UDC 547.836.3.07 : 547.829

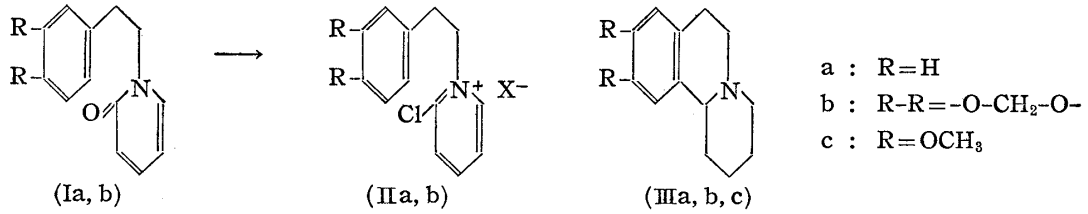
4. San-ya Akaboshi, Teruo Kutsuma, and Kazuo Achiwa : Synthesis in the Benzoquinolizine Group.*2 I. Synthesis of 1,2,3,4,6,7-Hexahydro-11b*H*-benzo[*a*]quinolizines.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

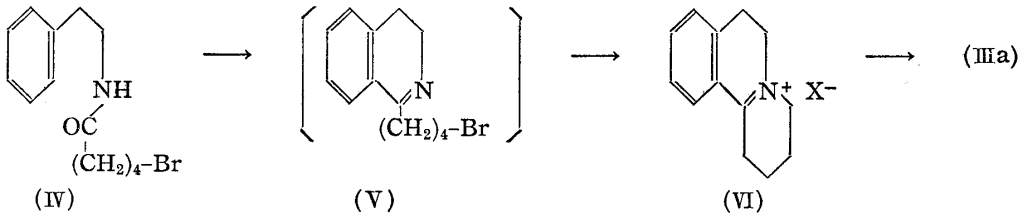
In earlier papers,[1~3] it had been erroneously reported that 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizines were obtained by catalytic hydrogenation of the products of the corresponding pyridones (Ia, Ib) with phosphoryl chloride. Reïnvestigation of the cyclization reaction of the pyridones (Ia, Ib) with phosphoryl chloride showed the formation of the corresponding 2-chloropyridinium salts (IIa and IIb) and not the cyclized product.[4,5]

Numerous attempts were made to effect cyclization of the pyridones (Ia and Ib) with various reagents including polyphosphoric acid, but no cyclized product could be isolated.

Thus, the synthesis of hexahydro-11b*H*-benzo[*a*]quinolizine (IIIa) was undertaken. Number of papers concerning the synthesis of (IIIc) have been published,[6~10] of which the method of Pyman was adopted for the present purpose.



The amide (IV) was prepared by the usual method from phenethylamine and 5-bromovaleryl chloride,[11] which remained oily and could not be induced to crystallize.



*1 Hongo, Tokyo (赤星三彌，久津間輝雄，阿知波一雄).

*2 This paper is an extension of the work published as a Communication to the Editor in this Bulletin, 7, 263(1959).

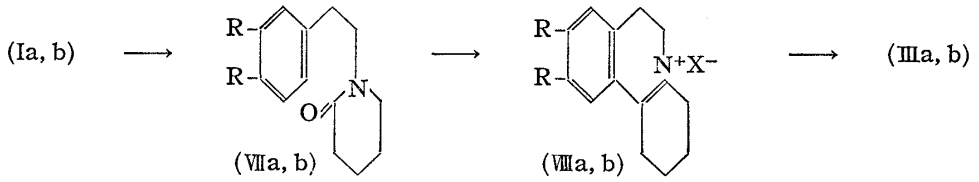
1) S. Sugasawa, S. Akaboshi, M. Suzuki : Yakugaku Zasshi, **72**, 1273(1952); S. Akaboshi : *Ibid.*, **72**, 1277(1952).
2) T. Govindachari, B. Thyagarajan : Proc. Indian Acad. Sci., **39** A, 232(1954) (C. A., **49**, 9653(1955)).
3) S. Sugasawa, N. Sugimoto : Ber., **72**, 979(1939).
4) S. Sugasawa, S. Akaboshi, Y. Ban : This Bulletin, **7**, 263(1959),
5) Y. Ban, O. Yonemitsu, T. Oishi, S. Yokoyama, M. Nakagawa : *Ibid.*, **7**, 609(1959).
6) R. Child, F. L. Pyman : J. Chem. Soc., **1931**, 36.
7) S. Sugasawa, K. Sakurai, N. Sugimoto : Yakugaku Zasshi, **59**, 247(1939).
8) S. Sugasawa, S. Akaboshi, M. Yamada : *Ibid.*, **71**, 1341(1951).
9) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 359(1958).
10) T. Fujii : *Ibid.*, **6**, 591(1958).
11) R. Merchant, J. N. Wickert, C. S. Marvel : J. Am. Chem. Soc., **49**, 1829(1927).

