[Chem. Pharm. Bull. 15(6) 879~883 (1967)] UDC 547.833.9.07

109. Tetsuji Kametani and Toyohiko Kikuchi: Studies on the Syntheses of Heterocyclic Compounds. CLXXXII.*1 A Modified Synthesis of So-called Corpaverine.

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Bischler-Napieralski cyclization of the phenethylamide (VII) having a benzyloxyl group in the 3-position of the benzene ring was found to take place in the position *para* and *ortho* to the benzyloxyl group, but both isoquinoline derivatives could not be separated in the stage of 3,4-dihydroisoquinolines (VIIIa and VIIIb), its methiodides (IXa and IXb), and 1,2,3,4-tetrahydroisoquinolines (Xa and Xb), even if various procedures as thin-layer chromatography were examined. Accordingly, after Xa and Xb had been hydrolysed, attempt to separate both compounds (I and XI) by thin-layer chromatography was successfully carried out.

After all, so-called corpaverine (I), namely, 8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1-(4-methoxybenzyl)-2-methylisoquinoline, was obtained besides its isomer (XI) in a comparatively better yield than that of our previous method. Furthermore, selective methylation of XIII with diazomethane also gave both compounds (I and XI), which were characterized as perchlorate and oxalate, respectively.

(Received November 14, 1966)

Corpaverine, $C_{20}H_{25}O_4N$, m.p. 138°, was isolated from *Corydalis aurea* WILLD. by Manske in 1938,[1] and chemical investigation[2] led to the proposed structure (I). Many attempts to synthesize it have been tried,[3,4] and its total synthesis recently revealed that corpaverine consisted of two components, (−)-capaurine (II) and sendaverine (III).[5~7] Furthermore, it has been reported that corpaverine is a molecular compound of both substances by thermal analysis.[8]

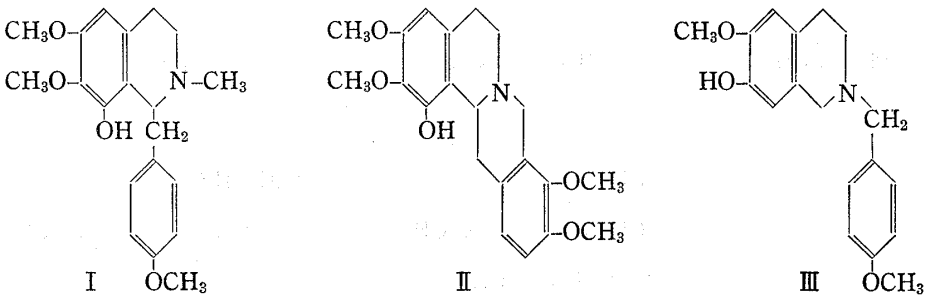

Chart 1.

The purpose of the present investigation was to study an alternative synthesis of so-called corpaverine (I), which was thought to be an important starting material for the other alkaloids, eventually leading to a modified synthesis of I.

*1 Part CLXXXI: Yakugaku Zasshi, **87**, 682 (1967).
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1) R. H. F. Manske: Can. J. Research, B, **16**, 81 (1938).
2) R. H. F. Manske: J. Am. Chem. Soc., **74**, 2864 (1952).
3) T. Kametani, S. Kano, T. Kikuchi: Yakugaku Zasshi, **86**, 423 (1966).
4) T. Kametani, S. Kano, Y. Watanabe: *Ibid.*, **86**, 417 (1966).
5) T. Kametani, K. Ohkubo, I. Noguchi, R. H. F. Manske: Tetrahedron Letters, **1965**, 3345; T. Kametani, K. Ohkubo: *Ibid.*, **1965**, 4317.
6) T. Kametani, K. Ohkubo, I. Noguchi: J. Chem. Soc. (C), **1966**, 715.
7) T. Kametani, K. Ohkubo: This Bulletin, **15**, 608 (1967).
8) T. Kametani, K. Ohkubo, R. H. F. Manske: Tetrahedron Letters, **1966**, 985.

In the previous paper[6] it has been reported that so-called corpaverine, namely, 1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (I) was synthesized in a poor yield by cyclization of 2-hydroxy-3,4,4′-trimethoxydesoxybenzoin (Ⅳ), and methylation of the resultant isoquinoline derivative (Ⅴ), followed by reduction of the methiodide (Ⅵ).

