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Reaction of 3-[3-(2-Nitrophenyl)-2-propenylidene]-2,4-pentanedione with Hydroxylamine Hydrochloride. Formation of a 2-Chloromethyleneindolin-3-one

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Reaction of 3-[3-(2-nitrophenyl)-2-propenylidene]-2,4-pentanedione (**3**) with hydroxylamine hydrochloride in methanol gave a 1:1 mixture of (*E*)-4-[3-methoxy-3-(2-nitrophenyl)-1-propenyl]-3,5-dimethylisoxazole (**4**) and (*E*)-4-[1-methoxy-3-(2-nitrophenyl)-2-propenyl]-3,5-dimethylisoxazole (**5**) in 49.3% yield. Similarly, when acetonitrile was used as the solvent in this reaction, 2-(3,5-dimethyl-4-isoxazolyl)-chloromethyleneindolin-3-one (**6**) (36.3%), (*E*)-4-acetyl-3-methyl-5-(2-nitrostyryl)isoxazole (**7**) (6.3%) and 4-[1-(hydroxyimino)ethyl]-3-methyl-7-(2-nitrophenyl)-1,2-oxazepine (**8**) (1.8%) were obtained.

Keywords——3-[3-(2-nitrophenyl)-2-propenylidene]-2,4-pentanedione; 2,1-benzisoxazole; isoxazole; 1,2-oxazepine; indole; indolin-3-one; isatin; reaction mechanism

In previous papers,[1] we described the utilization of α,β-unsaturated β-diketones, such as 3-phenylmethylene-2,4-pentandiones, for the preparation of some heterocycles. For example, 3-(2-nitrophenyl)methylene-2,4-pentanedione (**1**) was treated with hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) in acetonitrile to give 3-(3,5-dimethyl-4-isoxazolyl)-5-chloro-2,1-benzisoxazole (**2**) in 93% yield, as outlined in Chart 1. To extend the scope of this reaction we examined the reaction of *trans*-3-[3-(2-nitrophenyl)-2-propenylidene]-2,4-pentanedione (**3**) with $NH_2OH \cdot HCl$ in the present work.

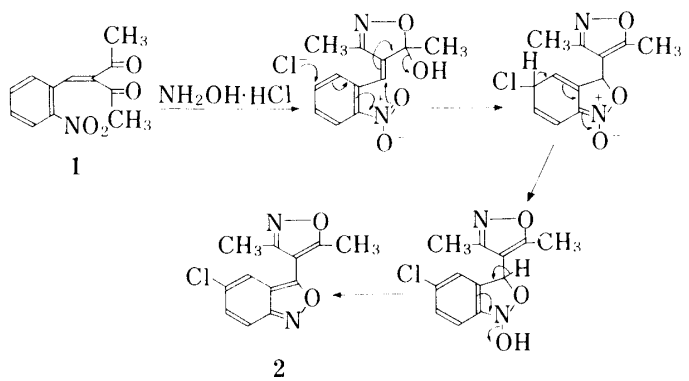

Chart 1

The Knoevenagel condensation of *trans*-2-nitrocinnamaldehyde[2] with acetylacetone in the presence of piperidine in ethanol gave **3** in 56.3% yield. Treatment of **3** with $NH_2OH \cdot HCl$ in methanol gave an oily material (in 49.3% yield), whose proton magnetic resonance (PMR) spectrum showed the presence of two components. Separation by silica gel column chromatography eluted with benzene gave 4-[3-methoxy-3-(2-nitrophenyl)-1-propenyl]-3,5-dimethylisoxazole (**4**), mp 63—64°C, [mass spectrum (MS) *m/z*: 288 (M^+)] from the first fraction and 4-[1-methoxy-2-(2-nitrophenyl)-2-propenyl]-3,5-dimethylisoxazole (**5**) as an oil [MS *m/z*: 288 (M^+)] from the second fraction in a ratio of 1:1. The structures were determined on the basis of the following observations; the signal due a to methine proton of **5** appeared as a doublet of doublets (J=6 and 1.5 Hz) at 4.80 ppm, while that of **4** appeared as a doublet (J=6 Hz) at 5.41 ppm shifted downfield (by 0.61 ppm) by the anisotropic effect of the nitro group. The observation that the two vinyl protons of **4** and **5** appeared as doublets with a coupling constant (J) of 16 Hz proved the compounds to be *E*-isomers.

