Notes

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Yoshifumi Maki, Mikio Suzuki, and Tomiyasu Yamada*1 : Reactions of Ethyl 3-Methyl-4*H*-benzo-1,4-thiazine-2-carboxylate with Hydrazine Derivatives.

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In 1897, Graff, *et al.*[1] reported that the reaction of ethyl 3-methyl-4*H*-benzo-1,4-thiazine-2-carboxylate (I) with phenylhydrazine results in a novel ring-conversion into 1-phenyl-3-methyl-4-phenylazo-2-pyrazolin-5-one (II : R=H). A similar ring-conversion was also observed by Takahashi, *et al.*[2] in the reaction of phenylhydrazine with ethyl 3-methyl-4*H*-pyrido[2,3-*b*]-1,4-thiazine-2-carboxylate, which is aza homolog of I. These papers did not offer any suggestions about the scope and mechanism of this reaction.

The present work, therefore, was undertaken to see if the reaction could occur on using hydrazine derivatives other than phenylhydrazine and the reaction mechanism was considered.

In the preparation of I, a modification of Graff's method[1] was used as described in the experimental part, since it gave a more satisfactory yield.

For explaining the reaction mechanism as described later, it is necessary to decide which tautomeric forms of I (amine form A or azomethine form B) is predominant.

Infrared spectrum of I clearly showed the presence of NH stretching band at 3400 cm^{-1} (Nujol) and at 3300 cm^{-1} (CCl_4). Also if I exists in form B, its nuclear magnetic resonance spectrum should exhibit a singlet signal attributed to one proton at C_2-position. However, its spectrum (in $CDCl_3$) indicated absence of the corresponding signal. These spectral data led to the reasonable conclusion that I exsists exclusively in the amine form A under the conditions of spectral measurement.

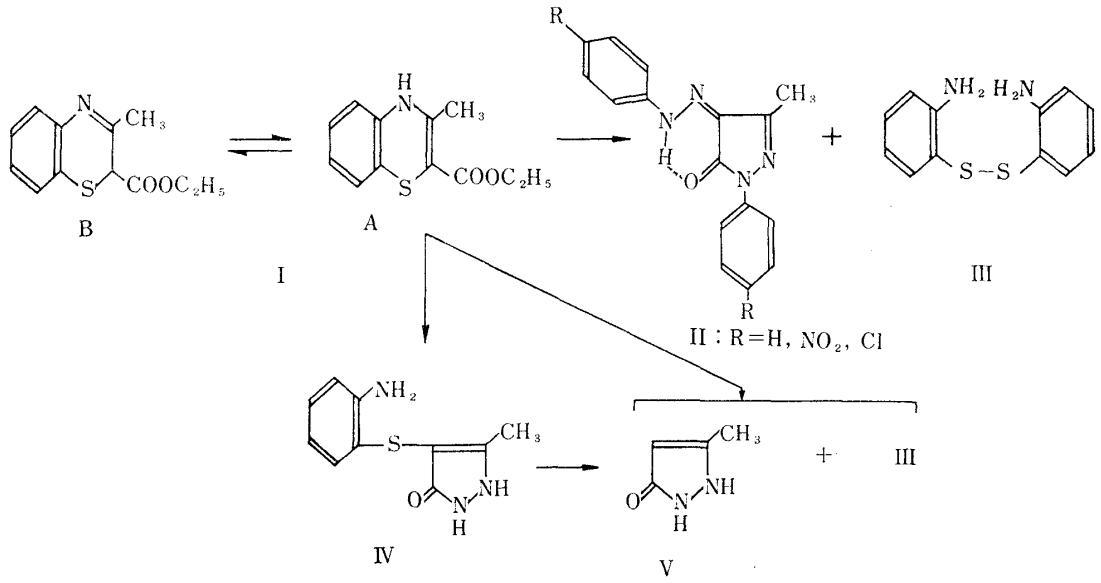

Chart 1.

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1) G. Graff, O. Unger : Ber., **30**, 2390 (1897).

2) T. Takahashi, E. Yoshii : This Bulletin, **2**, 382 (1954).

When I was allowed to react with *p*-chloro (or nitro) phenylhydrazine in the same way as in the case of phenylhydrazine,[1] the corresponding pyrazolone derivatives[3] (II: R=NO_2, Cl) and disulfide (III) were obtained.

II: R=NO_2, Cl were also prepared by condensation of *p*-nitro (or chloro) phenylhydrazine and ethyl 2-chloroacetoacetate according to Schoenbrodt's method,[4] and III was identical with authentic sample in melting point and infrared spectrum.

