[Chem. Pharm. Bull. 12(11)1296~1301(1964)] UDC 547.836.3.07

179. Yoshio Ban and Masako Seo: The Synthesis of β-Carboline Derivatives. IV.*1 Total Synthesis of Alstoniline.*2

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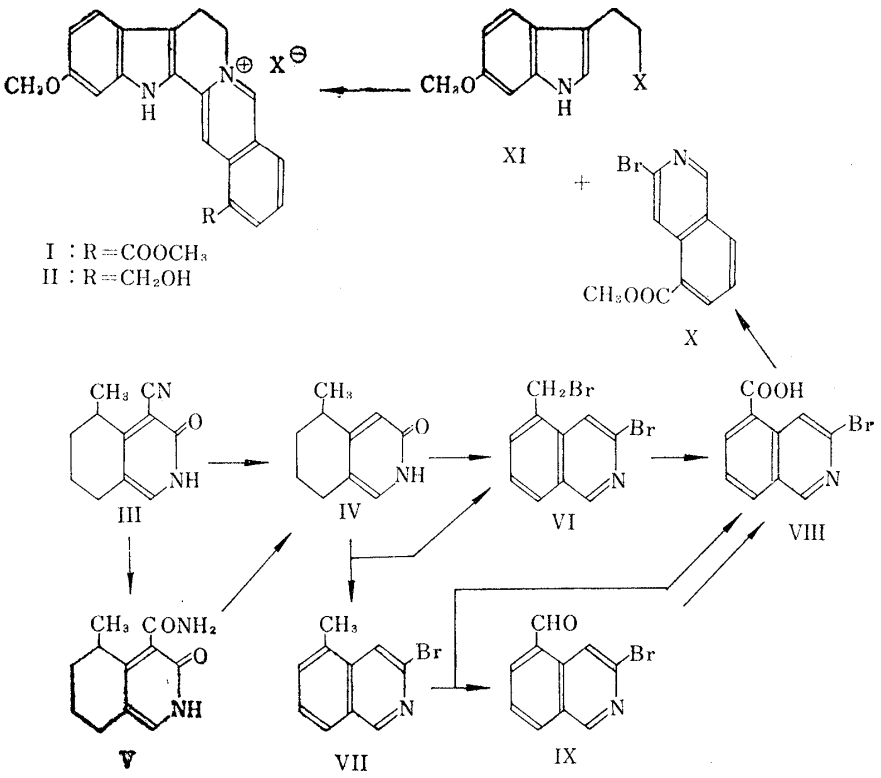
Alstoniline hydrochloride ($C_{22}H_{18}N_2O_3 \cdot HCl \cdot H_2O$), a brilliant red alkaloid of *Alstonia constricta* F. MUELL, was first isolated[1] and investigated by Elderfield and his co-workers, who established its structure (I, X=Cl) by degradation studies[2] and then by an elegant synthesis of alstonilinol iodide (II, X=I).[3] This alkaloid has an unsaturated ring system containing no asymmetric carbon atom, in which respect it constitutes one of two exceptions along with sempervirine[4] among the pentacyclic indoloquinolizine group of alkaloids.

In view of this interesting feature and because of interest in the biogenetic pattern[5] and in checking the pharmacological activities of these alkaloids, attention was turned



*1 Part III: This Bulletin, **11**, 1193 (1963).

*2 A preliminary communication of a portion of the results now reported has been published. Y. Ban, M. Seo: J. Org. Chem., **27**, 3380 (1962).

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2) *a*) N.J. Leonard, R.C. Elderfield: *Ibid.*, **7**, 556 (1942); *b*) R.C. Elderfield, S.L. Wythe: *Ibid.*, **19**, 683, 693 (1954); *c*) R.C. Elderfield, O.L. McCurdy: *Ibid.*, **21**, 295 (1956).

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to the synthesis of alstoniline itself by an application of a new synthetic method for β-carboline derivatives which has been being developed in this laboratory.[6]

In this paper we wish to report the detail of a total synthesis of this alkaloid.

