Orleans, La., a sample of versicolorin C derived from versiconal acetate from Dr. R. J. Cole, National Peanut Research Laboratory, Dawson, Ga., and a sample of versiconol from Dr. Y. Hatsuda, University of Tottori, Japan. We also wish to thank Dr. R. J. Cole for a prepublication copy of his paper on the carbon NMR of versiconal acetate. We thank Mr. T. Glass for obtaining the NMR spectra, and Miss Sue Ellen Jolly for assistance in the preparation of versicolorin A. This work was supported, in part, by contract 223-74-2146 from the Food and Drug Administration, Washington, D.C.

Registry No.—**3,** 6807-96-1; **4,** 10048-13-2; **6a,** 63324-95-8; **7b,** 63324-96-9; **9,** 22268-13-9; **10,** 63358-82-7; **12a,** 63324-97-0; **13,** 63324-98-1; **14b,** 63324-99-2; **16,** 63325-00-8; **17,** 63325-01-9; **18,** 6795-16-0; **19,** 63325-02-0; sodium borohydride, 16940-66-2.

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Studies on the Syntheses of Heterocyclic Compounds. 726.[1] Thermal Rearrangement of Aminomethyl Cyclopropyl Ketones and a Novel Synthesis of Pentazocine

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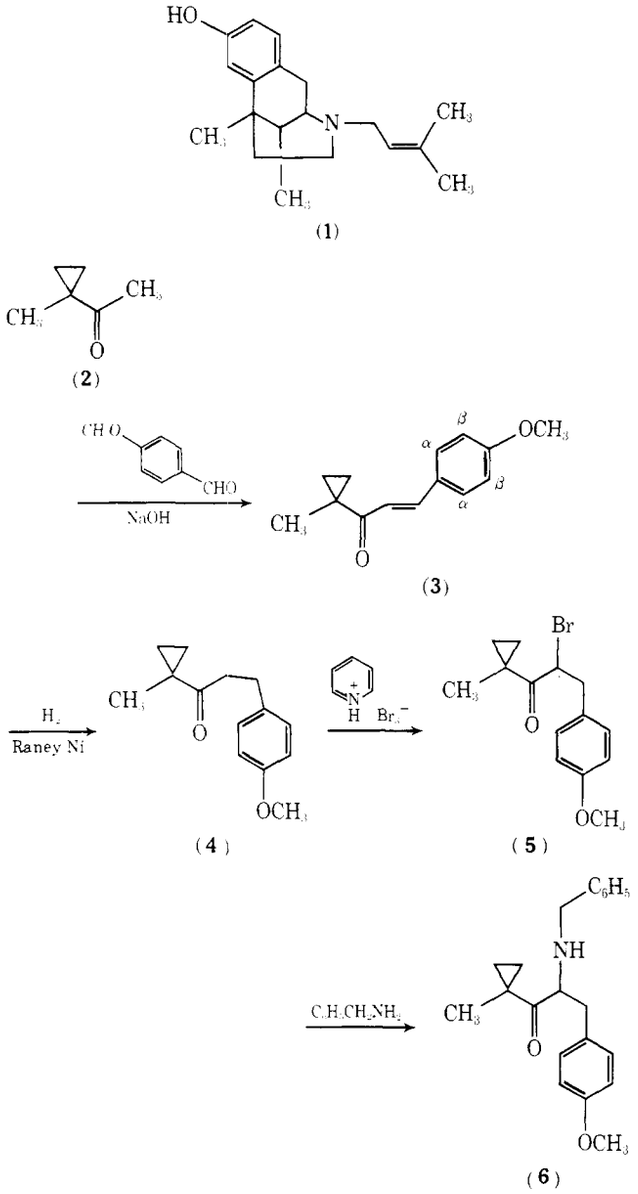
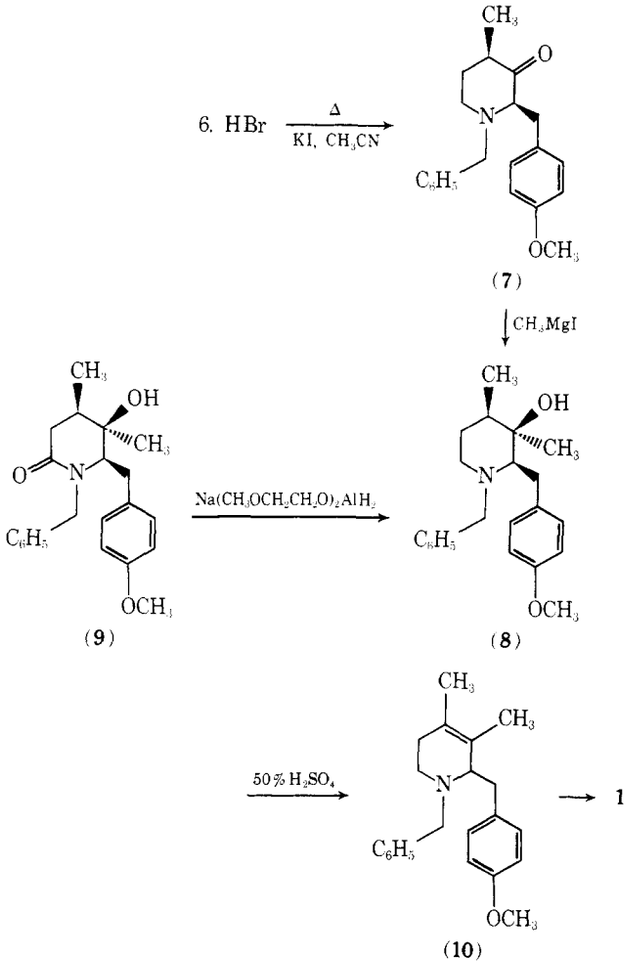
Thermal rearrangement of the hydrobromide of 2-benzylamino-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**6**), obtained from 1-acetyl-1-methylcyclopropane (**2**) through 3-(4-methoxyphenyl)-1-methylcyclopropyl-2-propenone (**3**), 3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**4**), and 2-bromo-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**5**), gave 1-benzyl-2-(4-methoxybenzyl)-4-methylpiperidin-3-one (**7**) in 71.2% yield, which was transformed to 1-benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (**10**) by Grignard reaction, followed by dehydration of the resulting 1-benzyl-3-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (**8**). Since **10** had been converted to pentazocine (**1**), this work constitutes a novel synthesis of pentazocine (**1**).

