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226. Sanya Akaboshi,^{*1} Toshio Kato,^{*2} and Akisuke Saiga^{*3} : Synthesis of the Heterocyclic Compounds by Pschorr Cyclization. II. Syntheses of Substituted-6,7-dihydrobenzo[*a*]quinolizinium Salts.^{*4}

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In the preceding paper,^{*5} the novel synthesis of the simple 6,7-dihydrobenzo[*a*]-quinolizinium salts (VI : R₁, R₂=H, X=I, and picrate) by Pschorr reaction of 1-(2-amino-phenethyl)pyridinium salt (V : R₁, R₂=H, X=Cl) was reported, where the internuclear cyclization onto α -position of a pyridinium ring occurred.

As regarding to the fact that many of a naturally occurring polycyclic heterocycles containing a nitrogen atom at a bridge head have the methylenedioxy or dimethoxy group as a substituent, the present paper deals with the application of Pschorr type reaction toward 1-(2-amino-4,5-methylenedioxyphenethyl) (Va'), 1-(2-amino-4,5-dimethoxyphenethyl) (Vb)-pyridinium and 1-(2-amino-4,5-dimethoxyphenethyl)picolinium (Vc) salts in order to elucidate some scope and limitation of this reaction.

At first, for the synthesis of one of the starting compounds (Va'), two synthetic methods were investigated; route 1) *via* 2-amino-4,5-methylenedioxyphenethyl alcohol and route 2) 1-(2-nitro-4,5-methylenedioxyphenethyl)pyridinium bromide. But due to the difficulty in halogenation in the former and in selective reduction of the nitro-group in the latter, respectively, the alternative route shown in Chart 1 (I→V) was adopted as the general synthetic method of the starting materials.

On treatment of phenethyl halides (I) with fuming nitric acid in acetic acid,¹⁾ specific substitution in the *para* position to methoxyl and methylenedioxy group occurred smoothly to give 2-nitrophenethyl halides (II) as crystalline form in good yields. Catalytic hydrogenation of II in acetic acid-acetic anhydride mixture over Adams' catalyst resulted in the simultaneous acetylation of the amino group generated by the reduction of nitro group to give acetamides (III), which were then converted into the corresponding quaternary salts (IV) by heating with pyridine or picoline in the boiling xylene. Hydrolysis of the quaternary compounds with 10% hydrochloric acid afforded the hydrochlorides of aminophenethylpyridinium and picolinium salts (IV) which served as the starting materials for the following Pschorr reaction.

Diazotization of 1-(2-amino-4,5-methylenedioxyphenethyl)pyridinium bromide hydrochloride (Va') was carried out by adding quantitative sodium nitrite solution into cold hydrochloric acid solution of Va'. By the gradual heating of the reaction mixture, the decomposition of diazonium compound which was shown by the evolution of nitrogen took place smoothly, followed by the treatment as described in the experimental part to give 9,10-methylenedioxy-6,7-dihydrobenzo[*a*]quinolizinium iodide (VIa'') in good yield (83.6%). In an attempt directly to use the reaction mixture of the hydrolysis of IVa' in the subsequent reaction without isolating Va', the final cyclized product was obtained in the form of bromide (VIa') in a yield of 62.2% (calculated from IVa'). Similarly,

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Moreover, ultraviolet spectra of these compounds had their maxima situated between 357 m μ and 367 m μ and showed very high-intensity absorption (log ϵ 3.96~4.11), which were considered to be due to the conjugation between benzene ring and pyridinium ring.

Further, to establish the structure of these products unequivocally, iodides, VIa'' and VIb'', were converted to the corresponding chlorides in the usual manner and subjected to hydrogenation over Adams' catalyst in 95% EtOH. The hydrochlorides, VIIa and VIIb, thus obtained were together with their picrate and perchlorate, found to be identical with authentic samples*⁴ which had been prepared from phenethylpiperidones, VIIIa and VIIIb, through the mixed melting point test and infrared spectra.