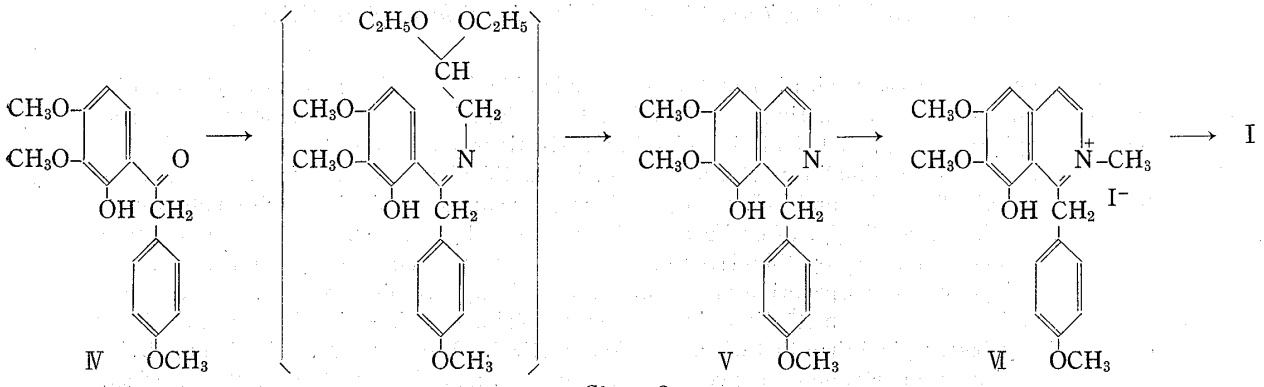
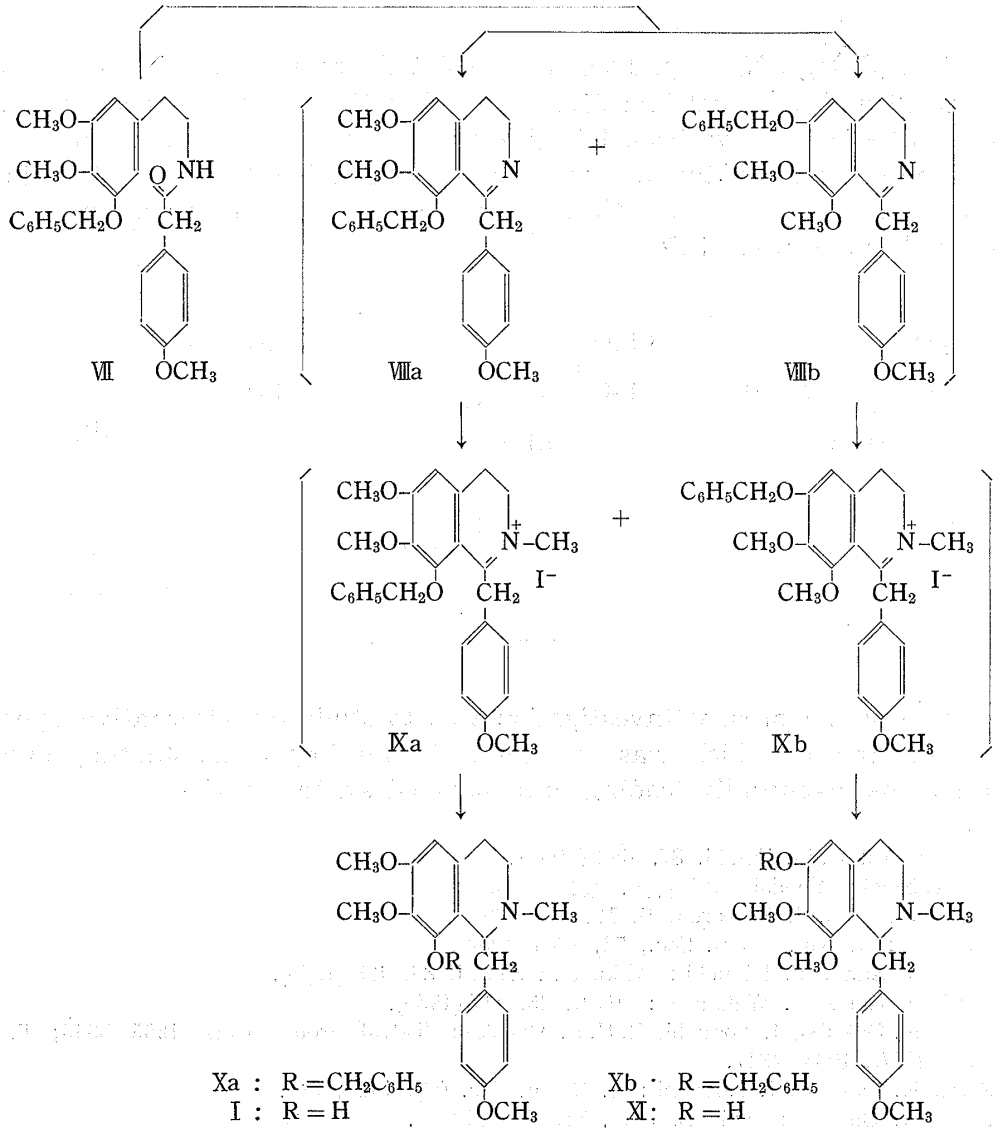


