Addition Reactions of Azoesters with 2-Thioquinazolinones

*Libero Italo Giannola, Gaetano Giammona, Bianca Carlisi and Salvatore Palazzo**

Istituto di Tecnica e Legislazione Farmaceutica, Università di Palermo, via Archirafi 32, Palermo, Italy

Reaction between diethyl azodicarboxylate (I) and 1,2,3,4-tetrahydro-2-thioquinazolin-4-one (II), as a cyclic model of thiourea, both in alcoholic medium and in inert solvents has been investigated. By carrying out the reaction in an inert solvent, it was possible to isolate an intermediate. Evidence is presented that the intermediate, in turn, was converted into the final products. Structures were unequivocally assigned by mass spectrometry.

J. Heterocyclic Chem., 18, 1557 (1981).

In preceding reports (1) we have described the use of substituted thioureas in the synthesis of heterocyclic compounds containing sulphur and nitrogen in order to study the pharmacological properties of the resulting compounds.

It is known (2) that substituted thioureas react with diethyl azodicarboxylate (I) to give an intermediate which undergoes thermal decomposition affording carbodiimides; on the other hand, azoesters generally react (3) with dienes *via* three pathways: the addition-abstraction reaction, an oxidation-reduction reaction and a Diels-Alder addition reaction.

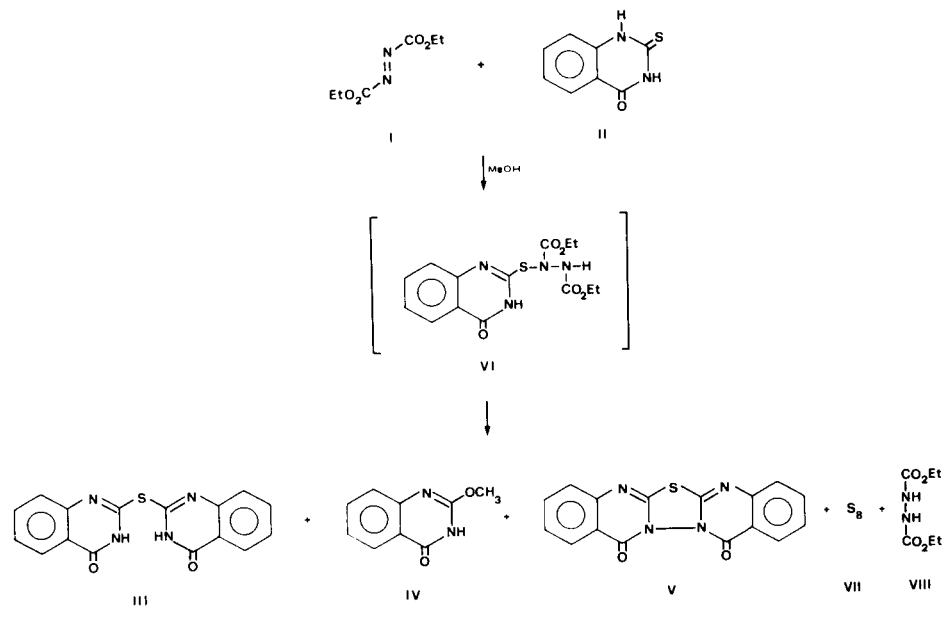
In our hands just two of these routes take place when 1,2,3,4-tetrahydro-2-thioquinazolin-4-one (II), representative of a cyclic model of thiourea, was allowed to react with diethyl azodicarboxylate (I). The reaction afforded three major products III, IV and V when carried out in alcoholic medium (Scheme 1).

Compound III was a colourless crystalline solid, $C_{16}H_{10}N_4O_2S$, mp 259-260°. It showed infrared bands at 3350-3250 (NH), 1698 (C=O) cm^{-1}; its ^{1}H-nmr spectrum (DMSO-d_6) exhibits a multiplet at δ 8.31-7.40 (H, aromatic) and a broad singlet centered at δ 12.49 which was exchanged with dueterium oxide (NH) in a ratio% 4/1. The ms spectrum showed fragments of importance from the standpoint of structural confirmation which correspond to the modes of cleavage shown in Scheme 2. These data allow an unequivocal assignment of the structure of bis (3,4-dihydro-4-oxo-2-quinazolinyl) sulphide.

