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# Synthesis of Compounds related to Antitumor Agents. VI.[1] The Conversion of 2,4-Dialkoxypyrimidines into N-Dialkyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidines in the Presence of *p*-Toluenesulfonic Acid Derivatives[2]

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The conversion of 2,4-dialkoxypyrimidines into 1,3-dialkyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidines was brought about in the presence of *p*-toluenesulfonic acid derivatives by simple heating. This reaction seems to proceed stabilized transition state in *p*-toluenesulfonic acid derivatives, and may give rise to a nucleophilic reaction by nitrogen on the migrating alkyl group.

**Keywords**——uracil; N-alkylpyrimidine; alkoxypyrimidine; the Hilbert-Johnson reaction; the Claisen rearrangement; *p*-toluenesulfonic acid derivatives

In connection of our studies of the synthesis of antitumor agents, we have synthesized some oxozolo[4,5-*d*]pyrimidines and pyrimido[5,4-*b*][1,4]oxazines and it became important for us to study the rearrangement of alkoxypyrimidines into uracils.

Many studies on the rearrangements of alkoxypyrimidines into uracils have been reported, while the most of them are application of the Hilbert-Johnson reaction[4] or the Claisen rearrangement[5] and other methods have not yet been investigated in detail. Thus it appeared interesting for us to study a new type of a rearrangement of alkoxypyrimidines in the presence of *p*-toluenesulfonic acid or its derivatives as catalytic agents.

That the lactim ether (I) undergoes rearrangement to its isomeric and stable lactam configuration (II) has been known for a long time. This transformation is not reversible and is brought about by the application of heat or through the influence of special catalytic agents, and have been observed to take place in both the acyclic and cyclic series of organic compounds.[6]

I II

Chart 1

The fused reaction of 2,4-dimethoxy-6-methylpyrimidine (IIIa)[7] in the presence of catallytic amount of *p*-toluenesulfonic acid (TSA) at 180—190° for a few minutes underwent smoothly to give rearranged product: 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidine (IVa) in 80% yield, which was identified with an authentic sample[8] by melting point, infrared (IR) and nuclear magnetic resonance (NMR) spectra. This reaction proceeded also by the presence of methyl *p*-toluenesulfonate (MTS) or ethyl *p*-toluenesulfonate (ETS) instead of TSA, and IVa was obtained in 75% yield.

1) Part V: T. Kato, N. Oda, and I. Ito, *Chem. Pharm. Bull.* (Tokyo), accepted.
2) Presented to the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
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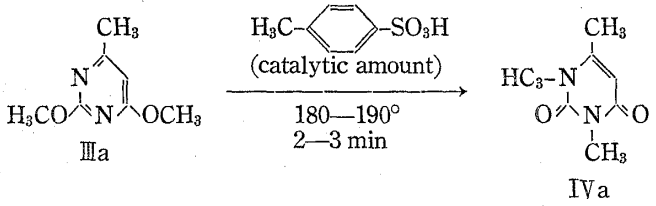
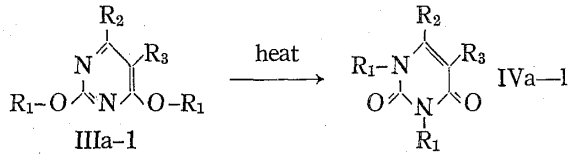



