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Synthesis of Some New Derivatives of Thiazolo[4,3-*b*]- and Thiazolo[2,3-*b*]quinazolone

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The new 5*H*-thiazolo[4,3-*b*]quinazoline-3,5(1*H*)-diones **3**, **4a–c**, **5a–c** and 5*H*-thiazolo[2,3-*b*]quinazoline-3,5(2*H*)-diones **9a–c**, **11a–c** were prepared by reaction of anthranilic acid with the 2-thiazolidinone-4-thione derivatives **1b**, **6a–c**, **7a–c** and the 5-substituted 2-(alkylmercapto)-2-thiazolin-4-ones **8a-c, 10a-c**, respectively.

Darstellung verschiedener neuer Thiazolo[4,3-b]- und Thiazolo[2,3-b]chinazolon-Derivate

Die neuen 5*H*-Thiazolo[4,3-b]chinazolin-3,5(1*H*)-dione **3**, **4a–c**, **5a–c** und 5*H*-Thiazolo[2,3-b]chinazolin-3,5(2*H*)-dione **9a–c**, **11a–c** werden durch Umsetzung von Anthranilsäure mit den 2-Thiazolidinon-4-thion-Derivaten **1b**, **6a–c**, **7a–c** und den 5-substituierten 2-Alkylmercapto-2-thiazolin-4-onen **8a–c**, **10a–c** synthetisiert.

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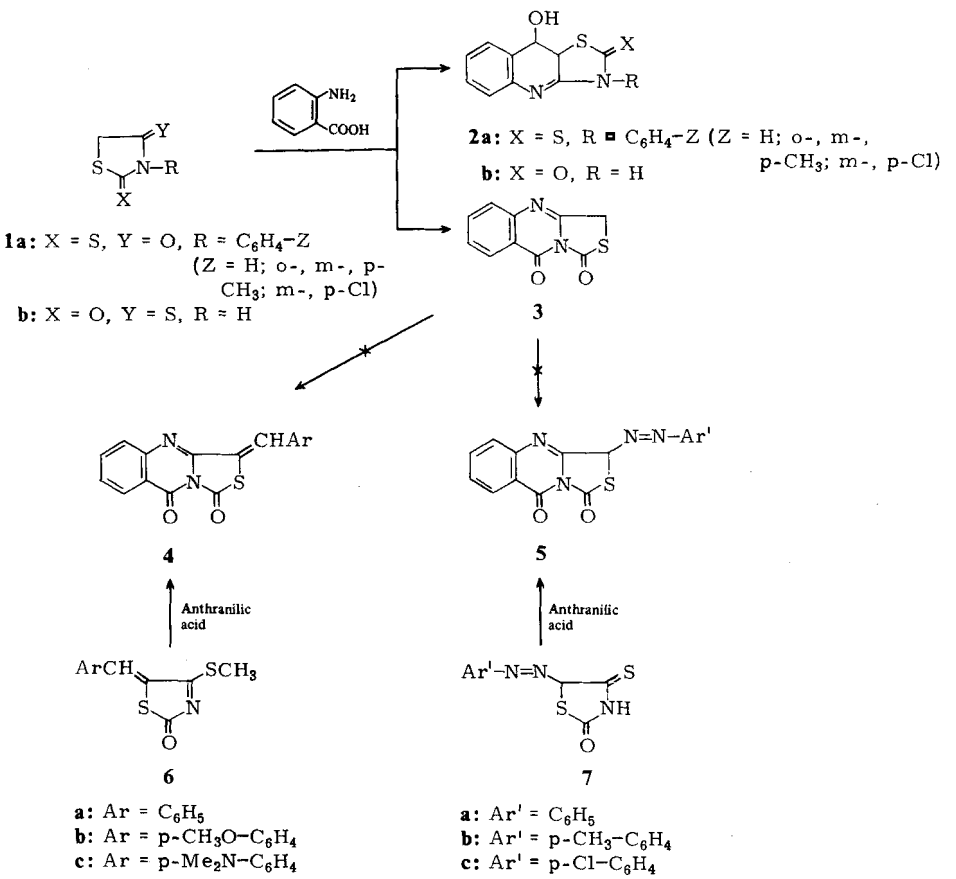
In view of the considerable biological importance of the quinazolone ring system as it is present in antibacterials[1,2], antivirals against influenza virus[3], and antimalarials[4], it was of interest in our previous work[5,6] to prepare condensed imidazoquinazolones of probable pharmacological effect. In the present investigation, our interest is continued to condense the quinazolone nucleus with the chemotherapeutically active heterocyclic nucleus thiazole[7,8] from the readily accesible thiazolidine thiones.

