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Studies on Pyrimidinylpyrazoles. II.[1] Ring Closures of N^2-Pyrimidinyl-3-oxobutyrohydrazides[2]

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The ring closure of N^2-pyrimidinyl-3-oxobutyrohydrazide derivatives by fusion was studied and a novel method for the synthesis of 1-pyrimidinyl-3-methylpyrazolin-5-one derivatives was found. This reaction mechanism was also investigated and a hypothesis was presented for the reaction process which includes an intermolecular rearrangement.

It was reported in the preceding paper of this series that N^2-pyrimidinyl-3-oxobutyrohydrazides prepared from hydrazinopyrimidines and ketene dimer give 2-pyrimidinyl-3-methylpyrazolin-5-ones by treatment with various bases. The present authors further studied the ring closure of N^2-pyrimidinyl-3-oxobutyrohydrazides by fusion and formed a novel method of synthesizing 1-pyrimidinyl-3-methylpyrazolin-5-ones. The present paper diels with the syntheses of these compounds and some considerations on the mechanism of this reaction.

Heating of N^2-(4,6-dimethyl-2-pyrimidinyl)-3-oxobutyrohydrazide (II) at above its decomposition point gave a compound, mp 112—114°, in a good yield. It was found that this compound is not the normally expected 2-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one (IV) but 1-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one (III) which was obtained by the other synthetic way in the preceding work.[1] Since it was suggested that the ring closure reaction of II by fusion was accompanied with the rearrangement of the hydrazinopyrimidine, this rearrangement reaction was examined further.

First, the compounds in which the N^1- or N^2-hydrogen in the hydrazine moiety of II was substituted by a methyl group, N^2-(4,6-dimethyl-2-pyrimidinyl)-N^1-methyl-3-oxobutyrohydrazide (V) and N^2-(4,6-dimethyl-2-pyrimidinyl)-N^2-methyl-3-oxobutyrohydrazide (IX) were synthesized from ketene dimer and corresponding methylpyrimidinylhydrazines. Fusion of V afforded a product as colorless crystals and this was identified with 2-(4,6-dimethyl-2-pyrimidinyl)-1,3-dimethyl-3-pyrazolin-5-one (VI) which was obtained by the treatment of IV with dimethyl sulfate in the preceding work.[1] Then, mixed fusion of IX and 4,6-dimethyl-2-(2-methylhydrazino)pyrimidine (VIII) gave N^2-(4,6-dimethyl-2-pyrimidinyl)-N^1-methyl-3-[1-methyl-1-(4,6-dimethyl-2-pyrimidinyl)hydrazono]butyrohydrazide (X) which was also prepared from V and 4,6-dimethyl-2-(1-methylhydrazino)pyrimidine (VII). The following facts were proved by these results. The compound whose N^1-hydrogen of the hydrazine moiety of II was substituted did not undergo the rearrangement reaction by fusion, while in the mixed fusion of the compound (IX) of which N^2-hydrogen was blocked with methyl group and the other hydrazine (VIII), the hydrazine moiety of IX rearranged to 3-carbonyl of the 3-oxobutyrohydrazide as hydrazone moiety. From the fact that co-existed VIII took part in the reaction of IX, it was suggested the reaction to be intermolecular rearrangement.

1) Part 1: T. Naito, T. Yoshikawa, S. Kitahara and N. Aoki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1467 (1969).
2) This work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 6, 1968.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

