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Michael Addition of [1*H*]Pyrrole[1)]

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[1*H*]Pyrrole (IIa) was reacted with 2-chloroethyl tosylate (III) in acetone in the presence of potassium hydroxide (condition A) to give 1-(4-oxo-2-methyl-2-pentyl)[1*H*]-pyrrole (IV) instead of 1-(2-tosyloxyethyl)[1*H*]pyrrole (IIb). IV was obtained from the reaction of IIa and mesityl oxide (V) in acetonitrile in the presence of potassium hydroxide (condition B).

With IIa under condition B, crotononitrile, ethyl crotonate, and 4,4-dimethyl-2-cyclohexenone (IX) gave 3-(1-[1*H*]pyrrolyl)butyronitrile (VIIa), 3-(1-[1*H*]pyrrolyl)butyric acid (VIIIa), and a mixture of 4,4-dimethyl-3-(1-[1*H*]pyrrolyl)cyclohexanone (X) and 1-cyanomethyl-4,4-dimethyl-3-(1-[1*H*]pyrrolyl)cyclohexanol (XI), respectively.

Keywords——Michael addition; [1*H*]pyrrole; conjugate addition; acetylpyrrole; cyclohexenone; crotononitrile; pyrrole *N*-alkylation

In connection with our studies on the synthesis of the 9,13-diazasteroid system, we found that the *N*-alkylation of the pyrrole ring of 2-(2-quinolyl)[1*H*]pyrrole (I) with methyl iodide or 2-chloroethyl tosylate (III) could be performed in the presence of potassium hydroxide (5 molar equivalents) in acetone (condition A).[2)] To examine the feasibility of *N*-alkylation of [1*H*]pyrrole (IIa) itself, IIa was treated with III under condition A. The material obtained after work-up exhibited an absorption maximum at 1700 cm^{-1} in the infrared (IR) spectrum, and in the nuclear magnetic resonance (NMR) spectrum it exhibited three singlet peaks at δ 1.56, 1.60 and 2.65 ppm with a relative intensity of 6: 3: 2 and two nearly singlet peaks at δ 5.98 and 6.66 ppm with a relative intensity of 2: 2. The mass spectrum (MS) showed the parent peak at *m/e* 165 as an intense peak. It was suggested from these physical data that the product was not the expected product, 1-(2-tosyloxyethyl)[1*H*]pyrrole (IIb), but 1-(4-oxo-2-methyl-2-pentyl)[1*H*]pyrrole (IV). The same product was obtained from the reaction of IIa and methyl iodide under condition A. It was verified that IV was formed by the Michael addition of IIa to mesityl oxide (V), the base-catalyzed product of acetone, in the presence of potassium hydroxide. In fact, IV could be obtained from the reaction of IIa and V in acetonitrile in the presence of potassium hydroxide (condition B) in 72.7% yield. In the NMR spectrum of IV, the signal due to the acetyl methyl group appeared at abnormally high field. This may be attributed to the anisotropy of the pyrrole ring. The difference in behavior with alkyl halide between I and IIa could be explained in terms of acidity of the pyrrole ring; the quinoline ring in I withdraws electrons from the pyrrole ring and the acidity of the pyrrole increases. As an example, 2-acetyl[1*H*]pyrrole (VIa) could be alkylated with methyl iodide under condition A to give 2-acetyl-1-methyl[1*H*]pyrrole (VIb) in good yield.

IIa could be alkylated with benzyl bromide under condition B to give 1-benzyl[1*H*]pyrrole (IIc) in an acceptable yield. IIc could also be obtained using a phase catalyst or crown ether[3)] catalyst starting with the same materials.