Chart 2.



Xa : R = $CH_2C_6H_5$
I : R = H

Xb : R = $CH_2C_6H_5$
Ⅺ : R = H

Chart 3.

Furthermore, Fujitani and Kishimoto[9] reported that the direction of cyclization of N-(5-benzyloxy-3,4-dimethoxyphenethyl)acetamide (Ⅶ) by Bischler-Napieralski reaction was examined and cyclization took place in the position *para* to benzyloxyl group in Ⅶ, forming Ⅺ.

Bischler-Napieralski cyclization of the amide (Ⅶ) with phosphoryl chloride in benzene was carried out, giving a mixture of Ⅷa and Ⅷb as a resinous syrup, which could not be separated and therefore characterized as the picrolonate. Reduction of the methiodide (Ⅸa and Ⅸb), which was obtained by methylation of Ⅷa and Ⅷb with methyl iodide, with sodium borohydride afforded a mixture of O-benzyl derivative (Xa and Xb) as a syrup which could not be separated. Accordingly, after hydrolysis of the above mixture, thin-layer chromatography on silica gel was examined to give two spots. The resultant mixture (I and Ⅺ) was then chromatographed on silica gel to give two components, showing Rf 0.58 and Rf 0.34. The former component of Rf 0.58 was characterized as its oxalate of Ⅺ, m.p. 173~175°, with correct analysis, and the latter one of Rf 0.34 was characterized as its perchlorate, m.p. 205~207°. The infrared (IR) spectrum of the latter free base was superimposable on that of our authentic sample (I)[6] obtained according to the procedure as was shown in Chart 2. Although there was a little difference between the nuclear magnetic resonance (NMR) spectra of both specimens (I) and (Ⅺ), the spectrum of the above compound (I) was also superimposable on that of the above authentic sample.[6]

These facts revealed that cyclization of the phenethylamide having a benzyloxyl group in the 3-position of the benzene ring was found to take place in the position *para* and *ortho* to benzyloxyl group in a comparatively good yield.

Secondly, Bischler-Napieralski reaction of N-(6,8-bisbenzyloxy-7-methoxyphenethyl)-2-(4-methoxyphenyl)acetamide (Ⅶ)[10] with phosphoryl chloride in benzene gave the 3,4-dihydroisoquinoline (XIII), which was characterized as its picrolonate. Reduction with sodium borohydride of the methiodide (XIV), which was obtained by methylation of XIII