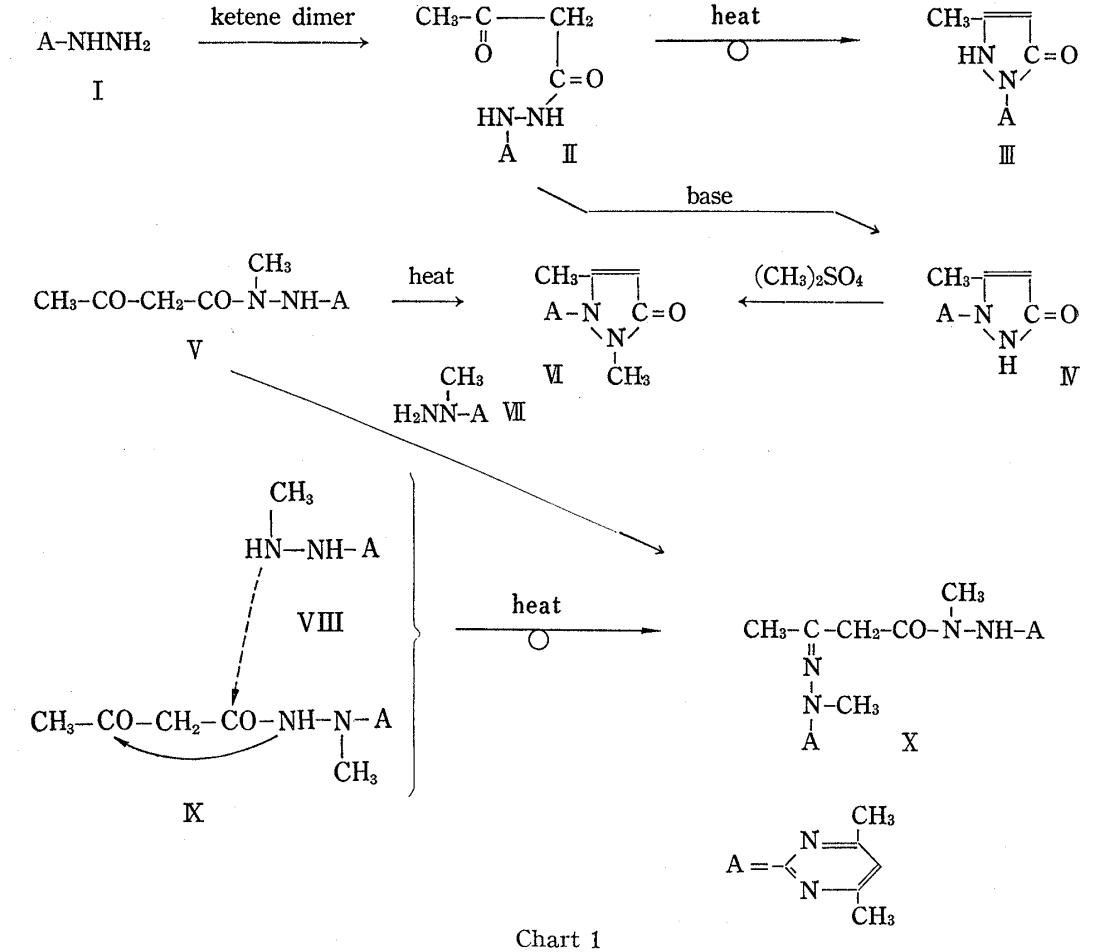


Chart 1

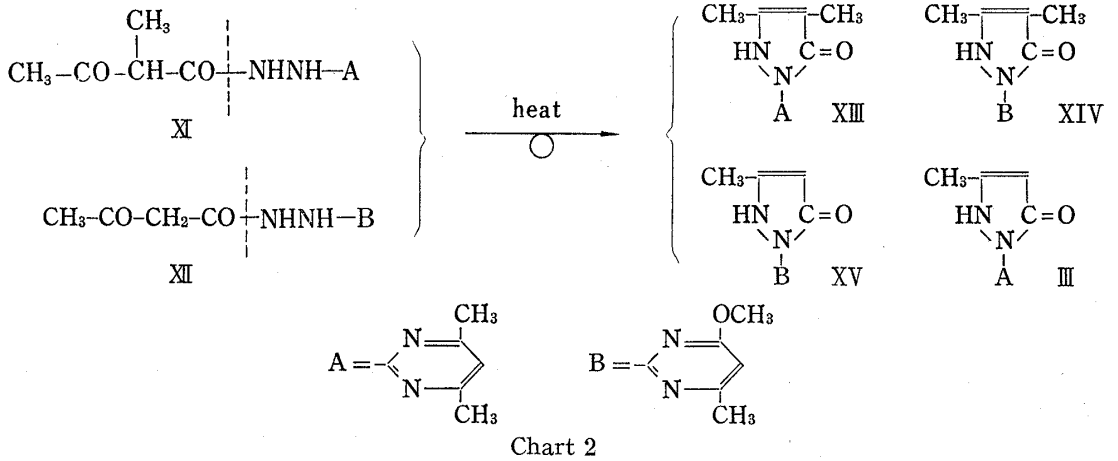


Chart 2

The above assumption was supported by the following experiments. N^2-(4,6-Dimethyl-2-pyrimidinyl)-2-methyl-3-oxobutyrohydrazide (XI) was prepared by methylation of II with methyl iodide. By fusion, XI underwent similar reaction as in the case of II and afforded 1-(4,6-dimethyl-2-pyrimidinyl)-3,4-dimethylpyrazolin-5-one (XIII), which was also prepared from ethyl 2-methyl-3-oxobutyrate and I in a similar manner as described in the preceding paper.[1] Then, equimolar mixture of XI and N^2-(4-methoxy-6-methyl-2-pyrimidinyl)-3-oxobutyrohydrazide (XII),[1] in which 2-methyl-3-oxobutyryl and pyrimidinylhydrazine moieties were different from those in XI was fused. The reaction product was chromatographed on silica gel column and was separated into an intermolecular cyclization product of XI

and XII, 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3,4-dimethylpyrazolin-5-one (XIV), and an intramolecular cyclization product (XIII) of XI, in 42% and 35% yield, respectively. The other expected products, XV and III, were determined by the comparison of thin-layer chromatograms of the reaction mixture with those of the specimens prepared by an other way.[1] From these results, it was confirmed that this reaction is an intermolecular rearrangement.

