Reactions of 3-Acetyltropolone and its Methyl Ethers with Hydroxylamine. Formation of 8*H*-Cyclohept[*d*]isoxazol-8-one and 8*H*-Cyclohept[*c*]isoxazol-8-one

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The reaction of 3-acetyltropolone (**1**) with hydroxylamine under the acidic condition gave 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one (**4**) and its oxime (**5**), and under the neutral condition gave **4** and 3-acetyltropolone oxime (**6**). The reaction of 3-acetyl-2-methoxytropone (**2a**) with hydroxylamine under the acidic condition gave **4**, **5**, and 4-methyl-1*H*-2,3-benzoxazin-1-one (**7**), and under the neutral condition gave **4**, **7**, 3-methyl-8*H*-cyclohept[*c*]isoxazol-8-one (**8**), and its oxime (**9**). The reaction of 7-acetyl-2-methoxytropone (**2b**) with hydroxylamine under the acidic condition gave **4** and **5**, and under the neutral condition gave **5**, **7**, and **9**.

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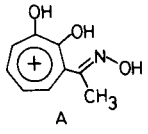
In a series on 3-acetyltropolone (**1**), we have recently reported that the reactions of **1** and its methyl ethers, 3- and 7-acetyl-2-methoxytropones (**2a** and **2b**), with hydrazines (3-5), and semicarbazide (6) gave 3-methyl-1,8-dihydrocycloheptapyrazol-8-one derivatives. Reactions of *o*-phenylenediamine also gave heterocycle-condensed troponoid compounds (7). The heterocycles in these products contain two nitrogen atoms. On the other hand, 8*H*-cyclohept[*d*]oxazol-8-one (8), 4*H*-cyclohept[*d*]-oxazol-4-one (9), and 4*H*-cyclohept[*d*]isoxazol-4-one derivatives (10) are also known as troponoid compounds condensed with heterocycles containing nitrogen and oxygen atoms.



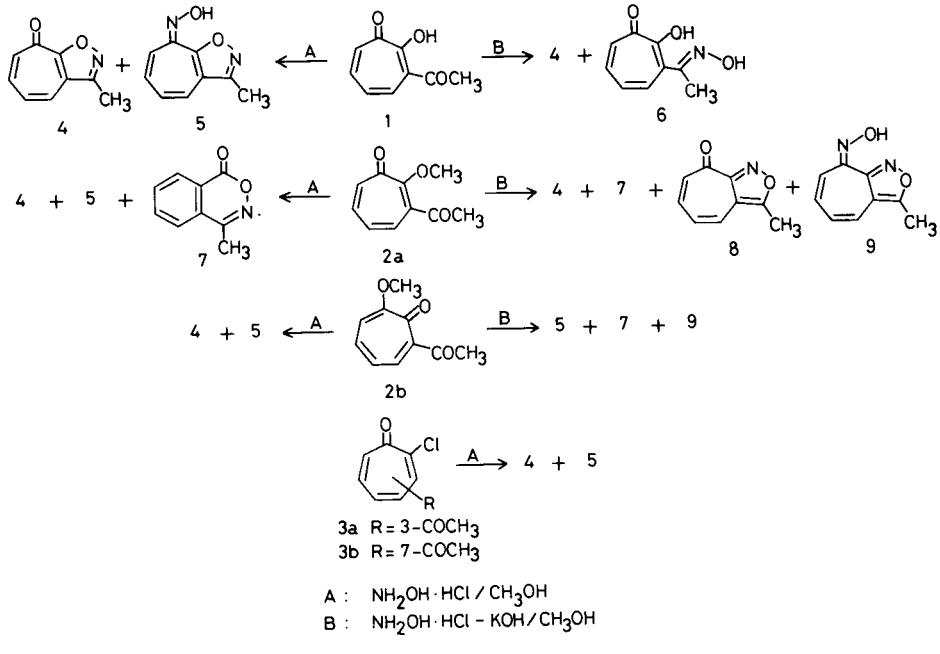
A

In the present work, we wish to report the formation of 8*H*-cyclohept[*d*]isoxazol-8-one and 8*H*-cyclohept[*c*]isoxazol-8-one derivatives by the reactions of 3-acetyltropolone (**1**) and its methyl ethers (**2a** and **2b**) with hydroxylamine. These 8*H*-cyclohept[*d*]isoxazol-8-ones and 8*H*-cyclohept-[*c*]isoxazol-8-ones are new types of troponoid compounds. The reactions of 3- and 7-acetyl-2-chlorotropones (**3a** and **3b**) with hydroxylamine are also described.

