95. Sadao Ohki, Yoshiya Noike, and Koji Yamakawa: Synthesis of Quinolizine Derivatives. IV.[1] Synthesis of 3-(N'-Methyl-2'-piperidyl)-quinolizidine.

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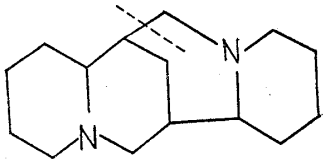
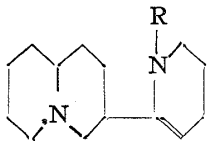
In this paper is described the synthesis of 3-(N'-methyl-2'-piperidyl)-quinolizidine (IV) which was prepared as a possible uterus constrictor. This compound can be regarded as a product obtained by the fission of sparteine (I) at the dotted line and is thought to be of interest in investigating the rôle of the two fused quinolizidine nuclei in sparteine from the pharmacological view point.



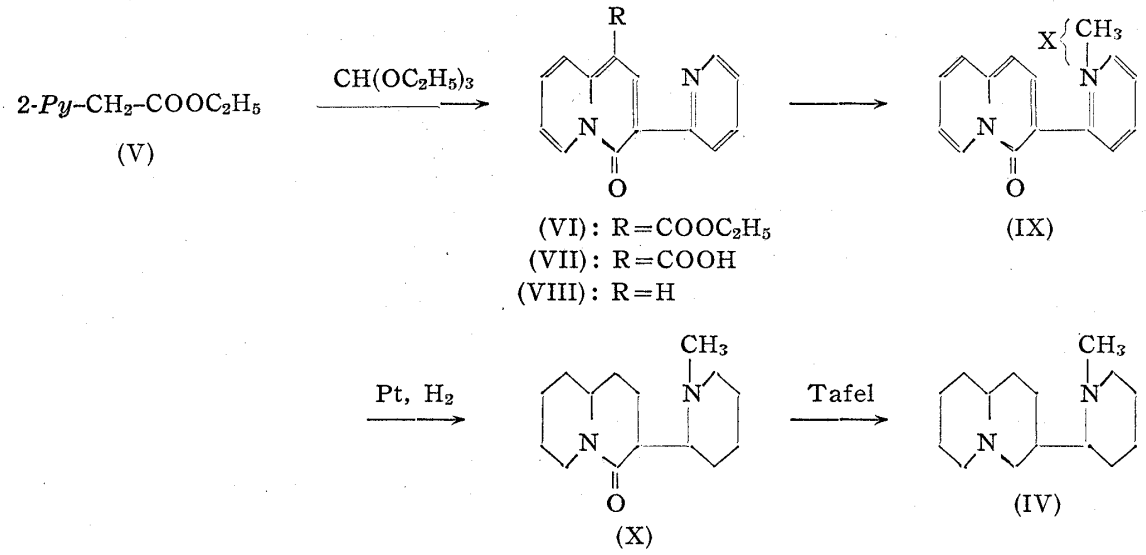
(I)



(II): R=H, (III): R=CH_3

Incidentally, Diskina and Konovalova[2] recently isolated an alkaloid piptantin, $C_{14}H_{24}N_2$, from *Piptanthus nanus* and elucidated its constitution as (II). They also prepared the corresponding N-methyl derivative (III) from (II).

Our first synthesis of (IV) was carried out as follows:



1-Carbethoxy-4-keto-3-(2'-pyridyl)-quinolizine (VI) was prepared from ethyl 2-pyridyl-acetate (V) and orthofomic ester according to Clemo *et al*[3]. Though 3-(2'-pyridyl)-4-keto-quinolizine (VIII) can be prepared in one step from (VI) by boiling the latter with hydrochloric acid according to Galinovsky *et al.*,[4] this reaction proceeds only with extreme sluggishness and so we first isolated the free carboxylic acid (VII), the alkaline hydrolytic product of (VI), and then decarboxylated this at 250°. The resultant compound (VIII) forms rhombic crystals of m.p. 112°, as was given also by Galinovsky.