3-Oxo-5-methyl-2,3,5,6,7,8-hexahydro-4-isoquinolinecarbonitrile (Ⅲ)*[4] which was prepared from 2-methylcyclohexanone by the method of Basu,[7] was subjected to hydrolysis, followed by the simultaneous decarboxylation. The reaction was carried out by heating with 75% sulfuric acid under a stream of nitrogen at 175~180° for 15 hour to give 5-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolone (Ⅳ), colorless needles, m.p. 126~127°, in 75% yield. In the other case that Ⅲ was heated with 75% sulfuric acid for one hour under the same condition as the above, there was obtained the corresponding amide (Ⅴ), colorless plates, m.p. 269~270°, along with a poor yield of Ⅳ, the former (Ⅴ) of which was further hydrolyzed and decarboxylated to yield the latter (Ⅳ). In addition to their infrared spectra and other physicochemical properties supporting the structures, Ⅳ and Ⅴ, this conversion confirmed the structural relationship of these compounds.

The oxo-base (Ⅳ) was heated with phosphoryl bromide in a sealed tube at 160~170° for 20 hour to furnish pale yellow needles, m.p. 157~158°, which were fully aromatized judging from its ultraviolet spectrum and assigned 3-bromo-5-bromomethylisoquinoline (Ⅵ) based upon the elemental analyses. In case of treating the same compound with phosphoryl chloride, a partially aromatized monochlorohydroisoquinoline was obtained, the result of which will be published in the following paper.[8] When, however, the above bromination reaction was conducted in an open vessel, a mixture of the monobromo-base (Ⅶ : colorless needles, m.p. 90~91°) and the dibromo-base (Ⅵ) was obtained, which was separable by chromatography on alumina.

The dibromo-base (Ⅵ) was heated with the freshly prepared selenium oxide in nitrobenzene at 170~175° for 1.5 hour to furnish the acid (Ⅷ), colorless needles, m.p. 251° in 63.5% yield. When the monobromo-base (Ⅶ) was heated with the same reagent, there were obtained the acid (Ⅷ) and the red brownish resin, the latter of which was separated by chromatography on alumina to two substances. The first one obtained as a yellow brownish oil showed the infrared spectrum similar to that of the starting material and it was discarded. The second one obtained as an orange solid, showed absorptions at 2730, and 1680 cm^{-1} and was assigned the aldehyde (Ⅸ). This assignment was further confirmed by the fact that this material was oxidized with hydrogen peroxide to yield the acid (Ⅷ).

The acid (Ⅷ) was treated with thionyl bromide and then with methanol to yield the corresponding ester (Ⅹ), colorless needles, m.p. 127°.

As has been obvious according to the above description, the synthetic route from Ⅲ *via* Ⅳ, Ⅵ, and Ⅷ to Ⅹ is most preferable.

Thus, a mixture of 3-(2-bromoethyl)-6-methoxyindole (Ⅺ) and the foregoing ester (Ⅹ) was heated at 75° in a current of nitrogen. At first, benzene was used as a solvent, but this was substituted by toluene in the course of reaction to raise the temperature to 95°. The heating at about this temperature was continued for totally 16~20 hour, during which time a red brownish solid deposited. This was washed with absolute ether, treated with silver chloride in methanol, and then recrystallized from methanol to afford the hydrochloride, fine orange red needles. The ultraviolet spectrum of this sample was identical with that of natural alstoniline hydrochloride (Ⅰ, X=Cl), derived from the

*[4] The m.p. 188° of this compound (Ⅲ) was different from the description (m.p. 212°) in the literature,[7] but all the data including elemental analyses obtained by us are compatible with Ⅲ.