Chart 2

TABLE I. The Reaction Conditions of 2,4-Dialkoxy-5,6-disubstituted-pyrimidines (IIIa-l) into 1,3-Dialkyl-1,2,3,4-tetrahydro-5,6-disubstituted-2,4-dioxopyrimidines (IVa-l) in the Presence of *p*-Toluenesulfonic Acid Derivatives (TSA, MTS or ETS)




| Compd. No. | Substituents R1 | R2 | R3 | | Amount(g) of catalyzer per 1 g of IIIa-1 | Reaction temperature (°C) | Yield (%) of product (IVa-1) |
|---|---|---|---|---|---|---|---|
| IIIa[7] | $CH_3$ | $CH_3$ | H | TSA | 0.1 | 180—190 | 80 |
| | | | | MTS | 0.1 | 180—190 | 76 |
| | | | | ETS | 0.1 | 180—190 | 75 |
| IIIb[9] | $CH_3$ | H | H | TSA | 0.1 | 180—190 | 74 |
| | | | | MTS | 0.1 | 180—190 | 73 |
| | | | | ETS | 0.1 | 180—190 | 76 |
| IIIc[9] | $C_2H_5$ | H | H | TSA | 0.1 | 180—190 | 80 |
| | | | | MTS | 0.1 | 180—190 | 76 |
| | | | | ETS | 0.1 | 180—190 | 75 |
| IIId[10] | $C_2H_5$ | $CH_3$ | H | TSA | 0.1 | 180—190 | 72 |
| | | | | MTS | 0.1 | 180—190 | 76 |
| | | | | ETS | 0.1 | 180—190 | 73 |
| IIIe[10] | $CH_3$ | H | Br | TSA | 0.08 | 190—195 | 63 |
| | | | | MTS | 0.08 | 190—195 | 65 |
| | | | | ETS | 0.08 | 190—195 | 62 |
| IIIf[10] | $CH_3$ | $CH_3$ | Br | TSA | 0.08 | 190—195 | 52 |
| | | | | MTS | 0.08 | 190—195 | 71 |
| | | | | ETS | 0.08 | 190—195 | 68 |
| IIIg | $CH_2CH_2CH_3$ | H | H | TSA | 0.1 | 180—190 | 51 |
| | | | | MTS | 0.1 | 180—190 | 64 |
| | | | | ETS | 0.1 | 180—190 | 68 |
| IIIh | $CH_2CH_2CH_3$ | $CH_3$ | H | TSA | 0.1 | 180—190 | 50 |
| | | | | MTS | 0.1 | 180—190 | 62 |
| | | | | ETS | 0.1 | 180—190 | 65 |
| IIIi[11] | $CH_2CH{=}CH_2$ | H | H | TSA | 0.1 | 140—150 | 60 |
| | | | | MTS | 0.1 | 140—150 | 59 |
| | | | | ETS | 0.1 | 140—150 | 64 |
| IIIj[11] | $CH_2CH{=}CH_2$ | $CH_3$ | H | TSA | 0.1 | 140—150 | 61 |
| | | | | MTS | 0.1 | 140—150 | 63 |
| | | | | ETS | 0.1 | 140—150 | 60 |
| IIIk | $CH_2CH{=}CH_2$ | H | Br | TSA | 0.08 | 150—160 | 42 |
| | | | | MTS | 0.08 | 150—160 | 63 |
| | | | | ETS | 0.08 | 150—160 | 58 |
| IIIl | $CH_2CH{=}CH_2$ | $CH_3$ | Br | TSA | 0.08 | 150—160 | 41 |
| | | | | MTS | 0.08 | 150—160 | 62 |
| | | | | ETS | 0.08 | 150—160 | 60 |

The reaction conditions of the conversion of some dialkoxypyrimidines (IIIa—l)[5,9–11] into the corresponding 1,2,3,4-tetrahydro-2,4-dioxopyrimidines (IVa—l)[5,9–11] in the presence of TSA, MTS, or ETS are summarized in Table I. When TSA was used, the yields of higher alkyl derivatives (IVe—l) were worse than those of lower alkyl derivatives (IVa—d). The reason seems due to the fact that ether bonds of IIIe—l are hydrolyzed by the acid catalyst.