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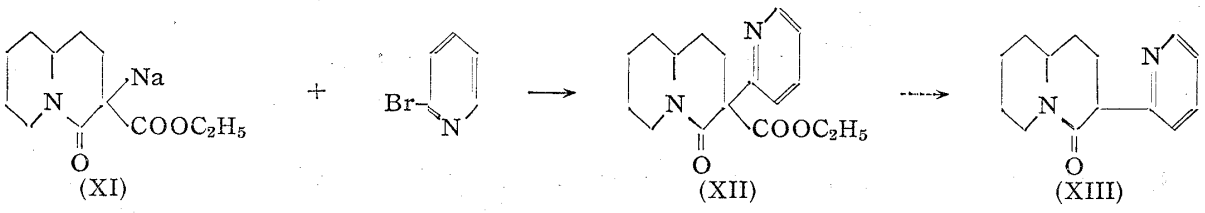
1) Part III: This Bulletin, 1, 260(1953).
2) Diskina, Konovalova: Daklady Acad. Nauk S.S.S.R., 81, 1069(1951).
3) Clemo, Morgan, Raper: J. Chem. Soc., 1936, 1025.
4) Galinovsky, Kainz: Monatsh., 77, 137(1947)(C.A., 43, 4269(1949)).

The methochloride (IX) of (VIII) gives strongly fluorescent solution in alcohol, which disappeared after absorbing hydrogen activated upon Adams' Pt at 40～45°. 3-(N'-Methyl-2'-piperidyl)-4-ketoquinolizidine (X), thus obtained, is a colorless oil of $b.p_{0.002}$ 160～165°, which represents the mixture of four or probably of more diastereoracemates[5], of which one gives crystalline platinum salt. The Tafel reduction of (X) in 50% sulfuric acid afforded colorless oil of $b.p_{0.1}$ 160° (oil-bath temp.), which gave no crystalline derivative. The analytical data of this oil approximated those of theoretical value.

In an effort to obtain at least one of the racemates of (IV) in crystalline form alternative methods of synthesis of this compound were explored.

Sodium 3-carbethoxy-4-ketoquinolzidine (XI)[6] was condensed with 2-bromopyridine, furnishing 3-(2'-pyridyl)-3-carbethoxy-4-ketoquinolizidine (XII). The hydrolysis of the latter and the decarboxylation of the free acid thus obtained to (XIII) were found to be unpromising and this route was abondoned.



(XI) (XII) (XIII)

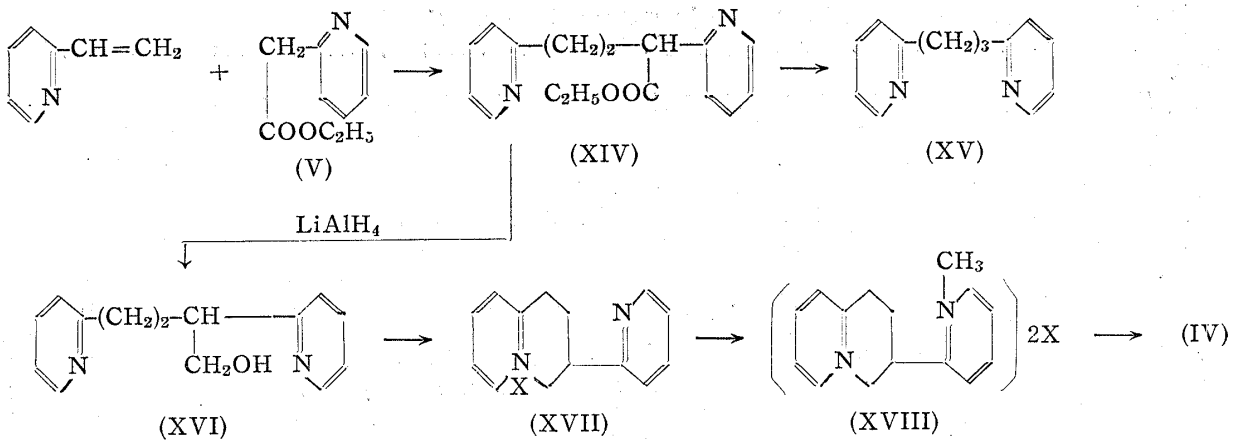
In the second alternative method 2-vinylpyridine was condensed with ethyl 2-pyridylacetate to furnish ethyl α,γ-di(2-pyridyl)-butyrate (XIV) in a good yield. On being boiled with hydrochloric acid this compound suffered hydrolysis and decarboxylation, giving 2-dipicolylmethane (XV), the crystalline picrate of which was proved to be identical with the one of the compounds prepared by Leonard[7] by condensing 2-vinylpyridine with α-picoline. The constitution of (XIV) was thus proved.

