10% aqueous sodium hydroxide, and then thoroughly extracted with ether. The combined ethereal solution was dried and evaporated, leaving faint yellow oil (0.5 g.) with a characteristic amine odor, which, when allowed to stand with methyl iodide, gave crystalline methiodide, forming faint yellow needles of m.p. 174~175° (decomp.). *Anal.* Calcd. for $C_{14}H_{16}NI$: C, 52.0; H, 4.9; N, 4.3. Found: C, 51.6; H, 5.0; N, 4.1.

The free base is fairly unstable and rapidly decolorizes on exposure to air. No crystalline methiodide was obtained from the decolorized product.

From 4',5'-methylenedioxy-9,10-dehydro- and 6-carbethoxy-9,10-dehydro-(2',1':1,2-benzoquinolinium) salts the corresponding unstable 9,10-dihydro derivatives seemed to be produced by the same method as oily substance, which, however, failed to give any crystalline derivative for identification.

Summary

An attempted selective hydrogenation of 9:10-double bond of 3,4-dihydro-9,10-dehydro-(2',1':1,2-benzoquinolinium) salts by means of $Na_2S_2O_4$ - Na_2CO_3 ended fruitless. In its stead ring cleavage took place, yielding *N*- β -phenethylpyridones with quantitative yield in smooth reaction. This cleavage reaction appeared to be a base-induced one, since sodium hydroxide or silver oxide worked as well, whereas smooth cleavage was effected by sodium carbonate only in the presence of sodium dithionite, and the labile quinolinium hydrogen sulfite formed first as an intermediate seems to be prerequisite in this case. The selective hydrogenation was achieved with $LiAlH_4$ in absolute ether. The compound thus produced (VIII) was found to be highly sensitive to oxidation, rapidly decolorizing on exposure to air.

(Received July 4, 1952)

363. San-ya Akahoshi: Synthesis in the Benzoquinolizine Group. XVIII. On the Relative Stability of Dibenzoquinolizinium Ring System.

(Pharmaceutical Institute, Medical Faculty, University of Tokyo*)

In the preceding paper** it was reported that 3,4-dihydro-9,10-dehydro-(2',1':1,2-benzoquinolinium) salt suffered smooth ring fission by basic reagents, furnishing *N*- β -phenethyl- α -pyridone in a good yield.

Thus, it appeared worth while to examine the behavior of similarly constructed dibenzoquinolizinium and isoquinolizinium salts toward the same reagents. Several of this type of compounds were, therefore, prepared from quinoline and isoquinoline, as shown in the following chart (compounds III and VI), and these were treated in the like manner as in the previous case, when the corresponding quinolones and isoquinolones were produced even more easily than in the case of pyridone.

On the other hand, the influences of some substituents on the stability of benzoquinolizinium ring were studied. As was expected, methylenedioxy group in 4',5'-positions stabilizes the ring system both in the mono- and dibenzoquinolizinium series, while carbethoxy group in 7-position of mono-benzoquinolizinium salt greatly diminishes the stability of the ring.

These results, together with the one described in the preceding paper**, are summarized in the Table.

Somewhat similarly constructed berberinium salt (VII) underwent smooth partial hydrogenation by means of $Na_2S_2O_4$ - Na_2CO_3 , giving a dihydro derivative (VIII), which was identified as its crystalline hydrochloride¹⁾ and the free base²⁾. The base is fairly

* Motofuji-cho, Bunkyo-ku, Tokyo. (赤星三彌). ** This Journal, **72**, 1273 (1952).

1) Gadamer: Arch. der Pharmazie **243**, 35 (1905); Perkin: J. chem. Soc. **113**, 722 (1918).

2) Karrer, et al.: Helv. Chim. Acta, **32**, 960 (1949); C. A. **43**, 6631 (1949).

unstable in the air, reduces silver nitrate solution, and yields the original berberinium salt (VII) on being treated with alcoholic iodine solution. Thus it seems probable that the double bonds of berberinium salt are located as shown in formula (VIII).

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-9,10-dehydro-(2',1':1,2-benzoquinolizinium) salt (IX) behaved quite differently from its corresponding 5,6,7,8-tetrahydro derivative (the second compound in the first column in the Table) toward $\text{Na}_2\text{S}_2\text{O}_4$ - Na_2CO_3 : Smooth reduction to (X) was effected which was identified with the authentic specimen.

The author is grateful to Prof. Sugawara for his advice and encouragement, and also to Mr. Himizu for his valuable assistance in the experimental work. The microanalyses were carried out by Mrs. Wu and Messrs. Sekijima, Takenaka, Kaneko, Huang, and Fukuda.

