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The Reactions of Activated Amides. VI.[1] The Reactions of 1-Methyl-2-pyrrolidone Dimethylacetal and 2-Methylmercapto-1-methyl-2-pyrroline with Dimethyl Acetylenedicarboxylate

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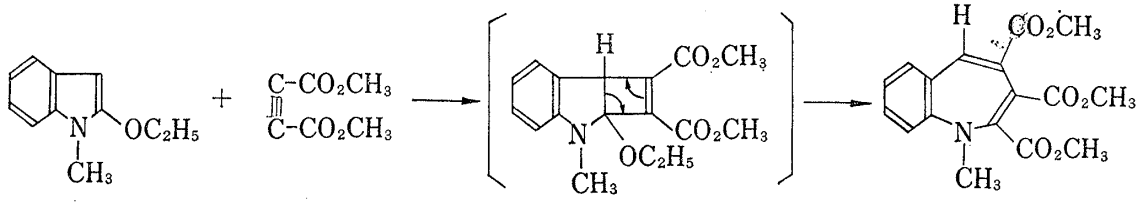
The reaction of 1-methyl-2-pyrrolidone dimethylacetal(IV) with dimethyl acetylenedicarboxylate(I) was carried out expecting the formation of the simple dihydroazepine derivative. However, the products actually obtained were the indoline derivative(VI), the isomeric pyrrolidone derivatives(VII and VIII) and the tetracarbomethoxy-1,3-butenyl pyrroline derivative (IX) when dioxane was used as the solvent, while the 1:1 adduct (X) was found to be the main product when the reaction was carried out in benzene. On the other hand, when 1-methyl-2-methylmercapto-2-pyrroline(XIII) was employed, the desired product(XIV) was obtained as a main product along with VI, VII, the Diels–Alder adduct(XV), and dimethyl 2,3-bis-methylmercaptosuccinate(XVI).

The reactions of dimethyl acetylenedicarboxylate (I) with various enamines have been studied extensively[3] and a novel condensation reaction of I with 2-ethoxyindole derivatives (II) to afford the benzazepine derivatives (III) has been reported by Plieninger and Wild.[4]



II I III

Chart 1

In the previous report of this series,[1] we described the reactions of cyclic amide acetals with electrophiles. As part of these works, we intended the condensation of I with 1-methyl-2-pyrrolidone dimethylacetal (IV)[5a] which is expected to have an analogous reactivity with II with expect to obtain the simple cyclic dienamine derivatives (V).[7]

The reaction took place when the acetal (IV) and I were refluxed in dioxane. The yellow solid (Mixture A) which deposited on the addition of ether and an oily material (Mixture B) obtained from the filtrate were subjected to silica gel chromatography, separately.

1) Part V: Takeshi Oishi, Hiroshi Nakakimura, Miwako Mori, and Yoshio Ban, *Chem. Pharm. Bull.* (Tokyo), **20**, 1735 (1972).
2) Location, *Kita-12, Nishi-6, Sapporo, Hokkaido.*
3) G.H. Alt, A.G. Cook, and M.E. Kuehne, "Enamines: Synthesis, Structure, and Reactions," ed. by A.G. Cook, Marcel Dekker, Inc., New York, 1969.
4) H. Plieninger and D, Wild, *Chem. Ber.*, **99**, 3070 (1966).
5) *a*) H. Bredereck, F. Effenberger, and H.P. Beyerline, *Chem. Ber.*, **97**, 3081 (1964); *b*) We carried out the abstruction of methanol from IV using metalic Na by the usual procedure[6] but only the unidentified mixture was obtained.
6) H. Meerwein, W. Florian, N. Schon, and G. Stop, *Ann*, **641**, 1 (1961).
7) Other methods of preparation of compounds of this type have been summerized by L.A. Paquette, "Principles of Modern Heterocyclic Chemistry," W.A. Benjamine, Inc., New York, 1968, pp. 344—347. The compound(V) was termed "cyclic dienamine" according to the literature. L.A. Paquet, *Tetrahedron Letters*, 2027, **1963**.