Further, in order to catch the hydrazinopyrimidine, which was expected to be formed, XII in acetone was heated in a sealed tube for 30 min at 180° and gave 2-propanone 4-methoxy-6-methyl-2-pyrimidinylhydrazone (XIX) in a quantitative yield. When XII in the mixture of acetone and ethanol was heated, it afforded ethyl acetate besides XIX.

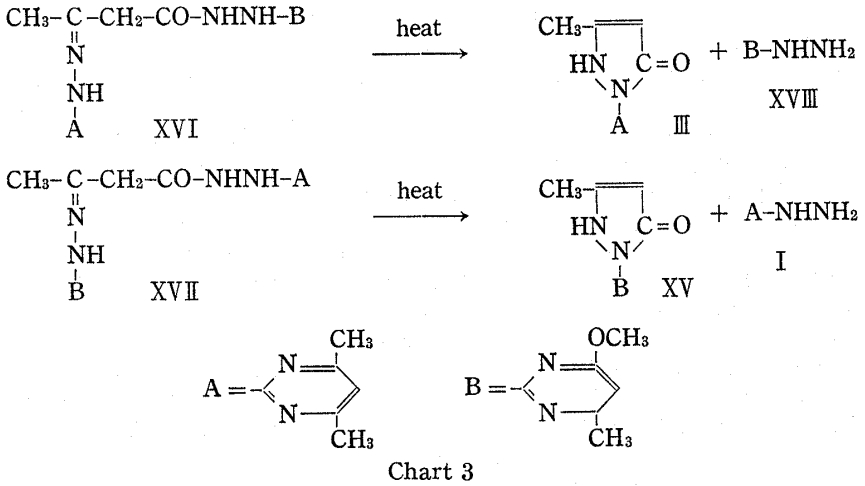


Chart 3

Then, we attempted the following experiments to consider the relation between this rearrangement and the liberated hydrazinopyrimidine. N^2-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-[(4,6-dimethyl-2-pyrimidinyl)hydrazono]butyrohydrazide (XVI)[4] and N^2-(4,6-dimethyl-2-pyrimidinyl)-3-[(4-methoxy-6-methyl-2-pyrimidinyl)hydrazono]butyrohydrazide (XVII),[4] which were prepared by treatment of the corresponding N^2-pyrimidinyl-3-oxobutyrohydrazides with hydrazinopyrimidines, were respectively fused. The reaction products from XVI were III and 2-hydrazino-4-methoxy-6-methylpyrimidine (XVIII), the latter having been present in the starting material as the hydrazone moiety. The molecule of III contained 4,6-dimethyl-2-hydrazinopyrimidine which formed the hydrazone moiety of XVI. XVII also afforded the corresponding products, XV and I quantitatively. Further, when only II was refluxed in benzene for 2 hr, the starting material was recovered quantitatively, while addition of a small amount of I in the reaction mixture of II led the reaction to the ring closure and afforded III in a quantitative yield.