Experimental

General method for the oxidation of *N*-β-phenethylquinolizinium salts (I)—Preparation of *N*-β'-phenethyl-α-quinolone (II : R=H)—To an aqueous solution of (I : R=H) bromide (3.14 g. or 0.01 mole equivalent in 50–100 cc. of water) was added a small portion of cold conc. aq. solution of potassium ferricyanide (9.9 g. or 0.03 mol. equiv.) with cooling, separating oily quinolizinium ferricyanide. This was triturated until it was induced to crystallize (yellow solid of m. p. 108–110° (decomp.)). The remaining solution of potassium ferricyanide was now introduced with cooling and stirring, furnishing yellow solid ferricyanide³⁾. A large excess of solid potassium hydroxide (30–40 g.) was then added with cooling so that the reaction temperature did not exceed 40°. The yellow ferricyanide being converted into a white solid and the reaction ended in about half an hour. The quinolone thus obtained was extracted with benzene, washed first with water, then with 10% hydrochloric acid, dried, and evaporated, leaving a light-colored oily quinolone, which soon solidified on standing. Purified from benzene-petroleum ether, forming colorless plates of m. p. 86–87°. Yield, 1.6 g. or 64%⁴⁾.

3) For the best result of oxidation it seems necessary to obtain the intermediate quinolizinium ferricyanide in crystalline form.

4) This quinolone has already been described by Sugawara (This Journal, 57, 1028 (1938)), and Sugawara, et al. (Ibid. 72, 190 (1952)), where yields of 48% and 56%, respectively, are mentioned.

N-(β -3,4-Methylenedioxyphenethyl)-quinolone (II: R-R=O-CH₂-O)⁵⁾—Colorless scales from benzene-petroleum ether, m. p. 137~138°. Yield, 90%.

N- β -Phenethyl-isoquinolones were prepared in the like manner.

N- β -Phenethyl-isoquinolone (V: R=H)—Colorless dices of m. p. 97~98° from benzene-petroleum ether, yield, 82%. *Anal.* Calcd. for C₁₇H₁₅ON: C, 81.0; H, 6.0; N, 5.6. Found: C, 82.0; H, 5.75; N, 5.0.

N-(β -3,4-Methylenedioxyphenethyl)-isoquinolone (V: R-R=O-CH₂-O)⁷⁾—Colorless needles of m. p. 91~92° from benzene-petroleum ether. Yield, 62%. *Anal.* Calcd. for C₁₈H₁₅O₃N: C, 73.7; H, 5.1; N, 4.8. Found C, 73.6; H, 5.3; N, 4.75.

General procedure of ring closure: Preparation of 3,4-dihydro-9,10-dehydro(2',1':1,2; 2'',1'':5,6-dibenzoquinolizinium) iodide (III)—The above-mentioned quinolone (II: R=H) (1.2 g.) was boiled with phosphoryl chloride (6~7 cc.) in an oil bath at 120~130° for 1.5 hrs., during which time the evolution of hydrogen chloride was hardly observed. On cooling, petroleum ether was added, separating viscous syrup, which was dissolved in 5% hydrochloric acid. To this solution potassium iodide was added, precipitating orange yellow crude iodide (III: R=H, X=I). Yield, 1.5 g. or 80%. Forms yellow needles of m. p. 185~186° (decomp.) from methanol. *Anal.* Calcd. for C₁₇H₁₄NI: N, 3.9. Found N, 3.6. The picrate forms needles of m. p. 135~136° (decomp.).

4',5'-Methylenedioxy-3,4-dihydro-9,10-dehydro-(2',1':1,2; 2'',1'':5,6-dibenzoquinolizinium) iodide (III: R-R=O-CH₂-O, X=I)—Yellow needles of m. p. 253~254° (decomp.)⁸⁾ as is described in the literature.

3,4-Dihydro-9,10-dehydro-(2',1':1,2; 2'',1'':7,8-dibenzo-isoquinolizinium) iodide—Yellow needles of m. p. 116~117° (decomp.) from alcohol-ether. Yield, 74%. *Anal.* Calcd. for C₁₇H₁₄NI; C, 49.3; H, 4.8; N, 3.4. Found: C, 48.8; H, 4.2; N, 3.8. The picrate is bright yellow needles of m. p. 142~143°. *Anal.* Calcd. for C₂₃H₁₆O₇N₄: N, 12.2. Found: N, 11.85.

4',5'-Methylenedioxy-3,4-dihydro-9,10-dehydro-(2',1':1,2; 2'',1'':7,8-dibenzoisoquinolizinium) iodide (VI: R=O-CH₂-O, X=I)—Yellow hair-like crystals from alcohol, m. p. 178~179° (decomp.). Yield, 66%. *Anal.* Calcd. for C₁₈H₁₄O₃NI: C, 53.6; H, 3.5; N, 3.5. Found: C, 53.25; H, 3.6; N, 3.4.

The ring fission of these quaternary salts was carried out as was described in the preceding paper.