On the other hand, when reaction of **3** with $NH_2OH \cdot HCl$ was carried out in acetonitrile at 55°C, a red material (**6**), mp 202—203°C, was obtained in 36.3% yield, together with 6.3% yield of **7**, mp 185—186°C, as well as 1.8% of **8**, 243—244°C. The red product proved to have the empirical formula $C_{14}H_{11}ClN_2O_2$ based on the results of elemental and MS spectral

analysis, and the ultraviolet (UV) absorption [λ_{max}^{EtOH} nm (log ε): 237 (3.92), 264 (4.06), 312 (3.75) and 462 (3.46)] indicated extensive conjugation. In the ^{13}C-nuclear magnetic resonance (CMR) spectrum, **6** exhibited fourteen signals as detailed in the experimental section. The infrared (IR) spectrum showed the disappearance of the NO_2 group and the presence of NH and carbonyl groups, the absorption of the latter being at 1690 cm^{-1}. The PMR spectrum showed the presence of four aromatic protons and two methyl protons (at 2.16 and 2.30 ppm) as well as an NH proton (at 10.02 ppm). In order to obtain definitive evidence of this structure, the following transformations were carried out. Thus, catalytic hydrogenation of **6** using 5% palladium carbon (Pd–C) gave a colorless product (**9**), $C_{14}H_{14}N_2O$, whose signals in the aromatic region showed a close similarity to those of indole[3] in the PMR spectrum. Further evidence for the structure **9** was provided by the UV spectrum [λ_{max}^{EtOH} nm (log ε): 272 (3.86), 282 (3.84) and 288 (3.73)], which was identical with that of 2-methylindole [λ_{max}^{EtOH} nm (log ε): 270 (3.85), 280 (3.84) and 287 (3.73)]. Therefore, the structure of **9** was established as 2-(3,5-dimethyl-4-isoxazolyl)methylindole. Further, chromic acid oxidation of **6** in acetic acid gave a red crystalline product (**10**) which was identified as isatin by mixed melting point determination and comparison of the IR spectrum with that of an authentic sample. Consequently, **6** was unambiguously confirmed to be 2-(3,5-dimethyl-4-isoxazolyl)-chloromethyleneindolin-3-one. Data on carbonyl frequency and the highest wavelength UV absorption maxima in reasonably good agreement with those of (*Z*)-2-[1-(3-ethyl-4-pyridyl)ethylidene]indolin-3-one (ν 1680cm^{-1} and λ 470 nm), which is a key intermediate in the synthesis of ellipticine.[4] The geometric configuration of **6** was elucidated by measurement of intramolecular Overhauser effects (NOE).

