Synthesis of 1,8- and 2,8-Dihydrocycloheptapyrazol-8-one Derivatives by the Reactions of 3-Acetyltropolone and its Methyl Ethers with Phenylhydrazine

Kimiaki Imafuku, Akio Yamane (1) and Hisashi Matsumura*

Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860, Japan

Received April 14, 1980

3-Acetyltropolone (**1**) reacted with phenylhydrazine to give 3-acetyltropolone phenylhydrazone (**3**) and 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one (**4**). The former (**3**) cyclized to afford the latter (**4**). The reaction of 3-acetyl-2-methoxytropone (**2a**) with phenylhydrazine gave **4**, 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one (**5**), and 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one phenylhydrazone (**6**). The compound (**5**) reacted with phenylhydrazine to afford **6**. The reaction of 7-acetyl-2-methoxytropone (**2b**) with phenylhydrazine gave 7-acetyl-2-methoxytropone phenylhydrazone (**7**), 7-acetyl-2-(*N'*-phenylhydrazino)-tropone phenylhydrazone (**8**), 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one phenylhydrazone (**9**), and **6**. The compound (**7**) was heated to afford **4** and reacted with phenylhydrazine to afford **8** and **9**. The compound (**8**) was also refluxed to give **9**.

J. Heterocyclic Chem., **17**, 1293 (1980).

Since 3-acetyltropolone (**1**) has an active methyl group and β-diketone structure, it is very useful as starting material for synthesis of heterocycle-condensed troponoid compounds. Previously, we reported that 3-acetyltropolone (**1**) and its methyl ethers (**2a** and **2b**) reacted with hydrazine (2) and methyl hydrazine (3) to give 1,8-dihydrocycloheptapyrazol-8-one derivatives. It is also known that 3-formyl-6-isopropyltropolone (4) and 3-acetyl-5,6,7-trichlorotropolone (5) reacted with phenylhydrazine to afford their phenylhydrazone, which cyclized to 1-phenyl-1,8-dihydrocycloheptapyrazol-8-ones. In this paper, we wish to describe the reactions of 3-acetyltropolone (**1**), 3-acetyl-2-methoxytropone (**2a**), and 7-acetyl-2-methoxytropone (**2b**) with phenylhydrazine.

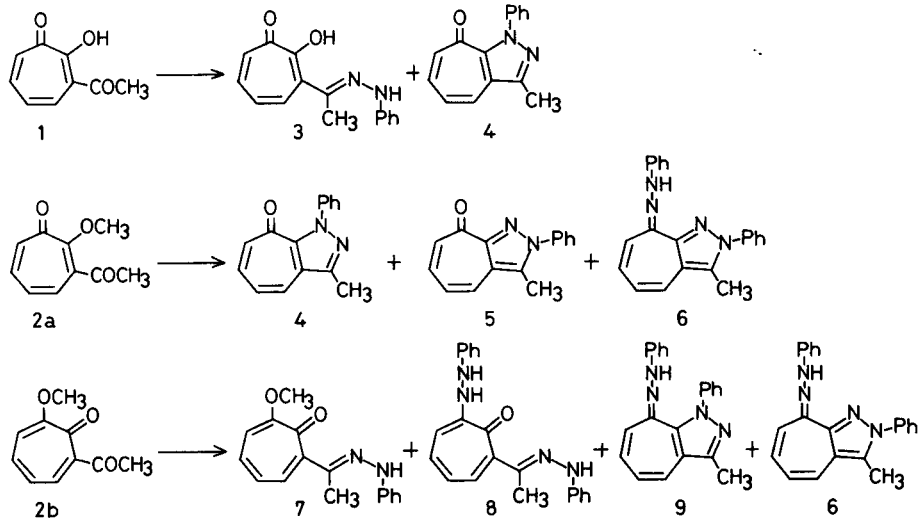
Results and Discussion.

Reaction of 3-Acetyltropolone (1) with Phenylhydrazine.

A mixture of 3-acetyltropolone (**1**) and phenylhydrazine in methanol was allowed to stand for 24 hours at room temperature to afford **3** (m.p. 119-120°) and **4** (m.p. 104-106°) in 53 and 7% yields, respectively. From elemental analysis ($C_{15}H_{14}N_2O_2$) and spectral data, the compound **3** was assigned to 3-acetyltropolone phenylhydrazone. The ir spectrum shows a characteristic absorption at 1600 cm^{-1} for tropolone but no acetyl carbonyl absorption near 1700 cm^{-1}. This compound gave coloration with iron(III) chloride.