Results and Discussion.

Reaction of 3-Acetyltropolone (1) with Hydroxylamine.

Refluxing of 3-acetyltropolone (**1**) and hydroxylamine hydrochloride in methanol for 3 hours gave **4** and **5** in 82 and 11% yields, respectively. The compound **4** was assigned to 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one from its elemental analysis ($C_9H_7NO_2$) and spectral data. The ir spectrum shows an absorption at 1640 cm^{-1} for the



3a R = 3-$COCH_3$
3b R = 7-$COCH_3$

A : $NH_2OH \cdot HCl / CH_3OH$
B : $NH_2OH \cdot HCl - KOH / CH_3OH$

Scheme

tropone carbonyl group but no acetyl carbonyl absorption near 1700 cm^{-1}. The ^1H nmr spectrum shows peaks at δ 2.57 (s, 3H) for the methyl group and 6.8-7.5 (m, 4H) for the seven-membered ring protons.

On the other hand, the compound (**5**) was determined to be 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one oxime from its elemental analysis ($C_9H_8N_2O_2$) and spectral data. The ^1H nmr spectrum shows peaks at δ 2.31 (s, 3H) for the methyl group, 6.0-7.3 (m, 4H) for the seven-membered ring protons, and 11.68 (s, 1H) for the OH group. Furthermore, refluxing of **4** and hydroxylamine hydrochloride in methanol also gave **5**. This indicates that the former is a precursor to the latter.

Under the neutral condition adjusted by the addition of an equimolar potassium hydroxide for hydroxylamine hydrochloride, a mixture of **1** and hydroxylamine in methanol was refluxed for 3 hours to give **4** and **6** in 21 and 65% yields, respectively. The compound (**6**) gave coloration with iron(III) chloride. The compound (**6**) was assigned to 3-acetyltropolone oxime from this coloration, elemental analysis ($C_9H_9NO_3$), and spectral data. The ir spectrum shows a characteristic absorption at 1600 cm^{-1} for tropolone but no acetyl carbonyl absorption. The ^1H nmr spectrum shows peaks at δ 2.05 (s, 3H) for the methyl group and 6.8-7.7 (m, 4H) for the seven-membered ring protons. Refluxing of **6** in methanol did not cyclize to **4** but cyclized to **4** quantitatively in the presence of hydrochloric acid. Thus it is thought that the compound (**6**) is a precursor to **4** and the formation of **4** from **6** preceeds *via* intermediate as **A**.

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

Refluxing of 3-acetyl-2-methoxytropone (**2a**) and hydroxylamine hydrochloride in methanol for 3 hours gave **4**, **5**, and 4-methyl-1*H*-2,3-benzoxazin-1-one (**7**) in 48, 18, and 5% yields, respectively. The compound (**7**) was identified by comparison of its mp and ^1H nmr spectrum with those of an authentic sample (11).

Under the neutral condition, refluxing of **2a** and hydroxylamine in methanol for 3 hours gave **4**, **7**, **8**, and **9** in 7, trace, 24, and 26% yields, respectively. The compound (**8**) was assigned to 3-methyl-8*H*-cyclohept[*c*]-isoxazol-8-one from its elemental analysis ($C_9H_7NO_2$) and spectral data. The ir spectrum shows an absorption at 1630 cm^{-1} for the tropone carbonyl group. The ^1H nmr spectrum shows peaks at δ 2.75 (s, 3H) for the methyl group and 6.2-7.4 (m, 4H) for the seven-membered ring protons. When uv and ^1H nmr spectra of **8** were compared with those of **4**, the uv spectrum of **8** shows an absorption maximum at longer wavelength region than that of **4** as shown in Figure 1, and the ^1H nmr spectrum of **8** shows a peak broadened towards higher magnetic field for the seven-membered ring protons than that of **4**. These results indicate that the compound (**8**) has lower aromaticity and larger character as conjugated polyene than the compound (**4**).