6) Y. Ban, M. Seo : Chem. & Ind. (London), **1960**, 235; Tetrahedron, **16**, 5, 11 (1961); This Bulletin, **11**, 1193 (1963).
7) U. Basu, B. Banerjee : Ann., **516**, 243 (1935).
8) Y. Ban, M. Seo : This Bulletin, **12**, 1378 (1964).

corresponding sulfate (I, X=1/2SO_4) which was generously supplied by Professor Elderfield (Fig. 1). But, the hydrochloride (I, X=Cl) is not suitable for identification since it decomposes over a wide range without melting. Therefore, the synthetic hydrochloride was converted to the picrate (I, X=picrate ion), red plates, m.p. 291° (decomp.), which

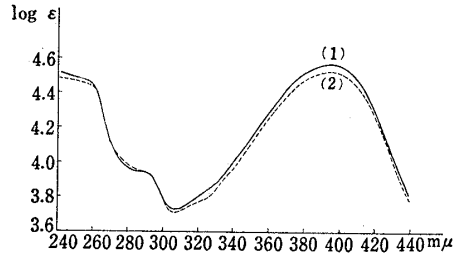

Fig. 1.

(1) ———— Natural alstoniline hydrochloride
(2) – – – – – Synthetic alstoniline hydrochloride

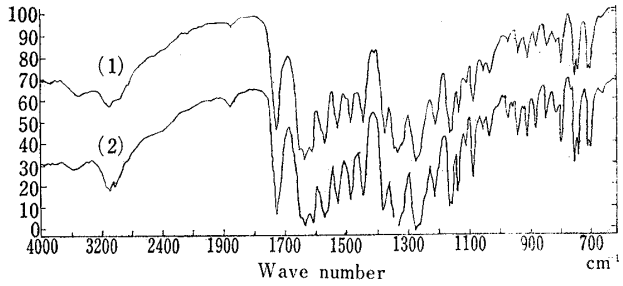

Fig. 2.

(1) Synthetic alstoniline picrate
(2) Natural alstoniline picrate

was directly compared with the picrate, red plates, m.p. 294° (decomp.), derived from the natural alkaloid. The identity of both samples was established by mixed melting point determination and was further confirmed by their identical infrared spectra shown in Fig. 2. This condensation was repeated twice, but the yield was almost the same, that was, ca. 40% as a crude product.

In the above second experiment that toluene was used as a solvent from the start of reaction, a benzene-soluble material was obtained as pale purple needle, m.p. 241° (decomp.), in a small quantity. This substance showed a positive reaction in the ferric chloride test, suggesting that the methoxyl group at 11-position was cleaved to the free hydroxyl group by a prolonged heating with X·HBr produced by the condensation. But the full structure of this compound has not yet been decided.

In this connection, it has been already reported*1 that the tosylate (XI, X=OTs) was condensed with 2-bromopyridine to afford the quinolizinium salt in 90% yield, which was much better than with the bromide (XI, X=Br) in the same condensation.

Accordingly, an attempt of substituting the tosylate (XI, X=OTs) for the bromide (XI, X=Br) in the foregoing procedure, was made to raise the yield of alstoniline (I), but in this case the yield was not improved against the above preliminary work.

Experimental*5

3-Oxo-5-methyl-2,3,5,6,7,8-hexahydro-4-isoquinolinecarbonitrile (III)——To a suspension of Na powder (5.6 g.) in abs. benzene was added under stirring a benzene solution of 2-methyl-6-aminomethylenecyclohexanone (33.5 g., 1 mole. equiv.), on which addition the color of the solution changed into orange-red from yellow. After the addition of the component, the mixture was stirred for 3 hr., and then ethyl cyanoacetate (27.5 g.) was added under ice-cooling. Immediately, the solution became yellow-turbid and the precipitate began to deposit. The whole mixture was stirred for 2 hr. after the addition, and allowed to stand at room temperature overnight. The mixture was refluxed for 4 hr. on a steam bath, and again left standing at room temperature overnight. To the mixture was added H_2O and the aqueous layer was separated. The benzene layer was washed with H_2O, and the washings were combined into the foregoing separated aqueous solution, which was acidified with conc. HCl. The separated oil was taken up in $CHCl_3$, and then extracted with BuOH. The combined extract was dried over Na_2SO_4 and the solvent was removed to yield a residue which was repeatedly recrystallized from EtOH to afford 8.175 g. (18%) of colorless prisms, m.p. 188° (lit.[7] m.p. 212°). IR : $\nu_{C\equiv N}$ 2215 cm^{-1}; $\nu_{C=O}$ 1640 cm^{-1} UV : λ_{max}^{EtOH} 345 mμ; λ_{min}^{EtOH} 270 mμ. *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.21; H, 6.39; N, 14.89. Found : C, 70.23; H, 6.79; N, 14.77.

