2-Methylimidazo[2,1-*b*]benzothiazole (XIV) from XVI——2-Acetylimino-3-acetonyl-2,3-dihydrobenzothiazole hydrobromide (XVI) (500 mg.) was refluxed with 2*N* HBr solution (20 ml.) for 20 min. The reaction mixture was evaporated under reduced pressure to dryness to afford a crystalline substance. Recrystallization from EtOH gave 2-methylimidazo[2,1-*b*]benzothiazole hydrobromide, m.p. 284~286° (400 mg.). *Anal.* Calcd. for $C_{10}H_9N_2SBr$: C, 44.62; H, 3.37; N, 10.41. Found : C, 44.39; H, 3.44; N, 10.83.

2-(2-Propynylthio)benzimidazole Hydrobromide (XVIII)——To 2-benzimidazolethiol (XVII)(7.5 g.) in abs. EtOH (200 ml.) was added propargyl bromide (6 g.) and the reaction mixture was heated on a water bath (80°) for 5 hr. The EtOH was evaporated under reduced pressure and the crystalline residue was recrystallized from abs. EtOH giving 2-(2-propynylthio)benzimidazole hydrobromide (XVIII) of m.p. 175~178° (11.3 g.). One more recrystallization from EtOH gave a sample of m.p. 179~180°. *Anal.* Calcd. for $C_{10}H_9N_2SBr$: C, 44.72; H, 3.38; N, 10.43. Found : C, 44.68; H, 3.38; N, 10.44. IR λ_{max}^{Nujol} μ : 3.13 (C≡C-H), 4.72 (C≡C).

3-Methylthiazolo[3,2-*a*]benzimidazole (XIX)——2-(2-Propynylthio)benzimidazole hydrobromide (XVIII) (1 g.) was suspended in abs. EtOH (40 ml.) and to this suspension was added Na (2 g.) in abs. EtOH (40 ml.). Then the reaction mixture was refluxed for 3 hr. About half the EtOH was evaporated under reduced pressure. The residue was poured into H_2O and the resulting crystalline substance was collected by filtration, washed with H_2O and dried (670 mg.). Recrystallization from 95% EtOH gave 3-methylthiazolo[3,2-*a*]benzimidazole (XIX) of m.p. 161~162° (542 mg.), which on admixture with the authentic sample[7] showed no depression in melting point. *Anal.* Calcd. for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found : C, 63.77; H, 4.35; N, 14.86. NMR : 7.31 τ ($-CH_3$).

The authors are grateful to Mr. M. Matsui, director of this laboratory and Prof. K. Tsuda of the University of Tokyo for encouragement throughout this work. The measurement of IR, UV and NMR spectra were carried out by Messrs. H. Higuchi, C. Fujimura, Misses. N. Sawamoto and Y. Nakajima. Microanalyses were made by Messrs. K. Ono, H. Nagashima, Misses. K. Saito, N. Gonda and H. Masuda to whom the authors' thanks are also due.

Summary

Intramolecular cyclization of propargylammonium halide derivatives was carried out giving methylated heterocyclic aromatic compounds with fused thiazole and imidazole nuclei. Some of these reactions were accompanied by rearrangement which might be caused by ring opening of the quaternary heterocyclic compounds.

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117. Akira Ogiso and Issei Iwai : An Approach to Synthesis of Diterpenoid Alkaloids. V.[*1] Total Synthesis of a Degradation Product of Atisine.[*2]

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A number of the investigations[1] on the synthesis of the diterpenoid alkaloids atisine and garryfoline have been carried out during last two or three years. Recently, Nagata and co-workers[2] have accomplished the total synthesis of atisine utililizing the angular

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cyanation reaction. Previously,[3] we reported that the characteristic A/E bicyclic ring system of the diterpenoid alkaloids could be successfully constructed using the Mannich reaction,[4] in which an A/B transfused tetracyclic compound (I) was obtained. Starting from this compound (I), we succeeded in the stereospecific synthesis of a degradation product (XII) of the naturally occuring diterpeniod alkaloids atisine and veatchine. This degradation product (XII) is a key compound proving that atisine and veatchine as well as the related diterpenoid alkaloids, garryfoline, atidine and ajaconine, all have the same A, B, C, E ring-structure and stereochemistry.[5] Moreover, this product possesses all of the asymmetric carbon atoms necessary for the total synthesis of these diterpenoid alkaloids.