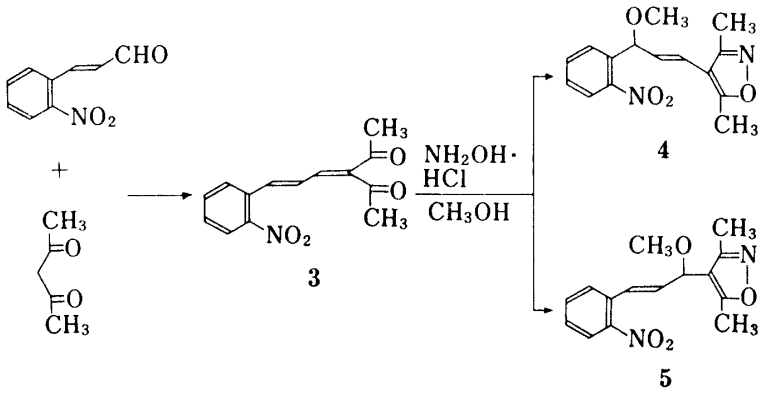

Chart 2

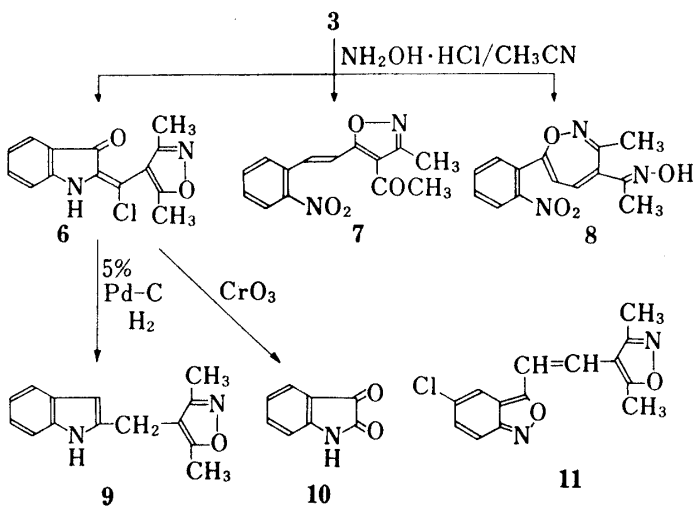

Chart 3

Thus, irradiation of the signals of methyl protons on the isoxazole ring caused no increase in the integration of NH proton signal, so it was considered that **6** might be the *z*-isomer. As will be described later, the anticipated 5-chloro-2,1-benzisoxazole (**11**) was not obtained in this case, in marked contrast to the results of the previous paper.[1] The structure of the minor product **7**, $C_{14}H_{12}N_2O_4$, was supported by the following spectral data: the IR spectrum showed a carbonyl absorption band at 1660 cm^{-1} and two strong bands at 1520 and 1350 cm^{-1} due to an NO_2 group. The PMR spectrum showed characteristic signals due to a *trans*-2-nitrostyryl moiety [7.32 (1H, d, J=16 Hz, Ph-CH=C<u>H</u>-) and 7.92 (1H, d, J=16 Hz, Ph-C<u>H</u>=CH-), in addition to four aromatic protons]. Although no molecular ion peak (*m/z* 272) was observed, an intense peak at *m/z* 226 due to loss of the nitro substituent was seen in its MS spectrum.[5] The most interesting fragments were those at *m/z* 124 and *m/z* 82, corresponding to [M^+-1] of 4-acetyl-3-methylisoxazole and the further loss of ketene. These data substantiate the structure of **7** as (*E*)-4-acetyl-3-methyl-5-(2-nitrostyryl)isoxazole. By means of MS [*m/e* 287 (M^+)] and elemental analysis, the molecular formula of another minor product **8** was proved to be $C_{14}H_{13}N_3O_4$. The IR spectrum showed, in addition to the absorption bands at 1530 and 1360 cm^{-1} due to an NO_2 group, a characteristic broad bands at 3100—2800 cm^{-1} indicating the presence of an =N-OH group.[6] The PMR spectrum exhibited a pair of doublets (J=8 Hz) due to a =CH-CH= moiety at 7.41 and 7.65 ppm. Further, major mass spectral fragments were markedly different from those of **7**.[7] On the basis of these observations the structure of **8** was tentatively assigned as 4-[1-(hydroxyimino)ethyl]-3-methyl-7-(2-nitrophenyl)-1,2-oxazepine.

The mechanism of the formation of the indolin-3-one, 5-styrylisoxazole and 1,2-oxazepine may be as follows: intramolecular cyclization of the monoxime A along path b gives the 5-styrylisoxazole (**7**), while path c followed by oxime formation gives the 1,2-oxazepine (**8**). On the other hand, cyclization along path a would give an intermediate γ-chlorocinnamylisoxazole C *via* an intermediate B. Prototropy may yield an intermediate D, Which would recyclize followed by dehydration to give 2,1-benzisoxazole F *via* an intermediate E. Rearrangement of 3-substituted 2,1-benzisoxazole to other heterocycles is well known.[8] For instance, reactions of 3-phenyl-2,1-benzisoxazole with nitric acid[9] or nitrous acid[10] give acridone. Thermolysis of 3-phenyl-2,1-benzisoxazole results in rearrangement to acridone,[11] and 3-methyl-2,1-benzisoxazole rearranges on strong heating to form indolin-3-one.[12] Recently, Smalley *et al.* have reported[13] the thermal rearrangement of some 3-styryl-2,1-benzisoxazoles to 2-arylidene-