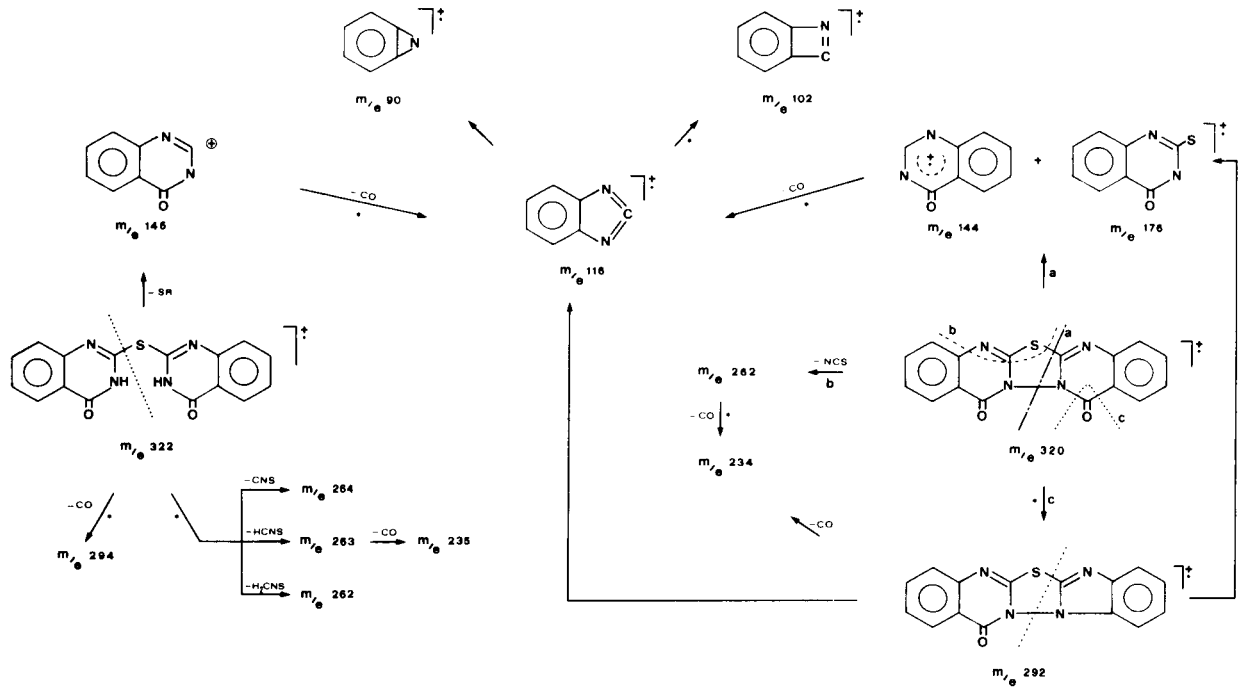
The structure of compound IV was assigned on the basis of its ir, ^{1}H-nmr, ms spectra and the analytical data in the literature (4). These data are consistent with those of 2-methoxy-3,4-dihydroquinazolin-4-one.