*5 All melting points are uncorrected.

5-Methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolone (IV)——A solution of 3-oxo-5-methyl-2,3,5,6,7,8-hexahydro-4-isoquinolinecarbonitrile (2.06 g.) in 10 ml. of 75% H_2SO_4 was heated at 170~180° under a stream of N_2 for 15 hr., during which time the evolution of CO_2 was checked from time to time by virtue of a barium hydroxide solution. In the first period of 2 or 3 hr. after the start of heating, the vigorous evolution of CO_2 was observed, and after 7 hr, very little gas evolution was recognized. The reaction mixture was made neutral with 15% NaOH and again made acidic with dil. HCl, on which treatment the separated black brown amorphous substance was filtered off, and the filtrate was extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and the solvent was removed to leave a residue which was purified by chromatography on alumina eluted with $CHCl_3$ to give 1.3 g. (75.0%) of colorless needles, m.p. 126~127°. IR: $\nu_{C=O}$ 1650 cm^{-1}. UV : λ_{max}^{EtOH} 308 mμ; λ_{min}^{EtOH} 254 mμ. *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.61; H, 7.97; N, 8.58. Found : C, 73.52; H, 8.32; N, 8.83.

When the heating time was limited to 1 hr. in the above procedure, there was obtained the corresponding amide, colorless plates, m.p. 269~270°, recrystallized from EtOH after treatment in the usual manner. IR : $\nu_{C=O}$ 1655 cm^{-1}. UV : λ_{max}^{EtOH} 323 mμ; λ_{min}^{EtOH} 266 mμ. *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 64.07; H, 6.99; N, 13.59. Found : C, 64.03; H, 6.81; N, 13.88.

3-Bromo-5-bromomethylisoquinoline (VI)——A mixture of 5-methyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolone (1.5 g.) and $POBr_3$ (40 g.) was heated at 160~170° in a sealed tube for 18 hr. After standing overnight, the whole mixture was poured onto ice, extracted with ether and with benzene, and the combined extract was dried over Na_2SO_4. The solvent was removed to yield a yellow solid which was recrystallized from benzene to afford 910 mg. (32.81%) of VI as pale yellow needles, m.p. 157~158°. *Anal.* Calcd. for $C_{10}H_7NBr_2$: Br, 53.15. Found : Br, 52.66. UV λ_{max}^{EtOH} mμ : 333, 321, 294, 282.5; λ_{min}^{EtOH} mμ : 325, 305, 289, 263. The acidic aqueous layer was made alkaline with NaOH solution and extracted with benzene and then with $CHCl_3$. The extract was dried over Na_2SO_4, and the solvent was removed to leave a resin which was chromatographed on alumina to yield 1.1 g. of a pale yellow resin. This solidified on standing and the resulting substance was neither VI nor VII judging from its IR spectrum. Its UV spectrum suggested that the material must be a derivative of isoquinoline, but the final assignment has remained to be decided.

3-Bromo-5-methylisoquinoline (VII)——The above reaction was carried out in an open vessel in the following : A mixture of 5-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolone (2 g.) and $POBr_3$ (26 g.) was heated at 180~190° for 15 hr. and the whole mixture was poured onto ice, extracted with ether, dried over Na_2SO_4, then the solvent was removed.

The residue was recrystallized from benzene to afford 190 mg. of the dibromo-base (VI), pale yellow needles, m.p. 158°.

The acidic aqueous layer was made alkaline with KOH and extracted with benzene and then with $CHCl_3$ to give a yellow brownish oil, after the usual treatment, which was purified by chromatography on alumina and repeatedly recrystallized from benzene-hexane to give 310 mg. of VII as colorless needles, m.p. 90~91°. *Anal.* Calcd. for $C_{10}H_8NBr$: C, 54.05; H, 3.60; N, 6.30. Found : C, 53.86; H, 3.56; N, 6.36. UV λ_{max}^{EtOH} mμ : 326 (3.40), 278 (3.59); λ_{min}^{EtOH} mμ : 303 (3.16), 254 (3.44).