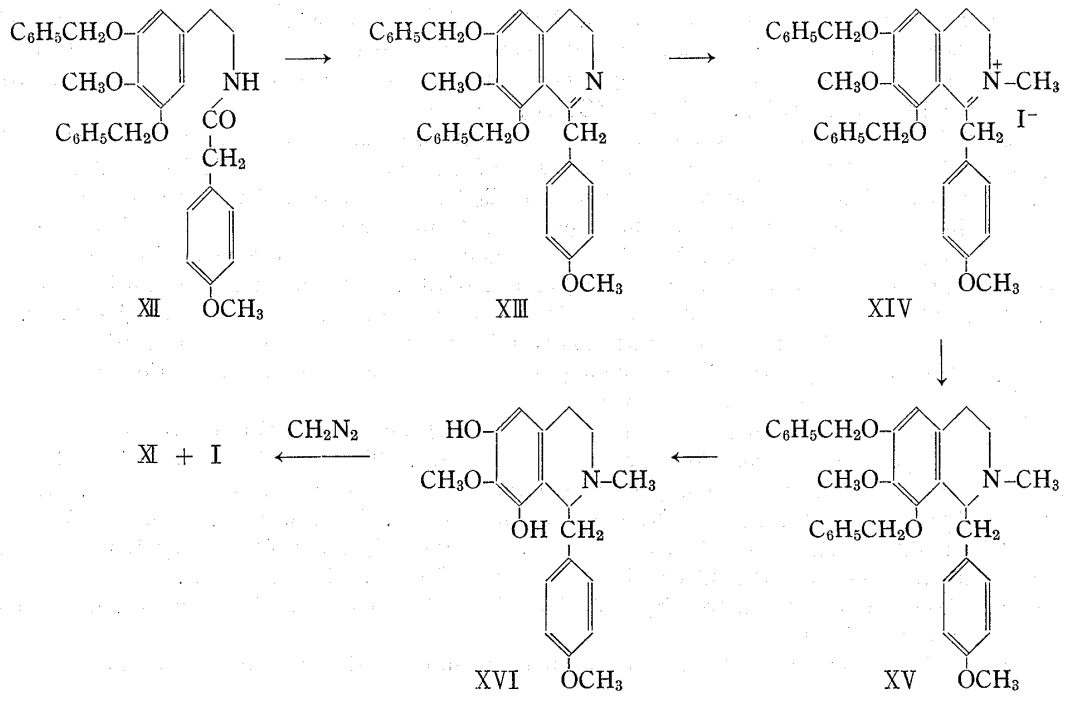


Chart 4.

9) K. Fujitani, T. Kishimoto: Yakugaku Zasshi, **84**, 329 (1964).
10) T. Kametani, S. Kano, T. Kikuchi: *Ibid.*, **86**, 979 (1966).

with methyl iodide, gave O,O-bisbenzyl-1,2,3,4-tetrahydroisoquinoline (XV) as a resinous syrup that could not be purified as a crystalline state. Therefore, hydrolysis of the preceding base (XV) with an ethanolic hydrochloric acid solution afforded the phenolic base (XVI) as colorless prisms, m.p. 163~165°.

Finally, the products which were obtained by methylation of 1 mole of XVI with 1 mole of diazomethane were separated on silica gel-chromatography, two components being obtained as the phenolic bases. Both specimens showed the spots of Rf 0.58 and Rf 0.34 on thin-layer chromatography, respectively. The oxalate of the former compound (Rf 0.58) was identical with the preceding compound (XI) on admixed melting point test and IR spectrum. The perchlorate of the latter compound (Rf 0.34) was also identical with an authentic sample. (I).

These facts reveal that a modified synthesis of so-called corpaverine has been accomplished.

Experimental*3

A Mixture of 8-Benzyloxy-6,7-dimethoxy- (VIIIa) and 6-Benzyloxy-7,8-dimethoxy-3,4-dihydro-1-(4-methoxybenzyl)isoquinoline (VIIIb)——A mixture of 5 g. of amide[9] (VII), 2 g. of $POCl_3$, and 50 ml. of benzene was heated under reflux on a water-bath for 3 hr. After an excess of *n*-hexane had been added to the above reaction mixture, it was allowed to stand overnight. The resultant precipitate was separated by decantation and washed with *n*-hexane for several times. To a solution of the above precipitate in a small amount of C_2H_5OH was added a saturated solution of picrolonic acid, and the precipitate was collected by filtration. Recrystallization of the picrolonate from EtOH gave 6.2 g. of yellow needles,*4 m.p. 198~200°. *Anal.* Calcd. for $C_{26}H_{27}O_4N \cdot C_{10}H_8O_5N_4$: C, 63.48; H, 5.18; N, 10.27. Found : C, 63.65; H, 5.28; N, 9.92. IR cm^{-1} ($CHCl_3$) : $\nu_{C=N}$ 1620.

