[Chem. Pharm. Bull. 20(4) 832—834 (1972)]

UDC 547.569.1.04 : 547.462.8.04

Further Studies on the Reaction of 2-Aminothiophenol with Dimethyl Acetylenedicarboxylate

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(Received July 21, 1971)

Several research groups[2,3,4] have studied the reaction of 2-aminothiophenol (I) with acetylenedicarboxylic acid and its diesters. Iwanami[2] has first described the isolation of two structural isomers in the reaction of I with diethyl acetylenedicarboxylate. The major and minor isomers have been assigned 3-ethoxycarbonylmethylene-3,4-dihydro-2-oxo-2H-benzo-1,4-thiazine (III) and 2-ethoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (II), respectively. After that, Kalbag and co-workers[3] have shown conclusively that Iwanami's major isomer must be represented by structure (II) based on its unequivocal synthesis. Reaction of I with acetylenedicarboxylic acid and its dimethyl ester have been also reported by Mushkalo and Brezemskaya.[4] Those previous studies, however, have never paid attention to the geometrical configuration related to an exomethylene double bond of the product.

The present work was undertaken to establish the stereochemistry of the product in the reaction of I with dimethyl acetylenedicarboxylate. We have confirmed that the reaction leads exclusively to the formation of *trans*-2-methoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (IV).

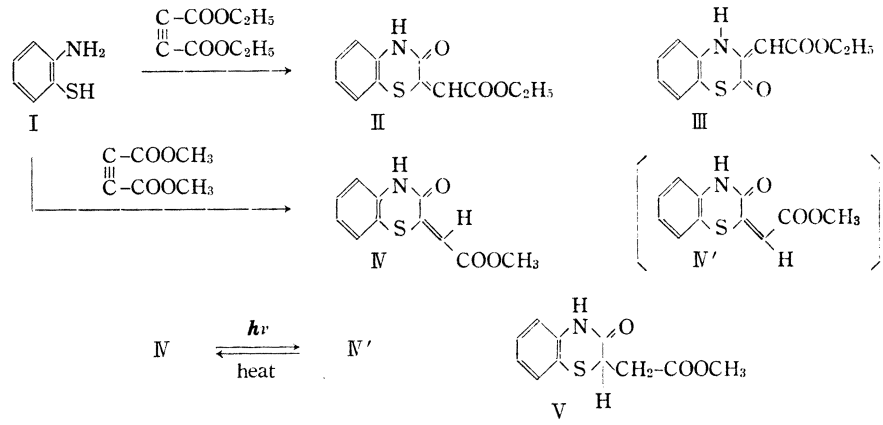

Chart 1

A solution of I in ether was allowed to react with dimethyl acetylenedicarboxylate at room temperature. The precipitated crude product (yield 90%) was shown to be homogeneous by thin-layer chromatographic analysis. The product was catalitically reduced by employment of Raney Ni to give 2-methoxycarbonylmethyl-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (V),

1) Location: *Sakanoshita, Mitahora, Gifu.*
2) Y. Iwanami, *Nippon Kagaku Zasshi*, **83**, 100 (1962).
3) S.M. Kalbag, M.D. Nair, P. Rajagoplan and C.N. Talaty, *Tetrahedron*, **23**, 1911 (1967).
4) L.M. Mushkalo and V.A. Brezemskaya, *Ukrain. Khim. Zh.*, **18**, 163 (1952).

which is identical, in every respects, with an authentic sample[5] prepared by the condensation of I with dimethyl fumarate. This fact and spectral data accommodate structure IV (without stereochemistry) for the product.

In order to obtain its geometrical isomer, the photochemical isomerization of IV was attempted.

A solution of IV in ethanol was irradiated with a 100 W high-pressure mercury lamp through a Pyrex filter under nitrogen for 20 hr. The precipitated solid mass was purified to give a product in 75% yield. The thin-layer chromatographic analysis of the reaction mixture revealed no formation of other products. A small amount of IV was recovered unchanged. The product thus obtained was converted into V by the catalytic reduction similar to the case of IV. Therefore, the product must be a geometrical isomer (IV′) related to an exo-methylene double bond in IV. Table I summarizes some physicochemical data of IV and IV′

Table I

	IV	IV′
mp (°C)	270	264
IR (cm^{-1}) nujol	3150 1680 (sh) 1660	3180 1730 1685
NMR (τ) DMSO-d_6	6.28 (3H, s) 3.13 (1H, s) −1.50 (1H, broad)	6.33 (3H, s) 5.46 (1H, s) −0.75 (1H, broad)
Mass Spectrum (M^+)	235	235

In the nuclear magnetic resonance spectra of IV and IV′, we observe a significant difference between their vinyl protons: a vinyl proton signal of IV (3.13 τ) is distinctly deshielded as compared to that of IV′ (5.46 τ), which is ascribable to the anisotropic effect of a lactam carbonyl grouping in IV. On refluxing in DMF for 3 hr, IV′ was transformed almost completely to IV. This fact clearly points that IV is thermodynamically more stable than IV′. Thus, the structure of IV and IV′ were established unambiguously.