On the other hand, Lecher, *et al.*[5] have reported that the dimer of 1-phenyl-3-methyl-pyrazolin-5-one (XX) was obtained from N^2-phenyl-3-(phenylhydrazono)butyrohydrazide by its fusion. It was considered that XX and phenylhydrazine were initially produced, and the dimer of II was formed. XX was also obtained as the reaction product of N^2-isonicotinoyl-3-oxobutyrohydrazide (XXI) and phenylhydrazine by Kato and his co-workers,[6] and they thought that the phenylhydrazone of XXI is an intermediate of the reaction.

By summarizing our investigation described above, it is presumed that this reaction will proceed *via* the following process.

4) Reaction of XVI with alkali gave III in good yield, while with hydrochloric acid afforded 2-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methylpyrazolin-5-one.[1] And treatment of XVII with alkali gave XV, while with hydrochloric acid afforded 2-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one.[1]

5) H.Z. Lecher, R.P. Parker and R.C. Conn, *J. Am. Chem. Soc.*, **66**, 1959 (1944).

6) T. Kato, H. Yamanaka and F. Hamaguchi, *Yakugaku Zasshi*, **83**, 741 (1963).

Initially, a small amount of I is liberated by thermal decomposition when II is fused, and the reaction of II and I produces N^2-pyrimidinyl-3-(pyrimidinylhydrazono)butyrohydrazide derivative, which is converted into 1-pyrimidinylpyrazolin-5-one derivative by a immediate liberation of the hydrazinopyrimidine. I thereby formed attacks II.

It is assumed that our presumption is favourably supported by the experimental results on II in benzene solution described above.

Experimental[7]

4,6-Dimethyl-2-(1-methylhydrazino)pyrimidine (VII)——To a stirred mixture of methyl hydrazine (20 g), EtOH (25 ml) and K_2CO_3 (30 g) was added dropwise a solution of 2-chloro-4,6-dimethylpyrimidine (31 g) in EtOH (25 ml) at 60—70° over a period of 30 min. The reaction mixture was stirred at the same temperature for another 30 min. The insoluble material was filtered off, and washed with EtOH. The filtrate and the washing were concentrated and the residue was chromatographed on Al_2O_3 (20 g). Elution with benzene and recrystallization of the eluate from ligroin gave VII (7.5 g, 90%) as colorless needles, mp 59—60°. *Anal.* Calcd. for $C_7H_{12}N_4$: C, 55.30; H, 7.89; N, 36.79. Found: C, 55.34; H, 7.94; N, 36.97.

4,6-Dimethyl-2-(2-methylhydrazino)pyrimidine (VIII)——To a solution of paraformaldehyde (0.72 g) in EtOH (40 ml), I (2.76 g) was added with stirring. The mixture was warmed at 70—75° for 15 min and concentrated *in vacuo* below 40°. The resulting crystals were filtered off, and washed with ligroin. Recrystallization from ligroin afforded Schiff base of I and formaldehyde as colorless prisms, mp 123—125°. *Anal.* Calcd. for $C_7H_{10}N_4$: C, 55.80; H, 6.67; N, 37.25. Found: C, 55.36; H, 6.30; N, 37.34.

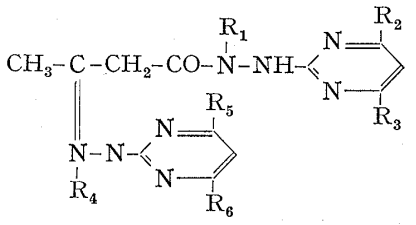
A mixture of the Schiff base (3.04 g), 10% Pd-C (1 g) and EtOH (20 ml) was subjected to catalytic hydrogenation under atmospheric pressure at room temperature. One molar equivalent of hydrogen was absorbed within about 8 hr. After removal of the catalyst, the solvent was evaporated and the residue was recrystallized three times from ligroin to give VIII (2.12 g, 70%) as colorless needles, mp 86—89°. *Anal.* Calcd. for $C_7H_{12}N_4$: C, 55.30; H, 7.89; N, 36.79. Found: C, 55.42; H, 8.01; N, 36.65.