The lithium aluminum hydride reduction of (XIV) yielded the corresponding alcohol (XVI) which, on being treated with thionyl chloride in chloroform solution, gave the chloride. The latter was then heated in benzene, furnishing the cyclized product (XVII)[8], the iodide (m.p. 158°) of which was heated with methyl iodide in methanol to give the bis-quaternary iodide (XVIII). The corresponding chloride in alcohol was then reduced catalytically over Adams' Pt catalyst; hydrogen being absorbed smoothly and colorless oil resulted. Though the free base was not induced to crystallize, the dipicrate was obtained as yellow plate-shaped crystals of m.p. 184～186°.

In this second method there exists only one racemate as far as the penultimate compound (XVIII), from which the ultimate compound was prepared by hydrogenation under mild conditions. Therefore, it appears that stereochemically purer (IV) was produced than by the first method.

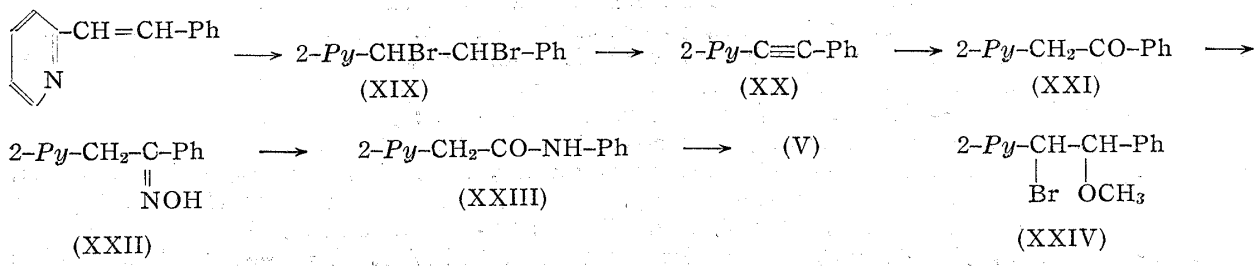
As for the preparation of ethyl 2-pyridylacetate, the starting material in the present syntheses, some comment will be made. As was described by Woodward *et al.*[9] this compound is most conveniently prepared by treating α-picolyl lithium with carbon dioxide, but since metallic lithium was not at our disposal, we had recourse to the Oparina's method[10], which was known to us only through *Chemisches Zentralblatt* which did not mention the working conditions in detail.

5) The study of the configuration of (X) by Stuart model revealed that there exists restricted rotation in the C–C bond between quinolizidine and piperidine rings.
6) Boekelheide, Rothchild: J. Am. Chem. Soc., 71, 879(1949); Ohki, Noike: J. Pharm. Soc. Japan, 72, 490(1950).
7) Leonard, Boyer: J. Am. Chem. Soc., 72, 4818(1950).
8) Cyclization to the other direction forming a four-memberd ring seems highly improbable.
9) Org. Syntheses, 29, 44.
10) Oparina: Chem. Zentr., 1935, I, 2536.