On the other hand, the reaction of I with *p*-tolylhydrazine did not afford the expected pyrazolone derivatives (II: R=CH_3) and 80% of I was recovered unchanged from the reaction mixture.

On heating I with hydrazine hydrate for 30 minutes, 3-methyl-4-(*o*-aminophenylthio)-2-pyrazolin-5-one (IV), m.p. 241~242°, was obtained in a fairly good yield.

IV shows a positive diazonium test for aromatic primary amines and infrared absorption bands at 3400, 3000, 2800~2500, and 1620 cm^{-1} (Nujol). Its ultraviolet absorption curve was in good agreement with that obtained tentatively adding the curve of 3-methyl-2-pyrazolin-5-one (V) to the curve of *o*-aminothiophenol. Furthermore, the structure of IV[5] was supported by the fact that when the duration of heating in the reaction of I with hydrazine hydrate was prolonged up to 5 hours, V and III, which were respectively identical with authentic samples, were obtained, and V and III were also formed by further treatment of IV with hydrazine hydrate. These findings indicate that IV easily suffers reductive cleavage of the C_4-S bond to give III and V.

On the contrary, no ring-conversion occurred in the reaction of I with methylhydrazine and semicarbazide under the condition similar to the case of hydrazine.

Lastly, we assumed the reaction mechanism consisting of the following steps, as shown in Chart 2: (1) Nucleophillic attack by amino group of hydrazine derivatives

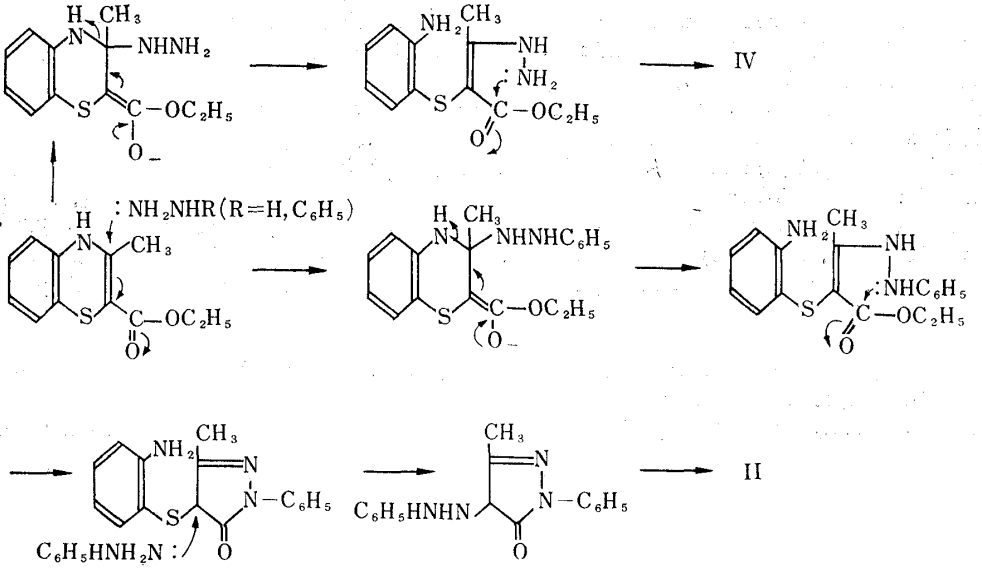

Chart 2.

3) R. Jones, *et al.* (Tetrahedron, **19**, 1497 (1963)) suggested that 1-phenyl-3-methyl-4-phenylazo-2-pyrazolin-5-one exsists exclusively in the hydrogen-bonded lactam hydrazone form (II: R=H) based on infrared and ultraviolet comparison with model compounds. The infrared spectra of the present pyrazolone derivatives (II: R=NO_2, Cl) also showed lactam carbonyl absorption band at 1670 cm^{-1} (in dil. CCl_4), indicating the presence of intramolecular hydrogen bond in agreement with Jones' viewpoint.

4) R. Schoenbrodt: Ann., **253**, 192 (1889).

5) Recently, A. R. Katrizky *et al.* (Tetrahedron, **21**, 1693 (1965)) discussed the problem of complex tautomerism of N-unsubstituted 2-pyrazolin-5-one on the basis of ultraviolet spectroscopy and basicity measurement.

at C_3-position, (2) cleavage of C_3-N bond, (3) ring-closure into pyrazolone, (4) replacement of 2-aminophenylthio group by phenylhydrazine derivatives (in the case of hydrazine, IV suffers reductive cleavage rather than replacement of *o*-aminophenylthio group by the hydrazine) and (5) oxidation.