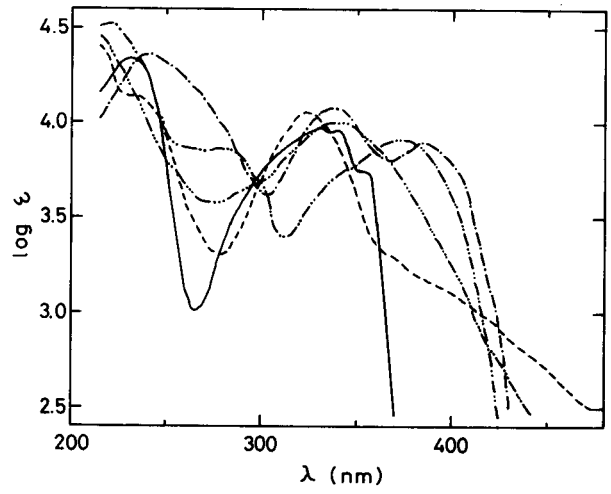


Figure 1. Electronic Spectra —— 4, ---- 5, -·-·- 6, -··-··- 8, -·····- 9.

On the other hand, the compound (**9**) was determined to be 3-methyl-8*H*-cyclohept[*c*]isoxazol-8-one oxime from its elemental analysis ($C_9H_8N_2O_2$) and spectral data. The ^1H nmr spectrum shows peaks at δ 2.55 (s, 3H) for the methyl group, 5.8-7.1 (m, 4H) for the seven-membered ring protons, and 11.87 (s, 1H) for the OH group. Furthermore, refluxing of **8** and hydroxylamine in methanol under the neutral condition gave **9**. It is thought that the compound (**8**) is a precursor to **9**.

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

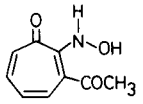
Refluxing of 7-acetyl-2-methoxytropone (**2b**) and hydroxylamine hydrochloride in methanol for 3 hours gave **4** and **5** in 74 and 20% yields, respectively.

Under the neutral condition, refluxing of **2b** and hydroxylamine in methanol for 3 hours gave **5**, **7**, and **9** in 52, trace, and 10% yields, respectively.

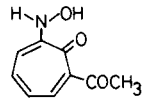
From the results of the above reactions, when the reactions were performed under the acidic condition, the major product obtained from **2a** and **2b** was the same as that from **1**. It is thought that **2a** and **2b** are initially hydrolyzed with acid, and then react with hydroxylamine to afford **4**.

On the other hand, when the reactions were performed under the neutral condition, it is thought, from the product yields, that the reactivity of **2a** and **2b** for hydroxylamine was larger at the C_2-position than at the acetyl carbonyl group. Also the formations of **8** and **9** from **2a** proceed *via* intermediate as **B**, while the formations of **5** and **9** from **2b** proceed *via* intermediate as **C**. However, the

intermediates, **B** and **C**, were not isolated.

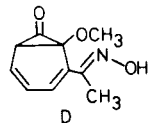


B

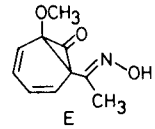


C

In addition, it is thought that the formation of **7** from **2a** and **2b** proceeds *via* intermediates, such as **D** and **E**.



D



E

Reactions of 3- and 7-Acetyl-2-chlorotropone (**3a** and **3b**) with Hydroxylamine.

Previously, we reported that 3- and 7-acetyl-2-chlorotropones (**3a** and **3b**) reacted with hydrazine and methylhydrazine to give 8*H*-cycloheptapyrazol-8-one derivatives (12). Now, a mixture of **3a** and hydroxylamine hydrochloride in methanol was refluxed for 3 hours to afford **4** and **5** in 22 and 7% yields, respectively. The same reaction of **3b** also gave **4** and **5** in 41 and 16% yields, respectively.

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 ^{1}H nmr spectra were recorded with a Hitachi R-24 spectrometer with TMS as an internal standard.

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

a) Acidic Conditions.

