Its Condensation with Aldehydes, Coupling with Diazonium Salts
and Cleavage by Amines

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(Z. Naturforsch. 32b, 94-97 [1977]; received March 5, 1976)

Thiazolo[2,3-b]quinazolines, Quinazolinylthioglycollanilides

Cyclodehydration of (4-oxo-3,4-dihydro-2-quinazolinylthio)acetic acid (1) afforded
5 H-thiazolo[2,3-b]quinazoline-3,5(2 H)-dione (2). Condensation of 2 with aldehydes gave
the 2-arylmethylene derivatives (6a-d) and coupling with diazonium salts gave the
hydrazones (9a, b). The thiazolone ring in 2 has been cleaved by amines to give α-(4-oxo-
3,4-dihydro-2-quinazolinylthio)acetonilides (11a-d). The arylmethene derivatives of the
angular isomer of 2, 5 H-thiazolo[3,2-a]quinazoline-1,5(2 H)-dione (4), were also prepared.

The thiazole ring system assumes considerable
importance by virtue of its presence in many
physiologically important compounds, namely,
thiamin, penicillin, etc. The quinazolone ring system
is also important as it is present in alkaloids like
vasicine and antimalarials like febrifugine and
arborine. This led us to try to synthesize some
thiazoloquinazolones likely to have biological
activity.

KENDALL et al.1 reported that (4-oxo-3,4-dihydro-
2-quinazolinylthio)acetic acid (1) was cyclized by
acetic anhydride to a thiazoloquinazolone. However,
the structure of the product was not defined. This
communication presents the results of the work
aimed to cyclize 1.

Treatment of 1 with acetic anhydride at 80 °C
gave 5 H-thiazolo[2,3-b]quinazoline-3,5(2 H)-dione
(2).

The use of concentrated sulphuric acid in the
cyclization at room temperature gave unchanged
acid (1), while boiling with acetic anhydride gave
charred material. However, when 1 was refluxed
with phosphorus oxychloride, the yield was 1,2,3,4-
tetrahydroquinazoline-2,4-dione (3).2

Compound 2 (m/e = 218) gave the correct elemen-
tal analysis for C_{10}H_{7}N_{2}O_{2}S. Its IR spectrum shows
a strong band at 1780 cm⁻¹ due to the thiazole ring
carbonyl*. Three other strong bands are present at
1695, 1665 and 1592 cm⁻¹, the first for
C=O at position 5 and the last two for C=N group; this
is in agreement with that reported by
CULBERTSON et al.3 for 4-quinazolones. No absorption bands
were observed in the region 2500-2700 cm⁻¹ which
indicates the absence of carboxylic groups.

Formulation of compound 2 in the linear rather
than the angular form (4) was based on the following
facts:

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* Absorption of carbonyl groups at such high wave
numbers has been reported before3,4.
i) 5 is the most favoured structure for 4-quinazolones,

ii) an authentic sample of 4 was prepared and proved to be different from our product (2) (mixed m.p.),

iii) the arylmethene derivatives of each of 2 and 4 were prepared by treatment with the appropriate aldehyde in refluxing acetic acid containing anhydrous sodium acetate. The benzylidene and p-chlorobenzylidene derivatives of 2 (6a, c) were found to be different from the corresponding derivatives of 4 (7a, b).

\[ \text{6a: } Ar = C_6H_5 \quad 6b: \text{ } Ar = C_6H_5(OC_2H_5) \quad 6c: \text{ } Ar = C_6H_4Cl-p \quad 6d: \text{ } Ar = C_6H_4Br-p \]

Compound 6a has two absorption bands in the IR region at 1760 and 1700 cm\(^{-1}\) assigned to the carbonyl groups at positions 3 and 5, respectively. The former suffered a downward shift with respect to that of 2 due to its conjugation with the exocyclic double bond.

The IR spectrum of 7a shows two bands at 1735 and 1695 cm\(^{-1}\) due to the carbonyl groups at positions 1 and 5, respectively. (The corresponding groups in 4 absorbed at 1785 and 1695 cm\(^{-1}\).)