To the main product V, the structure of 12*H*, 15*H*-[1,3,4]thiadiazolo[2,3-*b*:5,4-*b'*]diquinazoline-12,15-dione was assigned. Compound V showed in fact a carbonylic

SCHEME 1

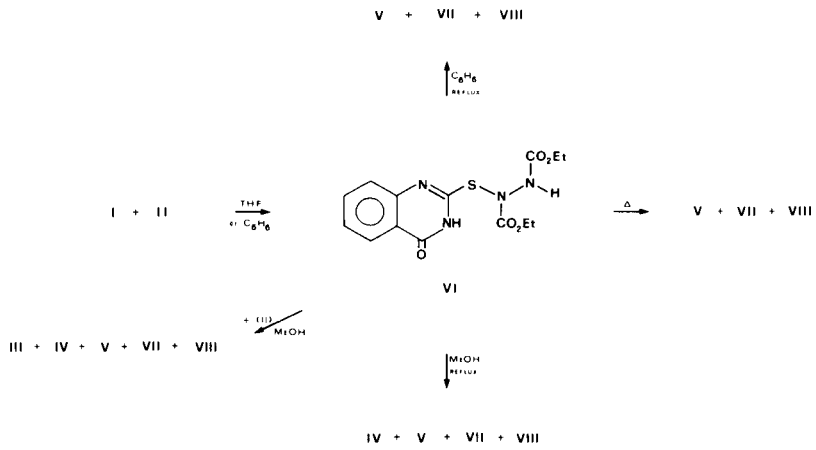


SCHEME 2



* METASTABLE SUPPORTED TRANSITIONS

SCHEME 3



but no NH band in the ir spectrum; its ^{1}H-nmr spectrum exhibits only signals for aromatic protons. The ms spectrum showed fragmentation which is in line with structure V. (Scheme 2).

Together with compounds III, IV and V, small amounts of VII and VIII were found as by products.

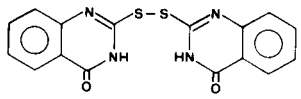
On the basis of literature analogies (2) we believe that, as thioureas afforded 1:1 adducts (thermically unstable) with diethyl azodicarboxylate, also compound II can undergo an addition reaction with I to give an intermediate from which III, IV and V could arise. However we were not able to isolate the intermediate by carrying out the reaction in alcoholic medium.

As we expected, by carrying out the reaction in an inert solvent such as tetrahydrofuran or benzene it was possible to confirm our hypothesis. In fact when compound I was allowed to react with II in tetrahydrofuran, compound VI was isolated. It was easily detectable by its ^{1}H-nmr which

showed the two ethyl groups of the azoester system and two unequivalent hydrogenatoms bound to the nitrogen-atom. The ms spectrum of VI recorded with an electron beam energy of 70 eV showed the same molecular ion as V and the same main fragmentation patterns; when recorded with an electron beam energy of 20 eV it showed the molecular ion peak at m/e 352. Compound VI melts at 144-145° and solidifies again at 155-160° to produce V(mp 301-302°); when heated in an oil bath at 170° for 1.5 hours, it yields V. When refluxed in an inert solvent for a few hours, compound VI was transformed into V; when refluxed in methanol VI was transformed into IV and V. Therefore compounds IV and V could arise from VI. In the methanolic reaction, VI was undetectable because it may: (a) undergo nucleophilic attack by methanol to yield IV; (b) react in a similar manner with II to yield III; (c) decompose to yield a probable carbodiimide which reacts with a molecule of VI to afford V, although attempts to separate the carbodiimide were unsuccessful owing its reactivity.

The experimental evidences are reported in the experimental section and summarized in Scheme 3.

It is claimed (5-6) that mercaptans reacting with I are transformed to the corresponding disulphides and that disulphides, in turn, treated with methanol lose an atom of sulfur to yield the corresponding sulphides. So an alternative pathway may involve the initial formation of disulphide (IX) which could explain the presence of compound III. We were not able to isolate IX in any of our reactions but this does not preclude its role as an intermediate.



IX

Diethyl azodicarboxylate is an useful oxidizing agent involving hydrogen abstraction from hydrogen donors, thus compound III could undergo an oxidation reaction by means of I to afford compound V. We have confirmed this hypothesis by allowing III to react with I under the same experimental conditions. Together with V it was possible in fact to detect the diethyl hydrazodicarboxylate (VIII), identified by comparison of its data with those of the literature.