3-Bromo-5-isoquinolinecarboxylic Acid (VIII)——To a solution of 3-bromo-5-bsomomethylisoquinoline (301 mg.)in nitrobenzene(5 ml.)was added the freshly prepared SeO_2 (180 mg., 1.6 moles), and the whole mixture was gradually heated to 165°, when the color of the solution was changed to red from yellow. It was observed that effervescence began to occur, separating Se metal about 170°. The mixture was kept on heating at 170~175° for about 1 hr., during which time the carboxylic acid was separated and deposited on the wall of the vessel. Finally, the temperature was raised to 180° and kept at this point for half an hour. The mixture was allowed to stand overnight so that the carboxylic acid may separate sufficiently. The precipitate was filtered, washed well with benzene to remove the nitrobenzene as a solvent. The crude acid was dissolved in EtOH to separate Se metal and then was treated with charcoal. The EtOH was removed to leave the crude material, which was recrystallized from EtOH to afford 160 mg. (63.5%) of colorless needles, m.p. 251° (decomp.). *Anal.* Calcd. for $C_{10}H_6O_2NBr$: C, 47.61; H, 2.38; N, 5.55; Br, 31.74. Found : C, 47.59; H, 2.48; N, 5.53; Br, 32.22. IR : $\nu_{C=O}$ 1685 cm^{-1}. UV λ_{max}^{EtOH} mμ : 334 (3.57), 325 (3.56), 293 (3.67), 282 (3.75). λ_{min}^{EtOH} mμ : 308 (3.55), 304 (3.21), 290 (3.66), 261 (3.56).

After collection of the acid, the filtrate was steam-distilled to expel the nitrobenzene, and the remaining aqueous solution was extracted with benzene to further remove a small amount of nitrobenzene and the unreacted material. Then, the aqueous solution was extracted with AcOEt and treated in the usual manner to give another 5 mg. of the carboxylic acid (VIII).

3-Bromo-5-isoquinolinecarboxaldehyde (IX)——A mixture of 3-bromo-5-methylisoquinoline (222 mg.) and the freshly prepared SeO_2 (122 mg.) in nitrobenzene was heated at 200~210° for 1 hr., during which time Se metal began to deposit at 205°. After cooling, the mixture was taken up in benzene, separating 70 mg. of the crystal which was filtered, dissolved in 10% $NaHCO_3$ and again precipitated with 10% HCl. The deposit was dissolved in EtOH, treated with charcoal, and then recrystallized from EtOH to give 26 mg. of colorless needles, m.p. 251° (decomp.), which was identified with the carboxylic acid (VIII) by the superimposable IR spectra. In the above procedure, the filtrate on the first collection of the acid (VIII)

was concentrated, and the residue was steam-distilled to expel the nitrobenzene, and the remaining aqueous solution was extracted with benzene, followed by the usual treatment to yield 80 mg. of red brownish resin, which was purified by chromatography on alumina (2 g.) eluted with $CHCl_3$ and again by chromatography on alumina (2 g.) eluted with benzene yielding 10 mg. of the yellow brownish oil (In its IR spectrum, the carbonyl absorption is very weak, and the whole chart is similar to that of the starting material.), and 40 mg. of the orange solid (IR : ν_{CHO} 2730 cm^{-1}; $\nu_{C=O}$ 1680 cm^{-1}). The former was thus discarded, and the latter was assigned the aldehyde (IX) by its IR spectrum, which was further confirmed by yielding the carboxylic acid (VIII) on oxidation with H_2O_2.

The Oxidation of IX with Hydrogen Peroxide——To a solution of the aldehyde (IX, 40 mg.) in acetone (2 ml.) was added 0.02 ml. of 30% H_2O_2, and the whole mixture was allowed to stand at room temperature for 1 hr., then heated at 36° for 6.5 hr. After cooling, 30% H_2O_2 (0.03 ml.) was added and the mixture was allowed to stand at room temperature for two nights. The acetone was removed under a stream of N_2 to leave the residue, to which was added H_2O (2 ml.). The resulting whole mixture was refluxed for 2 hr., and on cooling the mixture was extracted with benzene and the solvent was removed to leave the residue, whose IR spectrum was in agreement with that of the starting material. Subsequently, the reaction mixture was extracted with AcOEt, from which extract the solvent was removed to leave the solid (5 mg.). This was identified with the acid (VIII) by the superimposable IR spectra. The direct comparison by a mixed melting point test was impossible on account of shortage of the material.