Only a few examples of Michael addition reactions of IIa have appeared in the literature.[4)] The only acceptor used in this reaction was acrylonitrile and the reaction was carried out in dioxane or without solvent using Triton B as a catalyst. Crotononitrile was treated with IIa in the presence of methanolic Triton B in the absence of solvent (condition C). The product exhibited a single peak in gas-liquid chromatography (GLC). The retention time (t_R) was

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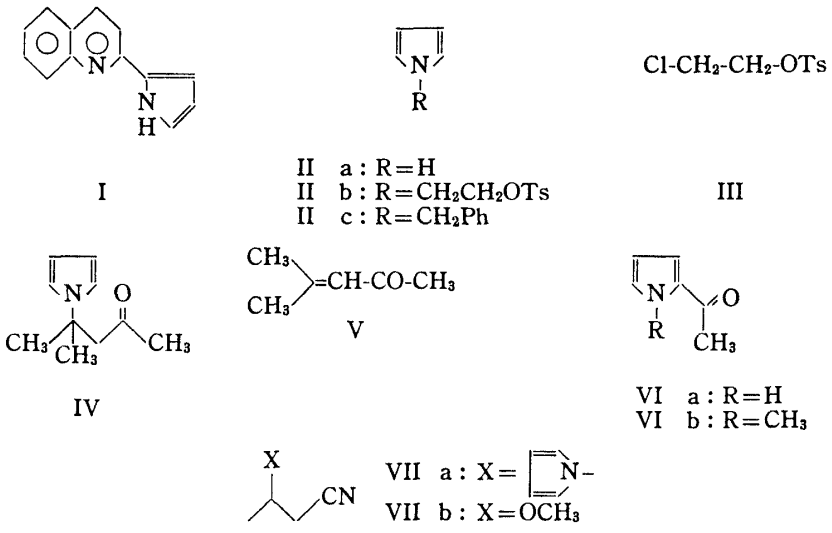

Chart 1

11 min (column temperature: 110°C). However, the NMR spectrum showed that the product was a mixture of at least two products. On the other hand, crotononitrile was treated with IIa under condition B to give a sole product, which was identified as 3-(1-[1*H*]pyrrolyl)butyronitrile (VIIa) from the elemental analysis and the physical data. The yield was 66.3%. The t_R of VIIa was also 11 min in GLC (column temperature: 110°C). The NMR spectrum of VIIa was partially identical with that of the mixture obtained in the former reaction. It was suggested from the analysis of the NMR spectrum that the other product in the former reaction was 4-methoxybutyronitrile (VIIb), and an authentic sample was prepared from crotononitrile and sodium methoxide. The formation of VIIb was ascribed to the use of methanolic Triton B. The yields of VIIa and VIIb from IIa under condition C were 51 and 25.5%, respectively. Thus, it was found that the potassium hydroxide-acetonitrile system, condition B, was more suitable for the Michael addition of IIa than the Triton B system.

Next, ethyl crotonate was chosen as an acceptor. In this case the Michael adduct, but the hydrolyzed product, 3-(1-[1*H*]pyrrolyl)butyric acid (VIIIa), was obtained in 85.0% yield.

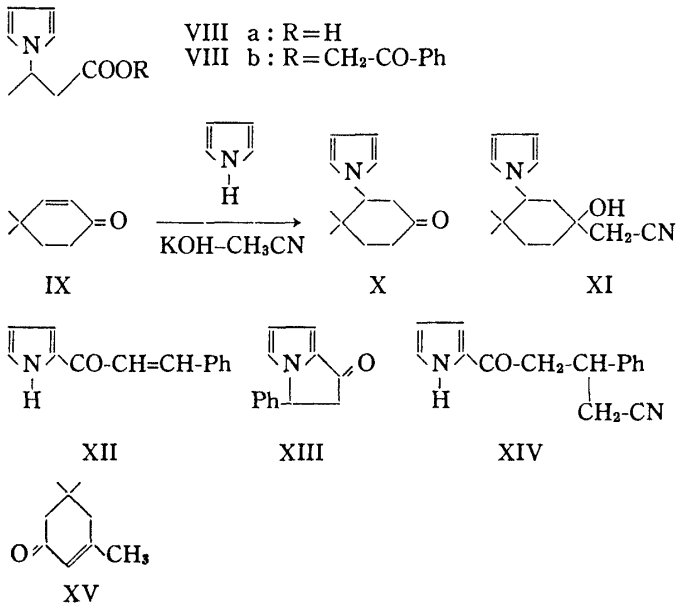

Chart 2

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The NMR spectrum showed a broad singlet peak at δ 11.43 ppm due to the proton of the carboxyl group. VIIIa was derived to the corresponding phenacyl derivative (VIIIb), which melted at 57—59°C.