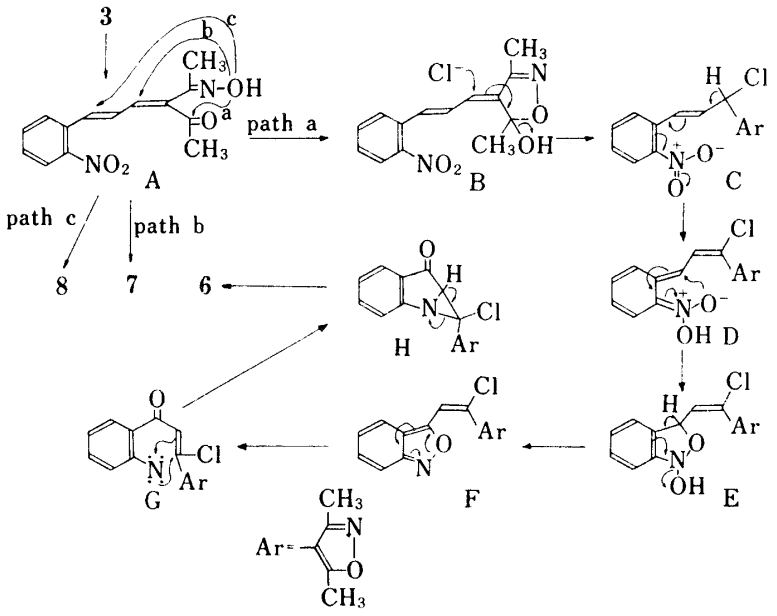

Chart 4

indoxyls in boiling anisol or 1-methylnaphthalene. Moreover, it was also reported[14] that 3-phenyliminoethyl- and 3-arylazo-2,1-benzisoxazoles thermally rearrange to 3-phenyl-4(3*H*)-quinazoline and 3-aryl-1,2,3-benzotriazine-4(3*H*)-ones. Thus, the pathway from F to **6** seems reasonable by analogy with the proposals of Smalley.[13] Namely, the formation of the indolin-3-one (**6**) probably involves ring-opening of 2,1-benzisoxazole (F) to the nitreno-ketone (G), followed by rearrangement of the tricyclic intermediate (H).

Experimental

All melting points were recorded on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO IRA-1 spectrophotometer and the UV spectra on a JASCO UVIDEC-505 spectrophotometer. The PMR spectra were taken at 90 MHz with a Hitachi R-24A spectrometer and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal standard. The CMR spectrum was recorded on a JEOL FX-100 spectrometer. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. The MS were recorded with a Hitachi RMU-7L spectrometer.

***trans*-3-[3-(2-Nitrophenyl)-2-propenylidene]-2,4-pentanedione (3)**——A suspension of 3.54 g of *trans*-2-nitrocinnamaldehyde and 2.0 g of acetylacetone in 30 ml of EtOH was treated with 10 drops of piperidine, and the mixture was stirred at room temperature for 2 d. The precipitate was collected by filtration, washed with cold EtOH and dried to give 2.95 g (56.8%) of **3**. Recrystallization from EtOH gave an analytical sample as pale yellow needles of mp 152—153°C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1700 (CO), 1650 (C=C), 1530 and 1360 (NO_2). PMR ($CDCl_3$) δ: 2.40 and 2.44 (each 3H, each s, $2\times CH_3$), 6.98—8.14 (7H, m, vinyl-H and Ar–H). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.93; H, 5.24; N, 5.34.

Reaction of 3 with Hydroxylamine Hydrochloride in MeOH——A mixture of 2.59 g of **3** and 2.1 g $NH_2OH\cdot HCl$ in 80 ml of MeOH was refluxed for 4 h. The solvent was evaporated off *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography eluted with $CHCl_3$ to remove tarry material, yielding 1.42 g (49.3%) of a pure oil, which consists of two components. The oily material was again subjected to silica gel column chromatography. The first fraction eluted with benzene yielded (*E*)-4-[3-methoxy-3-(2-nitrophenyl)-1-propenyl]-3,5-dimethylisoxazole (**4**) as colorless needles of mp 63—64°C (petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1530 and 1370 (NO_2). PMR ($CDCl_3$) δ: 2.30 and 2.40 (each 3H, each s, $2\times CH_3$), 3.36 (3H, s, OCH_3), 5.41 (1H, d, J=6 Hz, CH), 5.91 (1H, dd, J=6 and 16 Hz, Ph–CH(OCH_3)–C<u>H</u>=CH–), 6.41 (1H, d, J=16 Hz, Ph–CH(OCH_3)–CH=C<u>H</u>–), 7.32—7.95 (4H, m, Ar–H). MS: *m/z* 288 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.63; H, 5.57; N, 9.96. The second fraction eluted with benzene yielded (*E*)-4-[1-methoxy-3-(2-nitrophenyl)-2-propenyl]-3,5-dimethylisoxazole (**5**) as a pale brown oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1530 and 1350 (NO_2). PMR ($CDCl_3$) δ: 2.30 and 2.45 (each 3H, each s, $2\times CH_3$), 3.36 (3H, s, OCH_3), 4.80 (1H, dd, J=1.5 and 6 Hz, CH), 6.20 (1H, dd, J=6 and 16 Hz, Ph–CH=C<u>H</u>–), 7.06 (1H, dd, J=1.5 and 16 Hz, Ph–C<u>H</u>=CH–), 7.26—8.02 (4H, m, Ar–H). MS *m/z*: 288 (M^+).