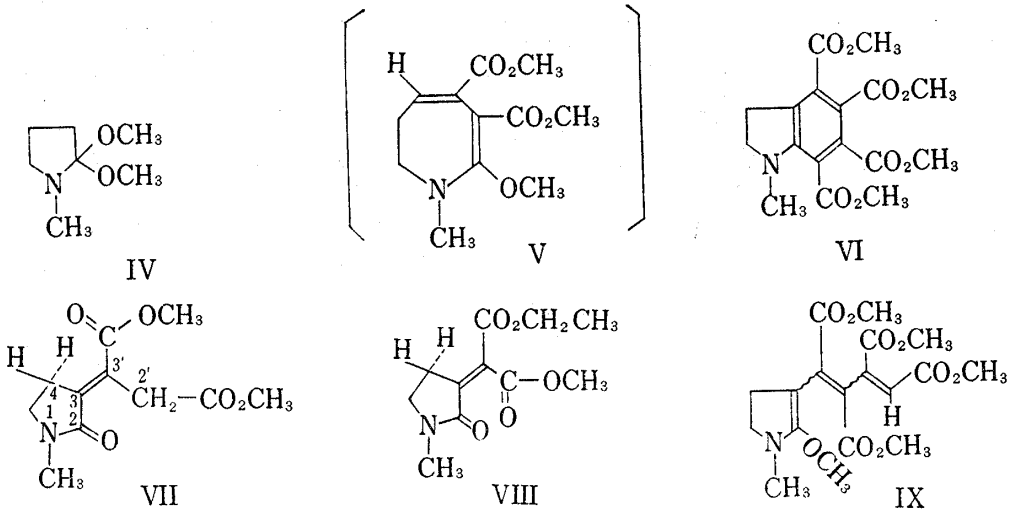


Chart 2

Mixture A: Elution with a mixture of ether and $CHCl_3$ (3: 1) afforded the crystalline tetracarbmethoxyindoline derivative (VI) and a mixture of VII and VIII as an oil, which partially solidified on standing for three weeks at room temperature. The structure of VI was easily determined from its extremely simple nuclear magnetic resonance (NMR) spectrum associated with its Mass spectral data (M^+=365). The structure VII was assigned to the deposited crystalline compound and VIII, to an remaining oil mainly from their NMR data. There were no signals due to vinylic proton in both VII and VIII, which preclude the presence of a double bond between C_2' and C_3'. The signals due to both C'_2-H (δ: 4.28, singlet) and C_4-H (δ: 3.1—3.4, broad) of crystalline compound appear significantely lower field than those (C_2'-H, δ: 3.87, singlet; C_4-H, δ: 2.70, triplet) of the oily compound. These shifts may be caused by the nearby located carbonyl groups and such are only expected from the structure visualized as VII.

Mixture B: Elution with a mixture of ether and benzene (2: 1) afforded a small amount of VI and an oil, which solidified on standing. The Mass spectrum of this compound (M^+= 375) reveals that it must be a 1: 2 adduct of IV and I and the NMR spectrum shows one proton singlet in addition to the several sharp signals due to six methyl groups. The appearance of the vinylic proton as a sharp singlet shows that there is no protons on the adjacent carbon atoms. From these data, the structure IX[8] was assigned to this compound. However, this tetra-ester shows a ultraviolet (UV) maximum at 306 nm whereas the compound (X)[8] (vide infra) exhibits at 382 nm. It is not surprising that X absorbs at this long wave length reagion (vide infra). Moreover, a further bathochromic shift would be expected for IX having still extended conjugated system than X. The remarkable hypsochromic shift actually observed would be ascribed for the non-planar structure due to a severe internal steric hindrance.

Then, the condensation was carried out in benzene to minimize the side reactions. An equimolar mixture of IV and I was refluxed for 1.2 hr in benzene. When most of the solvent was evaporated off and ether was added to the residue, a crystalline 1: 1 adduct separated out. UV maximum (382 nm) of this compound shows that it must contain an extensively conjugated chromophor and such could be expected from the structure X[9] having an ex-

8) We assigned the seven-membered enaminoester structure (V) and the ninemembered analogue for the compound X and IX, respectively, at the Third International Congress of Heterocyclic Chemistry (Sendai, Japan), 1971. Abstructs of papers, p. 128. These assignments were found to be erroneous by the subsequent studies.