It is well known that 2- and 4-aminopyridine form unstable diazonium salts and by immediate decomposition give rise to the corresponding hydroxypyridines. Recently, however, Herz and Marty⁵⁾ reported that 4-amino-3-phenethylpyridine 1-oxide had been successfully cyclized by the Pschorr reaction. Preceding to carry out above-mentioned Pschorr reaction onto a pyridinium ring, an attempt was made to bring about a ring closure involving attack onto a benzene ring, where the starting materials were expected to be more easily available. Thus 1-(3,4-methylenedioxyphenethyl)-2-aminopyridinium bromide (Xa') was prepared by heating 3,4-methylenedioxyphenethyl bromide (Ia') with 2-aminopyridine in alcohol,*⁶ and subjected to Pschorr-type reaction. But no characterizable product was obtained and the starting material was recovered as a picrate. This was considered to be due to the high resistance of Xa' to attack by nitrous acid because of tautomeric equilibrium illustrated in Chart 2 which is far shifted to the right to form pyridone-imine type (XIa').⁷⁾



Chart 2.

Experimental

2-Nitro-4,5-methylenedioxyphenethyl Bromide (IIa')—To a solution of 1.8 g. of 3,4-methylenedioxyphenethyl bromide (Ia') dissolved in 10 ml. of AcOH, a mixture of 1.8 ml. of fuming HNO₃ ($d=1.42$) and 2 ml. AcOH was added dropwise, and the reaction mixture was allowed to stand at room temperature for 1 hr., poured into ice water. Precipitated crystalline was filtered off, recrystallized from (iso-Pr)₂O-petr. ether, yield was 1.55 g. (72%). Pale yellow needles, m.p. 45~48°. *Anal.* Calcd. for C₉H₈NO₄Br: C, 38.44; H, 2.94; N, 5.11. Found: C, 39.65; H, 3.22; N, 5.13. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1525, 1330, 874.

2-Nitro-4,5-dimethoxyphenethyl Chloride (IIb)—This was obtained in 86.5% yield from 4,5-dimethoxyphenethyl chloride (Ib) by the method described above. Pale yellow needles, m.p. 111~112°. *Anal.* Calcd. for C₁₀H₁₂O₄NCI: C, 48.90; H, 4.92; N, 5.69; Cl, 14.46. Found: C, 49.30; H, 4.60; N, 5.60; Cl, 14.67. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1530, 1330, 880.

2-Acetamido-4,5-methylenedioxyphenethyl Bromide (IIIa')—1.2 g. of IIa' was dissolved in a mixture of 15 ml. of Ac₂O and 5 ml. of AcOH, and subjected to hydrogenation over 50 mg. PtO₂ at room temperature in an atmospheric pressure of hydrogen. 425 ml. of H₂ was absorbed. After filtration of catalyst and evaporation of solvent *in vacuo*, the residue was recrystallized from EtOH to give white

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needles, m.p. 171~172°. Yield: 0.57 g. (42.4%). *Anal.* Calcd. for $C_{11}H_{12}NO_3Br$: C, 46.17, H, 4.23, N, 4.86. Found: C, 46.03; H, 3.96; N, 4.73. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3280, 1660, 1640, 934, 861.

2-Acetamido-4,5-dimethoxyphenethyl Chloride (IIIb)—3.3 g. of IIIb was obtained from 3.5 g. of IIb by the procedure described above as white needles, m.p. 156~157° (from EtOH). Yield, 89.5%. *Anal.* Calcd. for $C_{12}H_{16}NO_3Cl$: C, 55.92; H, 6.21, N, 5.43. Found: C, 56.13; H, 6.26; N, 5.71. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3336, 1668, 1540, 865.

1-(2-Acetamido-4,5-methylenedioxyphenethyl)pyridinium Bromide (IVa')—The mixture of 2.18 g. of IIIa', 0.9 g. of pyridine and 50 ml. of dry toluene was refluxed for 15 hr. Precipitate which was separated gradually was filtrated while hot, washed with benzene and then Et_2O , recrystallized from EtOH to give white needles. Yield, 2.4 g. (86.5%), m.p. 274~275° (decomp.). *Anal.* Calcd. for $C_{16}H_{17}N_2O_3Br$: C, 52.61; H, 4.69; N, 7.67. Found: C, 52.41; H, 4.66; N, 7.53. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3270, 1677, 1630, 1534.

1-(2-Acetamido-4,5-dimethoxyphenethyl)pyridinium Chloride (IVb)—1.4 g. of IVb was obtained from 1.28 g. of IIIb by the method described above. White needles. m.p. 262° (decomp.). Yield, 83.3%. *Anal.* Calcd. for $C_{17}H_{21}O_3Cl$: C, 60.62; H, 6.24; N, 8.32. Found: C, 60.76; H, 6.09; N, 8.11. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3240, 1675, 1640, 1538.