N-(β -3,4-Methylenedioxyphenethyl)- α -pyridone—From *N*-(β -3,4-methylenedioxyphenethyl)-pyridinium bromide, m. p. 244~245° (decomp.), potassium ferricyanide, and potassium hydroxide, according to the method described above. The pyridinium ferricyanide forms colorless sandy solid of m. p. 186~187° (decomp.). Yield of the α -pyridone, 91%. Colorless flakes from benzene-petroleum ether, m. p. 147~148°. Does not dissolve in 10% HCl and gives no picrate. *Anal.* Calcd. for C₁₄H₁₃O₃N: C, 69.1; H, 5.25; N, 5.8. Found: C, 68.65; H, 5.2; N, 5.85.

Reduction of berberine chloride with Na₂S₂O₄-Na₂CO₃: Formation of dihydro-anhydro-berberine (VIII)—Berberine chloride of m. p. 205~206° (decomp.)⁹⁾ (0.5 g.) in water (150 cc.) was mixed with sodium carbonate solution (3 g. of soda and 15 cc. of water), giving orange red solution. Powdered sodium dithionite (2.5 g.) was now added in small portions to this solution. The solution soon became turbid, while the evolution of carbon dioxide was observed. After standing the whole for 24 hrs. at room temp., the yellowish precipitate was collected and washed, giving nearly colorless, amorphous substance, which is unstable in the air and rapidly changes to red. It reduces silver nitrate solution in the cold. Purified from acetone, forming faint yellow plates of m. p. 162~165° (decomp.) as has been described by Karrer²⁾. Gives sparingly soluble hydrochloride, which separates in bright yellow needles of m. p. 165~166° (decomp.) from dil. hydrochloric acid¹⁾.

When the hydrochloride (0.2 g.) in alcohol (15~20 cc.) was treated with alcoholic iodine solution (0.3 g. iodine in 10 cc. ethanol) in the presence of sodium acetate and kept standing for 24 hrs., yellowish brown solid separated. This was collected and triturated with aq. sulfurous acid, furnishing bright yellow crystalline solid, which was purified from aq. methanol, forming bright yellow crystals of m. p. 260~261° (decomp.), identical with the authentic specimen.

5) cf. Sugawara, Sugimoto: *Ber.*, **72**, 979 (1929).

6) The starting material, *N*- β -phenethyl-isoquinolinium bromide (IV: X=Br), forms colorless pillars of m. p. 70° from methanol-ether. Analysed as the corresponding iodide, yellow needles of m. p. 181° (decomp.) from alcohol. *Anal.* Calcd. for C₁₇H₁₆NI: C, 56.4; H, 4.4; N, 3.8. Found C, 55.8; H, 4.0; N, 3.9.

7) The starting isoquinolinium bromide is white needles of m. p. 228~229° (decomp.). *Anal.* Calcd. for C₁₈H₁₆O₂NBr: N, 3.9. Found: N, 3.85.

8) Sugawara, Sugimoto: *Ber.*, **72**, 979 (1939).

9) Merck's preparation of m. p. 202~204° (decomp.) was once purified from aq. methanol. The corresponding iodide forms yellow needles of m. p. 260~261° (decomp.) from methanol. Its picrate is yellow scales of m. p. 225~227° (decomp.).

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-9,10-dehydro-(2',1':1,2-benzoquinolizinium) salt and its reduction with $\text{Na}_2\text{S}_2\text{O}_4$ - Na_2CO_3 - N -(β '-3,4-Methylenedioxyphenethyl)- α -piperidone (1 g.), prepared by catalytic reduction of the corresponding α -pyridone, was refluxed with phosphoryl chloride (6 cc.) for 1.5 hrs., and the product was worked up as usual. The iodide (IX : X=I) separates in yellow needles of m.p. 251~252° (decomp.) from methanol. *Anal.* Cald. for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{NI}$: N, 3.9. Found: N, 3.85.

This iodide (0.3 g.) was dissolved in soda solution (50 cc. of 10%) and added with pulverized sodium dithionite in portions, shaken thoroughly and kept standing for 24 hrs. The resultant solution was extracted with benzene, washed, dried, and evaporated, leaving light yellow oily substance, and was identified as its Pt salt, which forms orange yellow needles of m.p. 223~224° (decomp.), and was proved to be identical with an authentic specimen of the Pt salt of (X), which was prepared from (IX : X=I) by catalytic reduction over the Adams catalyst.

Summary

Those dibenzoquinolizinium salts, prepared from β -phenethyl bromides and quinoline or isoquinoline via three stage-reactions, were cleaved rather more easily than the corresponding monoquinolizinium salts by means of $\text{Na}_2\text{S}_2\text{O}_4$ - Na_2CO_3 or sodium hydroxide. Somewhat similarly constructed berberine chloride, however, was reduced selectively by the former reagent, affording dihydro-anhydroberberine. 9:10-Double bond of 4',5'-methylenedioxy-3,4,5,6,7,8-hexahydro-9,10-dehydro-(2',1':1,2-benzoquinolizinium) salt (IX) was also reduced smoothly by this means. The influences of some substituents on the relative stability of benzoquinolizinium ring system were also discussed.

(Received July 4, 1952)