9) The isomeric structures (X') may also be taken into consideration but the sterically less hindered structure X was tentatively assigned for this compound.

tended methoxy-enaminoester moiety. The structure (V), although this type of chromophor is involved in it, was excluded clearly from the NMR spectrum. A sharp singlet appeared at 4.92 is only compatible with the vinylic proton in X. The reaction of X with I yielded the aforementioned indoline (VI), which confirmed the structure (X) for this adduct. From the filtrate, a small amount of VI was obtained along with the mixture of VII and VIII after silica gel chromatography. None of IX could be detected in this case. Mild hydrolysis of the adduct (X) by HCl–MeOH afforded a mixture of VII and VIII. The conversion of X into VII and VIII also took place by merely subjecting X to silica gel chromatography which in turn suggests that the lactams VII and VIII obtained by the condensation reaction in dioxane may be produced secondarily from the initially produced X because they were isolated after silica gel chromatography.

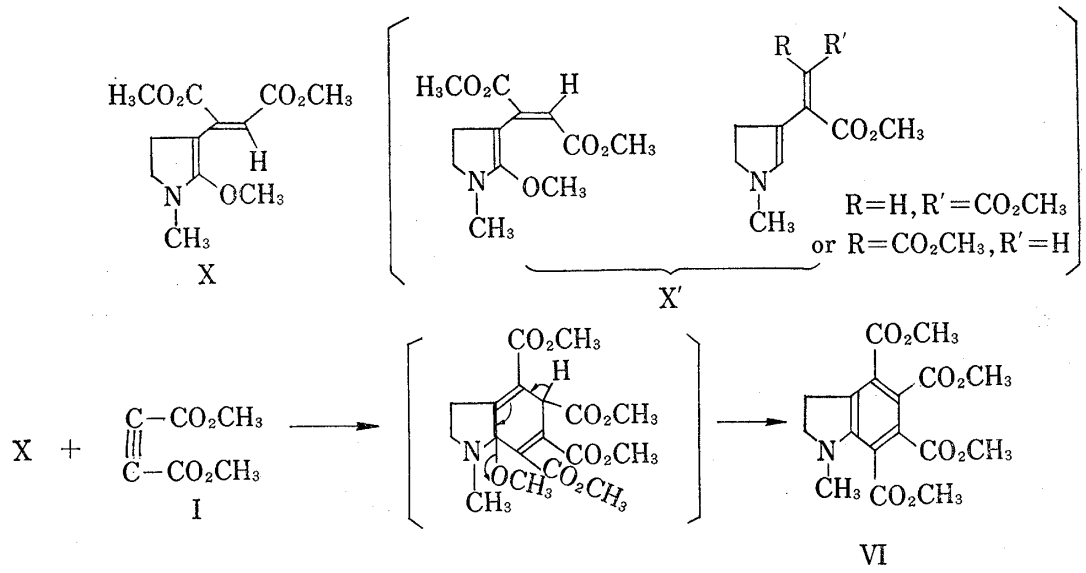


Chart 3

Any way, none of the expected seven-membered compound comparable to III could be obtained from the above reaction. The reason for this anomaly may be ascribed to the presence of methanol in the reaction media which was liberated from IV and could provide a proton to the intermediary salt (XII). Therefore, it was anticipated that the methoxy-enamine derivatives (II) or its congeners such as XII which could not liberate methanol should be employed for the purpose of obtaining a seven-membered compound.

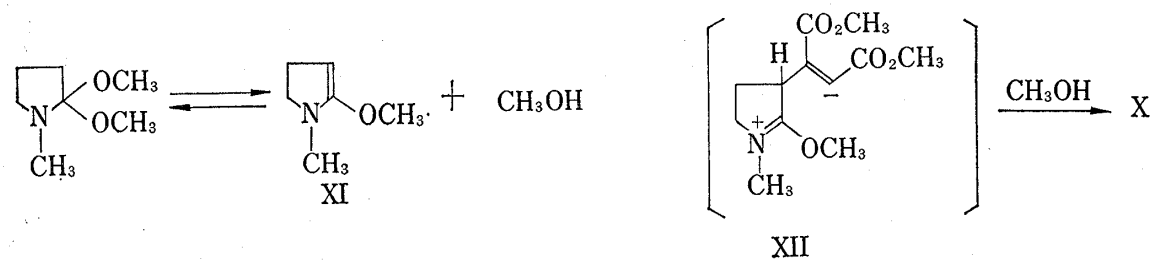


Chart 4

Since the preparation of XI has not been achieved yet,[5a,b] 2-methylmercapto-1-methyl-2-pyrroline (XIII)[10] was employed. A vigorous reaction took place when both components were mixed in dioxane and the desired cyclic dienamine (XIV) was obtained as a major pro-