Treatment of 2-amino-4-methoxy-6-methylpyrimidine[10] (V) by the above described condition gave 2-amino-3,4-dihydro-3,6-dimethyl-4-oxopyrimidine (VI) and 2-amino-4-(3′,4′-dihydro-4′-oxopyrimidin-2′-yl)amino-6-methylpyrimidine (VII), whose structure was proven by the fact that hydrolysis of VII in 10% HCl gave VI and 2-amino-4-hydroxy-6-methylpyrimidine[12] (VIII).

Although the rearrangement of V into VI was successful in the presence of TSA, MTS, or ETS, the heat of V with aniline or N-methylaniline in place of TSA, MTS, or ETS did not give rearranged products but resulted in the formation of 2-amino-4-anilino-6-methyl-pyrimidine[11] (X), 2-amino-4-(2′-amino-6′-methylpyrimidin-2′-yl)anilino-6-methylpyrimidine (XI) or 2-amino-4-N-methylanilino-6-methylpyrimidine (XII). Similarly the reaction of 4-amino-2-methoxy-6-methylpyrimidine (IX) with aniline or N-methylaniline afforded 4-amino-2-anilino-6-methylpyrimidine (XIII), 4-amino-2-(4′-amino-6′-methylpyrimidin-4′-yl)anilino-6-methylpyrimidine (XIV) or 4-amino-2-N-methylanilino-6-methylpyrimidine (XV) and no rearranged product was obtained.

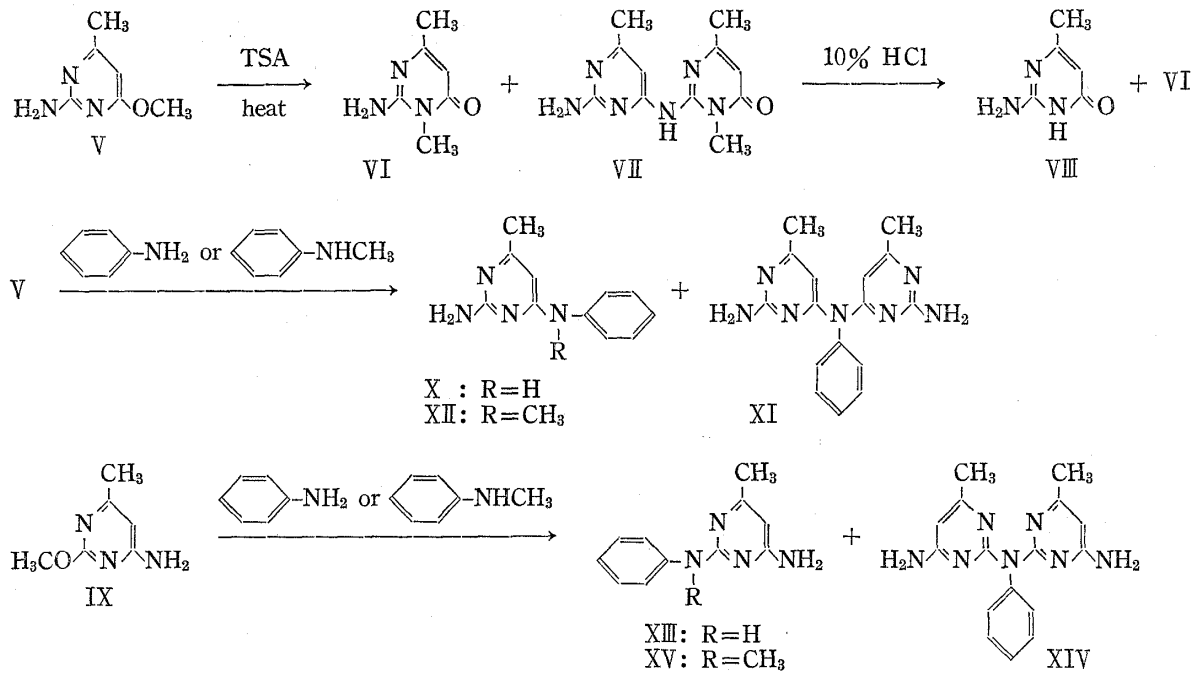



Chart 3

H.J. Minnemeyer, *et al.*[13] have reported the Claisen rearrangement in some pyrimidines in the presence of N,N-diethyl-*m*-toluidine (DEMT) or N,N-diethylaniline. Thus it was considered of interest to compare the Claisen rearrangement of 2,4-dicrotoxy-6-methylpyrimidine (XVI) in the presence of DEMT, and the reaction of XVI in the presence of TSA, MTS, or ETS.