N^2-(4,6-Dimethyl-2-pyrimidinyl)-N^1-methyl-3-oxobutyrohydrazide (V)——Prepared from ketene dimer and VIII in a similar manner previously reported in the case of the synthesis of II[1] in 29.6% yield. Colorless prisms (from ligroin), mp 129°. *Anal.* Calcd. for $C_{11}H_{16}O_2N_4$: C, 55.90; H, 6.78; N, 23.68. Found: C, 55.65; H, 7.09; N, 23.76.

N^2-(4,6-Dimethyl-2-pyrimidinyl)-N^2-methyl-3-oxobutyrohydrazide (IX)——Prepared from ketene dimer and VII in a similar manner described above in 62% yield. Colorless prisms (from MeOH-ligroin), mp 140°. *Anal.* Calcd. for $C_{11}H_{16}O_2N_4$: C, 55.90; H, 6.78; N, 23.68. Found: C, 55.85; H, 6.80; N, 23.60.

N^2-(4,6-Dimethyl-2-pyrimidinyl)-2-methyl-3-oxobutyrohydrazide (XI)——A solution of II (2.22 g), Na (0.23 g) in MeOH (20 ml) and MeI (5 g) was kept at room temperature for 30 min. The resulting crystals

Table I. N^2-Pyrimidinyl-3-(pyrimidinylhydrazono)butyrohydrazide Derivatives



Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	Yield[a] (%)	mp[b] (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
X	Me	Me	Me	Me	Me	Me	62	161—163[c]	$C_{18}H_{28}ON_8$	58.39	7.02	30.25	57.96	6.99	29.85
XVI[e]	H	OMe	Me	H	Me	Me	85	110—112[d]	$C_{16}H_{24}O_3N_8$	51.10	6.38	29.80	50.62	6.38	29.82
XVII	H	Me	Me	H	OMe	Me	75	100—103[d]	$C_{16}H_{22}O_2N_8$	53.70	6.15	31.30	54.12	6.80	31.22

a) Based on the N^2-pyrimidinyl-3-oxobutyrohydrazide derivative. *b*) All products are colorless needles.
c) recrystallization from ethyl acetate *d*) recrystallization from aq. MeOH
e) monocyarate

7) All melting points are uncorrected.

were collected by suction and recrystallized from MeOH to give XI (1.2 g, 51%) as colorless prisms, mp 189—193° (decomp.). *Anal.* Calcd. for $C_{11}H_{16}O_2N_4$: C, 55.90; H, 6.78; N, 23.68. Found: C, 55.86; H, 6.89; N, 23.82.

General Procedure of N^2-Pyrimidinyl-3-(pyrimidinylhydrazono)butyrohydrazide Derivatives——To a stirred suspension of N^2-pyrimidinyl-3-oxobutyrohydrazide derivative (5 mmole) in dioxane or benzene (5 ml) was added hydrazinopyrimidine derivative (5 mmole) in small portions at room temperature. After 2—3 hr, the suspension became a pale yellow solution, which was concentrated to syrup *in vacuo*, and the residue was treated with water. The separated crystals were recrystallized from a suitable solvent. Synthesized compounds are shown in Table I.

1-(4,6-Dimethyl-2-pyrimidinyl)-3,4-dimethylpyrazolin-5-one (XIII)——A mixture of ethyl 2-methyl-3-oxobutyrate (1.6 g), I (1.38 g) and EtOH (5 ml) was heated at 80—90° for 1 hr. Then, a solution of NaOH (500 mg) in H_2O (5 ml) was added to the reaction mixture at room temperature. After standing for 30 min, the mixture was acidified with AcOH and concentrated *in vacuo* to give a crystalline mass, which was filtered and washed with H_2O. Recrystallization from acetone-isopropyl ether (I.P.E.) afforded XIII (1.4 g, 64%) as colorless prisms, mp 144—148°, after drying *in vacuo* at 100°. *Anal.* Calcd. for $C_{11}H_{14}ON_4$: C, 60.50; H, 6.46; N, 25.68. Found: C, 60.21; H, 6.29; N, 26.23.