This work is also in connection with syntheses of antifungal substances of 1,4-thiazine derivatives. Screening tests ofan I d related compounds are now in progress.

Experimental

Ethyl 3-Methyl-4*H*-benzo-1,4-thiazine-2-carboxylate (I)——A mixture of *o*-aminothiophenol (3.8 g.) and ethyl 2-chloroacetoacetate (5.0 g.) was refluxed in EtOH (60 ml.) for 30 min. After cooling, the reaction mixture was poured into H_2O (120 ml.). The precipitate was collected and recrystallized from MeOH to I as yellow plates (4.6 g.), m.p. 144~145°(reported[1] m.p. 145°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3300, 1700. NMR (τ) (in $CDCl_3$): 8.70 (3H, triplet, J=7.0 c.p.s. $COOCH_2\underline{CH_3}$), 7.70 (3H, singlet, C=C-$\underline{CH_3}$), 5.79 (2H, quartet, J=7.0 c.p.s. $COO\underline{CH_2}CH_3$), 3.12 (3H, multiplet, ring protons, 3.55 (1H, multiplet, ring proton).

Reaction of Ethyl-3-Methyl-4*H*-benzo-1,4-thiazine-2-carboxylate (I) with Phenylhydrazine and Its Derivatives——i) A mixture of I (0.3 g.) and phenylhydrazine (1 g.) was refluxed in EtOH for 4 hr. The reaction mixture was concentrated *in vacuo*. After cooling, the deposited crystals were collected and recrystallized from MeOH to II: R=H as fine red needles (0.15 g.), m.p. 156~157°(reported[1] m.p. 155°). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3350, 1670. UV λ_{max}^{EtOH} mμ (ε): 251 (22,200), 394 (24,200). II: R=H was identical with an authentic sample prepared by Schoenbrodt's method[4] in melting point and IR spectrum.

The filtrate, obtained by removal of II: R=H, was evaporated to dryness, the residue was dissolved in $CHCl_3$, and chromatographed on silica gel. Separated crystals, m.p. 93°, were identified as those of disulfide III by IR comparison and mixed melting point determination with an authentic sample.

In a similar manner, I was converted into II: R=Cl, NO_2 and III by reaction with *p*-chloro(or nitro)-phenylhydrazine. II: R=Cl, orange needles (EtOAc), m.p. 238.5~239°. *Anal.* Calcd. for $C_{16}H_{12}ON_4Cl_2$: C, 55.35; H, 3.48. Found: C, 55.59; H, 3.68. II: R=NO_2, orange needles (EtOAc), m.p. ca. 300°. *Anal.* Calcd. for $C_{16}H_{12}O_5N_5$: C, 52.17; H, 3.28. Found: C, 52.10; H, 3.13.

Reaction of Ethyl 3-Methyl-4*H*-benzo-1,4-thiazine-2-carboxylate (I) with Hydrazine Hydrate——EtOH solution of I (1.0 g.) and 80% hydrazine hydrate (6 ml.) was refluxed at 60~70° for 30 min. The reaction mixture was concentrated *in vacuo*. After cool, the oily residue wes poured into H_2O, the precipitate was collected, and recrystallized from MeOH to IV as colorless prisms (0.6 g.), m.p. 241~242°. *Anal.* Calcd. for $C_{10}H_{11}ON_3S$: C, 54.28; H, 5.01. Found: C, 54.47; H, 5.25. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3000, 2800~2500, 1620. UV λ_{max}^{EtOH} mμ (ε): 227 (22,100), 249 (8890), 310 (3310).

When the duration of heating was prolonged up to 5 hr., I was converted into 3-methyl-2-pyrazolin-5-one V and III in a similar fashion with reaction of IV with hydrazine hydrate as follows.

EtOH solution of IV (0.3 g.) and 80% hydrazine hydrate (2 ml.) was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo*. When cooled, the deposited crystals were washed with $CHCl_3$, and recrystallized from EtOH to V as colorless needles (0.18 g.), m.p. 224~225°. IR ν_{max}^{Nujol} cm^{-1}: 2750~2600, 1620. UV λ_{max}^{EtOH} mμ (ε): 219 (3340), 245 (2850). V was identical with its authentic sample prepared by the condensation of ethyl 2-chloroacetoacetate and hydrazine hydrate.[6] III was also isolated from $CHCl_3$-soluble part in a similar manner as described for reaction of I with phenylhydrazine.

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6) L. Knorr: Ber., **16**, 2597 (1883).