The susceptibility of cyclopropane rings with suitable activating groups to several kinds of nucleophiles has been well documented[2–7] since the studies of Bone and Perkin.[8,9] Recently, Danishefsky reported[10–13] the nucleophilic homoconjugate reactions of cyclopropanes with two geminal activating groups and an enhanced activation of cyclopropanes with cyclic acylal. On the other hand, the acid-catalyzed thermal rearrangement of cyclopropylimines, which was originally reported by Cloke,[14,15] has been shown to be a useful reaction for the synthesis of Δ^1- or Δ^2-pyrrolines,[16–18] and aminomethyl cyclopropyl ketones have been transformed to 3-ketopiperidine rings.[19] In contrast to the well-studied thermal rearrangement of cyclopropylimines, there have been very limited studies regarding the thermal rearrangement of

Scheme I



Scheme II



aminomethyl cyclopropyl ketones and this prompted us to examine its possible use for the synthesis of more complex objectives.

Since pentazocine (1), 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine, was first synthesized by Archer et al.,[20] many kinds of synthetic methods[21-24] for this compound 1 have been reported because of its nonnarcotic analgesic activity. Herein we wish to report a simple and novel synthesis of pentazocine (1) by using the thermal rearrangement of aminomethyl cyclopropyl ketone **6** as a key reaction.

The key compound **6** in our synthesis was prepared as follows. Condensation of 1-acetyl-1-methylcyclopropane (**2**)[25,26] with *p*-methoxybenzaldehyde in the presence of sodium hydroxide, followed by the catalytic hydrogenation of the resulting styril ketone **3**, afforded the cyclopropylpropanone **4** in 81.35% overall yield. Bromination of the compound **4** with pyridinium hydrobromide perbromide in ether gave the bromide **5** [*m/e* 296 (M^+), 298 ($M^+ + 2$), ν_{max} ($CHCl_3$) 1685 cm^{-1}, δ ($CDCl_3$) 4.47 (1 H, q, J = 6 and 9 Hz, –CO–CHBr–)], which was subsequently treated with benzylamine in methanol to afford the key intermediate **6** in 75.6% yield (based on the propanone **4**).