Compounds 6a-d could be directly prepared from 8 by refluxing with chloroacetic acid, anhydrous sodium acetate and the appropriate aldehyde in acetic acid and acetic anhydride.

\[ \text{8} \quad \text{CICH}_2\text{COOH, ArCHO} \quad \text{AcNa, AcOH, Ac}_2\text{O} \quad \text{6a-d} \]

Compound 2 having an active methylene group coupled with areniendiazonium salts to give products formulated as the hydrazones (9a, b) rather than the azo compounds (10), due to the presence of NH absorption band at 3250 cm\(^{-1}\) in the IR spectrum of 9a. The same spectrum shows also two bands at 1750 cm\(^{-1}\) (C=O) and at 1700 cm\(^{-1}\) (C=O). The absorption of the thiazole ring carbonyl at a lower frequency, with respect to the same group in 2, may be a result of its conjugation with the hydrazono group.

\[ \text{9a: } Ar = C_6H_5 \quad 9b: \text{ } Ar = C_6H_4Br-p \]

The UV spectrum of 9a (ethanol) shows a maximum band at 410 nm. This provides more evidence for the hydrazone structure since while the monophenylazo compounds have a strong band at 270–280 nm, the monophenylhydrazones give a strong band at a wavelength higher than 320 nm.

The following is a recommended method for the preparation of the anilides 11 in quantitative yields. The method consists of adding various amines to a refluxing xylene solution of 2 where the thiazolone ring was opened to afford a-(4-oxo-3,4-dihydro-2-quinazolinylthio)acetonilides (11a-d).

\[ \text{2} \quad \text{ArNH}_2 \quad \text{ClCICH}_2\text{CONHar} \quad \text{8} \quad \text{11} \]

\[ \text{11a: } Ar = C_6H_5 \quad 11b: \text{ } Ar = C_6H_4CH_3-p \quad 11c: \text{ } Ar = C_6H_4Cl-p \quad 11d: \text{ } Ar = C_6H_4Br-p \]

This behaviour of 2 towards amines resembles that of other fused thiazoliones, such as 2,3-dihydro-5,6-diphenyl-imidazo[2,1-b]thiazol-3-one and 2,3-dihydrobenzimidazo[2,1-b]thiazol-3-one.

The anilides 11a-d were also directly prepared from 8 by boiling with the appropriate α-chloroacetamidine in alcoholic potassium hydroxide solution.

**Experimental**

Melting points are not corrected. IR spectra were recorded as KBr pellets with a Hitachi Grating IR spectrophotometer Model EPI-G3. UV spectra were measured in ethanol on Beckman recording spectrophotometer Model DK.
5 H-Thiazolo[2,3-b]quinazoline-3,5(2 H)-dione (2)

5 g of 1 were heated with 25 ml of acetic anhydride at 80–85 °C for 6 hours. The darkened reaction mixture was cooled and the brown solid was filtered off and dried well. It was then boiled with 150 ml of xylene and the solution was filtered from a brown residue. After cooling the filtrate, 2 was crystallized out in yellow prisms, m.p. 209 °C; yield 56%. When admixed with an authentic sample of 47, a depression in the m.p. was observed.

Analysis: C_{10}H_{6}N_{2}O_{2}S
Calcd C 55.03 H 2.78 N 12.84 S 14.69,
Found C 55.30 H 2.81 N 12.70 S 14.65.

1,2,3,4-Tetrahydroquinazoline-2,4-dione (3)

2 g of 1 and 10 ml of phosphorus oxychloride were refluxed for 15 min and then poured on ice with stirring. Yellow crystals of a sulphur-free compound (3) were separated, m.p. above 350 °C; yield 76%. No depression in the m.p. was observed when admixed with an authentic sample.

Analysis: C_{8}H_{6}N_{2}O_{2}
Calcd C 59.25 H 3.74 N 17.28,
Found C 59.15 H 3.66 N 17.10.

2-Arylmethylene-5 H-thiazolo[2,3-b]quinazoline-3,5(2 H)-diones (6a-d)

**General method a:** A mixture of 2.2 g (0.01 mole) of 2, 0.01 mole of the aromatic aldehyde and 3 g of anhydrous sodium acetate was refluxed in 30 ml of glacial acetic acid for 3 hours. The reaction mixture was then poured on cold water, the separated solid was filtered off, washed with water and crystallised from the proper solvent (cf. Table I).

**General method b:** A mixture of 1.8 g (0.01 mole) of 8, 1.0 g of chloroacetic acid, 2 g of fused sodium acetate and 0.01 mole of the aromatic aldehyde was refluxed in 20 ml of glacial acetic acid and 10 ml of acetic anhydride for 4 hours. The reaction mixture was then worked up as in method (a) to give 80–85% yields of 6a–d.

2-Arylmethylene-5 H-thiazolo[3,2-a]quinazoline-1,5(2 H)-diones (7a, b)

7a, b were prepared from 4 by the general method (a) used for the preparation of 6a–d, and they are listed in Table I.

2-Mercapto-3,4-dihydro-4-quinazolone (8)

A mixture of 4 g of anthranilamide, 3 ml of carbon disulphide, 1 g of potassium hydroxide and 50 ml of ethanol was refluxed till hydrogen sulphide was completely evolved (ca. 8 hours). The resulting solution was filtered while hot, the filtrate was cooled and the separated crystals were filtered off, dried and recrystallised from acetic acid, m.p. 283–284 °C (65%). Lit. m.p. 284 °C.