A mixture of **1** (329 mg, 2.0 mmoles) and hydroxylamine hydrochloride (279 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water, and evaporated to dryness. The residue was recrystallized from ethanol to afford 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one (**4**) as colorless plates, mp 177-178°; ir (chloroform): ν max 1640, 1590 cm^{-1}; uv (methanol): λ max 232 (log ϵ, 4.34), 329 (3.97), 340 nm (3.96); ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, CH_3), 6.8-7.5 ppm (m, 4H).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.27; H, 4.57; N, 8.40.

The filtrate was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ether. The first fraction was recrystallized from ethanol to afford 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one oxime (**5**) as orange crystals, yield 38 mg (11%), mp 219° dec; ir (potassium bromide): ν max 1590 cm^{-1}; uv (methanol): λ max 324 nm (log ϵ 4.05); ^{1}H nmr (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 6.0-7.3 (m, 4H), 11.68 ppm (s, 1H, OH).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.27; H, 4.71; N, 15.59.

The second fraction was recrystallized from ethanol to afford **4**. The combined yield of **4** was 264 mg (82%).

b) Neutral Conditions.

3-Acetyltropolone (**1**) (329 mg, 2.0 mmoles) was added to a mixture of hydroxylamine hydrochloride (278 mg, 4.0 mmoles) and potassium hydroxide (225 mg, 4.0 mmoles) in methanol (20 ml). The mixture was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with dilute sodium hydroxide solution and evaporated to dryness. The residue was recrystallized from ethanol to afford **4** (67 mg, 21%). The alkaline solution was acidified with hydrochloric acid and then extracted with chloroform. After removal of the solvent, the residue was recrystallized from ethanol to afford 3-acetyltropolone oxime (**6**) as colorless plates, yield 235 mg (65%), mp 163-164°; ir (potassium bromide): ν max 1600 cm^{-1}; uv (methanol): λ max 242 (log ϵ 4.36), 339 (4.08), 385 nm (3.90); ^{1}H nmr (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 6.8.-7.7 ppm (m, 4H).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.28; N, 7.76.

Cyclization of the Compound (**6**).

a) Neutral Conditions.

A solution of **6** (90 mg, 0.5 mmole) in methanol (10 ml) was refluxed for 3 hours and then worked up, as has been described above, not to give **4**. The compound (**6**) (87 mg, 96%) was recovered.

b) Acidic Conditions.

3-Acetyltropolone oxime (**6**) (90 mg, 0.5 mmole) in methanol (10 ml) was refluxed for 4.5 hours in the presence of hydrochloric acid, and then worked up, as has been described above, to give **4** (81 mg, 100%).

Reaction of the Compound (**4**) with Hydroxylamine Hydrochloride.

A mixture of **4** (81 mg, 0.5 mmole) and hydroxylamine hydrochloride (36 mg, 0.5 mmole) in methanol (10 ml) was refluxed for 10.5 hours. The solution was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ether. The first and second fractions were recrystallized from ethanol to afford **5** (21 mg, 23%) and **4** (40 mg, 49%), respectively.

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

a) Acidic Conditions.

A mixture of **2a** (360 mg, 2.0 mmoles) and hydroxylamine hydrochloride (278 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water, and evaporated to dryness. The residue was recrystallized from ethanol to afford **4**. The filtrate was concentrated and chromatographed for four times on two Wakogel B-10 plates (30 × 30 cm^2) with chloroform. The first fraction was recrystallized from benzene to afford 4-methyl-1*H*-2,3-benzoxazin-1-one (**7**) as colorless needles, yield 18 mg (5%), mp 162-163° [lit (11), mp 159-160°]; ir (chloroform): ν max 1740 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.60 (s, 3H, CH_3), 7.3-8.0 (m, 3H), 8.3-8.5 ppm (m, 1H, H-8).

The second fraction was recrystallized from ethanol to afford **4**. The combined yield of **4** was 156 mg (48%). The third fraction was recrystallized from ethanol to afford **5** (64 mg, 18%).

b) Neutral Conditions.