A mixture of 8-Benzyloxy-6,7-dimethoxy- (Xa) and 6-Benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydro-1-(4-methoxybenzyl)-2-methylisoquinoline (Xb)——To a solution of the preceding mixture (VIIIa and VIIIb) (5 g.) in 50 ml. of $(CH_3)_2CO$ and MeOH (1 : 1) was added 5 ml. of CH_3I, and the mixture was heated under reflux on a water-bath at 50~60° for 5 hr. Removal of the solvent gave the residue which was washed with ether. To a solution of the above residue (IXa and IXb) in 100 ml. of CH_3OH was portionwise added 7 g. of $NaBH_4$, and, after the addition, the mixture was mildly refluxed on a water-bath for 30 min. After the solvent had been distilled, an excess of 5% aq. NaOH solution was added to the resultant residue and extracted with ether. The extract was washed with water, dried over K_2CO_3, and evaporated to give 4 g. of a syrup, which showed one spot on thin-layer chromatogram of silica gel and, therefore, was used in the following reaction without separation. IR cm^{-1} ($CHCl_3$) : ν_{N-Me} 2950.

8-Hydroxy-6,7-dimethoxy- (I) and 6-Hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydro-1-(4-methoxybenzyl)-2-methylisoquinoline (XI) (Debenzylation of a Mixture of Xa and Xb)——A solution of 1.2 g. of the above 1,2,3,4-tetrahydroisoquinoline (Xa and Xb) in 20 ml. of C_2H_5OH-conc. HCl (1 : 1) was heated under reflux on a water-bath in the presence of N_2 for 2 hr., and the solvent was then removed by distillation to give a residue, which was dissolved in 5% aq. NaOH solution and extracted with ether. To the above alkaline solution which separated was added an excess of crystalline NH_4Cl, and an ammoniacal solution was extracted with ether. The extract was washed with water, dried over K_2CO_3, and evaporated to give 0.6 g. of syrup, which showed two spots having Rf 0.53 and Rf 0.34 on thin-layer chromatogram of silica gel (solvent, $CHCl_3$: Me_2CO=5 : 4). Therefore, separation by chromatography of the above mixture was tried to give two compounds showing Rf 0.34 and Rf 0.53, respectively.

To a solution of the former compound (Rf 0.34) in a small amonut of CH_3OH was added 70% aq. $HClO_4$ solution, and an excess of ether was added to the above mixture. The precipitate was collected by filtration. Recrystallization from C_2H_5OH gave 230 mg. of perchlorate as colorless cubes, m.p. 205~207°. *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot HClO_4$: C, 54.12; H, 5.90; N, 3.16. Found : C, 53.74; H, 5.44; N, 3.26. NMR*5(τ) ($CDCl_3$): 7.66 (3H, N-CH_3); 6.26, 6.19, 6.14 (9H, 3OCH_3); 6.80~8.00 (6H, 3-CH_2-); 3.82 (1H, C_5-H); 2.83 (2H, doublet, J=8.5 c.p.s., $C_{2'}$-H, $C_{6'}$-H), 3.24 (2H, doublet, J=8.5 c.p.s., $C_{3'}$-H, $C_{5'}$-H).

The IR and NMR spectra of the free base obtained from the above perchlorate were superimposable on those of an authentic sample (I).[6]

To a solution of the substance (Rf 0.53) in a small amount of ether was added an excess of saturated

*3 Melting points were not corrected.

*4 The free base obtained from this picrolonate showed one spot on thin-layer chromatography, even if various kinds of solvents were used.