10) R. Gompper and W. Elser, *Org. Syn.*, **48**, 97 (1968), John Willy and Sons, Inc., New York. The reactions of this compound with several electrophiles have been reported by Onaka and Kanda at the 91th Anual Meeting of Pharm. Soc. of Japan (Fukuoka), 1971. Abstructs of papers, p. 664.

duct. The presence of one proton triplet characteristic of this type of vinylic proton[11] clearly indicate the validity of the structure XIV for this compound. The Diels–Alder product (XV)[12] was also obtained along with VI and VII although the yield was very low. Its structure was suggested from the Mass (M^+=413), the NMR (one proton triplet due to the angular proton, δ: 4.2, J=4 Hz), and the UV (end absorption) spectra. The same compound was obtained when the cyclic dienamine (XIV) was reacted with I in dioxane, which clearly established the structure (XV) for this compound. It is noteworthy that the isomer (VIII) was not detected in this case but the condensation product (XVI) of I and CH_3SH was obtained.

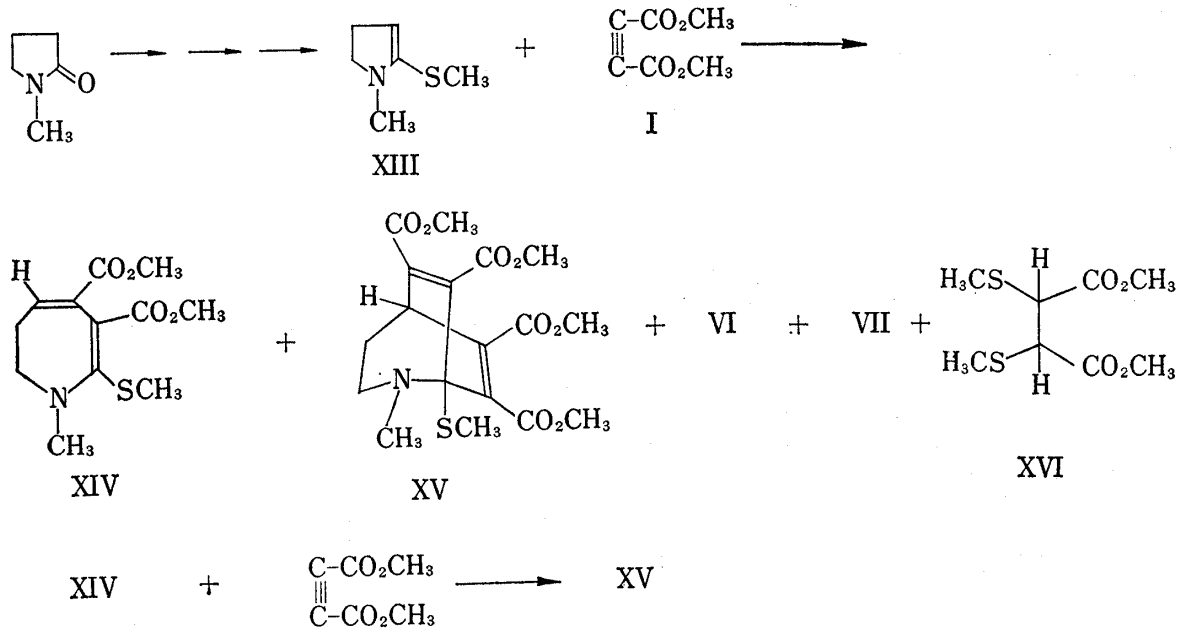


Chart 5

Thus, the seven-membered cyclic dienamine (XIV) was found to be prepared from the five-membered thiomethoxyenamine (XIII). Extension of these reactions for the preparation of the higher homologue of cyclic enaminoesters are being continued.

Experimental[13]

The Reaction of 1-Methyl-2-pyrrolidone Dimethylacetal(IV) with Dimethyl Acetylenedicarboxylate(I) in Dioxane——A mixture of IV (2.9 g) and a slight excess of I (3.0 g) was refluxed for 1.2 hr under nitrogen. The solvent was evaporated off and ether was added to the residue. When the solution was allowed to stand over night at room temperature, a yellow solid separated out (Mixture A). Evaporation of ether from the filtrate afforded an oil (Mixture B). These were chromatographed on silica gel separately.