Picrate: Yellow needles (from EtOH), m.p. 181°~182°. *Anal.* Calcd. for $C_{17}H_{21}N_2O_3 \cdot C_6H_2N_3O_7$: C, 52.16; H, 3.5; N, 13.25. Found: C, 52.05, H, 4.08; N, 13.31.

1-(2-Acetamido-4,5-dimethoxyphenethyl)picolinium Chloride (IVc)—1.45 g. (83%) of IVc was obtained from 1.28 g. of IIIb and 5.3 ml. of picoline by the treatment as in the case of IVa'. Colorless needles, m.p. 250~251° (decomp.). *Anal.* Calcd. for $C_{18}H_{23}N_2O_3Cl$: C, 58.67, H, 6.78; N, 7.59. Found: C, 58.71; H, 6.87; N, 7.64. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3240, 1680, 1650, 1540.

1-(2-Amino-4,5-methylenedioxyphenethyl)pyridinium Bromide Hydrochloride (Va')—1.125 g. of Va' was heated on a boiling water bath with 10% HCl for 3 hr. After cooling, the precipitated crystals were collected by filtration. The filtrate was concentrated under reduced pressure to a one-third its original volume and while hot an equal volume of EtOH was added. After standing overnight in a refrigerator, another crop of crystals were obtained. Overall yield was 0.99 g. (89.5%). Colorless granules, m.p. 257° (decomp.). *Anal.* Calcd. for $C_{14}H_{16}N_2O_2ClBr$: C, 46.75; H, 4.48; N, 7.79. Found: C, 46.94; H, 4.49; N, 7.10. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2800~2000, 1632.

1-(2-Amino-4,5-dimethoxyphenethyl)pyridinium Chloride Hydrochloride (Vb)—0.85 g. of Vb was obtained from 1.03 g. of IVb by the method described above. Yield, 85%. m.p. 253~253.5° (decomp.) (from MeOH-Et₂O mixture). *Anal.* Calcd. for $C_{15}H_{20}N_2O_2Cl$: C, 54.55; H, 5.76; N, 8.68.

Picrate: Yellow needles, m.p. 194~195.5° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}N_2O_2 \cdot 2C_6H_2N_3O_7$: C, 45.25; H, 3.35. Found: C, 45.42; H, 3.19.

1-(2-Amino-4,5-dimethoxyphenethyl)picolinium Chloride Hydrochloride (Vc)—Working up analogous to the case of Va', 1.05 g. of IVc gave 0.9 g. of Vc (86.5%). *Anal.* Calcd. for $C_{16}H_{22}N_2O_2Cl_2$: C, 55.65; H, 6.38; N, 8.12. Found: C, 56.12; H, 6.19; N, 7.96.

Picrate: m.p. 198~199° (from aq. AcOH). *Anal.* Calcd. for $C_{16}H_{22}N_2O_2 \cdot 2C_6H_2N_3O_7$: C, 46.03; H, 3.56; N, 15.34. Found: C, 45.60; H, 3.81; N, 15.21.

Pschorr Reaction

9,10-Methylenedioxy-6,7-dihydrobenzo[a]quinolizinium Salts (VIa~VIa'')—i) VIa'' from Va': 0.89 g. of Va' was suspended in 4.5 ml. of 20% HCl and to this solution 0.21 g. of NaNO_2 dissolved in 3 ml. of H_2O was added dropwise with stirring at 0° to 5°. After keeping at the same temperature for 10 min., the reaction mixture was warmed to room temperature and then to 70~80° gradually to complete the decomposition of diazonium compound until the evolution of N_2 had ceased. After cooling, the mixture was neutralized with 10% Na_2CO_3 . KI crystals were added and the pale yellow crystals separated immediately were collected by filtration, washed with EtOH and crystallized from EtOH to pale brown needles of VIa''. Yield, 0.72 g. (83.6%). *Anal.* Calcd. for $C_{14}H_{12}O_2NI$: C, 47.61; H, 4.00; N, 3.97; O, 9.06. Found: C, 47.32; H, 3.76; N, 3.45; O, 9.16. UV $\lambda_{\text{max}}^{\text{5\% EtOH}}$ $\text{m}\mu$ (log ϵ): 268~269 (4.13), 365~368 (4.04).

ii) VIa'' from IVa': 0.3 g. of IVa' was dissolved in 1 ml. of 10% HCl and subjected to hydrolysis by heating on a boiling water bath for 2 hr. After adding 0.5 ml. of conc. HCl, the mixture was submitted to diazotization with 70 mg. of NaNO_2 dissolved in 1 ml. of H_2O and subsequent decomposition in a manner as described above. The resultant mixture was evaporated to dryness under reduced pressure. The residue was extracted with hot EtOH to remove inorganic salts. On cooling of the extract, the pale yellowish green crystals of VIa' was separated out. Yield, 0.153 g. (60.3%). *Anal.* Calcd. for $C_{14}H_{12}O_2NBr \cdot \text{H}_2\text{O}$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.76; H, 4.23; N, 4.67.