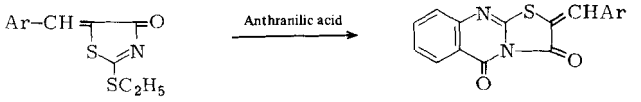
It was reported that 3-aryl-4-thiazolidinone-2-thiones **1a** reacted with anthranilic acid to give 2-thiono-3-aryl-4:5-(2′:3′)-4-hydroxyquinolylthiazolidines **2a**[9]. In this investigation, when the unsubstituted 2-thiazolidinone-4-thione **(1b)** was treated with anthranilic acid, 5*H*-thiazolo[4,3-b]quinazoline-3,5(1*H*)-dione **(3)** was obtained instead of **2b**. The structure of **3** was assigned based on the IR spectrum which revealed the presence of absorption bands characteristic for C=N at 1665 and 1590 cm^{-1} and C=O in position 5 at 1700 cm^{-1} (this is in agreement with the IR spectrum reported for 4-quinazolones)[10], in addition to the thiazole ring carbonyl at 1780 cm^{-1}. On the other hand, the band related to the NH group was entirely absent.

It was planned to synthesise the arylidene-**4** and arylazo-**5** compounds via condensation of **3** with aromatic aldehydes and subsequent coupling with aryldiazonium salts, but in



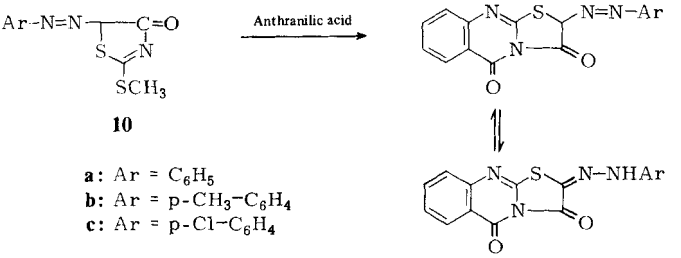
each case the starting material was recovered unchanged. Compounds **4a–c** and **5a–c** were alternatively synthesised in good yields via the reaction of anthranilic acid with the 5-arylidene-4-methylmercapto-3-thiazolin-2-ones **6a–c** and the 5-arylazo-2-thiazolidinone-4-thiones **7a–c** resp. (cf. Chart 1). The structures **4** and **5** were proven based on correct elementary analyses and IR spectra (see exp. part).

In a similar manner the syntheses of the 2-arylidene- and 2-arylazo-5*H*-thiazolo[2,3-b]quinazoline-3,5(2*H*)-diones **9**, **11** were performed. Thus, when the 5-arylidene-2-ethylmercapto-2-thiazolin-4-ones **8a–c** and the 5-arylazo-2-methylmercapto-2-thiazolin-4-ones **10a–c** were treated with anthranilic acid in presence of acetic acid, **9a–c** and **11a–c** were obtained. The assigned structures for **9** and **11** were inferred from correct analytical and spectral data. The IR spectra of **9a–c** and **11a–c** showed two bands at ~ 1750 and ~ 1700 cm^{-1} due to the presence of two carbonyl groups. The presence of an NH group at ~ 3250 cm^{-1} in the IR spectra of **11a–c**, and in addition the presence of a maximum band at 410 nm in the UV spectrum of **11a**, proved that **11** exists in the hydrazone form rather than the azo form[11,12]. An unequivocal support for structures **9** and **11** was anchieved via the preparation of authentic samples of **9a** and **11a** following the procedure previously reported by *Ali* et al[13].



8 **9**

a: Ar = C_6H_5
b: Ar = p-CH_3O-C_6H_4
c: Ar = p-Me_2N-C_6H_4



10

a: Ar = C_6H_5
b: Ar = p-CH_3-C_6H_4
c: Ar = p-Cl-C_6H_4

11

Experimental Part

MP: uncorr. *IR spectra:* Pye Unicam SP 1100 spectrophotometer. *Elementary analyses:* Microanalytical Centre, Cairo University.

5H-Thiazolo[4,3-b]quinazoline-3,5(1H)-dione **(3)**

A mixture of 0.01 mole 2-thiazolidinone-4-thione **1b**, and 0.01 mole anthranilic acid was heated in 30 ml ethanol or glacial acetic acid. During the reaction the odour of hydrogen sulphide could easily be detected and brown crystals were separated after 30 min. The heating was continued till the odour of

H_2S ceased (ca. 4 h). The reaction mixture was left to cool at room temp. The product was boiled for about 5 min with ethanol and filtered while hot to separate the highly insoluble product **3**, m.p. > 300 °C, yield 60 %. $C_{10}H_6N_2O_2S$(218.16)Calcd. C 55.0 H 2.78 N 12.8 S 14.7; Found C 55.2 H 2.70 N 12.9 S 14.5.

