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# 2-아릴-5, 6, 7, 8-테트라히드로-3-신놀린온들의 합성

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# Synthesis of 2-Aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones

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**요 약.** 2-치환 5, 6, 7, 8-테트라히드로-3-신놀린온 합성에 이용할 2-(2, 2, 2-트리클로로에틸리덴)시클로헥산온(**1**)을 시클로헥산온과 클로랄의 엔아민축합으로 얻고자 하였다. 그러나 1-모르폴리노-1-시클로헥센(**2**)과 클로랄을 축합한 결과 2-(1-히드록시-2, 2, 2-트리클로로에틸)시클로헥산온(**3**)이 생성되었으며, 이것을 탈수시킨 결과 2-(2, 2-디클로로비닐)-2-시클로헥센온(**4**)이 얻어졌다. 화합물 **1** 대신에 α-(4-모르폴린일)-α-(2-옥소시클로헥실)아세트산 모르폴린일륨(**5**)을 사용하여 아릴하드라진들과 반응시킴으로써 2-아릴-5, 6, 7, 8-테트라히드로-3-신놀린올들을 합성할 수 있었다.

**ABSTRACT.** The preparation of 2-(2, 2, 2-trichloroethylidene)cyclohexanone(**1**), as a key compound for synthesizing 2-substituted 5, 6, 7, 8-tetrahydro-3-cinnolinones, was attempted by the enamine condensation of cyclohexanone with chloral. However, the condensation of 1-morpholino-1-cyclohexene(**2**) with chloral afforded 2-(1-hydroxy-2, 2, 2-trichloroethyl) cyclohexanone (**3**), and its dehydration led to 2-(2, 2-dichlorovinyl)-2-cyclohexenone(**4**). 2-Aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones could be synthesized using morpholinium α-(4-morpholinyl)-α-(2-oxocyclohexyl)-acetate(**5**) in place of **1** with arylhydrazines.

## INTRODUCTION

One of the most widely used methods for preparing 3(2*H*)-pyridazinones is by condensation of 1, 4-ketoacids or their esters with unsubstituted or substituted hydrazines, followed by dehydrogenation of the resulting 4, 5-dihydro derivatives. Less frequently, unsaturated 1, 4-ketoacids are employed and these or their hydrazones afford 3(2*H*)-pyridazinones directly. Synthesis of 3(2*H*)-pyridazinones is also possible from unsaturated γ-lactones and 3-bromo-, 3-alkylthio-, or 3-hydroxy-1, 4-ketoacids.[1,2]

In the related synthesis, one of the authors and coworkers synthesized 2, 6-disubstituted 3(2*H*)-pyridazinones from γ, γ, γ-trichloro-α, β-unsaturated ketones and substituted hydrazines.[3~7] Only a limited number of 5, 6, 7, 8-tetrahydro-3-cinnolinones has been reported.[8~10] As an extension of previous work, we were interested in synthesizing 2-substituted 5, 6, 7, 8-tetrahydro-3-cinnolinones by the reaction of 2-(2, 2, 2-trichloroethylidene)cyclohexanone(**1**)

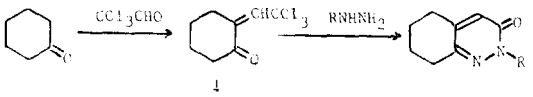


*Fig.* 1.

with substituted hydrazines.

Although we expected to obtain **1** from the condensation of 1-morpholino-1-cyclohexene(**2**) with chloral, the reaction product was 2-(1-hydroxy-2, 2, 2-trichloroethyl)cyclohexanone(**3**). Our attempts to obtain **1** by the dehydration of **3** were unsuccessful.

Schreiber and coworkers[10] have reported the synthesis of 5, 6, 7, 8-tetrahydro-3-cinnolinone by the reaction of morpholinium $\alpha$-(4-morpholinyl)-$\alpha$-(2-oxocyclohexyl)acetate(**5**) with hydrazine hydrate in the course of their study on the aminoalkylation. We wish to report the synthesis of 2-aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones using **5** in place of **1** and arylhydrazines.