Picrate: Yellow plates from Me_2CO , m.p. 227.5~228.5°. *Anal.* Calcd. for $C_{14}H_{20}O_2N \cdot C_6H_2N_3O_7$: C, 52.87; H, 3.11; N, 12.33. Found: C, 52.86; H, 3.52; N, 12.49.

iii) VIa from IVa: The saturated solution of KI was added to an aqueous solution of 0.43 g. of IVa'. The precipitated crystalline iodide (IVa'') which decomposed at 267~268° was collected by filtration. This (0.47 g.) was dissolved in 10 ml. of 50% EtOH and AgCl freshly prepared from 1.6 g. of AgNO_3 was

added. After being refluxed for 2.5 hr., inorganic salts were filtered off. Precipitate was washed repeatedly with 50% EtOH. The filtrate and washing solution were combined and evaporated to dryness under reduced pressure. The residual crude material was crystallized from EtOH to colorless needles of IVa, m.p. 270° (decomp.). Yield, 0.33 g. *Anal.* Calcd. for $C_{16}H_{17}O_3 \cdot N_2Cl$: C, 59.59; H, 5.35. Found: C, 58.94; H, 5.62.

0.40 g. of the foregoing chloride (IVa) was subjected to hydrolysis, diazotization and decomposition according to the same procedure as described in ii). The resultant reaction mixture was neutralized with 10% Na_2CO_3 and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH. After treatment with activated carbon, EtOH was evaporated to dryness. The residue was crystallized from EtOH-AcOEt mixture to colorless needles of VIa, m.p. 278~279° (decomp.). Yield, 0.18 g. (55.0%). *Anal.* Calcd. for $C_{14}H_{12}O_2NCl \cdot H_2O$: C, 60.11; H, 5.04; N, 5.01. Found: C, 59.26; H, 4.86; N, 5.34.

9,10-Dimethoxy-6,7-dihydrobenzo[a]quinolizinium Iodide (VIb'')—0.66 g. of Vb was diazotized in a usual manner and urea was added to decompose an excess nitrous acid. To this cold diazonium solution, Gattermann's copper prepared freshly was added in small portions at 0~3° until the evolution of N_2 gas had ceased. After removal of the catalyst by filtration the mixture was evaporated to dryness under reduced pressure, and the residue was extracted with hot EtOH. The EtOH extract was again evaporated to dryness *in vacuo* and the residue was dissolved in H_2O , treated with activated charcoal. After adding with KI crystals, the mixture was extracted with $CHCl_3$ repeatedly. Being washed with saturated $NaHSO_3$ solution, and dried over Na_2SO_4 , $CHCl_3$ was evaporated to dryness *in vacuo* and the resultant crude product was recrystallized from H_2O to pale yellow crystals of VIb'', m.p. 241~242.5°. Yield, 0.37 g. (50%). *Anal.* Calcd. for $C_{13}H_{16}O_2NI$: C, 48.78; H, 4.34; N, 3.79. Found: C, 48.86; H, 3.95; N, 4.08. UV $\lambda_{max}^{95\% EtOH}$ $m\mu$ (log ϵ): 285 (4.12), 364 (4.11).

Picrate: Yellow needles (from aq. EtOH), m.p. 202~204°. *Anal.* Calcd. for $C_{13}H_{16}O_2N \cdot C_6H_2N_3O_7$: N, 11.92. Found: N, 11.72.

2-Methyl-9,10-dimethoxy-6,7-dihydrobenzo[a]quinolizinium Iodide (VIc'')—0.85 g. of VIc'' was obtained from 1.3 g. of Vc in the same procedure as described in the case VIb''. Yield, 59.0%. m.p. 245~246°. *Anal.* Calcd. for $C_{14}H_{18}O_2NI$: C, 50.13; H, 4.70; N, 3.66. Found: C, 49.83; H, 4.86; N, 3.72. UV $\lambda_{max}^{95\% EtOH}$ $m\mu$ (log ϵ): 283 (4.02), 357 (3.96).