The amide (IV) was then cyclized by heating with a mixture of phosphoryl chloride and phosphorus pentoxide in boiling xylene according to the method of Whaley and Hartung[12] to yield the product (VI) directly in 51% yield. The intermediate (V) was not isolated, because it easily underwent the second cyclization to form (VI). The iodide (VI : X=I) was obtained as yellow needles of m.p. 176~177°.

Catalytic hydrogenation of (VI : X=Cl) over Adams' catalyst gave the dihydro base (IIIa) as an oily substance (b.$p_{1.5}$ 97~99°), whose hydrochloride came as colorless needles of m.p. 238~239°, and the picrate as yellow needles of m.p. 173°.

The methiodide of the base (IIIa) yielded phthalic acid on being oxidized with potassium permanganate. Thus the structure of (IIIa) was established.*3

The cyclization of piperidone (VIIa) to form (VIIIa) was next undertaken; phosphoryl chloride only gave an indefinite compound of m.p. 170°,*4 but a combination of phosphoryl chloride and polyphosphoric acid worked successfully, affording (VIIIa : X=I) in a yield of 41%.



The iodide and picrate of (VIIIa) were proved by admixture to be identical with (VI). Their IR and UV spectra were also identical in every respect.

Catalytic hydrogenation of (VIIIa : X=Cl) over Adams' catalyst was carried out smoothly, giving the corresponding dihydro base (IIIa). Hydrochloride of (IIIa) was obtained as colorless needles of m.p. 238°. These hydrochloride and picrate were also identical with the ones obtained from the reduction product of (VI).

As was expected, cyclization of the piperidone (VIIb) with phosphoryl chloride proceeded smoothly and the compound (VIIIb) was produced in a good yield (ca. 80%). Its iodide (VIIIb : X=I) formed yellow needles of m.p. 251°(decomp.) and the picrate formed yellow needles of m.p. 158~159°.

The chloride (VIIIb : X=Cl) was reduced catalytically by the same means to give the dihydro base (IIIb), which solidified when allowed to stand in a cold place. The free base (IIIb) formed colorless needles of m.p. 51~52°. The hydrochloride of (IIIb) was obtained as colorless prisms of m.p. 254°(decomp.).

Experimental*5

N-Phenethyl-5-bromovaleramide (IV)—To a stirred solution (7.7 g. of phenethylamine in 30 cc. of dehyd. benzene) chilled to 0° to 5° in an ice bath, a solution of 5-bromovaleryl chloride (4.0 g.) in dehyd. benzene (10.0 cc.) was added during 10 min. The benzene solution soon became turbid and phenethylamine hydrochloride separated as colorless needles. After the addition was completed, the mixture was stirred at room temp. for 1 hr. and worked up as usual. A faint yellow oily substance was obtained, which could not be crystallized. Yield, 5.7 g. or almost quantitative. The amide (IV) was used directly for the next cyclization step.

1-Phenethyl-2-piperidone (VIIa)—The solution of 1-phenethyl-2(1*H*)-pyridone[1] (Ia)(10.6 g. in 60 cc. of EtOH) was hydrogenated catalytically over Raney Ni catalyst (ca. 10 g.) at room temp. under ordi-

*3 This part concerns a correction of the erroneous description of the product of permanganate oxidation in a previous paper.[1]

*4 The structure of this compound is now being studied and details will be published in near future.

*5 All melting points are not corrected.