Birch reduction of the tetracyclic anisole derivative (I) with lithium and ethanol in liquid ammonia, followed by treatment with hydrochloric acid gave the α,β-unsaturated ketone (II) which showed an ultraviolet absorption maximum at 240 mμ (ε 16,400). The stereochemistry of C-9 hydrogen was assigned the more stable *trans*-configuration to C-10 hydrogen. The α,β-unsaturated ketone (II) was reduced with lithium tri-butoxyaluminum hydride to the allyl alcohol (III), m.p. 120~121°, showing infrared absorption bands at 3620 (hydroxy) and 1668 (double bond) cm^{-1}. This allylic alcohol would have a quasi-equatorial conformation, since the carbonyl group of the α,β-unsaturated keto-compound (II) is little hindered and the quasi-equatorial isomer (III), the more stable form, was predominantly formed (ca. 80%).[6]

Introduction of the angular substituent at C-8 was accomplished in 42% overall yield by Burgstahler method[7] as follows. Treatment of the allyl alcohol (III) with ethyl vinyl ether in the presence of mercuric acetate gave the vinyl ether (IV) which showed absorption bands at 1634 and 1611 cm^{-1} due to the two double bonds. The vinyl ether (IV) rearranged at 195° in decalin into the unsaturated aldehyde (V), m.p. 75~77°, possessing a *cis*-fused B/C ring juncture. Recently, Ireland, *et al.*,[8] have reported the successful construction of the C/D ring system of both atisine and garryfoline starting from the unsaturated aldehyde (XIII), therefore, the synthetic unsaturated aldehyde (V) must be a suitable precursor for the total synthesis of these alkaloids.

Catalytic hydrogenation of this aldehyde (V) over palladium-charcoal gave the saturated aldehyde, (VI), m.p. 109~110°, which reacted with phenylmagnesium bromide yielding the phenylcarbinol (VII). Dehydration of the phenylcarbinol (VII) by heating under reflux with *p*-toluenesulfonic acid in benzene for 10 hours afforded the styrene derivative (VIII). This compound (VIII) showed ultraviolet absorption maxima at 253 (14,800), 285 (1,470) and 294 mμ (1,120), and the infrared absorption band at 1648 cm^{-1} due to a conjugated double bond.

In order to remove the methyl group of the tertiary amine, the N-methyl of the stylene derivative (VIII) was converted into the N-cyano group by the von Braun method. The infrared spectrum of the N-cyano compound (IX), m.p. 180~181°, showed the characteristic cyanogen absorption at 2210 cm^{-1}. Decyanation was successfully carried out with lithium aluminum hydride[9] to form the secondary amine (X), which gave a hydro-

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chloride melting at 214~216°. The secondary amine was acetylated in the usual way to give the acetate (XI), m.p. 202~203°, which could be obtained in 71% overall yield from the N-methyl styrene derivative (VII). The styrene group of the acetate (XI) was cleavaged with sodium metaperiodate and potassium permanganate[10] to give the carboxylic acid, which was treated with diazomethane affording the methyl ester (XII) in 63% yield.