3-Acetyl-2-methoxytropone (**2a**) (356 mg, 2.0 mmoles) was added to a mixture of hydroxylamine hydrochloride (278 mg, 4.0 mmoles) and potassium hydroxide (225 mg, 4.0 mmoles) in methanol (20 ml) and refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water and evaporated to dryness. The residue was chromatographed on four Wakogel B-10 plates (30 × 30 cm^2) with ether. The first fraction was recrystallized from ethanol to afford 3-methyl-8*H*-cyclohept[*c*]isoxazol-8-one oxime (**9**) as brown prisms, yield 91 mg (26%), mp 178° dec; ir (potassium bromide): ν max 1650 cm^{-1}; uv (methanol): λ max 341 nm (log ϵ 4.00); ^{1}H nmr (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 5.8-7.1 (m, 4H), 11.87 ppm (s, 1H, OH).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.13; H, 4.67; N, 15.61.

The second fraction gave **7**, crude yield 8 mg (2%). The third fraction was a mixture of **4** and 3-methyl-8*H*-cyclohept[c]isoxazol-8-one (**8**), yield 102 mg (**4**: 7%, **8**: 24%). These yields were measured from the ^{1}H nmr spectral data and rechromatographed for four times on five Wakogel B-10 plates (30 × 30 cm^2) with chloroform. The first fraction was recrystallized from carbon tetrachloride to afford **8** as yellow prisms, yield 44 mg (14%), mp 125-127°; ir (chloroform): ν max 1655, 1630 cm^{-1}; uv (methanol): λ max 220 (log ϵ 4.52), 277 (3.86), 374 nm (3.91); ^{1}H nmr (deuteriochloroform): δ 2.75 (s, 3H, CH_3), 6.2-7.4 ppm (m, 4H).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.99; H, 4.39; N, 8.61.

Reaction of the Compound **8** with Hydroxylamine.

A mixture of **8** (32 mg, 0.2 mmole), hydroxylamine hydrochloride (28 mg, 0.4 mmole), and potassium hydroxide (22 mg, 0.4 mmole) in methanol (10 ml) was refluxed for 3 hours. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ether. The first fraction was recrystallized from ethanol to afford **9** (12 mg, 33%). The second fraction was recrystallized from carbon tetrachloride to afford **8** (15 mg, 45%).

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

a) Acidic Condition.

A mixture of **2b** (356 mg, 2.0 mmoles) and hydroxylamine hydrochloride (278 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water and evaporated to dryness. The residue was recrystallized from ethanol to afford **4**. The filtrate was concentrated and chromatographed on three Wakogel B-10 plates (30 × 30 cm^2) with ether. The first fraction was recrystallized from ethanol to afford **5** (72 mg, 20%). The second fraction was recrystallized from ethanol to afford **4**. The combined yield of **4** was 238 mg (74%).

b) Neutral Conditions.

7-Acetyl-2-methoxytropone (**2b**) (357 mg, 2.0 mmoles) was added to a mixture of hydroxylamine hydrochloride (278 mg, 4.0 mmoles) and potassium hydroxide (224 mg, 4.0 mmoles) in methanol (20 ml). The mixture was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water and evaporated to dryness. The residue was chromatographed for four times on four Wakogel B-10 plates (30 × 30 cm^2) with chloroform. The first fraction gave **7**, crude yield 7 mg (2%). The second and third fractions were recrystallized from ethanol to afford **9** (34 mg, 10%) and **5** (183 mg, 52%), respectively.

Reaction of 3-Acetyl-2-chlorotropone (**3a**) with Hydroxylamine.

To a suspension of **3a** (183 mg, 1.0 mmole) in methanol (10 ml) was added hydroxylamine hydrochloride (140 mg, 2.0 mmoles). The mixture was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in chloroform and washed with water. The chloroform solution was dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from ethanol to afford **4** (31 mg). The filtrate was chromatographed for four times on a Wakogel B-10 plate (30 × 30 cm^2) with chloroform to give **5** (12 mg, 7%) and **4** (5 mg) from the first and second fractions, respectively. The combined yield of **4** was 36 mg (22%).

Reaction of 7-Acetyl-2-chlorotropone (**3b**) with Hydroxylamine.

A mixture of **3b** (183 mg, 1.0 mmole) and hydroxylamine hydrochloride (140 mg, 2.0 mmoles) in methanol (10 ml) was refluxed for 3 hours and worked up, as has been described above, to give **4** (66 mg, 41%) and **5** (29 mg, 16%).

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