Bunnell and Fuchs (6) found that the ^{13}C nmr chemical shift differences between the α carbons of ketone and its

Scheme 1



0022-152X/80/061293-04$02.25

imine derivatives provide a convenient and reliable means of assigning imine stereochemistry and that carbons *syn* to the imine moiety are shifted to higher field ($\Delta\delta$ *syn*-α = 12-15 ppm) than carbons *anti* to the imine moiety ($\Delta\delta$ *anti*-α = 3-6 ppm). Now, we discuss the configuration of the phenylhydrazone group of the product (**3**). In the ^{13}C nmr spectra, 3-acetyltropolone (**1**) shows signals at δ 30.7 and 136.9 ppm for the methyl and C-3 carbon atoms, respectively, while the hydrazone (**3**) shows signals at δ 15.3 and 138.4 ppm for the methyl and C-3 carbon atoms, respectively. The differences between the ketone and the phenylhydrazone are as follows.

$$\Delta\delta\ CH_3 = 30.7 - 15.3 = 15.4 \text{ ppm}$$
$$\Delta\delta\ C\text{-}3 = 136.9 - 138.4 = -1.5 \text{ ppm}$$

This result indicates that the configuration of the hydrazone group is the (*E*)-form.

On the other hand, the compound (**4**) was determined to be 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one from its elemental analysis ($C_{15}H_{12}N_2O$) and spectral data. The ir spectrum shows an absorption at 1640 cm^{-1} for the tropone carbonyl group. The uv spectrum shows similar pattern to those of 3-methyl- (1) and 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-ones (2). The ^1H nmr spectrum shows peaks at δ 2.56 (s, 3H) for the methyl group, 6.5-7.5 (m, 4H) for the seven-membered ring protons, and 7.34 ppm (s, 5H) for the phenyl group.

The refluxing of **1** with phenylhydrazine for 2 hours gave the same products, **3** and **4**, in 57 and 14% yields, respectively. Furthermore, 3-acetyltropolone phenylhydrazone (**3**) was heated on a water bath to give the pyrazole (**4**). This indicates that the former is a precursor to the latter.

Reaction of 3-Acetyl-2-methoxytropone (**2a**) with Phenylhydrazine.

A mixture of 3-acetyl-2-methoxytropone (**2a**) and phenylhydrazine in methanol was allowed to stand for 24 hours at room temperature to give **4**, **5** (m.p. 182-184°), and **6** (m.p. 162-163°) in 17, 10, and 2% yields, respectively. The compound (**5**) was assigned to 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one, which is an isomer of **4**, from its elemental analysis and spectral data. The ir and ^1H nmr spectra are similar to those of **4**. However, the uv spectrum is different from that of the compound (**4**), as is shown in Figure 1.

From the elemental analysis ($C_{21}H_{18}N_4$), the mass-spectral determination of molecular weight (m/e M^+ 326), and other spectral data, the compound (**6**) was determined to be 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one phenylhydrazone. The ^1H nmr spectrum shows peaks at δ 2.27 (s, 3H) for the methyl group, 5.6-7.4 (m, 9H) for the seven-membered ring protons and the phenyl group in the phenylhydrazone group, 7.41 (s, 5H) for the 2-phenyl group, and 12.1 ppm (br, 1H) for NH group. The configuration of the phenylhydrazone group is a *syn*-form from a signal of the hydrogen bonded NH proton at δ 12.1 ppm.