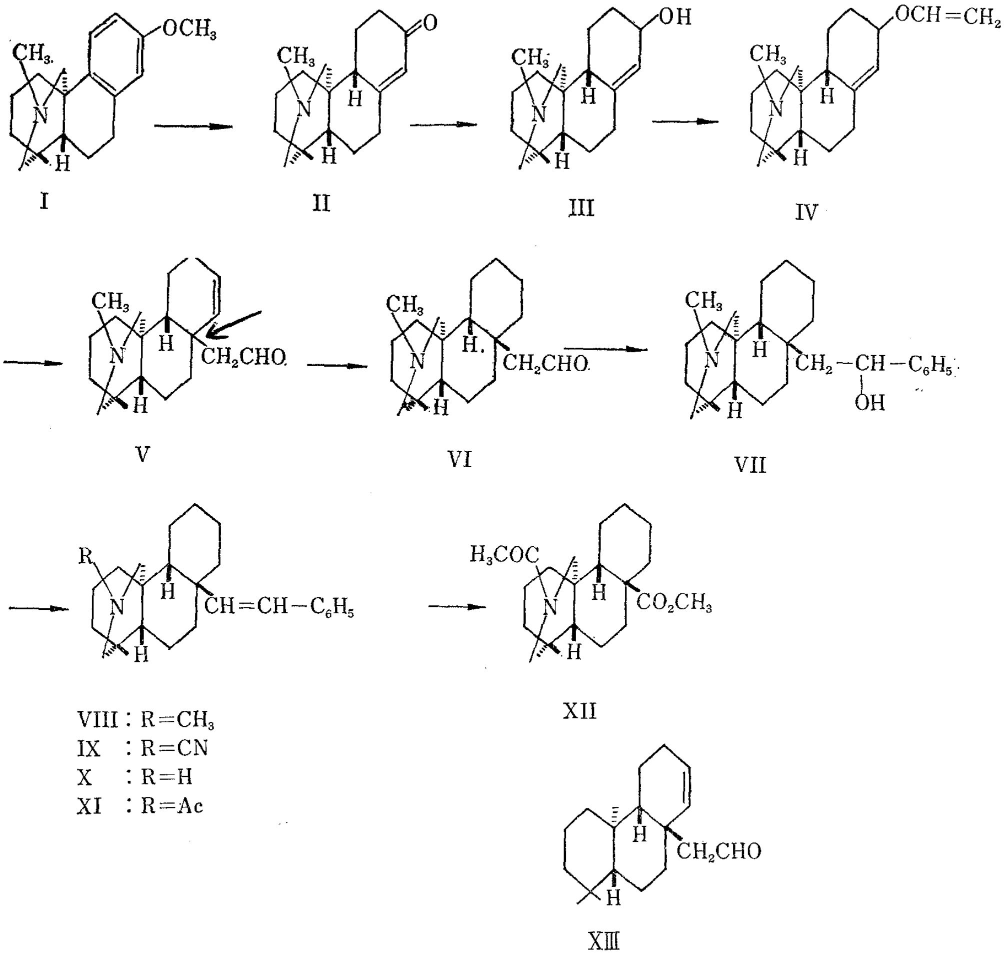

Chart 1.

Elemental analysis of this N-acetyl carboxylic ester (XII), m.p. 158~159°, was in agreement with the composition $C_{21}H_{33}O_3N$. Furthermore, the infrared spectrum measured in chloroform showed absorption bands at 1715 cm^{-1} (CO_2CH_3) and 1621 cm^{-1} ($NCOCH_3$), coinciding with that of a degradation product of both veatchine and atisine.

Experimental

Birch Reduction of the Tricyclic Anisole Compound (I)——To a mixture of 350 ml. of liq. NH_3 and 100 ml. of tetrahydrofuran was added a solution of 4.0 g. of the anisole compound (I) in 80 ml. of Et_2O and 100 ml. of tetrahydrofuran. Fifteen minutes after 3.0 g. of finely cut Li was added, 40 ml. of EtOH was gradually added and kept on stirring for 1 hr. Furthermore, 3.0 g. of Li was added and the stirring was continued for another 3 hr. The reaction mixture was allowed to stand overnight at room temperature to evaporate NH_3, poured into ice H_2O and extracted with Et_2O. The ethereal extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent yielded 4.0 g. of crystal mass.

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A solution of 4.0 g. of the crystal mass in 80 ml. of MeOH and 60 ml. of 10% HCl was boiled under reflux for 3 hr. After removal of the solvent, the reaction mixture was made alkaline with dil. NH_4OH and extracted with Et_2O. The ethereal extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from petr. ether yielded 2.4 g. of colorless prisms, m.p. 99~100°. UV : λ_{max}^{EtOH} 240 mμ (log ε 4.21). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1670 (C=O), 1633 (C=C). *Anal.* Calcd. for $C_{18}H_{27}ON$: C, 79.07; H, 9.95; N, 5.12. Found : C, 78.99; H, 9.81; N, 4.83.

Reduction of the α,β-Unsaturated Ketone (II)——To a solution of 4.0 g. of the α,β-unsaturated ketone (II) in 40 ml. of tetrahydrofuran was gradually added a solution of 8.0 g. of $LiAl(\textit{t}\text{-}BuO)_3H$ in 50 ml. of tetrahydrofuran at −10°. After the reaction mixture was allowed to stand overnight, the excess reagent was destroyed with cold H_2O. The resulted precipitate by addition of Et_2O was filtered, and the filtrate was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from petr. ether yielded colorless needles, m.p. 120~121°. This product was shown to be a pure product by thin-layer chromatography (silica gel G, $CHCl_3$-MeOH=3:1). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3620 (OH), 1668 (C=C). *Anal.* Calcd. for $C_{18}H_{29}ON$: C, 78.49; H, 10.62; N, 5.09. Found : C, 78.46; H, 10.51; N, 4.73.

The Vinyl Ether (IV) from the Allyl Alcohol (III)——A solution of the allyl alcohol (III) and 1.5 g. of freshly recrystallized $HgAc_2$ in 120 ml. of purified ethyl vinyl ether was refluxed for 10 hr., with an additional 0.5 g. of $HgAc_2$ being added every 2 hr. After extraction with cold aq. K_2CO_3, the solution was dried over K_2CO_3, and evaporated. The residual oil was chromatographed on basic alumina (90 g.). Petr. ether eluates yielded 3.0 g. of colorless oil. IR ν_{max}^{liquid} cm^{-1} : 1634, 1611 (C=C).