Next, thermolysis of compound **6** was carried out to proceed smoothly in high yield. A solution of hydrobromide of the compound **6** in acetonitrile was heated at 140–145 °C in a sealed tube in the presence of potassium iodide to give the piperidone **7** in 71.2% yield as a single product. The relative configuration between methyl and *p*-methoxybenzyl groups was assigned to be cis tentatively at this stage and this was confirmed by a subsequent transformation to the piperidin-3-ol **8**, which was in turn derived from the known compound **9**.[22] At first the piperidone **9**[22] was reduced with sodium bis(2-methoxyethoxy)aluminum hydride to afford **8**.

Finally, the piperidone **7** was treated with methylmagnesium iodide in ether to furnish the piperidin-3-ol **8** in 59% yield, which was shown to be identical with the authentic sample obtained above in its IR ($CHCl_3$) and NMR ($CDCl_3$) spectral comparisons and mixture melting points. The dehydration was effected by treating the piperidin-3-ol **8** with 50% sulfuric acid to give the olefinic compound **10** as a single product in 81% yield. Our product **10** was found to be identical with the authentic sample[27] in its IR ($CHCl_3$), NMR ($CDCl_3$) spectrum, and mixture melting point. Since this olefin **10** had been transformed to pentazocine (1),[27] this work constitutes a novel synthesis of pentazocine (1). Thus, we could demonstrate the thermal rearrangement of aminomethyl cyclopropyl ketone as a useful reaction for the synthesis of the compounds which contain a piperidine ring.

Experimental Section

Melting points are uncorrected. NMR spectra were taken with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), IR spectra with a Hitachi 215 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

3-(4-Methoxyphenyl)-1-methylcyclopropyl-2-propenone (3). A solution of 10.5 g of 1-acetyl-1-methylcyclopropane (**2**), 14.6 g of

p-methoxybenzaldehyde, 11 g of sodium hydroxide, 100 mL of water, and 80 mL of ethanol was stirred for 20 h at room temperature. After the addition of 200 mL of water, the reaction mixture was extracted with ether. The ethereal extract was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent and unreacted *p*-methoxybenzaldehyde gave 19 g of compound **3** as a yellow oil, which was used in the following reaction without purification. A part of the product was purified by preparative thin-layer chromatography on silica gel (ether–benzene, 1:2) for the spectral data and microanalysis: UV (MeOH) 323 nm; IR ($CHCl_3$) 1633 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.63–1.53 (4 H, m, cyclopropyl protons), 1.43 (3 H, s, CH_3), 3.81 (3 H, s, CH_3O), 6.70 (1 H, d, J = 14 Hz, –C**H**=CH–), 7.64 (1 H, d, J = 14 Hz, –CH=C**H**–), 6.90 (2 H, d, J = 8 Hz, aromatic β protons), 7.45 (2 H, d, J = 8 Hz, aromatic α protons); MS *m/e* 216 (M^+).

Anal. Calcd for $C_{14}H_{16}O_2 \cdot 0.25H_2O$: C, 76.25; H, 7.54. Found: C, 76.10; H, 7.39.

3-(4-Methoxyphenyl)-1-methylcyclopropylpropanone (4). A suspension of 18 g of compound **3** and 10 g of Raney nickel (W_2) in 400 mL of ethanol was shaken under a current of hydrogen for 24 h. After removal of the catalyst, the ethanol was evaporated off to give a pale yellow oil, which was distilled to afford 18 g (81.35% yield based on compound **2**) of compound **4** as a colorless oil: bp 115 °C (0.4 mmHg); IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.48–1.23 (4 H, m, cyclopropyl protons), 1.29 (3 H, s, CH_3), 2.41–3.08 (4 H, m, –CO–CH_2CH_2Ar), 3.72 (3 H, s, CH_3O), 6.76 (2 H, d, J = 9 Hz, aromatic β protons), 7.60 (2 H, d, J = 9 Hz, aromatic α protons); MS *m/e* 218 (M^+).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.70; H, 8.36.