## RESULTS AND DISCUSSION

The reaction of $\gamma, \gamma, \gamma$-trichloro-$\alpha, \beta$-unsaturated ketones with arylhydrazines has been reported to give 2, 6-disubstituted 3(2*H*)-pyridazinones in satisfactory yields.[3~7] $\gamma, \gamma, \gamma$-Trichloro-$\alpha, \beta$-unsaturated ketones have been prepared by the crossed aldol condensation of chloral with methyl ketones, and the dehydration of the resulting ketols. It was hoped that this reaction could be extended to synthesize 2-aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones using **1**.

Kiehlman and coworkers have reported that the direct condensation between cyclohexanone and chloral hydrate in acetic anhydride gave **3**,[11] and its thermal decomposition led to 2-(2, 2-dichlorovinyl)-2-cyclohexenone(**4**) instead of **1**.[12] We have found that the enamine condensation of **2** with chloral afforded **3**. Thus, chloral and **2** was reacted under reflux in cyclohexane, and the mixture was hydrolyzed with dil. HCl to give the two diastereomers of **3** (erythro and threo) in the approximate molar ratio 7 : 2. The same molar ratio was obtained by Kiehlman *et al.*[11] through the direct condensation of chloral with cyclohexanone in acetic anhydride. In contrast, the reaction of chloral with **2** under reflux in chloroform as solvent in the presence of dil. HCl gave the two diastereomers of **3** (erythro and threo) in the approximate molar ratio 2 : 8.

The attempted dehydration of threo **3** with *p*-toluenesulfonic acid resulted in the isomerization to erythro one. The dehydration of threo **3** with $H_2SO_4$ caused a concurrent dehydrochlorination to yield **4**. The analogous result has been obtained by Tanaka *et al.*[13] from the condensation of chloral with 1-morpholino-1-cyclopentene and subsequent dehydration of resulting ketol.

Schreiber and coworkers[10] has recently reported that the condensation of cyclohexanone with glyoxalic acid and morpholine gave **5**, and the reaction of it with hydrazine hydrate yielded 5, 6, 7, 8-tetrahydro-3-cinnolinone. We attempted to synthesize 2-aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones using **5** in place of **1**.

When **5** was reacted with arylhydrazine hydrochlorides in ethanol at 50~60°C, the

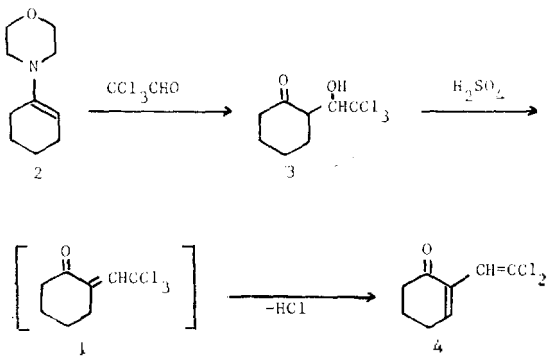
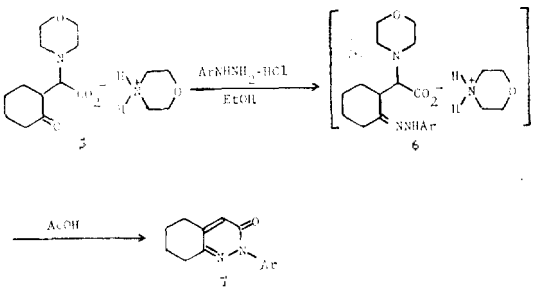


*Fig.* 2.



a. Ar=$C_6H_5$; e. Ar=$p$-$BrC_6H_4$;
b. $p$-$O_2NC_6H_4$; f. $m$-$O_2NC_6H_4$;
c. $p$-$CH_3C_6H_4$; g. $m$-$CH_3C_6H_4$;
d. $p$-$ClC_6H_4$.

