The mixture was repeatedly extracted with chloroform, the chloroform extract was dried with sodium sulfate and evaporated. The residue was treated with ether to give 3.50 g. of XIX, m.p. 163–165°, as a white precipitate. Recrystallization from isopropyl alcohol–ethyl acetate gave material of m.p. 169–170°. The infrared spectrum in chloroform showed no absorption on the 6.0–6.1 μ region. The ultraviolet spectrum in ethanol showed λ_{max} 280 mμ, log ϵ 3.51. The substance was readily soluble in water and its aqueous solution gave an immediate precipitate with silver nitrate. The crystals were hygroscopic.

Anal. Calcd. for $C_{17}H_{24}O_2NCl \cdot {}^1/_2H_2O$: C, 64.13; H, 7.92; Cl, 11.10. Found: C, 64.20; H, 8.45; Cl, 10.76.

The free base was a colorless oil which also showed no absorption in the 6.0–6.1 μ region.

The non-crystalline portion of the chloroform extract (after separation of XIX) was chromatographed on alumina. A small amount of the free base of XIX was eluted from the column first with benzene, followed by a major fraction (1.64 g.) that appeared to be XX, since its infrared spectrum was identical with that of XX, it did not react with malonic ester in the presence of ethanolic sodium ethoxide, and it consumed 0.91 mole of hydrogen over palladium charcoal in absolute ethanol to give an oil whose infrared spectrum was identical with that of XVIII.

XVII. *A. By hydrogenation of* XIX. A solution of 0.206 g. of XIX in 20 ml. of absolute ethanol absorbed 16.0 ml. (2.13 moles) of hydrogen in 3.5 hr. over 10% palladium-on-charcoal, whereupon hydrogenation ceased. Evaporation of the solvent gave 0.200 g. of XVII, m.p. 186–187°. Recrystallization from isopropyl alcohol–ethyl acetate gave material of m.p. 187–187.5°, alone or mixed with a sample prepared by method B. A mixed m.p. with XIX was depressed. The salt was hygroscopic; it was dried to constant weight at 90° immediately before analysis.

Anal. Calcd. for $C_{17}H_{28}O_2ClN$: C, 65.05; H, 8.99; N, 4.48. Found: C, 65.00; H, 9.05; N, 4.50.

B. By lithium aluminum hydride reduction of XVIII. A solution of 0.50 g. of XVIII in 10 ml. of tetrahydrofuran was added during 7 min. to a stirred solution of 0.120 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran. Heat was evolved. The reaction mixture was boiled under reflux for 7 hr., evaporated, acidified with dilute hydrochloride acid, and extracted with chloroform. Evaporation of the chloroform left a residue which after recrystallization from isopropyl alcohol–ethyl acetate gave 0.50 g. of crystals, m.p. 187–188°, alone or mixed with a sample prepared by method A. The infrared spectra of chloroform solutions of the two samples were identical.

Metal-ammonia reduction of XII. A large number of experiments were carried out in which XII was reduced with varying atomic proportions of lithium, sodium, and calcium. A typical run was carried out as follows. A solution of 10 g. of XII in about 100 ml. of tetrahydrofuran was added slowly to a solution of 0.80 g. of lithium in about 20 ml. of liquid ammonia. The blue color was discharged in about 2 hr. The excess ammonia was evaporated and the residue was treated with dilute hydrochloric acid and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated, and the residue was distilled to give 6.0 g. of a viscous liquid, b.p. 210–215°/1.5 mm.

This material deposited crystals after standing several days. The mixture was triturated with ether to give 1.8 g. of a white crystalline product, m.p. 133–135°. The filtrate was evaporated to give 4.0 g. of a thick oil, λ_{max} 280 mμ, log ϵ 3.60, λ_{max} 6.14 μ. The oil consisted mainly of XX contaminated with about 25% of XII (as evidenced by weak absorption at 312 mμ).

The crystalline material was recrystallized from ethyl acetate–ether to give material of m.p. 139.5–140°. It was phenolic, being insoluble in water or bicarbonate solution, but readily soluble in aqueous sodium hydroxide. Carbon dioxide precipitated it unchanged from alkaline solution. The substance showed a sharp O-H absorption in the infrared, and a sharp, strong lactam absorption at 6.15 mμ. It gave a green-brown color with ferric chloride which was unstable to water. The ultraviolet spectrum had λ_{max} 281.5 mμ, log ϵ 3.53, and was completely blank at longer wave lengths. Catalytic hydrogenation over palladium-on-charcoal ceased after the absorption of 1.00 mole of gas.

Anal. Calcd. for $C_{16}H_{21}O_3N$: C, 69.82; H, 7.64; N, 5.10. Found: C, 69.81; H, 7.70; N, 5.21.

The yield of the crystalline phenolic product (isolated by alkali extraction) increased at the expense of the yield of XX when the amount of lithium was increased. A preparation of XX was re-distilled and submitted for analysis. This material contained 9% of XII as determined spectrophotometrically.

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 70.58; H, 7.95; N, 4.85. Found: C, 70.35; H, 7.73; N, 5.01.

This material had λ_{max} 280 mμ, log ϵ 3.61, λ_{max} 6.14 μ. Hydrogenation in ethanol over palladium-on-charcoal ceased after the consumption of 0.92 mole of gas. The product, identified by its infrared spectrum, was XVIII.

Attempts to add sodiomalonic ester, potassium cyanide, or sodium bisulfite to XX were fruitless. In each case, chromatography gave only starting material. None of the chromatographic fractions had infrared spectra (*e.g.*, both ester and lactam absorption) expected of an adduct.

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