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3,4-dimethylpyrazolin-5-one (XIV)——A mixture of XVIII (1.54 g) and ethyl 2-methyl-3-oxobutyrate (1.6 g) was treated in the same way as described above, and gave XIV as colorless prisms (1.8 g, 77%), mp 148—152°. *Anal.* Calcd. for $C_{11}H_{14}O_2N_4$: C, 56.45; H, 6.03; N, 23.90. Found: C, 56.31; H, 6.03; N, 24.14.

2-Propanone 4-Methoxy-6-methyl-2-pyrimidinylhydrazone (XIX)——A solution of XVIII (1.54 g) in acetone (10 ml) was heated in a sealed tube at 90° for 2 hr and the reaction mixture was concentrated *in vacuo* to dryness. The residue was recrystallized from I.P.E. to give XIX as colorless prisms (1.5 g, 77%), mp 106—108°. *Anal.* Calcd. for $C_9H_{14}ON_4$: C, 55.70; H, 7.24; N, 28.82. Found: C, 55.46; H, 7.18; N, 28.70.

Reactions of II——A) Heating of II above the Melting Point: II (2.22 g) was placed in a test tube immersed in an oil bath (180°) for 5 min. The solid melted and there was considerable foaming. After cooling, the reaction mixture solidified was dissolved in $CHCl_3$ (40 ml) and extracted twice with 1N NaOH (10 ml). The $CHCl_3$ solution was dried over Na_2SO_4, and the solvent was evaporated. The crystalline residue was recrystallized from EtOH to give 45 mg (3.2%) of colorless needles, mp 111—113°. The IR spectrum of this compound was identical with that of I. The 1N NaOH extract was acidified with AcOH and the resulting precipitate was extracted with $CHCl_3$. After the extract was dried, the solvent was removed. After drying *in vacuo* at 50°, the residue (1.9 g, 95%) was recrystallized from I.P.E. to give colorless prisms, mp 112—114°, which were identified with III by mixed melting point test and comparison of IR and UV spectra.

B) Heating of II with I in Benzene: A suspension of II (111 mg) in dry benzene (20 ml) was refluxed for 2 hr and concentrated *in vacuo*. In this case, the starting material was recovered quantitatively.

A mixture of II (111 mg), I (10 mg) and dry benzene (20 ml) was refluxed for 2 hr. The clear solution was evaporated to dryness and the crystalline residue was dissolved in $CHCl_3$ (10 ml) and extracted twice with 1N NaOH (5 ml). The NaOH extract was acidified with AcOH and the precipitate was extracted with $CHCl_3$. From the $CHCl_3$ extract, III (93 mg, 91%) was obtained.

Heating of V above the Melting Point——V (200 mg) was heated in an oil bath (210°) for 40 min. After cooling, the reaction mixture was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with diluted HCl and the solvent was removed. The residue was dissolved in benzene and chromatographed on Al_2O_3. The eluate with benzene gave colorless prisms (92 mg, 50%), mp 104—109°. This was proved to be identical with VI by the mixed melting point determination and the UV and the IR spectra.

Heating of the Mixture of VIII and IX——A mixture of IX (1.18 g) and VIII (1.14 g) was placed in a test tube immersed in an oil bath (190°) for 10 min. Then, the excess of VIII was removed *in vacuo* at the same temperature. The syrupy residue (1.5 g) was chromatographed on cellulose powder which impregnated with $HCONH_2$, using benzene–cyclohexane–ligroin (1:1:1). The initial fraction (100 ml) was concentrated and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O and evaporated to syrup. The residue was crystallized from MeOH–H_2O and recrystallized from ethyl acetate to give 210 mg of colorless prisms, mp 161—163°. The product was identified with X described above by a mixed fusion and comparison of the IR spectra.