*Fig.* 3

precipitates were formed after 5~15 min. Although we were unsuccessful in purifing them, they are presumed to be arylhydrazones of **5** on the basis of the nmr spectrum of crude **6a**. These intermediate products were heated in acetic acid for 1~2 hr, and the major products were collected by column chromatography using chloroform or chloroform-hexane mixture as eluent.

The ir spectra of major products showed an absorption band at 1640~1670 $cm^{-1}$ which indicated strongly the presence of amide carbonyl of pyridazinones. Their nmr spectra showed C-4 aromatic proton at $\delta$ 6.4~6.7 ppm, C-6 and C-7 methylene protons at 1.6~1.8 ppm, and C-5 and C-8 methylene protones at 2.6~2.8 ppm, respectively. These informations, along with combustion analyses, indicate the structures of products to be those of 2-aryl-5, 6, 7, 8-tetrahydro-3-cinnolinones(**7**).

## EXPERIMENTAL

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the Lucky Central Research Institute. The nmr spectra were recorded on a Varian EM-360 spectrometer, and the data were given in $\delta$ units downfield from TMS. The ir spectra were obtained with Perkin-Elmer Model 283 infrared spectrophotometer.

The analytical determination by glpc were performed on a Yanagimoto G 180 gas chromatograph using a column packed with 5 % SE-30 (column temperature 140°C) and helium as carrier gas. Analytical tlc was done on silica gel 60(70-230 mesh ASTM, E. Merck).

1-Morpholino-1-cyclohexene[14] and morpholinium $\alpha$-(4-morpholinyl)-$\alpha$-(2-oxocyclohexyl) acetate[10] were prepared by the method described in the literature. Anhydrous chloral was prepared from the commercially available chloral hydrate by distillation from $H_2SO_4$. Other chemicals and solvents were used without further purification.

**Reaction of Chloral with 1-Morpholino-1-cyclohexene(2).**

1. To 50 m*l* of cyclohexane was added 5.0 g (30 mmol) of **2** with stirring, and a solution of 4.4 g (30 mmol) of chloral in 5 m*l* of cyclohexane was slowly introduced through the dropping funnel. After the mixture was refluxed for 4 hr, it was cooled to 40°C and then 6.2 m*l* of 20 % aqueous HCl was added. The mixture was stirred for 2 hr at room temperature and extracted with toluene. The extract was washed with water and dried over $MgSO_4$. Removal of the solvent left a crude product, which was recrystallized from cyclohexane to give 2.9 g (39 %) of **3**. It was found by glpc analysis to be a mixture of 70 % of erythro isomer and 30 % of threo one.

2. To a solution of 16.0 g (96 mmol) of **2** in 40 m*l* of chloroform was added a solution of 14.0 g (95 mmol) of chloral in 15 m*l* of chloroform through the dropping funnel over a 1-h interval. The mixture was stirred for 1h

and then 40 m*l* of 20 % aqueous HCl was added. After the mixture was refluxed for 5 hr, it was cooled to room temperature, and the organic layer was separated. The aqueous layer was adjusted to a pH of 6 with a 25 % aqueous NaOH and then extracted with chloroform. The combined extract was washed with water and dried over $MgSO_4$. Removal of the solvent left a crude product, which was recrystallized from cyclohexane to give 16.0g (68 %) of **3**. It was found by glpc analysis to be a mixture of 20 % of erythro isomer and 80% of threo one. Two isomers were separated by column chromatography (2.5×12 cm) using hexane-dichloromethane (v/v 1 : 1) as eluent and identified by comparison of their nmr spectra and melting points with those of authentic samples.

**Dehydration of Thero-2-(1-hydroxy-2, 2, 2-trichloroethyl)cyclohexanone(3)**. To 30 m*l* of conc. $H_2SO_4$ was added 1.5 g(6.1 mmol) of **3** (threo) at 0°C with stirring. After being stirred for 20 hr, the mixture was poured into 100 m*l* of ice water. The solution was extracted with ether, and the organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent left a crude product which showed three spots at Rf values of 0.1, 0.3, and 0.5 on tlc using petroleum ether as developer. The major product with the Rf value of 0.3 was collected by column chromatography (2.5×12 cm) using the same solvent as eluent and identified as **4** by comparison of its ir and nmr spectra with those of an authentic sample.