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11) S. Senda, K. Hirota, and K. Banno, *J. Med. Chem.*, **15**, 471 (1972).
12) A. Maggiolo and A.P. Phillips, *J. Org. Chem.*, **16**, 376 (1951).
13) H.J. Minnemeyer, J.A. Egger, J.F. Holland, and H. Tieckelmann, *J. Org. Chem.*, **26**, 4425 (1961); F.J. Dinan, H.J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **28**, 1015 (1963).

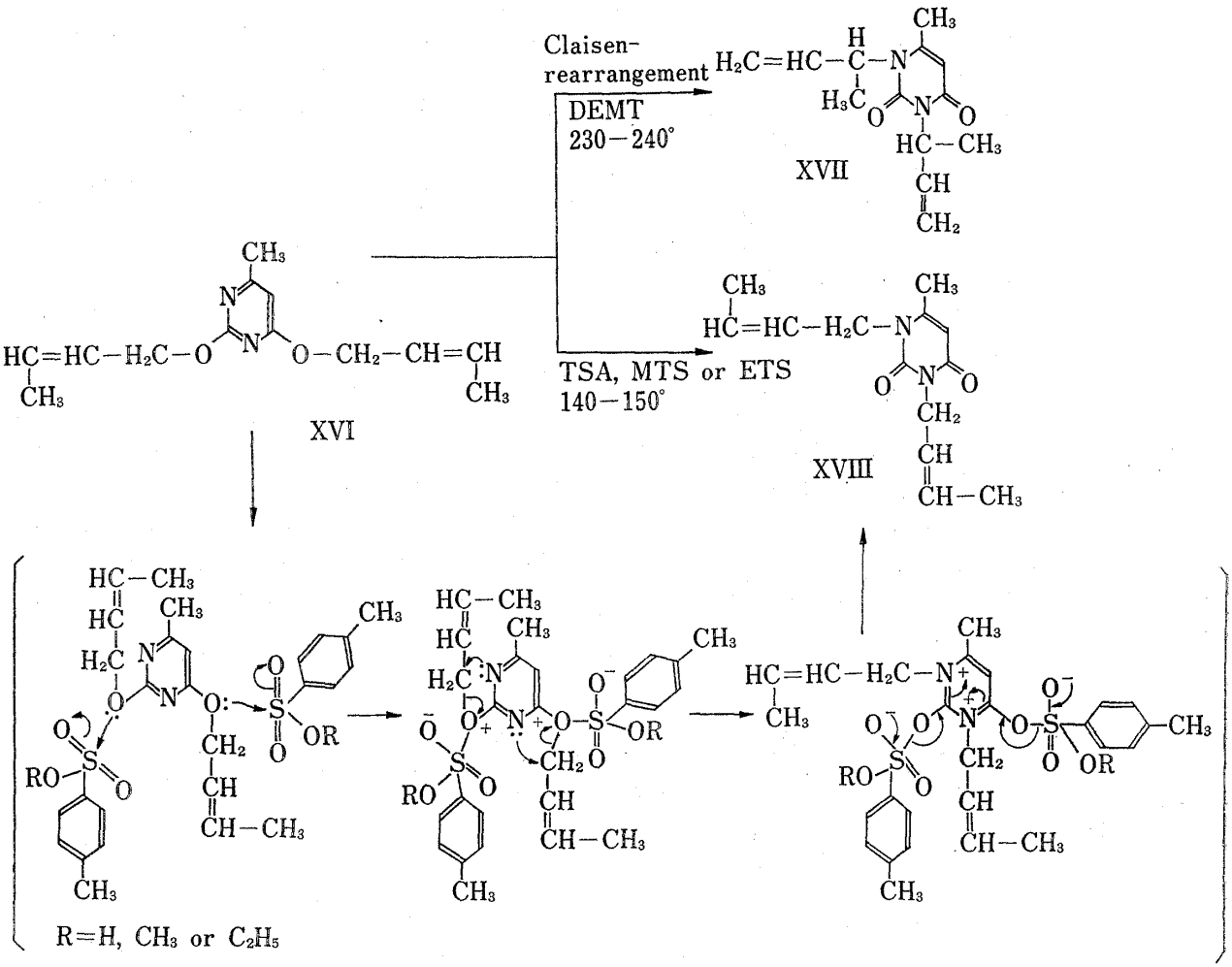


Chart 4

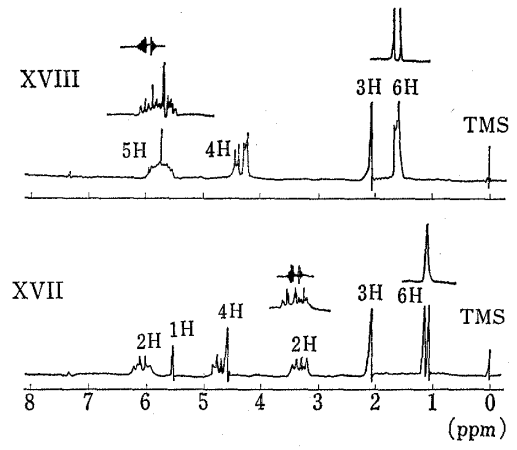


Fig. 1. NMR ($CDCl_3$) Spectra of XVII and XVIII

When XVI was heated in the presence of DEMT at 230—240°, 1,2,3,4-tetrahydro-1,3-dimethallyl-6-methyl-2,4-dioxopyrimidine (XVII) was prepared in 10% yield. But the compound that the rearrangement of a crotyl group to an adjacent carbon atom took place could not be separated. When TSA, MTS, or ETS was used at 140—150°, XVII was not obtained but 1,3-dicrotyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine (XVIII) in 50% yield. The structural confirmation of these isomers (XVII and XVIII) was carried out by NMR spectra. The methyl group on methallyl group of XVII was appeared as a sharp doublet ($J$=7 cps) but the methyl group on crotyl group of XVIII was appeared as a intricately split doublet coupled with olefinic proton on crotyl group, which was similar to that of XVI. Irradiation of olefinic proton of XVIII resulted in a clear doublet (see Fig. 1).