Heating of XI above the Melting Point——XI (118 mg) was placed in a test tube immersed in an oil bath (195—200°) for 5 min. The solid melted and there was considerable foaming. After cooling, the reaction mixture was recrystallized from acetone–I.P.E. to give colorless prisms (85 mg, 78%), mp 144—148°, which were identified with XIII by mixed melting point determination and comparison of the IR spectra.

Heating of the Mixture of XI and XII——A mixture of XI (1 g) and XII (1 g) was placed in a test tube immersed in an oil bath (200—205°) for 3 min. The solid melted and there was considerable foaming. After cooling, the syrupy residue was fractionated by silicagel (150 g) column chromatography using the following solvent systems: I.P.E.–AcOEt (5:1) and I.P.E.–AcOEt (5:2). From the fraction eluted with I.P.E.–AcOEt (5:1), a crude product (600 mg) was obtained, which was recrystallized from acetone–I.P.E.

to give 410 mg (41.8%) of colorless prisms, mp 146—151°, undepressed on admixture with a sample of XIV obtained before. The IR and UV spectra of this compound was identical with those of XIV.

From the fraction eluted with I.P.E.–AcOEt (5:2), the other crude product (650 mg) was obtained, which was washed with hot water (50—60°) and dried *in vacuo*. Recrystallization from acetone–I.P.E. afforded colorless prisms (320 mg, 35%), mp 142—147°. The product was identified with XIII by comparison of UV and IR spectra and mixed melting point determination.

From the water washing described above, the spots of XV and III were observed on thin-layer chromatography (Silica gel HF 254 (Merck), I.P.E.–AcOEt (5:1)).

Reactions of XII——A) Heating of XII in acetone: A solution of XII (1 g) in acetone (40 ml) was placed in a 100 ml stainless autoclave. The temperature was raised rapidly to 180° and maintained at the same temperature for 30 min. The mixture was concentrated *in vacuo* to dryness and the residue (0.81 g, 99%) melted at 105—107°, which showed no depression on admixture with XIX obtained above and the UV and IR spectra of the two were completely identical.

B) Heating of XII in acetone and EtOH: A solution of XII (1 g) in acetone (5 ml) and EtOH (10 ml) was heated at 90° for 40 hr in a sealed tube and the solvent was evaporated. The syrupy residue was dissolved in benzene and fractionated by silica gel (20 g) column chromatography using subsequently the following solvent systems: benzene–AcOEt (3:1) and AcOEt–acetone (1:1).

From the benzene fraction, ethyl acetate (230 mg, 44.6%) was obtained. It was identified with the authentic sample of ethyl acetate by comparison of IR spectra.

The fraction eluted with benzene–AcOEt (3:1) was concentrated *in vacuo* and the residue was crystallized from petroleum ether. Yield 120 mg (13%), mp 101—104°. It was identical with XV in mixed melting point test, UV and IR spectra.

The fraction eluted with AcOEt–acetone (1:1) was concentrated and the residue was crystallized from MeOH–petroleum ether to give colorless prisms (170 mg, 21.2%), mp 104—108°. The IR spectrum of the product was identical with that of XIX.

Heating of XVI above the Melting Point——XVI (2 g) was placed in test tube immersed in an oil bath (170°) for 5 min. The solid melted and there was considerable foaming. After cooling, the reaction mixture was dissolved in $CHCl_3$ (40 ml) and extracted three times with 1N NaOH (5 ml). The crystalline residue obtained from the $CHCl_3$ solution was recrystallized from EtOH to give colorless needles (710 mg, 86%), mp 111—113°. The crystals were identified with XVIII by comparison of the UV and IR spectra and by mixed melting point determination.

The 1N NaOH extract was acidified with AcOH and the precipitate was extracted with $CHCl_3$. The $CHCl_3$ extract afforded a crystalline product (1.06 g, 97%), mp 112—114°, undepressed on admixture with a sample of III. It was identical with that of III in UV and IR spectra.

Heating of XVII above the Melting Point——XVII (2 g) was treated with the same procedure as described in the case of XVI. I (630 mg, 81.5%) and XV (1.12 g, 91%) were obtained.

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