Methyl 3-Bromo-5-isoquinolinecarboxylate (X)——3-Bromo-5-isoquinolinecarboxylic acid (1.24 g.) was dissolved in $SOBr_2$ (23 g.) on heating at 70°, and the resulting solution was kept at 80~83° for 15 min., during which time the vigorous evolution of HBr gas was observed. The excess of $SOBr_2$ was removed *in vacuo* to leave the hemi-solidal residue, to which was added abs. MeOH. The whole solution was refluxed for 30 min. and then the excess MeOH was removed, to which residue was added H_2O. The separated oil was taken up in ether-benzene and the aqueous layer was further extracted with the same solvent several times. The extract was shaken with 10% $NaHCO_3$ to remove the unreacted carboxylic acid, and then dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from MeOH to afford 1.37 g. of yellow brownish crystals, which were again dissolved in MeOH and treated with active charcoal. The MeOH was removed and the residue was again recrystallized from MeOH to yield 1.29 g. (98.6%) of colorless needles, m.p. 127°. *Anal.* Calcd. for $C_{11}H_8O_2NBr$: C, 49.62; H, 3.00; N, 5.26; Br, 30.07. Found : C, 49.63; H, 3.17; N, 5.41; Br, 30.71. IR : $\nu_{C=O}$ 1710 cm^{-1}.

Alstoniline Hydrochloride (I, X= Cl)——A solution of 3-(2-bromoethyl)-6-methoxyindole (XI. X=Br; 239 mg.) and methyl 3-bromo-5-isoquinolinecarboxylate (X; 250 mg.) in abs. benzene (10 ml.) was heated at 70~75° under a stream of N_2 for 30 min., during which time no change was recognized. The temperature was raised to 75~80° and the whole was kept at this temperature for 10 hr. In ca. 2 hr., the red brown precipitate began to deposit on the wall of the vessel. Since the rate of deposition was not remarkable, the benzene as a solvent was substituted by toluene, and the whole mixture was heated at 90~95° for 6 hr. The toluene was removed, and abs. ether (10 ml.) was added, then the whole was refluxed for 15 min., and decanted. The ether extraction in the above manner was repeated three times to remove the starting material, and there was obtained 257 mg. of ether-insoluble red brownish solid, which was treated with AgCl in MeOH in the usual manner to yield the corresponding chloride as a reddish powder. The chloride was recrystallized from MeOH to give 80 mg. (43%) of crude alstoniline hydrochloride as a red purple powder. This powder (40 mg.) was subjected to chromatography on active charcoal (0.5 g.) eluted with MeOH to afford an orange-red powder, whose UV spectrum was identical with that of the natural alstoniline sulfate (I, X=1/2SO_4), kindly supplied by Professor Elderfield (Cf. Fig. 1).

The synthetic sample of the foregoing alstoniline hydrochloride (I, X=Cl, 40 mg.) was recrystallized from MeOH several times to afford fine orange-red needles, 4 mg. of which was dissolved in MeOH (1 ml.). To the resulting solution was added a solution of sodium picrate (2.5 mg.) in MeOH and the precipitate was collected on filtration, and recrystallized from MeOH twice to afford 3.5 mg. of red plates, m.p. 291° (decomp.), which was directly compared with the picrate, red plates, m.p. 294° (decomp.) derived from the natural alkaloid. The identity of both samples (I, X=picrate ion) was established by the mixed melting point determination and was further confirmed by their identical IR spectra which were shown in Fig. 2.