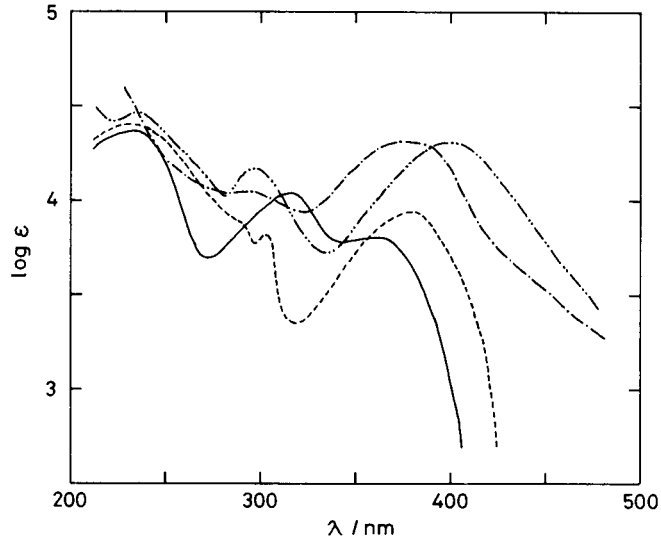


Figure 1. Electronic Spectra ——— **4** ----- **5** —·—·— **6** —··—··— **9**

The refluxing of **2a** and phenylhydrazine in methanol for 2 hours gave the same products, **4** (11%), **5** (18%), and **6** (9%). When the reaction was continued for 24 hours under reflux, the compound (**6**) was obtained as a major product (yield 35%) together with small amount of **4**, **5** not being obtained. Thus, it is thought that the compound (**5**) is a precursor to **6**. The pyrazolotropone (**5**) was treated with phenylhydrazine under reflux in methanol to afford **6** in 49% yield. However, the isomer (**4**) did not react with phenylhydrazine because of the steric hindrance of the phenyl group at the N_1-position.

Reaction of 7-Acetyl-2-methoxytropone (**2b**) with Phenylhydrazine.

When a mixture of 7-acetyl-2-methoxytropone (**2b**) and phenylhydrazine in methanol was allowed to stand for 2 hours at room temperature, four products, **6**, **7** (m.p. 150-152°), **8** (m.p. 162-165°), and **9** (m.p. 171-173°), were obtained in 6, 22, 4, and 4% yields, respectively. The compound (**7**) was assigned to 7-acetyl-2-methoxytropone phenylhydrazone from the elemental analysis ($C_{16}H_{16}N_2O_2$) and spectral data. The ir spectrum shows no acetyl carbonyl group near 1700 cm^{-1}. The ^1H nmr spectrum shows peaks at δ 2.11 (s, 3H) for the methyl group, 3.92 (s, 3H) for the methoxy group, 6.6-7.9 (m, 9H) for the phenyl group and the seven-membered ring protons, and 7.6 ppm (br, 1H) for the NH group. As shown in Figure 2, the uv spectrum is very similar to that of 3-acetyltropolone phenylhydrazone (**3**).

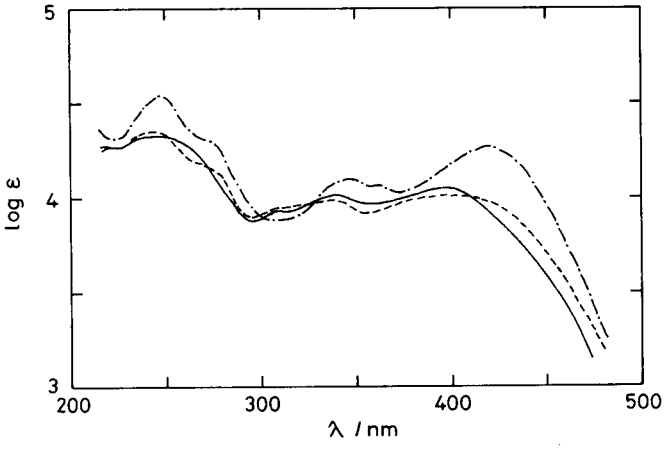


Figure 2. Electronic Spectra _____ **3** ----- **7** __·__·__ **8**

The compound **8** was determined to be 7-acetyl-2-(*N'*-phenylhydrazino)tropone phenylhydrazone from the elemental analysis ($C_{21}H_{20}N_4O$) and spectral data. It was found that the acetyl carbonyl and the methoxy groups disappeared from the ir and ^1H nmr spectra, respectively. The ^1H nmr spectrum also shows peaks at δ 2.20 (s, 3H) for the methyl group, 5.79 (br, 1H) for 2β-NH, 6.6-7.9 (m, 14H) for the two phenyl groups and the seven-membered ring protons, 7.40 (br, 1H) for NH-phenyl, and 8.45 ppm (br, 1H) for the 2α-NH group.

The compound **9** was assigned to 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one phenylhydrazone from the elemental analysis ($C_{21}H_{18}N_4$) and spectral data. In the mass spectrum, the parent peak was observed at 326. The ir spectrum shows no carbonyl absorption. The ^1H nmr spectrum shows peaks at δ 2.37 (s, 3H) for the methyl group, 5.8-7.4 (m, 9H) for NH-phenyl and seven-membered ring protons, 7.38 (s, 5H) for the 1-phenyl group, and 7.46 ppm (br, 1H) for the NH group.