12) W. Whaley, W. Hartung : J. Org. Chem., 14, 650(1949).

nary pressure, and 2 mol. equiv. of H_2 was absorbed rapidly. This was worked up as usual, and gave almost colorless oil, which distilled at 139°/2 mm. Hg to give 10.6 g. of a colorless oil. On being kept standing, the oil turned to a solid (m.p. 42~44°), which was purified from ether-petr. ether to colorless prisms of m.p. 44~45°. *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.71; H, 8.29; N, 6.92.

1-(3,4-Methylenedioxyphenethyl)-2-piperidone (VIIb)-1-(3,4-Methylenedioxyphenethyl)-2(1*H*)-pyridone[3] (IIa) (3.65 g.) in EtOH (120 cc.) was reduced catalytically over Raney Ni catalyst (ca. 2.4 g.) by the same means, and afforded colorless prisms of m.p. 96~97° (from hexane) in a good yield (3.41 g. or 85%). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found : C, 68.0; H, 6.74; N, 5.79.

1,2,3,4,6,7-Hexahydrobenzo[*a*]quinolizinium Iodide (VI : X=I and VIIIa : X=I)—i) Cyclization of the amide (IV) : The crude amide (IV) (2.0 g.) in dehyd. xylene (40 cc.) was mixed with freshly distilled $POCl_3$ (5.0 g.) and P_2O_5 (5.0 g.), and the whole was refluxed in an oil bath for 7 hr., when dark brown solid separated. After cool, xylene layer was decanted, the brown solid was dissolved in cold water (ca. 70 cc.) slightly acidified with HCl, shaken with benzene (50 cc.), and the benzene layer was discarded. The acid solution thus obtained was neutralized with K_2CO_3, extracted with benzene (ca. 50 cc.), and the benzene layer was discarded. This alkaline solution was acidified with HCl, an excess of KI was added to the solution, and a yellowish brown solid that separated out was taken up in $CHCl_3$, The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated *in vacuo*, leaving a crystalline solid, which was washed with acetone, giving orange yellow crystals of m.p. 163~170° (1.3 g.). The iodide (V : X=I) was purified from EtOH, forming yellow needles of m.p. 176~177°; yield, 1.12 g. (51%). *Anal.* Calcd. for $C_{13}H_{16}NI$: C, 49.85; H, 5.15; N, 4.47. Found : C, 50.35; H, 5.24; N, 4.79. IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=N), 778 (*ortho*-disubstd. benzene). UV : λ_{max}^{EtOH} 275 mμ (log ε 4.09).

Picrate : Yellow needles, m.p. 138~139° (decomp.) (from hydr. EtOH). *Anal.* Calcd. for $C_{19}H_{18}O_7N$: C, 55.07; H, 4.38; N, 13.52. Found : C, 55.31; H, 4.48; N, 13.37.

ii) Cyclization of (VIIa) with polyphosphoric acid and $POCl_3$: The foregoing piperidone (VIIa) (10 g.) in polyphorphoric acid (20 g.) was mixed with $POCl_3$ (50 g.) and the mixture was heated in an oil bath at 140°. After the vigorous reaction subsided, the temp. was elevated to 210~220° for 24 hr. The pale brown syrup that formed was extracted with ice water (ca. 300 cc.). The pale yellow H_2O solution was neutralized with K_2CO_3 and washed with benzene. From the benzene layer the piperidone (ca. 5.0 g.) was recovered. To this almost neutral H_2O solution an exess of KI was added and the yellowish solid that separated was taken up in $CHCl_3$, dried, and evaporated. The residual yellowish brown viscous oil turned to an orange solid of m.p. 170~174° (yield, 6.27 g. or 41.0%).

The iodide (VIIIa : X=I) was purified from EtOH to yellow needles of m.p. 176~177°. *Anal.* Calcd. for $C_{13}H_{16}NI$: C, 49.85; H, 5.15; N, 4.47. Found : C, 49.67; H, 5.22; N, 4.23. IR ν_{max}^{Nujol} cm^{-1} : 1669 (C=N), 778 (*ortho*-disubst. benzene). UV λ_{max}^{EtOH} 275 mμ (log ε 4.10).