Furthermore, 4,4-dimethyl-2-cyclohexenone (IX) was treated with IIa under condition B. In this case, 4,4-dimethyl-3-(1-[1*H*]pyrrolyl)cyclohexanone (X) as an oil and 1-cyanomethyl-4,4-dimethyl-4-(1-[1*H*]pyrrolyl)cyclohexanol (XI) as a crystalline compound were obtained in yields of 17.8 and 35.8%, respectively.

The intramolecular Michael type cyclization of 2-cinnamoyl[1*H*]pyrrole (XII), prepared from VIa and benzaldehyde, to 2,3-dihydro-3-phenyl-1-[1*H*]pyrrolizinone (XIII) was unsuccessful under condition B, and 3-cyano-2-phenylpropyl 2-[1*H*]pyrrolyl ketone (XIV), a product of the intermolecular Michael addition of acetonitrile, was obtained in a conversion yield of 21.2%. XIV exhibited an absorption at 1640 cm^{-1} in the IR spectrum and two doublet peaks at δ 2.66 and 3.23 ppm due to the protons of the two methylenes in the NMR spectrum.

Finally, under condition B IIa did not react with 3,5,5-trimethyl-2-cyclohexenone (XV) at all. This phenomenone is probably attributable to an inductive or a steric effect of the methyl group at the C_3 position. However, further work on this point is desirable.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (a hot stage type) and are uncorrected. Silica gel (Wako C-200) and pre-coated thin-layer chromatography (TLC) plates (Merck silica gel $60F_{254}$) were used for column chromatography and TLC. GLC was carried out with 5% SE-30 (stainless column, 3 mm×2 m) as the liquid phase at an N_2 flow rate of 40 ml/min with Shimadzu GC-6AM. IR spectra were determined by using a JASCO IRA-1 diffraction grating spectrophotometer: absorption data are given in cm^{-1}. NMR spectra were recorded on a JEOL C-60H spectrometer with tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants (J) are given in δ and Hz, respectively. MS were measured with a JEOL TMS-01SG (70 eV, direct inlet system) spectrometer. All solvents were removed by evaporation under reduced pressure.

General Procedures for Alkylation in the Presence of KOH in Me_2CO (Condition A)[5] or CH_3CN (Condition B)——Powdered KOH (5 mol eq) was added to a solution of substrate in Me_2CO or CH_3CN. After 5 min, a Michael acceptor or alkyl halide (1 mol eq) in the same solvent was gradually added dropwise. The organic mixture was transferred to the separating funnel containing benzene after 20 min. The organic layer was washed with brine then dried over Na_2SO_4. The residue obtained after removal of the solvent was fractionally distilled or recrystallized.

1-(4-Oxo-2-methyl-2-pentyl)[1H]pyrrole (IV)——[1*H*]Pyrrole (IIa, 3.55 g) was alkylated with 2-chloroethyl tosylate (III) under condition A. The product was fractionally distilled (at 5 mmHg). From the first (~80°C) and the second (80—100°C) distillates, IV (3.2 g, 36.6%) and vinyl tosylate (1.6 g) were obtained, respectively. The residue of this distillation was mainly III (*ca.* 7g).

IV: GLC (150°C); t_R 5.6 min. IR (film): $\nu_{C=O}$ 1700. NMR (CCl_4): 1.56 (6H, s, geminal CH_3), 1.60 (3H, s, Ac), 2.65 (2H, s, $-CH_2CO$), 5.98 (2H, t, J=2, pyrrolyl β-H), 6.66 (2H, t, J=2, pyrrolyl α-H). MS *m/e* (%): 165 (M^+, 84), 108 (M–Ac, 48), 67 (pyrrole, base peak), 43 (Ac^+, 100). IV was also obtained from the reaction of IIa and methyl iodide (1 mol eq) under condition A (the yield was 60.6%), and from the reaction of IIa and mesityl oxide (V) under condition B (the yield was 72.7%).