*5 NMR spectrum was measured by Varian A-60 spectrophotometer and $SiMe_4$ was used as internal reference.

solution of oxalic acid, and the precipitate was separated by filtration. Recrystallization from EtOH gave 200 ml. of oxalate of XI as colorless needles, m.p. 173~175°. *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot C_2H_2O_4 \cdot \frac{1}{2}H_2O$: C, 59.72; H, 6.38; N, 3.17. Found: C, 59.94; H, 6.64; N, 3.53. NMR (τ) ($CDCl_3$): 7.68 (3H, N-CH_3); 6.26 (3H, OCH_3), 6.14 (6H, $2OCH_3$); 6.80~8.00 (6H, 3-CH_2-); 3.58 (1H, C_5-H); 3.24 (2H, doublet, J=8.5 c.p.s., $C_{3'}$-H, $C_{5'}$-H); 2.83 (2H, doublet, J=8.5 c.p.s., $C_{2'}$-H, $C_{6'}$-H).

6,8-Bisbenzyloxy-3,4-dihydro-7-methoxy-1-(4-methoxybenzyl)isoquinoline (XIII)——A mixture of 5 g. of amide[10] (XII), 2 ml. of $POCl_3$, and 50 ml. of benzene*6 was heated under reflux on a water-bath for 3 hr. and an excess of *n*-hexane was added to the cooled reaction mixture, which was allowed to stand overnight. The resultant precipitate was separated by decantation and washed with *n*-hexane for several times. Recrystallization of its picrolonate from EtOH gave 6 g. of yellow needles, m.p. 183~185°. *Anal.* Calcd. for $C_{32}H_{31}O_4N \cdot C_{10}H_8O_5N_4$: C, 66.57; H, 5.19; N, 9.24. Found: C, 66.66; H, 5.11; N, 9.05. IR cm^{-1} ($CHCl_3$): $\nu_{C=N-}$ 1620.

6,8-Bisbenzyloxy-1,2,3,4-tetrahydro-7-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (XV)——To a solution of 5 g. of XIII in 50 ml. of Me_2CO-MeOH (1 : 1) was added 5 ml. of MeI and the mixture was heated on a water-bath at 50~60° for 5hr. After the reaction, the solvent was removed by distillation, and the residue (XIV) was washed with ether for several times.

Secondly, 6 g. of $NaBH_4$ was portionwise added to a solution of the above crude methiodide (XIV) in 100 ml. of CH_3OH, and the mixture was heated on a water-bath for 1 hr. Removal of the solvent gave the residue, which was admixed with 5% aq. NaOH solution and extracted with ether. The extract was washed with water, dried over K_2CO_3, and distilled to give 4 g. of XV as a syrup, which could not be purified as a crystalline state and, therefore, was used in the following reaction without purification.

1,2,3,4-Tetrahydro-6,8-dihydroxy-7-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (XVI)——A mixture of 3 g. of XV and 30 ml. of C_2H_5OH-conc. HCl solution was heated under reflux on a water-bath for 2 hr. Removal of the solvent in a current of N_2 gave the residue, which was dissolved in 5% aq. NaOH solution and extracted with ether. To an alkaline layer separated was added an excess of crystalline NH_4Cl, and the resultant ammoniacal solution was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and distilled to give the residue, whose recrystallization from $CHCl_3$ afforded 1.2 g. of XVI as pale brown needles, m.p. 161~163°. *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot \frac{1}{3}H_2O$: C, 68.04; H, 7.11; N, 4.18. Found: C, 68.03; H, 7.04; N, 4.01.

Methylation of XVI with Diazomethane——To a solution of 987 mg. of XVI in 100 ml. of CH_3OH was added an ethereal solution containing 126 mg. of CH_2N_2, and the mixture was allowed to stand in a refrigerator for 48 hr. Removal of the solvent gave the residue, which was dissolved in 5% aq. NaOH solution and extracted with ether. An excess of crystalline NH_4Cl was added to the above alkaline solution, and an ammoniacal solution thus obtained was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and distilled to give 605 mg. of a syrup, whose silica gel-chromatography using the solvent of $CHCl_3$-Me_2CO (5 : 4) gave two compounds showing Rf 0.34 and Rf 0.53. The former componnd was characterized as its perchlorate of I (yield, 250 mg.) and the latter as oxalate of XI (yield, 200 mg.).

Both specimens (I and XI) were completely identical with the authentic samples mentioned above on admixed melting point test, and their IR and NMR spectra also identical respectively.

*6 In a previous paper toluene was used as solvent, and the picrolonate of XIII was not characterized.