Picrate : Yellow needles (from hydr. EtOH), m.p. 139~140° (decomp.). *Anal.* Calcd. for $C_{19}H_{18}O_7N$: C, 55.07; H, 4.38; N, 13.52. Found : C, 55.26; H, 4.42; N, 13.25.

The iodide and picrate of (VIIIa) were found by admixture to be identical with (VI : X=I) and its picrate.

The IR and UV absorption spectra of the iodide (VIIIa : X=I) thus obtained were respectively well superimposable with those of the iodide (VI : X=I).

1,2,3,4,6,7-Hexahydro-11b*H*-benzo[*a*]quinolizine (IIIa)—i) Hydrogenation of (VI) : The foregoing iodide (VI : X=I) (0.6 g.) was converted as usual into the corresponding chloride which formed a pale yellow semi-solid (0.42 g. or nearly quantitative, based on the iodide (VI : X=I)). EtOH solution of the chloride (VI : X=Cl) (0.42 g. in 30 cc.) was smoothly hydrogenated catalytically over Adams' Pt catalyst (0.1 g.) at room temp. under ordinary pressure (1 mol. equiv. of H_2 being absorbed) giving hydrochloride (IIIa) of the dihydro base as colorless needles of m.p. 226~229°; yield, 0.4 g. or 93%. The hydrochloride was purified from EtOH-(iso-Pr)$_2$O (2:1), forming colorless small needles of m.p. 238~239°. *Anal.* Calcd. for $C_{13}H_{18}NCl$: C, 69.73; H, 8.11; N, 6.26. Found : C, 69.78; H, 7.88; N, 5.91. UV λ_{max}^{EtOH} mμ (log ε) : 262.5 (2.38), 270 (2.26).

Picrate : Yellow needles from EtOH-(iso-Pr)$_2$O (1:1), m.p. 173° (decomp.). *Anal.* Calcd. for $C_{19}H_{20}O_7N_4$: C, 54.80; H, 4.84; N, 13.46. Found : C, 55.03; H, 4.98; N, 13.31.

Free base : Colorless oil, b.$p_{1.5}$ 97~99°, which is unstable and colors on exposure to air.

Methiodide : Colorless prisms (from acetone), m.p. 133°. *Anal.* Calcd. for $C_{14}H_{20}NI$: C, 51.07; H, 6.12; N, 4.26. Found : C, 51.08; H, 6.04; N, 4.32.

ii) Hydrogenation of (VIIIa) : The foregoing iodide (VIIIa : X=I) was converted as usual into the corresponding chloride*6 and hydroganated catalytically over Adams' Pt catalyst by the same means. The product was worked up as described above, giving the hydrochloride (IIIa) of the dihydro base

*6 The chloride (Va : X=Cl) was obtained as faint yellow syrup, which formed pale yellow chloroplatinate of m.p. 213° (decomp.). *Anal.* Calcd. for $(C_{13}H_{16}N)_2PtCl_6 \cdot H_2O$: C, 39.40; H, 4.29; N, 3.50. Found : C, 39.15; H, 4.26; N, 3.43.

in a good yield (99.2%). It was purified from EtOH-(iso-Pr)$_2$O to form colorless small needles (IIIa-hydrochloride) of m.p. 238~239°. *Anal.* Calcd. for $C_{13}H_{18}NCl$: C, 69.73; H, 8.11. Found : C, 69.63; H, 8.45.

Picrate : Yellow needles (from EtOH-(iso-Pr)$_2$O) of m.p. 173° (decomp.).

These hydrochloride and picrate of (IIIa) from (VIIIa) were also found by admixture to be respectively identical with the ones (IIIa) obtained from (VI).

Oxidation of the Methiodide of (III) with $KMnO_4$—The methiodide of (IIIa) (380 mg.) was dissolved in 0.5% KOH solution (ca. 100 cc.), a solution of 5% $KMnO_4$ was added at room temp. with stirring (ca. 2.0 g. of $KMnO_4$ used), and the whole was heated on a water bath at 50~60° until the purple color practically disappeared. The reaction mixture was allowed to stand at room temp. overnight, the precipitated MnO_2 was filtered off, and washed well with hot water. The filtrate was concentrated under reduced pressure to ca. 20 cc. and acidified to Congo Red with 10% H_2SO_4, then extracted continuously with ether. Thus, colorless crystals of m.p. 190~195° (decomp.) were obtained. Yield, 120 mg.

