Notes

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Studies on the Syntheses of Heterocyclic Compounds. DXXV.[1] Syntheses of Berberine and Related Compounds. III.[2] Dealkylation of N-Substituted Protoberberinium Salts

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Nandinine (I) was synthesized by Mannich reaction reported in a previous paper[2] and was converted into berberine (II) by methylation with diazomethane, followed by dehydrogenation.[4] The methylation of I with diazomethane was not so suitable from the industrial point of view, and therefore we investigated the methylation of I with dimethyl sulfate available easily in industry. In this methylation, N-methylation could occur in addition to the expected O-methylation, and so it was necessary to investigate the N-demethylation in order to get berberine. Thus, we examined the dealkylation of N-methyl and N-benylcanadines (V and VI) obtained by treatment of canadine (III) with dimethyl sulfate or benzyl chloride as the preliminary experiments, and here reported these results.

One of the present authors[5,6] reported the dealkylation of the quaternary bases with thiophenol in basic medium and Shamma[7] also achieved the N-demethylation of N-methylcanadinium chloride with sodium thiophenolate. Therefore, we investigated the demethylation and debenzylation of V and VI, respectively, by application of this method.

Canadine (III), obtained by sodium borohydride reduction[8] of berberinium chloride (VII), was treated with dimethyl sulfate in chloroform to give N-methylcanadinium methosulfate (V), which was treated with thiophenolate under refluxing in methyl ethyl ketone for 20 hr in a current of nitrogen to give the demethylated product, canadine (III), in 47% yield.
Moreover, N-benzylcanadinium chloride (VI), which was prepared by benzylation of III with benzyl chloride, gave canadine (III), in 75% yield, in treatment with thiophenolate under refluxing in methyl ethyl ketone. The same reaction of V and VI with phenolate was also examined, but our expected products were given in poor yield perhaps due to the weak nucleophile of phenolate anion.

On the ground of the above results, the conversion of I into IV was investigated from the industrial point of view. The methylation of I with dimethyl sulfate in the presence of potassium carbonate in acetone gave N-methylcanadinium methosulfate (V) which had already been converted into canadine (III). In this case, O-methylation of I with dimethyl sulfate

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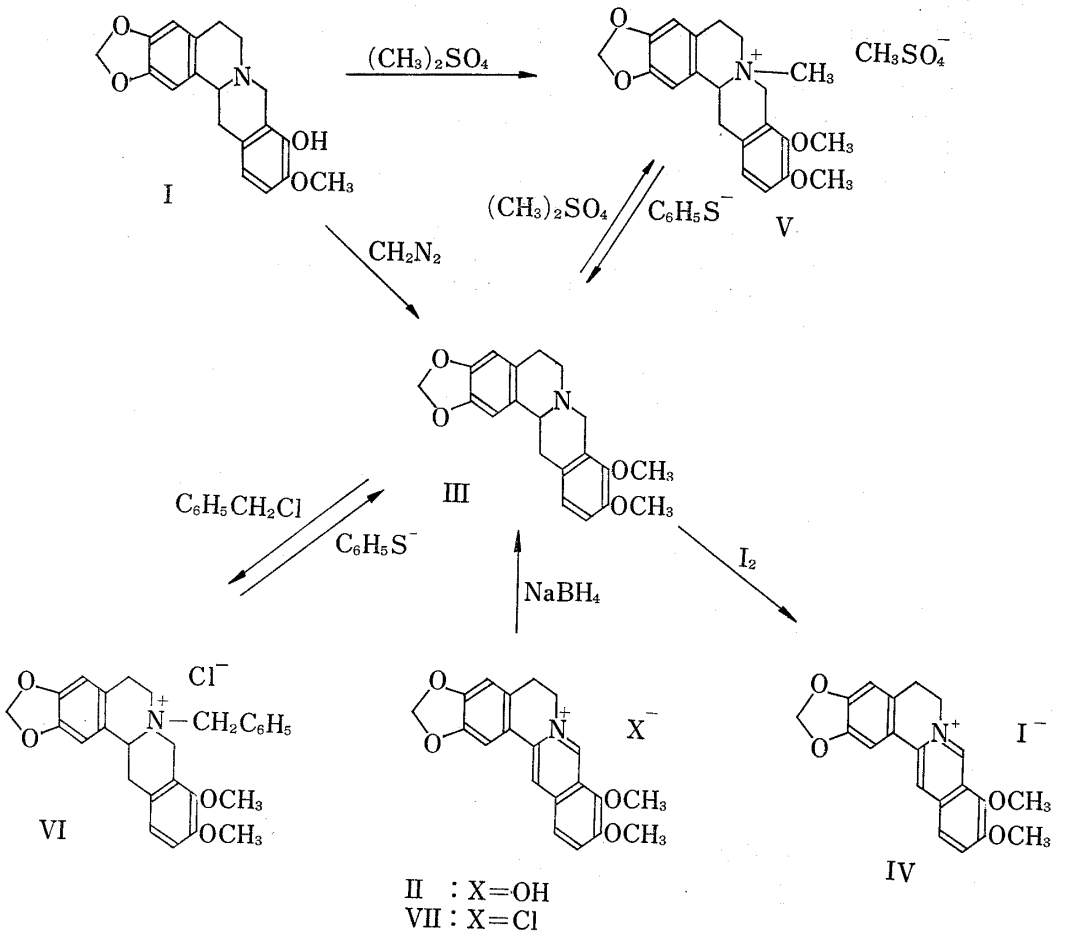

Chart 1

in chloroform did not occur in the presence or absence of base such as sodium methoxide or potassium carbonate.