It is obvious that in the presence of aniline derivatives such as DEMT, the Claisen rearrangement occurred, on the contrary in the presence of *p*-toluenesulfonic acid derivatives such

as TSA, MTS, or ETS, an intramolecular 1,3-shift[14] (from oxygen to nitrogen) was participated.

It is said that the Hilbert-Johnson reaction is the conversion of alkoxypyrimidine into N-alkylpyrimidine through the quarternary salt activated by using of alkyl halide. However, our method which seems to be proceed *via* a stabilized transition state in TSA, MTS or ETS, may be considered as a nucleophilic reaction by nitrogen on the migrating alkyl group.

## Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and are uncollected. IR spectra were taken on a JASCO infrared spectrophotometer IR-S. NMR spectra were run on a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

**General Procedure of 2,4-Dialkoxy-5,6-disubstituted-pyrimidines (IIIa—l)**——A mixture of 0.1 mol of 2,4-dichloro-5,6-disubstituted-pyrimidine,[15] 0.3 mol of sodium and 100 ml of absolute alcohol was refluxed for 1—3 hr. After evaporation of the solvent, water was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness. The residues were recrystallized or distilled: A mixture of 1.6 g of 2,4-dichloro-6-methylpyrimidine,[16] 0.7 g of sodium and 10 ml of absolute methanol was refluxed for 1 hr. After evaporation of the solvent, 10 ml of water was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from *n*-pentane to give IIIa.