**2-Phenyl-5, 6, 7, 8-tetrahydro-3-cinnolinone (7a)**. To 10 m*l* of ethanol heated to 50~60°C was added 1.08 g (3.3 mmol) of **5** in small portions with stirring. To this solution was added 0.48 g (3.3 mmol) of phenylhydrazine hydrochloride with stirring to give a precipitate after 10 min. After being allowed to sit at room temperature for 1 hr, it was filtered, washed with acetone, and dried in a vacumn desicator. The precipitate was added to 10 m*l* of acetic acid, and the mixture was heated at 50°C for 1 hr. It was cooled to room temperature, and the solvent was removed. The major product was collected by column chromatography (2.5 ×12 cm) using chloroform-hexane (v/v 9 : 1) as eluent and recrystallized from hexane; Yield: 0.52 g (70%); mp 120~121°C; NMR($CDCl_3$) $\delta$1.8(m, 4H, $2CH_2$), 2.8(m, 4H, $2CH_2$), 6.7 (s, 1H, CH), 7.4(m, 5H, $C_6H_5$); IR(KBr pellet) 2940, 1657, 1578, 1300, 1130, 752, 690 $cm^{-1}$

*Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.29; H, 6.25; N, 12.37. Found: C, 74.42; H, 6.30; N, 12.49.

**2-(*p*-Nitrophenyl)-5, 6, 7, 8-tetrahydro-3-cinnolinone(7b)**. Following the procedure described before, the intermediate product was obtained from 2.15g (6.58 mmol) of **5** and 1.25 g (6.58 mmol) of *p*-nitrophenylhydrazine hydrochloride in 20m*l* of ethanol. It was heated in 20 m*l* of acetic acid at 60°C for 1 h. The major product was collected by column chromatography using chloroform-hexane (v/v 8 : 2) as eluent and recrystallized from methanol; Yield: 0.89 g (50%); mp 124°C; NMR ($CDCl_3$) $\delta$ 1.7(m, 4H, $2CH_2$), 2.7(m, 4H, $2CH_2$), 6.7 (s, 1H, CH), 8.0(m, 4H, $C_6H_4$); IR(KBr pellet) 2940, 1670, 1575, 1500, 1340, 1300, 1140, 1100, 850, 700 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.84; N, 15.49. Found: C, 62.06; H, 4.82; N, 15.98.

**2-(*p*-Tolyl)-5, 6, 7, 8-tetrahydro-3-cinnolinone(7c)**. Following the procedure described before, the intermediate product was obtained from 1.08g (3.3 mmol) of **5** and 0.52 g (3.3 mmol) of *p*-tolylhydrazine hydrochloride in 10 m*l* of ethanol. It was heated in 10 m*l* of

acetic acid at 50°C for 30 min. The major product was collected by column chromatography using chloroform-hexane (v/v 8 : 2) as eluent and recrystallized from hexane; Yield: 0.48 g (61 %); mp 121°C; NMR ($CDCl_3$) $\delta$ 1.8(m, 4H, $2CH_2$), 2.4(m, 3H, $CH_3$), 2.7(m, 4H, $2CH_2$), 6.7(s, 1H, CH), 7.3(m, 4H, $C_6H_4$); IR(KBr pellet) 2940, 1656, 1590, 1500, 1300, 1130, 930 $cm^{-1}$.

*Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.72; N, 11.66. Found: C, 74.63; H, 6.68; N, 11.78.