The structures of the products were assigned based upon their mass spectra which showed a typical fragmentation. These data allow an unequivocal assignment of the structures. It is interesting that peaks at m/e 116, 102 and 90 are common to the compounds III and V and were besides found in other compounds bearing a quinazoline ring structure (7). The modes of cleavage are shown in Scheme 2.

Compounds III, V and VI have not been reported in the literature and will be submitted for pharmacological screening.

Work is in progress to evaluate the reactivity of II with dimethyl acetylenedicarboxylate.

EXPERIMENTAL

All melting points were determined on an Electrothermal capillary apparatus and are uncorrected. Ir spectra were taken with a Perkin-Elmer infrared spectrophotometer Models 157-299 as nujol mulls. The nmr spectra were recorded at 80 MHz at probe temperature on a Varian FT 80/A instrument with tetramethylsilane as the internal standard. Mass spectra were run on a JEOL JMS-01SG-2 mass spectrometer. Elemental analyses were performed with a Perkin-Elmer Model 240 CHN analyser. Thin layer chromatoghraphy utilizing 0.25 mm silica gel Merck plates with fluoresent indicator and a solvent system consisting of benzene 7 parts to ethylacetate 3 parts, were utilized for chromatographic confirmation of the purity of compounds.

12*H*,15*H*-[1,3,4]Thiadiazolo[2,3-*b*:5,4-*b'*]diquinazoline-12,15-dione (V).

A solution of I (1.74 g, 0.01 mole) in 20 ml of methanol was added dropwise to a stirred suspension of II (1.78 g, 0.01 mole) in 200 ml of methanol. The mixture was refluxed for 3 hours and then allowed to stand for 2 hours at room temperature. The resulting solid material was filtered, washed with methanol, dried and then recrystallized repeatedly from ethanol yielding 1.1 g (31%) of V as colorless crystals; mp 301-302°; ir: 1710 cm^{-1} (C=O); nmr (DMSO-d_6): δ 8.34-7.60 (m, 8H, aromatic); ms: m/e (relative intensity) 320 (100%) (M^+), 292 (4%), 262 (6%), 234 (10%), 206 (38%), 176 (17%), 162 (15%), 149 (28%), 144 (16%), 116 (6%), 102 (12%), 90 (30%).

Anal. Calcd. for $C_{16}H_8N_4O_2S$: C, 60.00; H, 2.52; N, 17.50; S, 10.01. Found: C, 60.15; H, 2.34; N, 17.61; S, 10.16.

Bis(3,4-dihydro-4-oxo-2-quinazolinyl) Sulphide (III).

The methanolic mother liquor of the above reaction, after removal of compound V, was evaporated *in vacuo* to dryness. The residual solid mixture was then treated with boiling chloroform (3 × 20 ml) to remove the soluble part A of material. The insoluble solid of two compounds separated by fractional cystallization from methanol. The compound less soluble in methanol was recrystallized form methanol to give 0.6 g (17%) of colorless crystals identified as the title compound, mp 259-260°; ir: 3350-3250 (NH), 1698 cm^{-1} (C=O); nmr (DMSO-d_6): δ 12.49 br(s, 2H, exchanged with deuterium oxide, NH), 8.31-7.40 (m, 8H, aromatic); ms: m/e (relative intensity) 322 (28%) (M^+), 294 (17%), 264 (13%), 263 (18%), 235 (16%), 145 (52%), 144 (11%), 119 (40%), 116 (11%), 102 (7%), 90 (100%).

Anal. Calcd. for $C_{16}H_{10}N_4O_2S$: C, 59.63; H, 3.13; N, 17.39; S, 9.95. Found: C, 59.68; H, 2.95; N, 17.51; S, 10.12.

2-Methoxy-3,4-dihydroquinazolin-4-one (IV).

From the methanolic mother liquor of compound III, after dilution with 20 ml of water colorless product IV separated. The product washed, dried and recrystallized from methanol (0.54 g, 15%) melted at 213-214°. Compound IV was identified based upon literature data. Its melting point did not depress an authentic pure sample (4). The infrared spectra of the samples were identical.