2-Bromo-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (5). To a solution of 5 g of compound **4** in 200 mL of ether was added in small portions 7.5 g of pyridinium hydrobromide perbromide under ice cooling and the resulting mixture was stirred for 4 h at the same temperature. After filtration, the filtrate was washed with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 7.5 g of bromide **5** as a yellow oil, which was used in the following reaction without further purification because of its instability. A part of this product was purified by preparative thin-layer chromatography on silica gel ($CHCl_3$) for spectral data and microanalysis: IR ($CHCl_3$) 1685 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.6–1.3 (4 H, m, cyclopropyl protons), 1.35 (3 H, s, CH_3), 2.8–3.7 (2 H, m, ArCH_2–), 3.76 (3 H, s, CH_3O), 4.47 (1 H, q, J = 6 and 9 Hz, –C**H**Br–), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.1 (2 H, d, J = 8 Hz, aromatic α protons); MS *m/e* 296 (M^+), 298 ($M^+ + 2$).

Anal. Calcd for $C_{14}H_{17}O_2Br$: C, 56.58; H, 5.77. Found: C, 56.45; H, 5.87.

2-Benzylamino-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone)6). A solution of 7.5 g of bromide **5** and 11.3 g of benzylamine in 200 mL of methanol was refluxed for 5.5 h. After removal of methanol, the residue was dissolved in 100 mL of 10% hydrochloric acid, whose solution was washed with *n*-hexane. The aqueous layer was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent and unreacted benzylamine afforded a yellow oil, which was purified by column chromatography on 100 g of silica gel. Elution with hexane–benzene (2:3) gave 5.6 g (75.6% based on compound **4**) of benzylamino derivative **6** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.5–1.2 (4 H, m, cyclopropyl protons), 1.23 (3 H, s, CH_3), 2.68–3.0 (2 H, m, >C**H**CH_2Ar), 3.3–3.75 (3 H, m, –C**H**CH_2– and >NCH_2Ar), 3.8 (3 H, s, CH_3O), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.1 (2 H, d, J = 8 Hz, aromatic α protons), 7.2 (5 H, s, aromatic protons); MS *m/e* 323 (M^+). Hydrochloride formed colorless crystals: mp 163–164 °C.

Anal. Calcd for $C_{21}H_{25}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 68.31; H, 7.38; N, 3.80. Found: C, 68.10; H, 7.23; N, 3.83.

1-Benzyl-2-(4-methoxybenzyl)-4-methylpiperidin-3-one (7). A solution of 325 mg of benzylamino derivative **6** hydrobromide and 130 mg of potassium iodide in acetonitrile was heated at 140–145 °C in a sealed tube for 3 days. After filtration of inorganic compound, the solvent was distilled off and the residue was dissolved in 20 mL of 10% hydrochloric acid, whose solution was washed with *n*-hexane. The aqueous layer was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil, which was subjected to column chromatography on 10 g of silica gel. Elution with benzene gave a solid, which was recrystallized from benzene–hexane to afford 185 mg (71.2%) of **7** as colorless needles, mp 104–105 °C: IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6.5 Hz, CH_3), 1.5–3.6 (8 H, m, methylene and methine protons), 3.73 (2 H, s, >NCH_2Ar), 3.78 (3 H, s, CH_3O), 6.78 (2 H, d, J = 9 Hz, aromatic β protons), 7.03 (2 H, d, J = 9 Hz, aromatic α protons), 7.21 (5 H, s, aromatic protons); MS *m/e* 323 (M^+).

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.20; H, 7.73; N, 4.13.

1-Benzyl-3-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (8). (A) From 7. To a solution of methylmagnesium iodide (prepared from 85 mg of Mg turnings and 500 mg of methyl iodide) in 5 mL of dry ether was added dropwise a solution of 100 mg of **7** in 5 mL of dry ether and stirred for 5 h at room temperature. The reaction mixture was poured into 10 mL of ice–water and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil, which was subjected to column chromatography on 2 g of silica gel. Elution with benzene–ethyl acetate (95:5) gave 62 mg (59%) of **8** as a colorless oil, which was identical with **8** obtained from **9** as below in its IR, NMR spectrum, and mixture melting point.