5 H-Thiazolo[2,3-b]quinazoline-2,3,5(2 H)-trione-2-arylhydrazones (9a, b)

The aromatic amine (0.005 mole) was dissolved in 5 ml of concentrated hydrochloric acid and 5 ml of water, cooled to 0 °C and treated with a cold solution of 0.5 g of sodium nitrite in 5 ml of water. This diazotised amine was gradually added to an ice-cold solution of 0.005 mole of 2 in 30 ml of pyridine. The reaction mixture was refrigerated for 1 hour and then poured into water. The product was filtered off, washed with water, dried and crystallised from the proper solvent.

The 2-phenylhydrazone (9a) was prepared in 70% yield, crystallized from dilute DMF, m.p. 270 °C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Solvent of cryst.</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon Analysis [%]</th>
<th>Analysis [º]</th>
<th>Sulphur Analysis [%]</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caled Found</td>
<td>Caled Found</td>
<td>Caled Found</td>
</tr>
<tr>
<td>6a</td>
<td>248</td>
<td>(AcOH)</td>
<td>73</td>
<td>C_{17}H_{10}N_{2}O_{2}S</td>
<td>66.65</td>
<td>66.46</td>
<td>3.30</td>
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<tr>
<td>6b</td>
<td>241</td>
<td>(PhNO₂)</td>
<td>63</td>
<td>C_{12}H_{14}N_{2}O_{3}S</td>
<td>62.28</td>
<td>62.50</td>
<td>3.86</td>
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<tr>
<td>6c</td>
<td>280</td>
<td>(Dioxan)</td>
<td>78</td>
<td>C_{17}H_{9}ClN_{2}O_{2}S*</td>
<td>59.91</td>
<td>59.67</td>
<td>2.67</td>
</tr>
<tr>
<td>6d</td>
<td>276</td>
<td>(PhNO₂)</td>
<td>80</td>
<td>C_{17}H_{9}BrN_{2}O_{2}S</td>
<td>53.00</td>
<td>53.23</td>
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<tr>
<td>7a</td>
<td>288</td>
<td>(PhNO₂)</td>
<td>68</td>
<td>C_{17}H_{10}N_{2}O_{2}S</td>
<td>66.65</td>
<td>66.41</td>
<td>3.30</td>
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<tr>
<td>7b</td>
<td>285</td>
<td>(PhNO₂)</td>
<td>70</td>
<td>C_{17}H_{9}ClN_{2}O_{2}S</td>
<td>59.91</td>
<td>59.71</td>
<td>2.67</td>
</tr>
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</table>

* Cl: Caled 10.40, Found 10.31%.
Analysis: \( \text{C}_{14}\text{H}_{10}\text{N}_{4}\text{O}_{2}\text{S} \)

Calcd C 59.60 H 3.13 N 17.38 S 9.93.

Found C 59.87 H 3.32 N 17.15 S 9.81.

The 2-\( p \)-bromophenylhydrazone (9b) was obtained in 74% yield, crystallized from DMF, m.p. 243 °C.

Analysis: \( \text{C}_{16}\text{H}_{10}\text{N}_{4}\text{O}_{2}\text{S} \)

Calcd C 61.72 H 4.22 N 13.50 S 10.30.


\( \alpha \)-(4-Oxo-3,4-dihydro-2-quinazolinylthio) acetanilides (I1a-d)

a) From 2: General procedure

To a boiling solution of 1.1 g of 2 in ca. 40 ml of xylene was added 0.005 mole of the amine. White crystals separated while refluxing was continued for 15 min. The reaction mixture was cooled, filtered and the product (quantitative yield) was recrystallized from the proper solvent.

I1a was recrystallized from dilute acetic acid, m.p. 243 °C.

Analysis: \( \text{C}_{16}\text{H}_{11}\text{N}_{3}\text{O}_{2}\text{S} \)

Calcd C 61.72 H 4.22 N 13.50 S 10.30.


b) From 8: General procedure

A mixture of 0.9 g of 8, 0.005 mole of the appropriate \( \alpha \)-chloroacetanilide and 0.3 g of potassium hydroxide in ca. 30 ml of ethanol was refluxed for 3 hours. The reaction mixture was then poured into water and the separated solid was filtered off, dried and crystallized from the proper solvent to give I1a-d (yields 60-70%).

The authors wish to express their thanks to Dr. A. A. El-Sayed, Formerly, Lecturer in Chemistry, Faculty of Science, Cairo University, for his previous interest in this work.

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