Diethyl Hydrazodicarboxylate (VIII).

The chloroform solutions of the part above called A, were combined and concentrated in a rotary evaporator to about 10 ml to afford a crude product. Recrystallization from benzene yielded colorless needles (0.32 g, 9.1%), mp 131-132° identified as VIII by comparison of the ir spectrum with that of an authentic pure sample obtained from ethyl chloroformate and hydrazine hydrate (8). The melting point was not depressed when mixed.

The chloroform mother liquor of compound VIII evaporated to dryness yielded a small amount of pale yellow needles characterised as sulphur (VII).

Diethyl[(3,4-Dihydro-4-oxo-2-quinazolinyl)thio]bicarbamate (VI).

(I) A solution of diethyl azodicarboxylate (I) (1.74 g, 0.01 mole) in tetrahydrofuran (20 ml) was added dropwise to an ice-cooled stirred solution of II (1.78 g, 0.01 mole) in tetrahydrofuran (100 ml). When the addition was complete, stirring of the resulting solution was continued for 2 hours. After standing overnight at room temperature, the solvent was evaporated *in vacuo* and the residue washed with cooled diethyl ether (3 × 10 ml). By this method it was possible to prepare an analytically pure sample of VI (2.1 g, 60%). Compound VI melts at 144-145°, solidifies again at 155-160° to melt definitively at 301-302°. Additional product was obtained after evaporation of the ethereal solution; ir: 3280 and 3140 (NH), 1750 and 1720 (C=O ester), 1665 cm^{-1} (C=O amide); nmr (deuterochloroform): δ 12.04 br (s, 1H, exchanged with deuterium oxide, NH), 8.29 (dd, J_{5-6} = 8.0 Hz, J_{5-7} = 2.0 Hz, 1H, C_5-H), 7.69-7.44 (m, 3H, aromatic), 6.52 (s, 1H, removed by deuterium oxide, NH of the hydrazo group), 4.47-4.07 (m, 4H, $-CH_2-$), 1.42-1.18 (m, 6H, $-CH_3$); ms: (20 eV) m/e (relative intensity) 352 (10%) (M^+), 178 (100%), 176 (7%), 122 (46%), 120 (76%), 119 (43%), 105 (25%), 92 (21%).

Anal. Calcd. for $C_{14}H_{16}N_4O_5S$: C,47.73; H,4.58; N, 15.90; S, 9.09. Found: C, 47.62; H, 4.46; N, 16.02; S, 9.27.

(II) When the reaction between I and II was carried out with the above procedure using benzene instead of tetrahydrofuran, the same crude VI was obtained. It was treated as above (see I) mp undepressed when mixed. Compound VI was easily converted into IV, V, VII and VIII.

Transformation of VI into V, VII and VIII.

(I) A solution of VI (0.1 g 0.00028 mole) in 10 ml of benzene was refluxed for 3 hours. The solid product which formed (0.038 g, 38%) was filtered, washed, dried and recrystallized from ethanol and melted at 301-302° undepressed with a sample of V. The infrared spectra of the two samples were identical.

The benzene mother liquor, cooled, afforded colorless needles mp 131-132° undepressed with a sample of VIII.

After removal of compound VIII, the solvent was concentrated *in vacuo* to dryness. The resulting solid material was characterized as sulphur (VII).

(II) Compound VI (0.1 g, 0.00028 mole) was heated at 170° for 1.5 hours on an oil bath. After cooling the reaction mixture was treated with boiling benzene. The insoluble material (0.04 g, 40%) mp 301-302° was consistent with V. From the benzene solution compounds VII and VIII were separated and purified in the aforementioned manner (see I).

Transformation of VI into IV, V, VII and VIII.

A solution of diethyl (3,4-dihydro-4-oxo-2-quinazolinyl)thiobicarbamate (VI) (0.1 g, 0.00028 mole) in methanol (20 ml) was refluxed for 3 hours and then allowed to stand for 2 hours at room temperature. The solid material after recrystallization from ethanol afforded (0.0038 g, 38%) of V, mp 301-302° undepressed when mixed. The infrared bands were identical.