This crude acid was treated with (Ac)$_2$O forming colorless needles of m.p. 128~129° (from benzene-hexane) which was identical with authentic specimen of phthalic anhydride by admixture.

9,10-Methylenedioxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium Iodide (VIIIb : X=I)—The piperidone (VIIb) (1.7 g.) in dehyd. benzene (10 cc.) was mixed with freshly distilled $POCl_3$ (7.0 g.) and the mixture was refluxed in an oil bath at 120~130° for 3 hr., the benzene and excess of $POCl_3$ were removed *in vacuo*, and the residue was dissolved in cold H_2O containing some HCl. This solution was shaken with benzene and the benzene layer was discarded. To the yellow aqueous solution thus obtained, an excess of KI was added, separating a yellow crystal of m.p. 218~221° (decomp.) in a yield of 1.90 g. or 88%. The iodide (Va : X=I) was purified from H_2O forming small pale yellow needles of m.p. 251° (decomp.). *Anal.* Calcd. for $C_{14}H_{16}O_2NI$: C, 47.06; H, 4.51; N, 3.92. Found : C, 47.42; H, 4.39; N, 3.87. UV λ_{max}^{EtOH} mμ (log ε) : 248 (4.32), 298 (3.46), 355 (4.05).

Picrate : Yellow needles (from EtOH), m.p. 155~156°. *Anal.* Calcd. for $C_{20}H_{18}O_9N_4$: C, 52.40; H, 3.96; N, 12.22. Found : C, 52.51; H, 3.90; N, 12.59.

9,10-Methylenedioxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (IIIb)—The foregoing iodide (VIIIb : X=I) (1.74 g.) was converted as usual into the corresponding chloride, which formed pale yellow crystalline solid (1.30 g.). This was dissolved in EtOH (ca. 50 cc.) and was catalytically reduced over Adams' Pt (0.15 g.), when a smooth and rapid uptake of H_2 (126 cc., 1 mol. equiv.) took place, and this was worked up as usual. The hydrochloride (1.30 g.) formed colorless prisms of m.p. 242~245° (decomp.) (almost quantitative). On being purified from EtOH, this formed colorless prisms of m.p. 254° (decomp.). *Anal.* Calcd. for $C_{14}H_{18}O_2NCl$: C, 62.81; H, 6.74; N, 5.23. Found : C, 62.80; H, 6.56; N, 5.18. UV λ_{max}^{EtOH} mμ (log ε) : 235 (3.52), 290 (3.67).

The free base was obtained from the hydrochloride of (IIIb) as colorless plates of m.p. 51~53° (from petr. ether). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found : C, 73.13; H, 7.44; N, 6.01.

Picrate : Bright yellow needles (form EtOH), m.p. 198~199° (decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_9N_4$: C, 52.17; H, 4.38; N, 11.85. Found : C, 52.63; H, 4.40; N, 12.17.

Methiodide : Colorless prisms (from MeOH), m.p. 232~233°. *Anal.* Calcd. for $C_{15}H_{20}O_2NI$: N, 3.75. Found : N, 3.84.

The authors are grateful to Professor S. Sugasawa for his interest and encouragement throughout this work. Thanks are also due to the members of the Central Analysis Room of this Faculty, and also to Mrs. F. Hisamichi and Mr. T. Yoda of Tokyo Research Laboratory of Tanabe Seiyaku Co., for microanalytical data.

Summary

Synthesis of 1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizines (IIIa and IIIb) was described. N-Phenethyl-5-bromovaleramide (IV) and 1-phenethyl-2-piperidone (VIIa) were cyclized with a mixture of phosphoryl chloride-phosphorus pentoxide and phosphoryl chloride-polyphosphoric acid, respectively, and were reduced catalytically. Thus, the hexahydro base (IIIa) was obtained.

9,10-Methylenedioxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (IIIb) was obtained in a good yield from the cyclized product of the corresponding piperidone (VIIb) by the same method.

(Received May 11, 1959)