Addition of a thiol to an acetylenic compound,[6] in general, results in the preferential formation of a *trans*-addition product, although the *trans-cis* ratio of the products depends upon the reaction conditions employed. The present study provides an example demonstrating the highly stereoselective *trans*-addition of a thiol to an acetylenic bond.

Furthermore, we attempted the photochemical addition of I to dimethyl acetylenedicarboxylate. To a solution of I in ethanol dimethyl acetylenedicarboxylate was added by protions under the irradiation similar to the previous case for 10 hr. The reaction occured with complication and seven products were identified as IV, IV′ and dimethyl fumarate by comparison with authentic samples, respectively. Detailed analysis of the undetermined products is now in progress.

Experimental

2-Methoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (IV)——To a solution of 2-aminothiophenol (I) (0.6 g) in ether (10 ml) was added dimethyl acetylenedicarboxylate (0.7 g) with stirring at room temperature. After stirring for 2 hr, the resulting precipitate was collected by filtration and recrystallized from EtOH to give IV (1.1 g) as yellow needles, mp 270°. *Anal.* Calcd. for $C_{11}H_9O_3NS$: C, 56.16; H, 3.85; N, 5.95. Found: C, 56.37; H, 4.07; N, 6.01.

Photochemical Isomerization of IV to *cis*-Isomer (IV′)——A solution of IV (0.2 g) in EtOH (200 ml) was irradiated with a 100 W high pressure mercury lamp through a Pyrex filter under nitrogen for 20 hr.

5) J. Bourdais, *Bull. Soc. Chim. France*, **1962**, 1709.
6) For example, see, A.A. Oswald, K. Grisbaum, B.H. Hadson, Jr. and J.M. Bregman, *J. Am. Chem. Soc.*, **86**, 2877 (1964).

The precipitated solid mass was collected by filtration and recrystallized from acetone to give IV′ (0.15 g) as colorless prisms, mp 265°. *Anal.* Calcd. for $C_{11}H_9O_3NS$: C, 56.16; H, 3.85; N, 5.95. Found: C, 56.36; H, 4.12; N, 6.07. The filtrate gave 0.02 g of unchanged IV.

Catalytic Reduction of IV and IV′——A mixture of IV (0.5 g) and Raney Ni (1.0 g) in MeOH (50 ml) was shaken with hydrogen at room temperature. During the reduction, IV dissolved to give a clear colorless solution, and the reduction was completed within 30 min. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was recrystallized from MeOH to give 2-methoxycarbonylmethyl-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (V) as colorless needles, mp 145°. Yield, 0.4 g. This compound was identified by comparing its infrared spectrum with that of an authentic sample.[5]

In a similar manner, IV′ (100 mg) was reduced to give V (75 mg).

[Chem. Pharm. Bull. 20(4) 834—836 (1972)]

UDC 547.963.3.04 : 615.31.011.5

Complexation of Chlorpromazine with Adenosine and Its Phosphates[1]

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(Received July 27, 1971)

The molecular basis for the lowering action of chloroprmazine (CPZ) on the membrane permeability has not been cleared yet. The surface activity of CPZ itself has been thought to be ascribable to the permeability reduction for some time.[3] However, Blei[4] has demonstrated a marked decrease in the surface tension of solutions of CPZ in the presence of adenosine-5′-triphosphate (ATP), and suggested that the formation of CPZ–ATP complex of greater surface activity than CPZ alone is attributed to the reduction of membrane permeability. Hence, in the present work, the formation of complexes of CPZ with adenosine, adenosine-5′-monophosphate (AMP), and ATP has been investigated by the aid of ultraviolet absorption spectra.

Experimental

Materials——Adenosine, AMP, and ATP were of reagent grade, Ajinomoto Co., Ltd. CPZ (hydrochloride) was kindly supplied by Shionogi & Co., Ltd. They were used without further purification. Phosphate buffer (0.1M, pH 6.5) was used for the solvent unless otherwise described.

Measurement of Absorption Spectra——The absorption spectra were recorded with a Hitachi EPS-3T spectrophotometer in 0.5 cm cells at room temperature.

Determination of Equilibrium Constant——Hitachi model 139 spectrophotometer was employed for the measurements of absorbance decrease at 307 mμ of 10^{-3}M CPZ in the presence of 4×10^{-3}—4×10^{-2}M adenosine, AMP, or ATP at 25° and 37°. The values of equilibrium constant, K_C, for the complex formation were estimated by the aid of the Benesi-Hildebrand method.[5] Free energy change, ΔG, for the complexation was calculated from the value of K_C.

1) *a*) This forms Part XI of "Spectroscopic Studies on Molecular Interactions"; *b*) Part X: I. Moriguchi, S. Fushimi, and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **20**, 411 (1972).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo, 141, Japan.*
3) W. Scholtan, *Kolloid-Z.*, **142**, 84 (1955); F. Vilallonga, E. Fried, and J.A. Izquierdo, *Arch. Intern. Pharmacodyn.*, **130**, 260 (1961); P.M. Seeman and H.S. Bialy, *Biochem. Pharmacol.*, **12**, 1181 (1963).
4) I. Blei, *Archiv. Biochem. Biophys.*, **109**, 321 (1965).
5) H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949); I. Moriguchi and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **17**, 2173 (1969).