(B) From 1-Benzyl-5-hydroxy-6-(4-methoxybenzyl)-4,5-dimethylpiperidin-2-one (9). A solution of 1.3 g of amide **9** in 25 mL of dry xylene was added to a solution of 12 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 15 mL of dry xylene, and the resulting mixture was heated under reflux for 4 h under a current of nitrogen. After the reaction mixture was acidified with 10% hydrochloric acid, the organic layer separated was extracted with water. Both aqueous layers were combined and basified with 10% ammonium hydroxide solution and extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow oil, which was subjected to column chromatography on 20 g of silica gel. Elution with benzene–ethyl acetate (95:5) afforded 662 mg (50.3%) of **8** as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 4.0 Hz, C**H**$_3$CH<), 1.25 (3 H, s, C**H**$_3$C(OH)<), 3.8 (3 H, s, CH_3O), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.6 (2 H, d, J = 8 Hz, aromatic α protons), 7.65 (5 H, s, aromatic protons). Hydrochloride: mp 180–182 °C.

Anal. Calcd for $C_{22}H_{29}NO_2 \cdot HCl \cdot 0.5\ H_2O$: C, 68.64; H, 8.06; N, 3.64. Found: C, 68.68; H, 7.94; N, 3.71.

1-Benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (10). A solution of 30 mg of carbinol **8** in 5 mL of 50% sulfuric acid was heated at 80 °C for 2 days under stirring. The reaction mixture was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oil, which was purified by preparative thin-layer chromatography on silica gel (petroleum ether–ether, 3:1) to afford 23 mg (81%) of **10** as a colorless oil: NMR ($CDCl_3$) δ 1.63 (6 H, s, 2× CH_3), 3.58 (2 H, s, >NCH_2Ar), 3.77 (3 H, s, CH_3O), 6.66 (2 H, d, J = 9.1 Hz, aromatic β protons), 7.08 (2 H, d, J = 9.1 Hz, aromatic α protons), 7.1 (5 H, s, aromatic protons). Hydrochloride, mp 152–153 °C (lit.,[27] mp 152–154 °C) identical with an authentic sample[27] in its IR, NMR spectrum, and mixture melting point.

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Registry No.—**1**, 359-83-1; **2**, 1567-75-5; **3**, 63215-74-7; **4**, 63181-46-4; **5**, 63181-47-5; **6**, 63181-48-6; **6** HCl, 63181-49-7; **6** HBr, 63197-36-4; **7**, 63181-50-0; **8**, 63181-51-1; **8** HCl, 63181-52-2; **9**, 63181-53-3; **10**, 22185-48-4; **10** HCl, 23909-52-6; *p*-methoxybenzaldehyde, 123-11-5; benzylamine, 100-46-9.

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Reduction of Acylguanidines to Alklyguanidines with Lithium Aluminum Hydride

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Six acylguanidines bearing different alkylation patterns, namely dodecanoylguanidine (1), *N*-dodecanoyl-*N'*,*N''*-dimethylguanidine (2), *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (3), β-alacreatinine (5), creatinine (6), and methylcreatinine (7), have been reduced to the corresponding alkylguanidines with lithium aluminum hydride in yields ranging from 51 to 62%. A seventh reduction substrate, *N*-octanoyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine (4), gave only nonguanidine reduction products resulting from cleavage of the guanidine moiety, including *N*-(dimethylaminomethyl)octanamide (25). Syntheses of the various substrates are described and reaction mechanisms and general synthetic utility are discussed.

Although a literature search revealed no examples of reduction of an acylguanidine with lithium aluminum hydride ($LiAlH_4$), a statement[1] that the guanidine group is inert to $LiAlH_4$ suggested to us that the reduction of an acylguanidine to an alkylguanidine might be possible. The utility of such a conversion is illustrated by the occurrence of the alkylguanidine moiety in a wide variety of biological systems and the presence of the guanidine group in antihypertensive drugs such as clonidine[2] and guanethidine.[3]

Results and Discussion

Preparation of Reduction Substrates. The acylguanidines **1–7**, selected because they represent a broad range of substitution patterns, were in most cases easily prepared. Compounds **1**[4] and **2** were prepared by acylating the appropriate guanidine free base with methyl dodecanoate following the general procedure for acylating guanidines with esters.[5] To acylate the *sym*-tetramethylguanidine and prepare substrate **4**, the acid chloride was required. Compounds **1**, **2**, and **4** displayed the spectral properties expected for such acylguanidines.[6]

Considerable difficulty was encountered in the preparation of *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**), the major problem being the selective conversion of **10** to **3**. The preparation of **9** proceeded according to conventional methods,[7,8] and then **9** hydriodide was converted by ion exchange to the acetate to obtain increased solubility in acetic anhydride.