2-Phenacylpyridine (XXI) was prepared by Boehringer Sohn's method[11] from 2-styrylpyridine via 2-styrylpyridine dibromide (XIX) and 2-phenethinylpyridine (XX). For dehydrobromination of (XIX) to (XX) amyl alcoholic potassium hydroxide gave a better result in shorter time than ethanolic alkali, as is mentioned in the literature. Our attempt to obtain 2-(β-methoxy-α-bromo-β-phenethyl)-pyridine (XXIV) by treating the dibromide (XIX) either with methanol or sodium methoxide in order to simplify the preparation of (XXI) failed, chiefly giving 2-(α(or β)-bromostyryl)-pyridine.

The Beckmann rearrangement of the oxime (XXII) was best carried out by means of phosphorus pentachloride in ether, giving the anilide (XXIII) in about 85% yield, which in turn was converted to ethyl 2-pyridylacetate (V) by bubbling dry hydrogen chloride through the ethanolic solution at 70~75°. Heating at 80° or above resulted mainly in decarboxylation, yielding α-picoline as the main product.



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Experimental

3-(2'-Pyridyl)-4-ketoquinolizine(VIII)—1-Carbethoxy-3-(2'-pyridyl)-4-ketoquinolizine (VI: 1.7 g.) was hydrolyzed by boiling with 5% alcoholic potassium hydroxide (0.48 g. KOH) solution for 1 hr., separating yellow potassium salt. After being heated for an additional hour, alcohol was evaporated and the residue was dissolved in water and filtered. The yellow filtrate was made acid with acetic acid, separating gelatinous precipitate, which was collected on a filter, washed, and dried at 110°. Crude yield of the carboxylic acid (VII) was 1.4 g. This was then heated gradually in a distilling flask, when at 240~250° the whole decomposed with effervescence. The residue was distilled under 1 mm., giving yellow syrupy distillate (VIII), which solidified on standing. Purified from benzene-petroleum ether, it forms orange yellow rhombs of m.p. 112°, which is soluble in ether, alcohol, benzene, and chloroform. By extracting the flask residue with benzene some more substance was recovered. Yield, 0.96 g. *Anal.* Calcd. for $C_{14}H_{10}ON_2$: N, 12.6. Found: N, 12.9.

11) Boehringer Sohn: Brit. Pat. 311,387; Chem. Zentr., 1930, II, 812.

Methiodide: From (VIII) and methyl iodide in methanol, as usual. Orange yellow plates of m.p. 236° from alcohol. *Anal.* Calcd. for $C_{15}H_{13}ON_2I$: C, 49.45; H, 3.6; N, 7.7. Found: C, 49.3; H, 4.0; N, 7.7.

3-(N'-Methyl-2'-piperidyl)-4-ketoquinolizidine (X)—The above-mentioned methiodide of (VIII) was converted into the corresponding chloride, which was reduced catalytically in HCl-acid alcoholic solution over Adams' Pt at 40~50°. The absorption of hydrogen proceeded smoothly and the original yellow fluorescent solution became colorless. The filtrate from the catalyst was evaporated and the residue was dissolved in a small amount of water, basified, salted out, and extracted with ether. Yield of colorless oil of $b.p_{0.002}$ 160~165° was 0.9 g. Gives orange yellow dice-shaped Pt-salt of m.p. 207~208°(decomp., after decolorizing at about 199°) from water, which was the only crystalline derivative so far obtained. *Anal.* Calcd. for $(C_{15}H_{25}ON_2)_2H_2PtCl_6$: C, 39.5; H, 5.7; N, 6.15; Pt, 21.4. Found: C, 39.6; H, 5.8; N, 6.0; Pt, 21.8.

3-(N'-Methyl-2'-piperidyl)-quinolizidine (IV)—A solution of the foregoing compound (X: 0.3 g.) in sulfuric acid (8 cc. of 50%) was reduced at a lead cathode (0.2 amp./cm²), 50% sulfuric acid being the anolyte. The resultant catholyte was basified, salted out, and extracted with ether. A colorless oil of $b.p_1$ 160°(oil-bath temp.) was obtained. *Anal.* Calcd. for $C_{15}H_{28}N_2$: C, 76.3; H, 11.8; N, 11.8. Found: C, 77.4; H, 11.9; N, 11.8. No crystalline derivative was obtained.