Pyrolysis of the Vinyl Ether (IV)——A solution of 3.0 g. of the vinyl ether (IV) in 30 ml. of redistilled decalin was heated in a sealed tube at 195° for 5 hr. Evaporation of solvent on a steam bath at reduced pressure left 3.0 g. of a colorless oil. Recrystallization from MeOH gave plates, m.p. 75~77°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1715 (HC=O), 1660 (C=C). *Anal.* Calcd. for $C_{20}H_{31}ON$: C, 79.67; H, 10.37; N, 4.65. Found : C, 79.71; H, 10.51; N, 4.46.

Catalytic Reduction of the Unsaturated Aldehyde (V)——A mixture of 2.9 g. of the unpurified unsaturated aldehyde (V) and 3.0 g. of 10% Pd-C in 90 ml. of EtOH was hydrogenated at atmospheric pressure. After the uptake of 1 mole of H_2 ceased, the catalyst was filtered, the filtrate was evaporated to dryness, and chromatographed on neutral alumina (grade II, 100 g.). Hexane eluates yielded 1.4 g. of the saturated aldehyde (VI), forming prisms from petr. ether, m.p. 109~110°. IR : $\nu_{max}^{CHCl_3}$ 1719 cm^{-1} (HC=O). *Anal.* Calcd. for $C_{20}H_{33}ON$: C, 79.15; H, 10.96; N, 4.62. Found : C, 79.43; H, 10.85; N, 4.79.

Grignard Reaction of the Aldehyde (VI)——To a grignard's solution, prepared from 510 mg. of Mg and 3.5 g. of bromobenzene in 30 ml. of Et_2O, was added a solution of 1.2 g. of the aldehyde (VI) in 30 ml. of Et_2O under ice-cooling. After standing overnight at room temperature, the reaction mixture was poured into NH_4Cl saturated cold H_2O and extracted with Et_2O. The ethereal extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residual oil was chromatographed on alumina (grade II, 45 g.). Hexane eluates gave 50 mg. of an oil, and benzene eluates yielded 1.3 g. of an amorphous solid which was shown to be a pure substance by thin-layer chromatography (silica gel G, $CHCl_3$-MeOH =5:1). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3620 (OH), 1610, 1500 (aromatic C=C). *Anal.* Calcd. for $C_{26}H_{39}ON$: C, 81.83; H, 10.30; N, 3.67. Found : C, 81.71; H, 9.93; N, 3.99.

Dehydration of the Phenylcarbinol (VII)——A solution of 1.2 g. of the phenylcarbinol (VII) and 500 mg. of toluene-*p*-sulfonic acid in 50 ml. of benzene was boiled azetoropically with an additional benzene for 10 hr. The reaction mixture was washed with aq. $NaHCO_3$, H_2O, dried over Na_2SO_4 and evaporated to dryness. The residual oil was chromatographed on alumina (grade II, 40 g.) in hexane to give 900 mg. of a colorless oil. UV $\lambda_{max}^{cyclohexane}$ (log ε) : 253 (4.17), 285 (3.17), 294 (4.05). IR ν_{max}^{liquid} cm^{-1} : 1646 (C=C), 1581, 1500 (aromatic C=C).

N-Cyanation of the Styrene Derivative (VIII)——To a solution of 900 mg. of the styrene derivative (VIII) in 15 ml. of $CHCl_3$ was added a solution of 500 mg. of BrCN in 10 ml. $CHCl_3$, and the mixture was heated under reflux for 5 hr. The reaction mixture was washed with 5% HCl, H_2O, and dried over Na_2SO_4. Evaporation of the solvent to dryness yielded the crystalline N-cyano compound (IX) which was recrystallized from Me_2CO to give 800 mg. of colorless prisms, m.p. 180~181°. IR : ν_{max}^{KBr} 2210 cm^{-1} (C≡N). *Anal.* Calcd. for $C_{26}H_{34}N_2$: C, 83.37; H, 9.15; N, 7.48. Found : C, 83.14; H, 9.03; N, 7.63.