The refluxing of a mixture of **2b** and phenylhydrazine in methanol gave **6** (1%), **7** (2%), **8** (19%), and **9** (34%) after 1 hour. The prolonged reaction (2 hours) gave **9** (41%) as a major product together with **6** (1%), **7** (2%), and **8** (6%).

Furthermore, the compound (**7**) was heated on a water bath to afford **4** (67%) and reacted with phenylhydrazine under reflux in methanol to afford **8** (3%) and **9** (30%) after 1 hour. The compound (**8**) also cyclized to **9** (59%) under reflux in methanol. Thus, it is found that the compound (**7**) is a precursor to **4**, **8**, and **9**, while the compound (**8**) is one to **9**.

EXPERIMENTAL

The melting points were determined with a Yanagimoto MP-S2 melting-point measuring apparatus and are uncorrected. The ir spectra were taken on a JASCO IRA-1 spectrophotometer, and the uv spectra on a Hitachi EPS-3T spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded with a Hitachi R-24 and with a JEOL JNM-FX-100 spectrometer, respectively, with TMS as an internal standard. The mass spectra were run on a JEOL JMS-01-SG-2 spectrometer.

Reaction of 3-Acetyltropolone (**1**) with Phenylhydrazine.

a.

A mixture of **1** (323 mg., 2.0 mmoles) and phenylhydrazine (436 mg., 4.0 mmoles) in methanol (20 ml.) was allowed to stand for 24 hours at room temperature. After the removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with 3*M* hydrochloric acid and water, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene-petroleum ether to afford 3-acetyltropolone phenylhydrazone (**3**) as yellow needles, yield 271 mg. (54%), m.p. 119-120°; ir (chloroform: 1600 cm^{-1} (C=O); uv (methanol): λ max 242 (log ϵ 4.33), 335 (4.01), 396 nm (4.05); ^1H nmr (deuteriochloroform): δ 2.22 (s, 3H, CH_3), 6.7-7.4 (m, 8H), 7.4 (br, 1H, NH), 7.87 (m, 1H, H-4), 9.0 ppm (br, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 15.29, 113.30, 120.49, 121.03, 127.31, 129.14, 137.11, 138.39, 139.49, 143,88, 144.67, 169.40, 171.71 ppm.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.79; H, 5.53; N, 11.15.

The evaporation residue of the filtrate from the recrystallization of **3** was chromatographed on a Wakogel B-10 plate (20 × 20 cm^2) with chloroform to afford 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) as orange yellow prisms (from hexane), yield 33 mg. (7%), m.p. 104-106°; ir (chloroform): 1640 (C=O), 1600 cm^{-1}; uv (methanol): λ max 233 (log ϵ 4.38), 305 (4.01), 316 (4.04), 365 nm (3.82); ^1H nmr (deuteriochloroform): δ 2.56 (s, 3H, CH_3), 6.5-7.5 (m, 4H), 7.34 ppm (s, 5H, Ph).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.13; H, 5.11; N, 11.96.

b.

A mixture of **1** (339 mg., 2.1 mmoles) and phenylhydrazine (443 mg., 4.1 mmoles) in methanol (20 ml.) was refluxed for 2 hours and then worked up as has been described above to give **3** (298 mg., 56%) and **4** (66 mg., 13%).

Cyclization of the Compound (**3**).

The hydrazone (**3**) (227 mg., 0.9 mmole) in 50% acetic acid (16 ml.) was heated on a water bath for 1 hour. The reaction mixture was neutralized with sodium hydrogencarbonate solution and then extracted with chloroform. After the evaporation of the solvent, the residue was recrystallized from hexane to afford **4** (131 mg., 62%).

Reaction of 3-Acetyl-2-methoxytropone (**2a**) with Phenylhydrazine.

a.