Mixture A: Elution with a mixture of ether and $CHCl_3$ (3:1) afforded 391 mg (5.4%) of 1-methyl-4,5,6,7-tetracarbmethoxyindoline(VI), mp 168—171°, IR ν_{max}^{neat} cm^{-1}: 1740, 1720; Mass Spectrum, M^+=365; NMR ($CDCl_3$) δ: 2.8 (3H, singlet, NCH_3), 3.78 (3H, singlet, CO_2CH_3), 3.83 (9H, singlet, CO_2CH_3). *Anal.* Calcd. for $C_{17}H_{18}O_8N$: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.71; H, 5.11; N, 3.68. Further elution with the same solvent system yielded 365 mg (7.5%) of an oily material, which partially solidified on standing at room temperature for three weeks. The solid was recrystallized from ether affording methyl 2-(1′-methyl-2′-oxo-3′-pyrrolidinylidene)succinate(VII), mp 82—83°, Mass Spectrum, M^+=241; NMR ($CDCl_3$) δ: 4.29 (2H, singlet, $\rangle C\text{-}CH_2\text{-}C(=O)-$), 3.76 (3H, singlet, CO_2CH_3), 3.66 (3H, singlet, CO_2CH_3), 3.1—3.61 (4H, broad),

11) G.A. Berchtold and G.F. Uhliq, *J. Org. Chem.*, **28** 1459 (1963).
12) A related Diels–Alder product has been produced by the reaction of I with the enamine derivative. A.K. Bose, G. Mina, M.S. Manhas, and E. Rzucidlo, *Tetrahedron Letters*, **1963**, 1467.
13) Melting points are uncorrected. All NMR spectra were measured with a Hitach H-60 or R-20b spectrometer. Chemical shifts are reported as values measured from tetramethylsilane as an internal standard.

2.95 (3H, singlet, NCH_3), UV_{max}^{EtOH} nm (ε): 240 (8880), 267 (7320). *Anal.* Calcd. for $C_{11}H_{15}O_5N$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.60; N, 6.25; N, 5.97. The isomeric structure VIII was assigned to the oily compound. NMR ($CDCl_3$) δ: 3.87 (2H, singlet, $\rangle C(=O)-CH_2-C-$), 3.77 (3H, singlet, CO_2CH_3), 3.66 (3H, singlet, CO_2CH_3), 3.45 (2H, triplet, H-C_5-H), 3.04 (3H, singlet, NCH_3), 2.70 (2H, triplet, H-C_4-H).

Mixture B: Elution with a mixture of ether and benzene (2:1) afforded a small amount of the indoline (VI). Further elution with the same solvent system yielded 385 mg (4.9%) of 1-methyl-2-methoxy-3-(1′,2′,3′,4′-tetracarbmethoxy-1′,3′-butadienyl)-2-pyrroline(IX), yellow prisms, mp 124—126° (recrystallized from benzene–ether), Mass Spectrum, $M^+=395$; IR ν_{max}^{neat} cm^{-1}: 1730, 1710, 1660, 1630; NMR ($CDCl_3$): 6.67 (1H, singlet, $\rangle C(H)=C(O)-C-$), 4.0 (3H, singlet, OCH_3), 3.82, 3.67, 3.65, 3.60 (total 12H, four singlet, CO_2CH_3), 3.0 (3H, singlet, NCH_3); UV_{max}^{EtOH} nm (ε): 306 (10000). *Anal.* Calcd. for $C_{18}H_{23}O_9N$: C, 54.40; H, 5.83; N, 3.53. Found: C, 54.46; H, 6.03; N, 3.46.