Ethyl α,γ-Di(2-pyridyl)-butyrate (XIV)—A mixture of 2-vinylpyridine (1.9 g.), ethyl 2-pyridylacetate (6 g.), and sodium (0.08 g. as small pieces) was heated gradually up to 130~135° during 5 hrs., when sodium disappeared, giving dark brown solution. On cooling the whole was mixed with ether and a few small pieces of ice, and the mixture was shaken thoroughly. Aqueous layer was basified and extracted with ether, and the ethereal solution was combined with the original ether layer. This was washed with saturated sodium chloride solution, dried, and evaporated. The dark red brown residue was distilled in vacuo, giving orange yellow oil of $b.p_3$ 165~168°; yield, 3.5 g. or 72% based upon vinylpyridine that entered into reaction. About 2 g. vinylpyridine was recovered. Gives yellow plate-shaped picrate of m.p. 124~127°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_2 \cdot 2C_6H_3O_7N_3$: C, 46.15; H, 3.3. Found: C, 46.0; H, 3.4.

When heated with 20% hydrochloric acid for 2.5 hrs., this compound suffered decarboxylation, giving 2-dipicolylmethane (XV), which gave dipicrate of m.p. 208~209°, as is mentioned in the literature[7].

2,4-Di(2-pyridyl)-butanol (XVI)—A solution of (XIV: 3.5 g.) in ether (20 cc.) was added to a solution of lithium aliminum hydride (0.3 g.) in ether (20 cc.) at a room temperature with stirring. An additional ethereal solution of lithium aluminum hydride solution (0.4 g. of $LiAlH_4$) was added and the whole was warmed at 35° for 1 hr., giving reddish solution. After decomposing with water, the resultant solution was acidified with 10% sulfuric acid. The aqueous layer separated was basified, salted out, and then extracted with chloroform, which was dried and evaporated. The residue came over at 181~183° (0.2 mm.) as faint yellow viscous oil; yield, 1.7 g. Gives dipicrate of m.p. 167~169°, which comes as orange yellow plates from glacial acetic acid. Dipicrate of phenylurethane: The phenylurethane was obtained as oily uncrystallizable substance, which, however, gave crystalline dipicrate. Yellow plates of m.p. 173° from glacial acetic acid. *Anal.* Calcd. for $C_{21}H_{21}O_2N_3 \cdot 2C_6H_3O_7N_3$: C, 49.2; H, 3.35; N, 10.4. Found: C, 48.3; H, 3.4; N, 11.0.

3-(2'-Pyridyl)-1,2,3,4-tetrahydroquinolizinium Chloride (XVII: X=Cl)—A solution of (XVI: 1.4 g.) in chloroform was treated with thionyl chloride (1 g.) with cooling. The mixture was then warmed at 60~65° for 2.5 hrs., rapidly separating red brown oily substance. The solvent and excess of thionyl chloride were evaporated in vacuo, the residue was dissolved in ice-cold water, and filtered through a wet filter.

The filtrate was basified, extracted with benzene, and dried over potassium carbonate. The dried benzene solution was now refluxed on a water bath, gradually separating oily substance, which turned crystalline after about 10 hrs.' heating. The heating was continued for 40 hrs. altogether and the supernatant benzene layer was decanted. The crystalline residue was washed three times with the same solvent, giving 0.7 g. of the chloride, which was deliquescent and was used directly for the next stage. Picrate: Yellow plates from glacial acetic acid, m.p. 182~185°. *Anal.* Calcd. for $C_{14}H_{15}N_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$: C, 46.7; H, 3.0; N, 16.6. Found: C, 47.0; H, 3.1; N, 16.2.