**General Procedure of 1,3-Dialkyl-1,2,3,4-tetrahydro-5,6-disubstituted-2,4-dioxopyrimidines (IVa—l) by Rearrangement**——A mixture of 1 g of IIIa—l and a catalytic amount of TSA, MTS or ETS was heated on an oil bath for a few min. After cooled, the product was purified by recrystallization or distillation; A mixture of 1 g of IIIa and 0.1 g of TSA was heated on an oil bath at 180—190° for a few min. After cooled, the mixture was recrystallized from benzene to give 0.8 g (80%) of IVa as colorless prisms, mp 114—115° (lit. 113—115°).

**2-Amino-3,6-dimethyl-3,4-dihydro-4-oxopyrimidine (VI) and 2-Amino-4-(3′,6′-dimethyl-3′,4′-dihydro-4′-oxopyrimidin-2′-yl)amino-6-methylpyrimidine (VII) by Rearrangement**——A mixture of 0.7 g of V and 50 mg of TSA, MTS, or ETS was heated on an oil bath at 180—190° for a few min. After cooled, the mixture was washed with methanol, the deposited crystals were recrystallized from methanol to give VI and VII. VI; mp 172—174°, 85 mg (12%), colorless needles. NMR ($CDCl_3$: DMSO-$d_6$=1: 2) $\delta$: 2.15 (3H, singlet, C–$CH_3$), 3.47 (3H, singlet, N–$CH_3$), 5.20—5.70 (2H, broad singlet, $NH_2$, exchanged with $D_2O$), 6.00 (1H, singlet, aromatic proton). *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.85; H, 6.70; N, 29.88. VI I; mp>300°, 0.52 g (42%), yellow prisms. NMR (DMSO-$d_6$) $\delta$: 2.20, 2.30 (6H, each singlet, 2×C–$CH_3$), 3.56 (3H, singlet, N–$CH_3$), 6.20, 6.25 (2H, each singlet, 2×aromatic proton). *Anal.* Calcd. for $C_{11}H_{14}ON_6$: C, 53.65; H, 5.73; N, 34.13. Found: C, 53.42; H, 5.92; N, 34.25.

**Reaction of VII with 10% HCl**——A mixture of 0.3 g of VII and 15 ml of 10% HCl was heated at 80—90° for 2 hr. After evaporation of the solvent, the residues were washed with a saturated $NaHCO_3$ solution and the deposited crystals were collected. It was recrystallized from ethanol to give 85 mg (50%) of VI and 42 mg (28%) of VII.[12]

**4-Amino-2-methoxy-6-methylpyrimidine (IX)**——A mixture of 1.4 g of 4-amino-2-chloro-6-methylpyrimidine,[16] 0.8 g of sodium and 15 ml of absolute methanol was refluxed for 2 hr. After evaporation of the solvent, 10 ml of water was added to the residue and unsoluble crystals were collected. It was recrystallized from benzene to give 0.6 g (43%) of IX as colorless plates, mp 144—146°. *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.79; H, 6.52; N, 30.20. Found: C, 52.01; H, 6.62; N, 30.41.