The whole procedure was repeated using toluene instead of benzene from the start of reaction. Namely, a solution of XI (X=Br, 486 mg.) and X (886 mg.) in dry toluene (20 ml.) was heated at 90~98° under a stream of N_2 for 25 hr. The red brownish powder deposited and was collected by filtration. The solid was mixed with ether, and the whole refluxed to remove the ether-soluble unreacted material. The extraction was repeated several times. The ether-insoluble substance was treated with AgCl in MeOH to afford 495 mg. of black brownish caramel, which was subjected to chromatography on active charcoal (2 g.) and cellulose powder (5 g.). The elution with MeOH gave the red purple powder (160.9 mg.), which was mixed with dry benzene, and the mixture was refluxed to remove the benzene-soluble material on warming. The benzene extract afforded a purple powder which was recry-

stallized from MeOH–benzene to yield 42 mg. of pale purple needles, m.p. 241° (decomp.). This compound showed a positive reaction in the $FeCl_3$ test, but the structure has not yet been decided. The benzene-insoluble orange red powder (12.5 mg., 1.65%) was recrystallized from MeOH to afford 8 mg. (1.06%) orange red needles, which decomposed over a wide range without melting on melting point determination, but its UV spectrum was identical with that of the natural alkaloid (Fig. 1). *Anal.* Calcd. for $C_{22}H_{19}O_3N_2Cl \cdot 2.5H_2O$: C, 60.06; H, 5.46. Found : C, 60.01; H, 5.13.

Synthetic sample : UV λ_{max}^{EtOH} mμ (log ε) : 395 (4.53), 290 (3.94, shoulder); λ_{min}^{EtOH} mμ (log ε) : 306 (3.72). The natural alkaloid : UV λ_{max}^{EtOH} mμ (log ε) : 395 (4.57), 290 (3.94, shoulder); λ_{min}^{EtOH} mμ (log ε) : 306 (3.73). (lit.[2c]) UV λ_{max} mμ (log ε) : 380 (4.4), 280 (3.88, shoulder); λ_{max} mμ (log ε) : 306 (3.68). This hydrochloride was derived to the picrate, m.p. 291°, identical with an authentic sample (m.p. 294°) of the natural alkaloid. Also, methyl 3-bromo-5-isoquinolinecarboxylate (X, 570 mg.) was recovered from the ether extract in the above procedure.

(ii) 2-(6-Methoxyindol-3-yl)ethyl *p*-toluenesulfonate (XI, X=OTs) was substituted for 3-(2-bromoethyl)-6-methoxyindole (XI, X=Br) as a component in this condensation.

To a solution of methyl 3-bromo-5-isoquinolinecarboxylate (X, 532 mg.) in dry toluene (20 ml.) was added a solution of 2-(6-methoxyindol-3-yl)ethyl *p*-toluenesulfonate (XI, X=OTs; 530 mg.) in dry dioxane (3 ml.), from which the dioxane was evaporated *in vacuo*. The residual mixture was heated at 60~70° under a stream of N_2 for 16 hr. The red brownish powder deposited and was collected by filtration. The substance was mixed with benzene and ether, then refluxed to remove the unreacted starting material.

There was obtained 386 mg. of a red purple powder, whose UV spectrum (λ_{max}^{EtOH} mμ : 515, 330 (shoulder); λ_{min}^{EtOH} mμ : 392, 295) was different to a small extent from that of alstoniline. This was treated with the freshly prepared AgCl in MeOH, the MeOH was concentrated and the residue was purified by chromatography on charcoal to afford 5.5 mg. (1.4%) of orange red needles, which were identified with the natural alkaloid in the foregoing manner. Methyl 3-bromo-5-isoquinolinecarboxylate (180 mg.) was recovered from the above benzene-ether extract.

The authors express their deep gratitude to Prof. R. C. Elderfield for his gracious gift of alstoniline sulfate, and to Dr. W. T. Sumerford, Mead Johnson Research Center, for kindly supplying 6-methoxyindole. Thanks are also due to the members of the Central Analysis Room of this Faculty for elemental analyses, and to the Ministry of Education for Grant-in-Aid for the Institutional Research in aid of this work.

Summary

The total synthesis of alstoniline, an alkaloid of *Alstonia constricta* F. MUELL, was achieved by applying a new synthetic method of β-carboline derivatives which has been being developed in this laboratory.

(Received July 15, 1964)