3-(2'-Pyridyl)-1,2,3,4-tetrahydroquinolizinium Iodide Methiodide (XVIII: X=I)—The foregoing chloride (0.2 g.) in water was mixed with potassium iodide and the quinolizinium iodide thus formed was extracted with chloroform, which was dried, and evaporated. The crystalline residue was purified from hydrous methanol, forming faint reddish brown dice of m.p. 158°; yield, 0.2 g. This (0.2 g.) was heated at 100° with methyl iodide (0.15 g.) in methanol for 2 hrs., giving crystalline methiodide (XVIII: X=I), which was purified from hydrous ethanol, forming yellowish pillar-shaped crystals of m.p. 229°, after sintering at about 180°. *Anal.* Calcd. for $C_{15}H_{18}N_2I_2 \cdot 1/2H_2O$: C, 37.1; H, 3.9. Found: C, 37.1; H, 3.5.

3-(N'-Methyl-2'-piperidyl)-quinolizidine (IV)—The aforesaid iodide (0.15 g) was converted into the corresponding chloride as usual and reduced catalytically over Adams' Pt in HCl-acid alcoholic

solution, 40 cc. of hydrogen being absorbed smoothly. The reduction product was obtained as an oily substance. Dipicrate: Yellow plates, m.p. 184~186°. *Anal.* Calcd. for $C_{15}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 46.7; H, 4.9; N, 16.1. Found: C, 46.5, H, 4.8; N, 16.6.

2-Phenacylpyridine Oxime (XXII)—From phenacylpyridine (XXI: 53 g.), hydroxylamine hydrochloride (20 g.), and sodium acetate (20 g.) in alcohol as usual. Colorless rhombs of m.p. 118° from ethanol. Yield, 50 g. or 88%.

2-Pyridylacetanilide (XXIII)—The foreoging oxime (3 g.) in absolute ether (100 cc.) was added with phosphorus pentachloride (3 g.) in small portions, with cooling and stirring, separating yellow crystalline solid, which became yellower and then turned into greenish pasty mass, when warmed at 25~30° on a water bath. The mixture was then decomposed by the addition of ice water and the aqueous layer was extracted with chloroform, after being neutralized with sodium carbonate. The crude product obtained was purified from ethanol, forming colorless rhombs of m.p. 131~134°; yield, 2.55 g. or 85%.

Ethyl 2-Pyridylacetate (V)—A solution of the above amide (9.1 g.) in absolute ethanol (150 cc.) was saturated with dry hydrogen chloride with cooling, separating white crystalline solid, which disappeared by further introduction of hydrogen chloride while being warmed at 70~75° on a water bath. After being kept at this temperature for 3 hrs., ethanol was distilled off, leaving white crystalline hydrochloride, which was dissolved in ice-cold water, neutralized, salted out, and the base was collected in ether. Ethyl 2-pyridylacetate was obtained as a faint yellow liquid of $b.p_{10}$ 120~122°; yield, 3.8 g. or 71%. Gives crystalline picrate of m.p. 137~138°.

Summary

3-(N'-Methyl-2'-piperidyl)-quinolizidine (IV), which can be regarded as one of the fission products of sparteine, was synthesized by two different methods. i) 1-Carbethoxy-4-keto-3-(2'-pyridyl)-quinolizine (VI) was hydrolyzed and decarboxylated to 3-(2'-pyridyl)-4-keto-quinolizine (VIII), the methochloride of which was reduced catalytically, giving 3-(N'-methyl-2—piperidyl)-4-ketoquinolizidine (X). The latter furnished the objective product (IV), of which no crystalline derivative was obtainable. ii) 2-Vinylpyridine was condensed with ethyl 2-pyridylacetate according to Michael, giving ethyl α,γ-di(2-piridyl)-butyrate (XIV). The lithium aluminum hydride reduction product of the latter gave the corresponding alcohol, the chloride of which furnished 3-(2'-pyridyl)-1,2,3,4-tetrahydroquinolizinium chloride (XVII) by intramolecular quaternization on being heated. The methochloride of the latter was reduced catalytically, yielding the ultimate compound (IV), of which the dipicrate was obtained as yellow plates of m.p. 184~186°, showing the product by the latter method to be stereochemically purer.

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