Dehydrogenation of canadine (III) with iodine gave berberinium iodide (IV) in good yield,[4] and thus we have achieved a semi-industrial synthesis of berberine.

Experimental[9]

N-Methylcanadinium Methosulfate (V)——a) Synthesis of V from Canadine (III): A mixture of 1 g of III, 70 ml of $CHCl_3$, and 0.55 g of $(CH_3)_2SO_4$ was refluxed for 1 hr. After the reaction the solvent was distilled off to give a residue, which was washed with ether and collected by filtration. Recrystallization from MeOH gave 990 mg (67%) of V as colorless prisms, mp>250°. *Anal.* Calcd. for $C_{22}H_{27}O_8NS$: C, 56.77; H, 5.85; N, 3.01. Found: C, 57.04; H, 5.91; N, 3.34.

b) Synthesis of V from Nandinine (I): A mixture of 400 mg of I, 30 ml of acetone, 600 mg of $(CH_3)_2SO_4$, and 700 mg of K_2CO_3 was heated under reflux for 5 hr. After the removal of acetone, the residue was washed with ether and admixed with a small amount of hot water. After cooling, a solid precipitated was collected, washed with water, dried, and recrystallized from MeOH to give 375 mg (60%) of V as colorless prisms, mp>250°, which were identical with the above authentic sample by infrared (IR) spectral comparison and on its thin-layer chromatographic (TLC) behavior.

9) Melting points are not corrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi H-60 and IR spectra with a Hitachi-215.

10) This was dried *in vacuo* on P_2O_5 at 60° for 24 hr.

N-Benzylcanadinium Chloride (VI)——A mixture of 500 mg of III and 3 g of benzyl chloride was heated on a water-bath for 5 hr, and the reaction mixture was then washed with ether and collected by filtration. Recrystallization from MeOH–ether gave 410 mg (60%) of VI as hygroscopic pale yellow needles, mp 210°. *Anal.* Calcd. for $C_{27}H_{28}O_4NCl \cdot 2/3H_2O$[10]: C, 67.84; H, 6.19; N, 2.93. Found: C, 67.63; H, 6.61; N, 2.55. NMR (ppm) (in DMSO-d_6): 3.3 (6H, s, 9- and 10-OCH_3), 5.4 (2H, broad, s, $C\underline{H}_2C_6H_5$), 6.06 (2H, s, OCH_2O), 7.2 (5H, s, $CH_2C_6\underline{H}_5$).

Canadine (III)——a) A mixture of 500 mg of V, 150 ml of EtOH, and 500 ml of sodium thiophenolate was stirred for 1 hr at room temperature and the solvent was then distilled off under reduced pressure to give a residue whose solution in 100 ml of MeCOEt was refluxed for 20 hr. After removal of the solvent, the remaining residue was admixed with water and extracted with $CHCl_3$. Evaporation of the extract, the residue was dissolved in 10% HCl aq. solution, and the acidic solution was washed with ether, made basic with sat. Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to give a yellowish solid, the recrystallization of which from MeOH gave 170 mg (47%) of III as colorless prisms, mp 169—170°. *Anal.* Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.81; H, 6.10; N, 4.11. This sample was identical with an authentic sample,[8] which was obtained by reduction of berberinium chloride (VII), in IR spectral and TLC comparison. Furthermore, the mixed melting point test of both specimens showed no depression.

b) A mixture of 500 mg of VI, 120 ml of EtOH, and 500 mg of sodium thiophenolate was treated in a similar manner as above to give a yellowish solid, which was recrystallized from MeOH to give 280 mg (75%) of III as colorless prisms, mp 167—170°, identical with the above sample.

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Reaction of Biguanides and Related Compounds. VII.[1] The Condensation of Arylbiguanide with α,β-Unsaturated Carboxylic Ester in Dimethylformamide

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Phillips[3] has reported that methyl cinnamate reacted easily with guanidine by heating in ethanol to give 2-amino-4-hydroxy-6-phenyl-5,6-dihydropyrimidine in a low yield. Sugino[4] has also shown that the reaction of methyl acrylate with guanidine gave the almost quantitative yield of 2-amino-3-(N-amidinocarbamoylethyl)-6-oxo-3,4,5,6-tetrahydropyrimidine by using dimethylformamide (DMF) as a solvent under more moderate conditions. On the other hand, it is known that alkyl acrylate reacted with phenylbiguanide in alcohol in the presence of sodium alkoxide to give 2-amino-4-anilino-6-(β-alkoxyethyl)-*s*-triazine.[5] Biguanides would be anticipated to behave just like as guanidine, because the guanidine moiety is involved in the molecule. In fact it has been reported that arylbiguanide reacted with ethyl acetoacetate to give 2-arylguanidino-6-methyl-4-pyrimidinol.[6,7] The reaction between

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