Vinyl Tosylate: NMR (CCl_4): 2.3 (3H, s, $-CH_3$), 4.8 (1H, q, J=5, 2), 4.8 (1H, q, J=14, 2), 6.55 (1H, q, J=14, 5), 7.3 (2H, d, J=8), 7.7 (2H, d, J=8).

1-Benzyl[1*H*]pyrrole (IIc)——The yield was 61%. GLC (160°C): t_R 9.0 min (*cf.*, $PhCH_2Br$: t_R 3.1 min). NMR (CCl_4): 4.92 (2H, s, $>CH_2$), 6.08 (2H, t, J=2, pyrrolyl β-H), 6.52 (2H, t, J=2, pyrrolyl α-H), 6.7—7.4 (5H, m, phenyl H). ($CDCl_3$): 4.90 (2H, s), 6.15 (2H, s), 6.60 (2H, t), 6.8—7.4 (5H, m). [*cf.*, lit.[6] NMR ($CDCl_3$): 4.54 (2H, s), 6.23 (2H, t), 6.48 (2H, t), 6.75—7.15 (5H, m)].

2-Acetyl-1-methyl[1*H*]pyrrole (VIb)——2-Acetyl[1*H*]pyrrole (VIa) [prepared from IIa and acetic anhydride[7]] was methylated quantitatively to VIb with methyl iodide under condition A. NMR (CCl_4): 2.33 (3H, s, Ac), 3.86 (3H, s, $>N-CH_3$), 6.03 (1H, t-like, C_4–H), 6.83 (2H, m, C_3,5–H).

3-[1-[1*H*]Pyrrolyl)butyronitrile (VIIa) and 3-Methoxybutyronitrile (VIIb)——A mixture of IIa (0.67 g), crotononitrile (0.67 g), and 40% Triton B methanolic solution (0.2 ml) was stirred at 35—40°C for 1 h. The benzene layer containing the reaction product was washed with brine and dried. The residue obtained after removal of the solvent was microdistilled. bp <100°C (5 mmHg). 1.1 g. VIIa (51%) and VIIb (25.5%). GLC (110°C), t_R: 11 min. VIIa could be obtained from the same starting materials under condition B (the

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yield was 66.3%).

VIIa: bp <110°C (9 mmHg). IR (film) $\nu_{C\equiv N}$ 2260, δ_{CH} 720. NMR (CCl_4): 1.53 (3H, d, J=7, $\underline{CH_3}$-CH<) 2.56 (2H, d, J=7, $-CH_2-CN$), 4.33 (1H, m, >N-CH<), 6.10 (2H, t, J=2, pyrrolyl β-H), 6.67 (2H, t, J=2, pyrrolyl α-H). *Anal.* Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.36; H, 7.63; N, 20.58.

VIIb: IR (film): $\nu_{C\equiv N}$ 2260. NMR (CCl_4): 1.27 (3H, d, J=6, $\underline{CH_3}$-CH<), 2.43 (2H, d, J=6, $-CH_2-CN$), 3.45 (3H, s, $-OCH_3$), 3.60 (1H, m, >CH-O). An authentic VIIb was prepared from crotononitrile and NaOMe in MeOH.

3-(1-[1*H*]Pyrrolyl)butyric acid (VIIIa)——A mixture of IIa (0.67 g) and ethyl crotonate (1.2 g) was treated under condition B. No compound could be found in the benzene layer extracted from the basic solution. The basic solution was acidified with conc. HCl. The acidic layer was extracted with AcOEt, from which VIIIa was obtained. GLC (150°C) 3.7 min. The yield was 85.0%. NMR ($CDCl_3$): 1.42 (3H, d, J=6, CH_3-), 2.66 (2H, d, $>CH_2$), 4.50 (1H, m, >CH-N<), 5.97 (2H, t, J=1.5, pyrrolyl β-H), 6.55 (2H, t, J=1.5, pyrrolyl α-H), 11.43 (1H, s, -COOH).