Reaction of 3 with Hydroxylamine Hydrochloride in Acetonitrile——A mixture of 5.18 g of **3** and 2.78 g of $NH_2OH\cdot HCl$ in 150 ml of CH_3CN was stirred at 55°C for 15 h. The solvent was evaporated off *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* to provide an oil, which crystallized on addition of EtOH. The collected precipitate was recrystallized from benzene to give 2.03 g (36.3%) of 2-(3,5-dimethyl-4-isoxazolyl)-chloromethyleneindolin-3-one (**6**) as red needles of mp 202—203°C. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1690 (CO), 1625 (C=C). UV λ_{max}^{EtOH} nm (log ε): 237 (3.92), 264 (4.06), 312 (3.75), 462 (3.46). PMR (DMSO-d_6) δ: 2.16 and 2.30 (each 3H, each s, $2\times CH_3$), 6.80—7.66 (4H, m, Ar–H), 10.02 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 10.2 (q), 11.7 (q), 108.7 (s), 111.4 (s), 112.1 (d), 120.0 (d), 121.1 (s), 124.4 (d), 136.0 (s), 136.6 (d), 152.6 (s), 158.7 (s), 168.6 (s), 182.0 (s). MS *m/z*: 274 (M^+). *Anal.* Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20. Found: C, 61.28; H, 3.94; N, 10.10. The filtrate was concentrated *in vacuo* and the residual oil was subjected to silica gel column chromatography. The first fraction eluted with benzene yielded 344 mg (6.3%) of (*E*)-4-acetyl-3-methyl-5-(2-nitrostyryl)isoxazole (**7**) as pale yellow needles of mp 185—186°C (AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1660 (CO), 1520 and 1350 (NO_2). UV λ_{max}^{EtOH} nm (log ε): 270 (4.11). PMR (DMSO-d_6) δ: 2.44 and 2.73 (each 3H, each s, CH_3 and/or $COCH_3$), 7.32 (1H, d, J=16 Hz, Ph–CH=C<u>H</u>–), 7.92 (1H, d, J=16 Hz, Ph–C<u>H</u>=CH–), 7.66—8.18 (4H, m, Ar–H). MS *m/z*: 226 (M^+-NO_2), 184 (M^+-NO_2 and ketene), 124 and 82 ([M^+-1] of 4-acetyl-3-methylisoxazole and the further loss of ketene). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.65; H, 4.40; N, 10.23. The second fraction eluted with $CHCl_3$ yielded 104 mg (1.8%) of 4-[1-(hydroxyimino)ethyl]-3-methyl-7-(2-nitrophenyl)-1,2-oxazepine (**8**) as pale yellow needles of mp 243—244°C (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3100—2800 (=N–OH), 1530 and 1360 (NO_2). PMR (DMSO-d_6) δ: 2.20 and 2.38 (each 3H, each s, $2\times CH_3$), 7.41 and 7.65 (each 1H, each d, J=8 Hz, =CH–CH=), 7.55—8.22 (4H, m, Ar–H), 11.52 (1H, s, OH). MS *m/z*: 287 (M^+), 241 (M^+-NO_2), 223 (M^+-NO_2 and H_2O), 209 (M^+-NO_2 and MeOH), 183 (M^+-NO_2 and CH_3–C=N–OH). *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.51; H, 4.61; N, 14.87.

2-(3,5-Dimethyl-4-isoxazolyl)methylindole (9)——A solution of 1 g of **6** in 100 ml of EtOH was shaken with H_2 over 400 mg of 5% Pd-C for 10 h in a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo*. The residual oil was subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ yielded 198 mg (24.5%) of **9** as colorless needles of mp 130°C (AcOEt–*n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 3220 (NH). UV λ_{max}^{EtOH} nm (log ε): 272 (3.86), 282 (3.84), 288 (3.73). PMR (DMSO-d_6) δ: 2.11 and 2.24 (each 3H, each s, $2\times CH_3$), 3.85 (2H, s, CH_2), 6.08 [1H, br s, C(3)–H of indole ring], 6.85—7.52 (4H, m, Ar–H), 10.86 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.57; H, 6.17; N, 12.31.

Chromic Acid Oxidation of 6——To a solution of **6** in 5 ml of AcOH was added 5 ml of 20% CrO_3–AcOH solution, and the mixture was stirred at room temperature for 3 h. Excess CrO_3 was decomposed by the addition of EtOH under ice cooling, then the mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and saturated $NaHCO_3$, then dried over Na_2SO_4. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography eluted with $CHCl_3$ to give 45 mg of a red crystalline solid. Recrystallization from EtOH gave **10**, mp 198—199°C, which was identical with an authentic sample of isatin as determined by mixed melting point determination and comparison of their IR spectra.

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References and Notes

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