The methanolic mother liquor was removed under reduced pressure and the solid residue treated with boiling chloroform (2 × 10 ml) to remove soluble material. The residual product after crystallization from methanol (0.0024 g, 24%) melted at 213-214° undepressed with a sample of IV. The infrared spectra of the two samples were identical. The combined chloroform solutions when concentrated yielded VIII, mp 131-132°. The mp was not depressed when mixed with an authentic pure sample. The chloroform mother liquor from which compound VIII separated when evaporated to dryness gave a small quantity of pale yellow needles of sulphur.

Reaction of Diethyl[(3,4-Dihydro-4-oxo-2-quinazolinyl)thio]bicarbamate (VI) with 1,2,3,4-Tetrahydro-2-thioquinazolin-4-one (II).

A solution of VI (0.3 g, 0.00085 mole) in methanol (10 ml) was added to a suspension of II (0.15 g, 0.00085 mole) in methanol (10 ml) and refluxed with stirring for 1 hour. The solvent was then evaporated *in vacuo*. The resulting mixture purified under the conditions previously described (reaction between I and II in methanol), afforded compounds III, IV, V, VII and VIII. The melting points and spectral data of these compounds were found indentical with those of authentic pure samples. The mp was undepressed when mixed.

Reaction of Bis(3,4-dyhydro-4-oxo-2-quinazolinyl) Sulphide (III) with Diethyl Azodicarboxylate (I).

A solution of I (0.05 g, 0.00031 mole) in 5 ml of methanol was added dropwise to a stirred solution of III (0.1 g, 0.00031 mole) in 20 ml of methanol. The mixture was refluxed for 3 hours and then allowed to standing for two hours. A solid material separated which was collected, washed with methanol, dried and crystallized from ethanol yielding 0.07 g (66%) of V, mp 301-302° undepressed with an authentic pure sample. The infrared spectra of the two samples were identical. The methanolic mother liquor from which compound III separated, was evaporated *in vacuo* and the residual solid crystallized from benzene and yielded VIII (0.043 g, 41%) mp 131-132°. The mp was undepressed when mixed with a pure sample.

REFERENCES

(1a) S. Palazzo and G. Lombardo, *Gazz. Chim. Ital.*, **93**, 207 (1963); (b) S. Palazzo, L. I. Giannola and S. Caronna, *Atti Accad. Sci. Lett. Arti Palermo*, **33**, 421 (1974); (c) L. I. Giannola, S. Palazzo, P. Agozzino, L. Lamartina and L. Ceraulo, *J. Chem. Soc., Perkin Trans.* I, 1428 (1978).

(2) O. Mitsunobu, K. Kato and M. Tomari, *Tetrahedron*, **26**, 5731 (1970).

(3) B. Franzus, *J. Org. Chem.*, **28**, 2954 (1963).

(4a) M. Claesen and H. Vanderhaeghe, *Bull. Soc. Chim. Belg.*,**68**, 220 (1959); (*Chem. Abstr.*, **54**, 9938 (1960)); (b) R. H. Mc. Kee, *J. Prakt. Chem.*, **84**, 821 (1911).

(5) F. Yoneda, K. Suzuki and Y. Nitta, *J. Am. Chem. Soc.*,**88**, 2328 (1966).

(6) P. K. Srivastava and Saleem, *Tetrahedron Letters*2725 (1968).

(7a) L. I. Giannola, M. L. Bajardi and S. Palazzo, *J. Heterocyclic Chem.*, **14**, 506 (1977); (b) L. Ceraulo, P. Agozzino, M. Ferrugia and L. I. Giannola, 4th National Congress of Mass Spectrometry, Catania, 12-14 September 1977, Italy.

(8) Th. Curtius and K. Heidenreich, *J. Prakt. Chem.*, **52**, 476 (1895).