A solution of **2a** (346 mg., 1.9 mmoles) and phenyl hydrazine (438 mg., 4.1 mmoles) in methanol (20 ml.) was allowed to stand for 24 hours at room temperature. After the removal of the solvent, the residue was chromatographed on two Wakogel B-10 plates (30 × 30 cm^2) with chloroform. The first fraction was recrystallized from benzene-petroleum ether to afford 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one phenylhydrazone (**6**) as orange scales, yield 15 mg. (2%), m.p. 162-163°; ir (chloroform): 3220 (NH), 1603 cm^{-1}; uv (methanol): λ max 236 (log ϵ 4.45), 298 (4.29), 400 nm (4.30); ^1H nmr (deuteriochloroform): δ 2.27 (s, 3H, CH_3), 5.6-7.4 (m, 9H), 7.41 (s, 5H, 2-Ph), 12.1 ppm (br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 10.38, 112.81, 119.53, 121.19, 122.65, 123.63, 124.31, 128.20, 128.98, 129.28, 134.59, 136.25, 137.03, 138.83, 144.68, 148.82 ppm.

Anal. Calcd. for $C_{21}H_{18}N_4$: C, 77.27; H, 5.50; N, 17.17. Found: C, 77.25; H, 5.56; N, 17.19.

The second fraction was rechromatographed on a Wakogel B-10 place (30 × 30 cm^2) with chloroform-ether to give two fractions. One of them was recrystallized from hexane to afford **4** (78 mg., 17%). Another frac-

tion was recrystallized from benzene-petroleum ether to afford 3-methyl-2-phenyl-2,8-dihydrocycloheptapyrazol-8-one (**5**) as pale yellow prisms, yield 46 mg. (10%), m.p. 182-184°; ir (chloroform): 1640 (C=O), 1605 cm^{-1}; uv (methanol): λ max 229 (log ε 4.41), 246 (4.38), 288 (3.92), 303 (3.79), 379 nm (3.94); ^1H nmr (deuteriochloroform): δ 2.53 (s, 3H, CH_3), 6.3-7.4 (m, 4H), 7.41 ppm (s, 5H, Ph); ^{13}C nmr (DMSO-d_6): δ 11.16, 115.20, 119.63, 119.88, 126.26, 128.40, 136.34, 141.17, 147.56 ppm.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86.

b.

A mixture of **2a** (356 mg., 2.0 mmoles) and phenylhydrazine (550 mg., 5.1 mmoles) in methanol (20 ml.) was refluxed for 2 hours. After the evaporation of the solvent, the residue was worked up as has been described above to give **4** (50 mg., 11%), **5** (83 mg., 18%), and **6** (58 mg., 9%).

c.

The same reaction of **2a** (335 mg., 1.9 mmoles) and phenylhydrazine (512 mg., 4.7 mmoles) in methanol (20 ml.) under reflux gave **4** (10 mg., 2%) and **6** (213 mg., 35%) after 24 hours.

Reaction of the Pyrazolotropone (**5**) with Phenylhydrazine.

The pyrazolotropone (**5**) (70 mg., 0.3 mmole) was refluxed with phenylhydrazine (107 mg., 1.0 mmole) in methanol (10 ml.) for 24 hours. The evaporation residue was chromatographed on a Wakogel B-10 plate (20 × 20 cm^2) with chloroform. The upper fraction was recrystallized from benzene-petroleum ether to give **6** (48 mg., 49%). The compound (**5**) (12 mg., 17%) was recovered from the lower fraction.

Reaction of 7-Acetyl-2-methoxytropone (**2b**) with Phenylhydrazine.

a.

The methyl ether (**2b**) (347 mg., 1.9 mmoles) and phenylhydrazine (432 mg., 4.0 mmoles) were dissolved in methanol (20 ml.) and allowed to stand for 24 hours at room temperature. After the removal of the solvent, the residue was chromatographed on two Wakogel B-10 plates (30 × 30 cm^2) with chloroform. The first fraction was recrystallized from benzene-petroleum ether to give **6** (39 mg., 6%). The second fraction was also recrystallized from benzene-petroleum ether to give 3-methyl-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one phenylhydrazone (**9**) as reddish orange needles, yield 25 mg. (4%), m.p. 171-173°; ir (chloroform): 1605 cm^{-1}; uv (methanol): λ max 285 sh (log ε 4.06), 384 nm (4.32); ^1H nmr (deuteriochloroform): δ 2.37 (s, 3H, CH_3), 5.8-7.4 (m, 9H), 7.38 (s, 5H, 1-Ph), 7.46 ppm (br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 11.60, 113.06, 119.10, 119.58, 119.97, 121.39, 126.02, 126.41, 127.23, 128.55, 128.74, 131.38, 133.72, 137.66, 141.41, 144.68, 148.34 ppm; ms: m/e M^+ 326.

