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ON THE STRUCTURE OF THE PRODUCT OF THE REACTION OF 2-AMINOTHIOPHENOL WITH DIETHYL ACETYLENE DICARBOXYLATE*

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Abstract—The major product (m.p. 220–222°) of the reaction of 2-aminothiophenol (I) with diethyl acetylenedicarboxylate has been conclusively shown to be 2-ethoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (II) and not 3-ethoxycarbonylmethylene-3,4-dihydro-2-oxo-2H-benzo-1,4-thiazine (III) as reported.[2]

OVER three years ago Iwanami[2] claimed to have isolated two isomeric products from the reaction of 2-aminothiophenol (I) with diethyl acetylenedicarboxylate and described the major product (m.p. 220·5–222°) as 3-ethoxycarbonylmethylene-3,4-dihydro-2-oxo-2H-benzo-1,4-thiazine (III) and the minor product (m.p. 268–269°) as 2-ethoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (II) (herein designated A and B respectively). These structural assignments were based on the structure of the acid V (m.p. 278°) which had been proposed[3] for the product obtained in 98% yield from the reaction of I with acetylenedicarboxylic acid in ether. Iwanami[2] hydrolysed both A and B to the corresponding acids and reasoned that since the m.p. (280–281°) of the acid he had prepared from B was close to that (278°) of 2-carboxymethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (V) that the Russian authors[3] had reported, they should be one and the same and that the structure of his minor product (B) should, therefore, be represented by II. The major product (A) then, according to him, should have the alternate structure III.

In connection with a project involving the synthesis of benzo-1,4-thiazine derivatives for biological evaluation, we had occasion to repeat the reaction of I with diethyl acetylenedicarboxylate under the conditions prescribed[2] and found that only one crystalline compound could be isolated. A comparison of the m.p. (220–222°) and the IR spectrum (KBr disc; ν_{max} 3265 cm^{-1}, 1665 cm^{-1} and 1655 cm^{-1}) of this compound with those that Iwanami[2] had described for his major product (A) leaves no doubt that they are one and the same.

Catalytic hydrogenation of A in the presence of Raney Ni furnished, after the slow uptake of a mole of hydrogen, a dihydroester which was identical, in all respects, with 2-ethoxycarbonylmethyl-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (VII) prepared by the condensation of I with diethyl fumarate.[4] Compound VII, on basic hydrolysis, yielded an acid C whose m.p. (195–197°) is in good agreement with that (196°) of 2-carboxymethyl-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (VI) which had earlier

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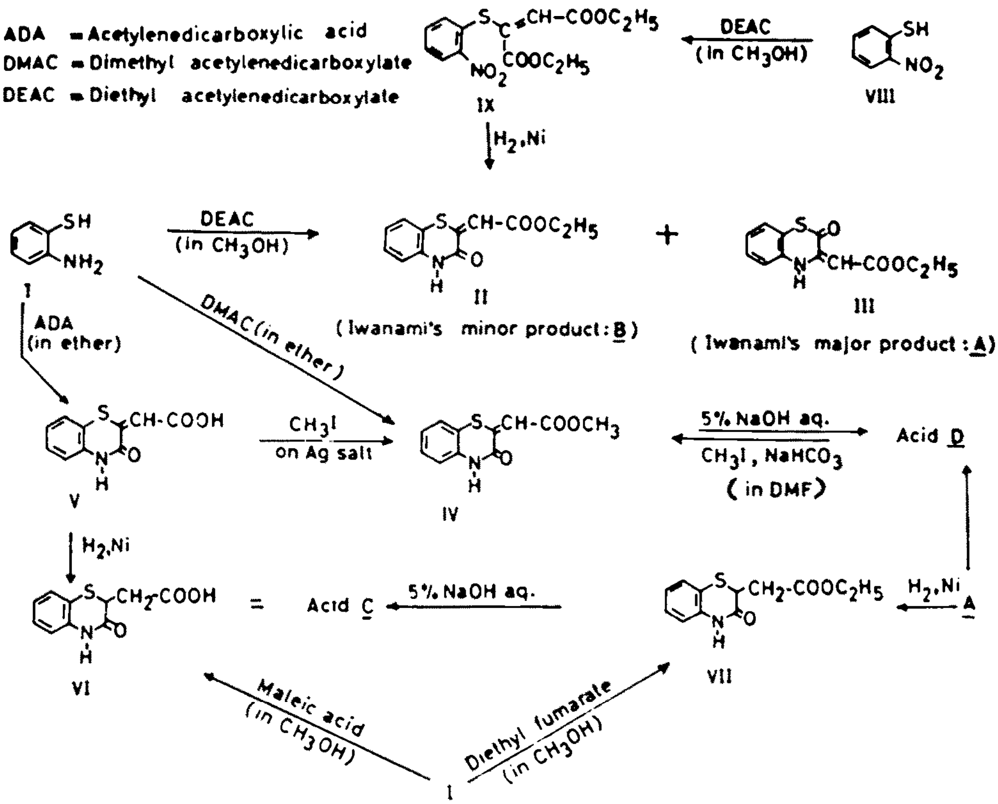
[2] Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 100 (1962); *Chem. Abstr.* **59**, 3916 (1963).