**Reaction of V or IX with Aniline**——A mixture of 0.003 mol of V or IX and 10 ml of aniline was heated at 170—180° for 6 hr through nitrogen gas. After cooled, 20 ml of ether was added to the mixture and the deposited crystals were collected. The crystals were recrystallized from methanol to give X[11] and XI, or XIII and XIV. XI; mp>300°, 0.19 g (21%), pale yellow plates. NMR (DMSO-$d_6$) $\delta$: 2.30 (6H, singlet, 2×C–$CH_3$), 6.20 (2H, singlet, 2×pyrimidine $C_5$–H), 7.20—7.50 (5H, multiplet, benzene ring protons). *Anal.* Calcd. for $C_{16}H_{17}N_7$: C, 62.52; H, 5.58; N, 31.90. Found: C, 62.73; H, 5.73; N, 31.55. XIII; 0.32 g (53%), colorless prisms, mp 213—215°. NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, singlet, C–$CH_3$), 6.12 (1H, singlet, pyrimidine $C_5$–H), 7.25—7.55 (5H, multiplet, benzene ring protons). *Anal.* Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.78; H, 5.97; N, 27.81. XIV; 0.17 g (18%), mp >300°, yellow needles. *Anal.* Calcd. for $C_{16}H_{17}N_7$: C, 62.52; H, 5.58; N, 31.90. Found: C, 62.37; H, 5.63; N, 32.01.

**Reaction of V or IX with N-Methylaniline**——A mixture of 0.003 mol of V or IX and 10 ml of N-methylaniline was heated at 170—180° for 6 hr through nitrogen gas. After cooled, 20 ml of ether was added to the

14) J.W. Schulenberg and S. Archer, "Organic Reactions," vol. 14, John Wiley and Sons, Inc., New York, N. Y., 1965, p. 3.
15) J.R. Marshall and J. Walker, *J. Chem. Soc.*, **1951**, 1015.
16) S. Gabriel and J. Colman, *Ber.*, **32**, 2921 (1899).

mixture and the deposited crystals were collected. The crystals were recrystallized from methanol to give XII or XV. XII; 0.29 g (45%), mp 225—227°, yellow prisms. NMR (DMSO-$d_6$) $\delta$: 2.25 (3H, singlet, C-$CH_3$), 3.25 (3H, singlet, N-$CH_3$), 6.27 (1H, singlet, pyrimidine $C_5$-H), 7.20—7.45 (5H, multiplet, benzene ring protons). *Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 66.98; H, 6.82; N, 26.35. XV: 0.24 g (38%), yellow prisms, mp 232—235° (decomp.). *Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.15; H, 6.40; N, 26.07.

**2,4-Dicrotoxy-6-methylpyrimidine (XVI)**——A solution of 6.5 g of 2,4-dichloro-6-methylpyrimidine in 10 ml of 2-butene-1-ol was dropped into a solution of 2 g of sodium in 15 ml of 2-butene-1-ol under cooling. The mixture was stirred for 1 hr at room temperature and the solvent was evaporated to dryness. To the residues was added 20 ml of water and extracted with $CHCl_3$. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was fractionated by distillation. $bp_{0.3}$ 85—87°, 5.7 g (61%). pale brown oil. *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74. Found: C, 66.93; H, 7.98.

**1,2,3,4-Tetrahydro-1,3-dimethallyl-6-methyl-2,4-dioxopyrimidine (XVII) by Rearrangement**——A mixture of 1 g of XVI and 10 ml of DEMT was heated at 230—240° on an oil bath for 6 hr through nitrogen gas. After cooled, most of the solvent was vacuum distilled. The residue was allowed to cool and stand at room temperature for 2 hr. During this time the product (XVII) crystallized. The crystals were mixed with a small amount of petroleum ether to facilitate filtration and collected. The product was washed with a minimum amount of isopropyl ether to give 0.1 g (10%) of XVIII as a colorless needles, mp 39—41°. *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.50; N, 11.88.

**1,3-Dicrotyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine (XVIII) by Rearrangement**——A mixture of 1 g of XVI and 0.1 g of TSA, MTS, or ETS was heated at 140—150° on an oil bath for a few min. After cooled, the mixture was fractionated by distillation to give 0.5 g (50%) of XVIII as a colorless oil, $bp_{0.01}$ 82—85°. *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74. Found: C, 66.72; H, 7.56.

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