Anal. Calcd. for $C_{21}H_{18}N_4$: C, 77.27; H, 5.56; N, 17.17. Found: C, 76.97; H, 5.60; N, 17.09.

The third fraction was rechromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with chloroform-ether (6:1) to give two fractions. One of them was recrystallized from benzene to give 7-acetyl-2-methoxytropone phenylhydrazone (**7**) as yellow prisms, yield 114 mg. (22%), m.p. 150-152°; ir (chloroform): 1605 cm^{-1}; uv (methanol): λ max 242 (log ε 4.37), 270 sh (4.20), 330 (3.99), 402 nm (4.02); ^1H nmr (deuteriochloroform): δ 2.11 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.6-7.9 (m, 9H), 7.6 ppm (br, 1H, NH).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.50; H, 6.07; N, 10.56.

Another fraction was also recrystallized from benzene to afford 3-acetyl-7-(*N'*-phenylhydrazino)tropone phenylhydrazone (**8**) as yellow needles, yield 27 mg. (4%), m.p. 162-165°; ir (chloroform): 1605 cm^{-1}; uv (methanol): λ max 247 (log ε 4.55), 270 sh (4.33), 345, (4.11), 420 nm (4.28); ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3), 5.79 (br, 1H, 2β-NH), 6.6-7.9 (m, 14H), 7.40 (br, 1H, NH-Ph), 8.45 ppm (br, 1H, 2α-NH).

Anal. Calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.37; H, 5.90; N, 16.24.

b.

A mixture of **2b** (714 mg., 4.0 mmoles) and phenylhydrazine (858 mg., 7.9 mmoles) in methanol (40 ml.) was refluxed for 1 hour. After removal of the solvent, the residue was worked up as has been described above to give **6** (16 mg., 1%), **7** (17 mg., 2%), **8** (264 mg., 19%), and **9** (440 mg., 34%).

c.

The reaction of **2b** (354 mg., 2.0 mmoles) and phenylhydrazine (426 mg., 3.9 mmoles) in methanol (20 ml.) under reflux for 2 hours gave the same products, **6** (9 mg., 1%), **7** (10 mg., 2%), **8** (40 mg., 6%), and **9** (268 mg., 41%).

Cyclization of the Compound (**7**).

The phenylhydrazone (**7**) (100 mg.) in acetic acid (10 ml.) was heated on a water bath for 1 hour. The reaction mixture was neutralized with sodium hydrogencarbonate solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from hexane to afford **4** (48 mg., 55%).

Reaction of the Compound (**7**) with Phenylhydrazine.

A mixture of **7** (134 mg., 0.5 mmole) and phenylhydrazine (54 mg., 0.5 mmole) in methanol (20 ml.) was refluxed for 1 hour. After the evaporation of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with chloroform. The first fraction was recrystallized from benzene-hexane to give **9** (49 mg., 30%). The second fraction was also recrystallized from benzene to give **8** (6 mg., 3%).

Cyclization of the Compound (**8**).

A solution of **8** (100 mg.) in methanol (5 ml.) was refluxed for 24 hours. The evaporation residue was purified by the chromatography on a Wakogel B-10 plate (20 × 20 cm^2) with chloroform-ether and recrystallization from benzene-petroleum ether to afford **9** (56 mg., 59%).

Acknowledgement.

We wish to thank Dr. Tetsuo Nozoe, Professor Emeritus of Tohoku University, for his advice and encouragement. We are also indebted to Professor Hitoshi Takeshita of Kyushu University for the ^{13}C nmr spectral measurements.

REFERENCES AND NOTES

(1) Present address: Wakunaga Pharmaceutical Co., Ltd., Kodamachi, Takata-gun, Hiroshima 729-64.

(2) A. Yamane, M. Nagayoshi, K. Imafuku and H. Matsumura, *Bull. Chem. Soc. Jpn.*, **52**, 1972 (1979).

(3) A. Yamane, K. Imafuku and H. Matsumura, *ibid.*, **53**, 1461 (1980).

(4) S. Matsumoro, *Sci. Repts. Tohoku Univ., I*, **42**, 222 (1958).

(5) G. O. Schenck, B. Brahler and M. Cziesla, *Angew. Chem.*, **68**, 247 (1956).

(6) C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, **42**, 2614 (1977).