**2-(*p*-Chlorophenyl)-5,6,7,8-tetrahydro-3-cinnolinone (7d).** Following the procedure described before, the intermediate product was obtained from 2.16g (6.58 mmol) of **5** and 1.18 g(6.58 mmol) of *p*-chlorophenylhydrazine hydrochloride in 20 m*l* of ethanol. It was heated in 20 m*l* of acetic acid at 60°C for 1.5 h. The major product was collected by column chromatography using chloroform as eluent and recrystallized from ethyl acetate; Yield: 0.86g(51%); mp 170°C; NMR($CDCl_3$) $\delta$1.8(m, 4H, $2CH_2$), 2.7(m, 4H, $2CH_2$), 6.7(s, 1H, CH), 7.5(m, 4H, $C_6H_4$); IR (KBr pellet) 2920, 1645, 1570, 1305, 1125, 992, 830 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{13}N_2OCl$: C, 64.49; H, 5.04; N, 10.76. Found: C, 64.19; H, 4.97; N, 10.64.

**2-(*p*-Bromophenyl)-5,6,7,8-tetrahydro-3-cinnolinone(7e).** Following the procedure described before, the intermediate product was obtained from 1.08 g(3.3mmol) of **5** and 0.74 g (3.3 mmol) of *p*-bromophenylhydrazine hydrochloride in 10 m*l* of ethanol. It was boiled under reflux in 10 m*l* of acetic acid for 2 hr. The major product was collected by column chromatography using chloroform as eluent and recrystallized from hexane; Yield: 0.70 g (68 %); mp 159~160°C; NMR($CDCl_3$) $\delta$ 1.8(m, 4H, $2CH_2$), 2.7(m, 4H, $2CH_2$), 6.7(s, 1H, CH), 7.5(s, 4H, $C_6H_4$); IR (KBr pellet) 2920, 1650, 1565, 1470, 1305, 1120, 990, 825, 700 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{13}N_2OBr$: C, 55.09; H, 4.30; N, 9.18. Found: C, 55.32; H, 4.23; N, 9.35.

**2-(*m*-Nitrophenyl)-5,6,7,8-tetrahydro-3-cinnolinone (7f).** Following the procedure described before, the intermediate product was obtained from 2.16 g (6.58 mmol) of **5** and 1.12 g (6.58 mmol) of *m*-nitrophenylhydrazine hydrochloride in 20 m*l* of ethanol. It was boiled under reflux in 20 m*l* of acetic acid for 1.5 h. The major product was collected by column chromatography using chloroform-hexane (v/v 9 : 1) as eluent and recrystallized from hexane. Yield: 1.16 g (65 %); mp 120°C; NMR($CDCl_3$) $\delta$ 1.8(m, 4H, $2CH_2$), 2.8(m, 4H, $2CH_2$), 6.8(s, 1H, CH), 7.7~8.6(m, 4H, $C_6H_4$); IR(KBr pellet) 2930, 1655, 1590, 1510, 1340, 1300, 1120, 870 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.84; N, 15.49. Found: C, 62.06; H, 4.79; N, 15.92.

**2-(*m*-Tolyl)-5,6,7,8-tetrahydro-3-cinnolinone(7g).** Following the procedure described before, the intermediate product was obtained from 1.08 g (3.3 mmol) of **5** and 0.52 g (3.3mmol) of *m*-tolylhydrazine hydrochloride in 10 m*l* of ethanol. It was boiled under reflux in 10 m*l* of acetic acid for 1.5hr. The major product was collected by column chromatography using chloroform-hexane (v/v 8 : 2) as eluent and recrystallized from hexane; Yield: 0.47 g (60 %); mp 95~96°C; NMR ($CDCl_3$) $\delta$ 1.7(m, 4H, $2CH_2$), 2.4(s, 3H, $CH_3$), 2.7(m, 4H, $2CH_2$), 6.4(s, 1H, CH), 7.3(m, 4H, $C_6H_4$); IR(KBr pellet) 2920, 1640, 1575, 1410, 1300, 1120, 860, 780, 700 $cm^{-1}$.

*Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H,

6.72; N, 11.66. Found: C, 74.60; H, 6.69; N, 11.65.

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