The Reaction of IV with I in Benzene——A solution of IV (2.9 g) and a slight excess of I (3.0 g) in benzene was refluxed for 1.2 hr. After the addition of ether, the deposited solid was collected to yield 2.9 g (56.9%) of dimethyl (1-methyl-2-methoxy-4,5-dihydro-3-pyrrolidinyl)maleate(X), mp 142—143° (recrystallized from benzene–ether). Mass Spectrum $M^+=255$, IR ν_{max}^{neat} cm^{-1}: 1730, 1680, NMR ($CDCl_3$) δ: 4.92 (1H, singlet, $\rangle C(H)=C(O)-C-$), 3.86 (3H, singlet, OCH_3), 3.70 (3H, singlet, CO_2CH_3), 3.65 (3H, singlet, CO_2CH_3), 2.72 (3H, singlet NCH_3). UV $_{max}^{EtOH}$ nm (ε): 382 (30800). *Anal.* Calcd. for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.55; H, 6.75; N, 5.47. The filtrate was chromatographed on silica gel to afford a small amount (38 mg) of the indoline(VI) and 150 mg (3.1%) of a mixture of VII and VIII.

Hydrolysis of X——To a solution of X (105 mg) in 4 ml of ethanol was added 0.2 mg of 10% HCl. After being stirred for 4 hr at room temperature, the solution was neutralized by the addition of 10% of NaOH. The mixture was shaken with 50 ml of CH_2Cl_2 and the organic layer was dried and evaporated. The residual oil was chromatographed on alumina. Elution with a mixture of ether and CH_2Cl_2 (4:1) afforded 60 mg of a mixture of VII and VIII.

The Reaction of 2-Methylmercapto-1-methyl-2-pyrroline(XIII) and I——A mixture of XIII (3.1 g) and I (3.7 g) in dioxane was stirred for 30 min at 80°. When ether was added to this solution the indoline (VI) (420 mg) precipitated out. The filtrate was subjected to alumina chromatography. Elution with a mixture of ether and hexane (10:1) afforded 155 mg (2.7%) of dimethyl 2 3-dimethylmercaptosuccinate (XVI), mp 106—108°, Mass Spectrum, $M^+=238$; NMR ($CDCl_3$) δ: 3.78 (6H, singlet, CO_2CH_3), 3.6 (2H, singlet, -Ç-H), 2.20 (6H, singlet, SCH_3). *Anal.* Calcd. for $C_8H_{14}O_4S_2$: C, 40.39; H, 5.88. N, 26.89. Found: C, 40.31; H, 5.96; N, 26.68. Further elution with the same solvent system yielded a mixture of the Diels–Alder adduct(XV), the expected azepine derivative (XIV), the crystalline lactam (VII), and VI. The repeated alumina chromatography was carried out for the isolation of each component and finally, 275 mg (2.8%) of XV [mp 163—164°, Mass Spectrum, $M^+=413$; NMR ($CDCl_3$) δ: 4.17 (1H, triplet, $J=4$ Hz, -Ç-H), 3.78, 3.72 (total 12H, two peaks, CO_2CH_3), 2.51 (3H, singlet, NCH_3), 1.96 (3H, singlet, SCH_3); UV, only end absorption. *Anal.* Calcd. for $C_{18}H_{23}O_8N$: C, 52.30; H, 5.57; N, 3.39; S, 7.75. Found: C, 52.27; H, 5.50; N, 3.60; S, 7.95] and 916 mg (14.1%) of 1-methyl-2-methylmercapto-3,4-dicarbomethoxy-6,7-dihydroazepine(XIV)[an oil, Mass Spectrum, $M^+=271$; NMR ($CDCl_3$) δ: 6.34 (1H, triplet, $J=4$ Hz, $-CH_2-Ç=$), 3.68 (3H, sinblet, CO_2CH_3), 3.62 (3H, singlet, CO_2CH_3), 3.40 (2H, triplet, $J=5$ Hz, $\rangle N\underline{CH_2}CH_2-$), 3.17 (3H, singlet, NCH_3), 2.4—2.7 (2h, broad, $CH_2C\underline{H_2}-Ç=$), 2.45 (3H, singlet, SCH_3); UV $_{max}^{EtOH}$ nm (ε): 269 (6050), 339 (7210)], 280 mg (4.8%) of VII, and 208 mg of VI were obtained.

Thr Reaction of XIV with I——A mixture of XIV (180 mg) and I (87 mg) in dioxane was heated for 30 min at 80° under nitrogen. After being stirred for 6 hr at room temperature, the solvent was evaporated off *in vacuo* and a residual colorless solid was triturated with ether to afford the adduct (XV) (80 mg). This experiment clearly indicate the validity of the structures of both XIV and XV.