[3] L. K. Mushkalo and V. A. Brezemskaya, *Ukrain. Khim. Zh.* **18**, 163 (1952); *Chem. Abstr.* **48**, 13692 (1954).

[4] J. Bourdais, *Bull. Soc. Chim. Fr.* 1709 (1962).



been prepared[3] by the catalytic hydrogenation of V. A sample of VI was prepared by the direct method of Bourdais[4] involving the condensation of I with maleic acid and found to be identical with the acid C.

Saponification of A with 5% aqueous sodium hydroxide afforded an acid D, m.p. 292–294° (dec) (reported[2]: 288–290°), which was identical, in all respects, with the acid prepared by the basic hydrolysis of 2-methoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (IV) which had been prepared[3] both by the methylation of the acid V and by the direct condensation of I with dimethyl acetylenedicarboxylate. Methylation of D in dimethyl formamide with methyl iodide in the presence of sodium bicarbonate furnished a methyl ester identical, in all respects, with IV.

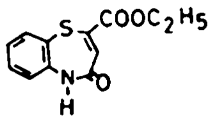
These facts considered together would suggest that either Iwanami's[2] structure III for his major product A or Mushkalo and Brezemskaya's[3] structure V for their acid (and, hence, structure IV for the corresponding ester) must be incorrect. In order to decide between these two structure possibilities an unambiguous synthesis of the ethyl and methyl esters of V became necessary and was successfully carried out.

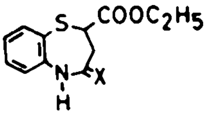
2-Nitrothiophenol (VIII), on condensation with diethyl acetylenedicarboxylate in methanol, furnished diethyl 1-(2-nitrophenyl)mercaptoethylene-1,2-dicarboxylate (IX) which on controlled catalytic hydrogenation (3-mole-uptake) yielded a compound identical in all respects with B. When dimethyl acetylenedicarboxylate was used in the place of the diethyl ester, the final product was identical in all respects with

IV.[3] Hence, Iwanami's[2] major product **A** (in our case, the only product) cannot have the structure III proposed by him but, instead, can be truly represented only by the structure II. It follows, then, that the structures V and IV advanced by Mushkalo and Brezemskaya[3] for the products of the reaction of I with acetylene dicarboxylic acid and dimethyl acetylenedicarboxylate, respectively, are correct.

It is pertinent to mention here that although we have clearly established that the acid **D** should be the same as V described by the Russian chemists,[3] the m.p. (278°) of V that they reported is lower than that (292–294° dec) we and Iwanami[2] had observed for **D**.

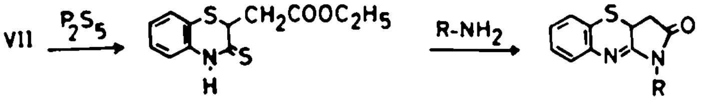
A remote possibility of **A** having the structure X incorporating the seven-membered 1,4-thiazepine system, can be strictly excluded on the basis of the sequence of reactions that Bourdais[6] had carried out starting with VII. He treated VII with


X


XI

XI a, X = O

XI b, X = S



XII XIII

phosphorous pentasulphide to obtain the thiolactam XII which reacted readily with ammonia and primary amines yielding tetrahydropyrrolo[3,2-b]benzo-1,4-thiazine derivatives of the type XIII. Although it is possible that X could be hydrogenated to the dihydroderivative XIa which, in turn, could furnish the corresponding thiolactam XIb, cyclisation of XIb with ammonia or primary amines is not feasible. Since VII is the dihydro derivative of **A** it follows that **A** cannot have structure X.

EXPERIMENTAL

All m.ps were determined in open capillary tubes and are uncorrected.