VIIIa was phenacylated with phenacyl bromide to VIIIb, which was recrystallized from Et_2O. VIIIb: mp 57—59°C. IR (Nujol): $\nu_{C=O}$ 1738, 1705. NMR (CCl_4): 1.65 (3H, d, J=7, CH_3-), 2.80 (2H, d, J=8, $-CH_2CO$), 4.58 (1H, q, J=7, >N-CH<), 5.18 (2H, s, $>CH_2$), 6.00 (2H, t, J=2, pyrrolyl β-H), 6.44 (2H, t, J=2, pyrrolyl α-H), 7.3—8.2 (5H, m, phenyl H). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.89; H, 6.17; N, 5.06.

4,4-Dimethyl-3-(1-[1*H*]pyrrolyl)cyclohexanone (X) and 1-Cyanomethyl-4,4-dimethyl-3-(1-[1*H*]pyrrolyl)-cyclohexanol (XI)——IIa (0.67 g) was treated with 4,4-dimethyl-2-cyclohexenone (IX, 1.24 g)[8] under condition B. XI was obtained by recrystallization of the residue from Et_2O–hexane and the mother liquor was purified through a medium pressure SiO_2 column to give X and XI from the benzene eluates. The yields of X and XI were 17.8% and 35.8%, respectively. X: bp <140°C (3 mmHg). GLC (200°C): 2.6 min. IR (film): $\nu_{C=O}$ 1720, δ_{CH} 722. NMR (CCl_4): 0.90 and 1.07 (each 3H, s, $-CH_3$), 3.97 (1H, q, J=12, 6.5, >CH-N<), 6.02 and 6.51 (each 2H, br s, pyrrolyl H). *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.97; H, 9.07; N, 7.30. XI: mp 133—135°C. GLC (200°C): 7.2 min. IR (Nujol): ν_{OH} 3450, $\nu_{C\equiv N}$ 2260. NMR ($CDCl_3$): 0.90 (6H, s, 2×CH_3), 2.58 (2H, s, $-CH_2CN$), 4.12 (1H, q, J=10, 6, >CH-N<), 6.17 and 6.67 (each 2H, t, J=1.5, pyrrolyl H). *Anal.* Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.51; H, 8.86; N, 11.90.

2-Cinnamoyl[1*H*]pyrrole (XII)——To a mixture of VIa (0.9 g, 8.3 mmol) and benzaldehyde (0.88 g, 8.3 mmol), 10% NaOH (0.67 ml, 1.65 mmol) was added dropwise at room temperature. The mixture was stirred overnight. The precipitate was collected on a filter, and recrystallized from aq. EtOH. mp 140—142°C. The yield was 32.6%. IR (Nujol): $\nu_{C=O}$ 1600. NMR ($CDCl_3$): 6.35 (1H, m, C_4-H), 7.12 (2H, m, $C_{3,5}$-H), 7.2—8.1 (7H, m), 10.73 (1H, br s, >NH). MS *m/e*(%): 197 (M^+, base peak), 196 (M−1, 51).

3-Cyano-2-phenylpropyl 2-[1*H*]Pyrrolyl Ketone (XIV)——A solution of XII (0.47 g) in CH_3CN (30 ml) was treated under condition B. The crystallized residue obtained after removal of the solvent was recrystallized from aq. EtOH to give XII. The mother liquor was purified through an SiO_2 column to give XIV from the benzene fraction. XII: 145 mg, XIV: 84 mg (yield: 21.2%). IR (film): $\nu_{C=O}$ 1640, $\nu_{C\equiv N}$ 2270. NMR (CCl_4–$CDCl_3$): 2.66 and 3.23 (each 2H, d, $>CH_2$), 3.67 (1H, m, >CH-), 6.23 (1H, q, J=2.5, C_4-H), 6.96 (2H, t, J=2.5, $C_{3,5}$-H), 7.30 (5H, s, phenyl H), 10.76 (1H, br s, >NH).

XIV-2,4-Dinitrophenylhydrazone: mp 172—176°C (recrystallized from aq. EtOH). *Anal.* Calcd for $C_{21}H_{18}N_6O_4$: C, 60.28; H, 4.34; N, 20.09. Found: C, 59.97; H, 4.32; N, 20.19.

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References and Notes

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