Reduction of the N-Cyano Derivative (IX)——To a solution of 400 mg. of $LiAlH_4$ in 40 ml. of Et_2O was gradually added a solution of 750 mg. of the N-cyano derivative (IX) in 7 ml. of tetrahydrofuran and 3 ml. of Et_2O at room temperature. The reaction mixture was heated under reflux for 4 hr. under stirring, after cooling, the excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O. After filtration, the mixture was extracted with 5% HCl. The extract was washed with Et_2O and evaporated at reduced pressure to give a crystalline residue which was recrystallized from MeOH to yield 700 mg. of prisms, m.p. 214~216°. IR ν_{max}^{KBr} : 1584 cm^{-1} (NH_2^+). *Anal.* Calcd. for $C_{25}H_{35}N\cdot HCl$: C, 77.79; H, 9.18; N, 3.63. Found : C, 77.01; H, 9.59; N, 3.43.

Acetylation of the Secondary Amine (X)——A solution of 650 mg. of the secondary amine (X) in 5 ml. of pyridine and 5 ml. of Ac_2O was allowed to stand overnight at room temperature. 450 mg. of prisms were crystallized in the reaction mixture. The mother liquor was poured into ice H_2O and extracted with Et_2O.

The extract was washed with 5% HCl, H_2O, dried over Na_2SO_4 and evaporated to give 150 mg. of prisms. The combined prisms were recrystallized from MeOH to obtain 580 mg. of acetate (XI), m.p. 202~203°. IR : $\nu_{\max}^{KBr}$ 1648 cm^{-1} ($NCOCH_3$). *Anal.* Calcd. for $C_{27}H_{37}ON$: C, 82.81; H, 9.61; N, 3.58. Found : C,82.57; H, 9.52; N, 3.44.

The N-Acetyl Carboxylic Ester (XII) from the N-Acetyl Styrene Derivative (XI)——To a solution of 540 mg. of the styrene derivative (XI) and 100 mg. of K_2CO_3 in 200 ml. of dioxane and 80 ml. of H_2O was added a solution of 2.1 g. of $NaIO_4$ and 50 mg. of $KMnO_4$ in 80 ml. of dioxane and 80 ml. of H_2O. The reaction mixture was stirred for 20 hr. at room temperature. After the excess oxidation reagent was decomposed with $NaHSO_3$, the solvent was concentrated in reduced pressure. The residue was poured into H_2O, extracted with Et_2O. The ethereal extract was dried over Na_2SO_4 and evaporated to give 550 mg. of an amorphous product.

The nonpurified carboxylic acid was dissolved in 50 ml. of Et_2O and a solution of CH_2N_2 in 20 ml. of Et_2O, prepared from 2 ml. of nitrosomethylurethane, was gradually added to the solution under ice-cooling. The reaction mixture was allowed to stand overnight and the excess CH_2N_2 and solvent were concentrated to dryness. The residual oil was chromatographed on alumina (grade I, 30 g.). Benzene elutes gave 80 mg. of methyl benzoate, and Et_2O elutes gave 430 mg. of N-acetyl carboxylic ester (XII) which was recrystallized from Me_2CO to yield 300 mg. of colorless prisms, m.p. 158~159°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1715 (CO_2CH_3), 1612 ($NCOCH_3$). *Anal.* Calcd. for $C_{21}H_{33}O_3N$: C, 72.58; H, 9.57; N, 4.03. Found : C, 72.85; H, 9.55; N, 3.59.

We thank Mr. M. Matsui, the Director of this Laboratory for his encouragement and Dr. S. W. Pelletier, Professor of the University of Georgia for kindly sending us the infrared spectra of the degradation product of atisine and veatchine and for his valuable discussion.

Summary

The tetracyclic anisole compound (I) was converted into the N-acetyl carboxylic ester (XII). The infrared spectrum of the latter was coincided with that of a degradation product of atisine and veatchine.

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UDC 543.41[547.92]-4

118. **Kazukichi Kato** : A New Color Reaction of Steroid with Anhydrous Aluminum Chloride and Anisaldehyde. III.*[1] A Method for the Colorimetric Determination of Allylestrenol.

(*Shinagawa Factory, Sankyo Co., Ltd.**[2])

In the first paper of this series,[1] a colorimetric determination of ethylestrenol(17α-ethyl-17β-hydroxyestr-4-ene) with anhydrous aluminum chloride and anisaldehyde was reported. Since several derivatives of estrenol are used for various therapeutic purposes, a method of assay which is selective and generally applicable to them is urged to be established.

The present work deals with a method for the colorimetric determination of allylestrenol(17α-allyl-17β-hydroxyestr-4-ene) which is used as a pure gestagen. There was no report on the assay of this steroid, and for lack of the selective color reaction the

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*[1] Part II : This Bulletin, **12**, 582 (1964).

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[1] K. Kato : This Bulletin, **12**, 578 (1964).