Diethyl 1-(2-nitrophenyl)mercaptoethylene-1,2-dicarboxylate (IX) A soln of 2-nitrothiophenol (2·2 g) in MeOH (20 ml) was added to a soln of diethyl acetylenedicarboxylate (2·4 g) in MeOH (20 ml) with agitation. The mixture, which warmed up gradually, was set aside for 2 hr, then heated to boiling and filtered to remove a small quantity of insoluble material. The solid that separated on cooling the filtrate was filtered and recrystallized from pet. ether containing a little benzene. Yellow crystals (1·6 g), m.p. 76–79°. (Found: C, 51·90; H, 4·77; N, 4·64. $C_{14}H_{15}NO_6S$ requires: C, 51·69; H, 4·65; N, 4·31%.)

Dimethyl 1-(2-nitrophenyl)mercaptoethylene-1,2-dicarboxylate was prepared through a similar procedure by using dimethyl acetylenedicarboxylate instead of the diethyl ester. Yellow crystals from methanol, m.p. 93–95°. (Found: C, 48·50; H, 3·60; N, 4·72. $C_{12}H_{11}NO_6S$ requires: C, 48·49; H, 3·73; N, 4·71%.)

2-Ethoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (II). A soln of IX (1·1 g) in MeOH (150 ml) was hydrogenated at atm press in the presence of Raney Ni (0·5 g) until the uptake of H required to reduce the nitro to the amino group (224 ml) was complete (3 hr). The mixture was then filtered to remove the catalyst and the filtrate concentrated to a small bulk under reduced press, cooled and filtered. The residue was recrystallized from MeOH. Yellow crystals, m.p. 220–222°. The

[6] J. Bourdais, *Bull. Soc. Chim. Fr.* 1756 (1965).

m.p. on admixture with a specimen of A prepared by the method of Iwanami[3] from 2-aminothiophenol and diethyl acetylenedicarboxylate, was undepressed. The IR spectra (KBr) of both the samples were identical.

2-Methoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazine (IV) was prepared by the catalytic reduction of dimethyl 1-(2-nitrophenylmercaptoethylene-1,2-dicarboxylate in a similar manner—yellow crystals from MeOH, m.p. 264–266°. The m.p. on admixture with a sample prepared by the method of Mushkalo and Brezemskaya[5] from 2-aminothiophenol and dimethyl acetylenedicarboxylate, was undepressed. The IR spectra (nujol) of both the samples were identical.

Acid D. Compound A (2·5 g) prepared through Iwanami's[3] procedure was dissolved in 5% NaOHaq and the clear soln was set aside for 3 hr, acidified with 2N HCl and filtered. The residue was washed thoroughly with water, dissolved in requisite quantity of sat $NaHCO_3$aq and filtered. The filtrate was acidified with HCl and the solid that separated was collected, washed successively with water, MeOH, acetone and ether and dried. The product was insoluble in most of the organic solvents. Yellow crystals (1·8 g), m.p. 292–294° (dec). (reported[5]: 288–290°). M.p. on admixture with a sample of V obtained by the saponification of IV[5] with 5% NaOHaq, was undepressed. The IR spectra (nujol) of both the samples were identical.

Methylation of acid D. Anhydrous K_2CO_3 (1·5 g) and MeI (0·6 ml) were added to a soln of the above acid (1·5 g) in warm DMF (15 ml) and the mixture was then heated on the water bath for 3 hr, cooled and poured into water containing crushed ice. The mixture was filtered after a few min and the residue washed well with water and recrystallized from MeOH—yellow crystals (0·9 g), m.p. 264–266°. M.p. on admixture with a sample of IV,[5] was undepressed. The IR spectra (nujol) of both the samples were identical.

Catalytic hydrogenation of A. Compound A[3] (37·4 g) suspended in MeOH (500 ml) was hydrogenated at atm press in the presence of Raney Ni (60·0 g) added in 4 portions until the uptake of a molar equiv (3360 ml) of H was complete (88 hr). The mixture was then filtered and the filtrate evaporated to dryness under reduced press. The residue was recrystallized from AcOEt–hexane. Colourless crystals (30·5 g), m.p. 127–129°. M.p. on admixture with a sample of VII prepared according to the method of Bourdais,[4] was undepressed. The IR spectra (nujol) of both the samples were identical.

Acid C. The above ester (3·0 g) was added to a soln of 2·5% NaOHaq (20 ml) containing MeOH (20 ml) and the mixture set aside for 5 hr, filtered to remove traces of insoluble material and the filtrate acidified with 2N HCl. The solid that separated was filtered, washed with water and recrystallized from a small quantity of MeOH. Colourless crystals (1·8 g), m.p. 195–197° (reported[6]: 196°). M.p. on admixture with a sample of VI prepared by the direct method of Bourdais[4] involving the condensation of 2-aminothiophenol with maleic acid, was undepressed. The IR spectra (nujol) of both the samples were identical.

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