Picrate: Yellow needles (from EtOH), m.p. 174~175°. *Anal.* Calcd. for $C_{15}H_{20}NO_2 \cdot C_6H_2O_7N_3$: C, 54.54; H, 4.13; N, 11.57. Found: C, 54.36; H, 4.47; N, 11.33.

9,10-Methylenedioxy-1,2,3,4,6,7-11bH-hexahydrobenzo[a]quinolizine Hydrochloride (VIIa)—To a solution of 0.12 g. of VIa dissolved in 5 ml. of 95% EtOH, 20 mg. of PtO_2 was added and the mixture was shaken in H_2 atmosphere at room temperature. After 38.8 ml. of H_2 had been absorbed, the catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH-isoPrOH to colorless needles. Yield, 80 mg. (70%), m.p. 254~256°. *Anal.* Calcd. for $C_{14}H_{18}O_2NCl$: C, 62.80; H, 6.78; N, 5.23. Found: C, 63.42; H, 7.03; N, 5.04.

Picrate: Yellow needles (from EtOH), m.p. 198~199° (decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_9N_4$: C, 52.17; H, 4.38; N, 12.17. Found: C, 52.58; H, 4.21; N, 12.25.

Perchlorate: Colorless needles, m.p. 231~233° (from EtOH). *Anal.* Calcd. for $C_{14}H_{18}O_6NCl$: C, 50.68; H, 5.47; N, 4.22. Found: C, 50.40; H, 5.80; N, 4.46.

These hydrochloride, picrate and perchlorate showed no depression of melting point when mixed respectively with the authentic samples which were prepared from piperidone (VIIa), and their IR and UV spectra were also identical with these of authentic samples.

9,10-Dimethoxy-1,2,3,4,6,7-11bH-hexahydrobenzo[a]quinolizine Hydrochloride (VIIb)—The foregoing iodide (VIb'') was converted into the corresponding chloride by the customary method and reduced catalytically as described above. The picrate of the product thus obtained was found to be identical with an authentic sample by admixture and IR spectrum of hydrochloride (VIIb) was well superimposable with that of an authentic sample.

2-Amino-1-(3,4-methylenedioxyphenethyl)pyridinium Bromide (Xa')—The mixture of 3.25 g. of Ia', 2.0 g. of 2-aminopyridine and 30 ml. of EtOH was refluxed for 6 hr. on a water bath. The mixture was evaporated to dryness *in vacuo*, the residue was washed with benzene and purified by recrystallization from EtOH to colorless needles, m.p. 212~213.5°. Yield, 2.7 g. (59%). *Anal.* Calcd. for $C_{14}H_{15}O_2N_2Br$: C, 52.02; H, 4.68; N, 8.67. Found: C, 51.85; H, 4.84; N, 8.56.

Picrate: Yellow needles, m.p. 175~177°. *Anal.* Calcd. for $C_{14}H_{15}O_2N_2 \cdot C_6H_2N_3O_7$: C, 50.96; H, 3.64; N, 14.86. Found: C, 51.61; H, 3.76; N, 14.87.

Trial of Pschorr Reaction of 2-Amino-1-(3,4-methylenedioxyphenethyl)pyridinium Bromide (Xa')—0.14 g. of Xa' was dissolved in a hot mixture of 0.8 ml. of 20% HCl and a small amount of MeOH. The solution was then cooled to 0° and 40 mg. of $NaNO_2$ dissolved in 0.5 ml. of H_2O was added dropwise. After stirring for 30 min., the mixture was warmed to room temperature and allowed to stand 2 hr. The crystals separated were collected (0.10 g.), and purified as a picrate by crystallization from EtOH, m.p. 175~177°, which was found to be identical with a picrate of Xa' by admixture.

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Summary

The Pschorr reaction of 1-(2-amino-4,5-methylenedioxyphenethyl)pyridinium (Va'), 1-(2-amino-4,5-dimethoxyphenethyl)pyridinium (Vb) and 1-(2-amino-4,5-dimethoxyphenethyl)picolinium (Vc) salts was carried out and the corresponding cyclized product was obtained respectively.

2-Amino-1-(3,4-methylenedioxyphenethyl)pyridinium salt was prepared and its Pschorr reaction was investigated.

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