1-Arylidene-5H-thiazolo[4,3-b]quinazoline-3,5(1H)-diones **4a–c**

A mixture of 0.01 mole of the 5-arylidene-4-methylmercapto-3-thiazolin-2-ones[14] **6a–c**, and 1.37 g anthranilic acid in 20 ml glacial acetic acid was heated. During the reaction a yellow solid was separated after about 15 min. The heating was continued till the odour of methane thiol could not longer be detected (ca. 3 h). The reaction mixture was cooled to room temp. and the precipitated solid was crystallised from dimethyl formamide as yellow crystals of **4a–c**. The products **4a–c** listed in Table 1 are insoluble in sodium hydroxide (2 %) and sodium carbonate solutions. IR of **4a**: 1660 (C=N), 1700 and 1770 cm^{-1} (2 C=O).

1-Arylazo-5H-thiazolo[4,3-b]quinazoline-3,5(1H)-diones **5a–c**

A solution of 0.01 mole of **7a–c**[15] and 0.01 mole anthranilic acid in 50 ml acetic acid was refluxed till the hydrogen sulphide was completely evolved (ca. 4 h). The reaction mixture was cooled to room temp. and poured over water, the separated brown solid was crystallised from dimethyl fromamide as **5a–c**. The solid products **5a–c** listed in Table 1 are insoluble in sodium hydroxide (2 %) and sodium carbonate solutions. IR of **5a**: 1660 (C=N), 1700 and 1770 cm^{-1} (2 C=O).

Table 1: *1-Arylidene-* **4a–c** *and 1-arylazo-* **5a–c** *of 5H-thiazolo*[4,3-b]*quinazoline-3,5(1H)-diones* **3**

Compound	m.p. (°C)	Yield (%)	Formula (Mol..Wt.)	Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	S Calcd.	S Found
4a	215	75	$C_{17}H_{10}N_2O_2S$ (306.27)	66.7	66.7	3.30	3.4	9.2	9.2	10.5	10.5
4b	252	78	$C_{18}H_{12}N_2O_3S$ (336.29)	64.3	64.2	3.57	3.5	8.3	8.4	9.5	9.6
4c	262	73	$C_{19}H_{15}N_3O_2S$ (349.33)	65.3	65.4	4.30	4.4	12.0	12.1	9.2	9.0
5a	260	70	$C_{16}H_{10}N_4O_2S$ (322.27)	59.6	59.5	3.13	3.2	17.4	17.4	9.9	10.0
5b	272	66	$C_{17}H_{12}N_4O_2S$ (336.30)	60.7	60.6	3.57	3.5	16.7	16.6	9.5	9.6
5c	282	68	$C_{16}H_9N_4O_2SCl$* (356.77)	53.9	53.9	2.52	2.6	15.7	15.8	9.0	9.1

* Cl: Calcd. 10,0, Found 10.1.

2-Arylidene-5H-thiazolo[2,3-b]quinazoline-3,5(2H)-diones **9a–c**

A mixture of 0.01 mole of 5-arylidene-2-ethylmercapto-2-thiazolin-4-ones[16] **8a–c** and 0.01 mole anthranilic acid was heated in 40 ml glacial acetic acid. When the reaction was completed (evolution of C_2H_5SH ceased, ca. 6 h), the mixture was left to cool at room temp. The product was crystallised from the proper solvent as **9a–c**. **9a** was crystallised from acetic acid, m.p. 250 °C, yield 78 %. No depression in m.p. was observed when admixed with an authentic sample[13].

9b was crystallised from dimethyl formamide, m.p. 232 °C, yield 75 %. $C_{18}H_{12}N_2O_3S$(336.29)Calcd. C 64.3 H 3.57 N 8.3 S 9.5; Found C 64.3 H 3.6 N 8.2 S 9.4.

9c was crystallised from dimethyl fromamide, m.p. 272 °C, yield 72 %. $C_{19}H_{15}N_3O_2S$(349.33)Calcd. C 65.3 H 4.30 N 12.0 S 9.2; Found C 65.2 H 4.2 N 12.1 S 9.3.

5H-Thiazolo[2,3-b]quinazoline-2,3,5(2H)-trione-2-arylhydrazones **11a–c**

A solution of 0.01 mole of **10a–c**[17] and 0.01 mole anthranilic acid in 50 ml glacial acetic acid was refluxed till the odour of methane thiol could not longer be detected (ca. 6 h). The reaction mixture was worked up as in case of **5**. The products were recrystallised from dimethyl formamide as brownish red crystals of **11a–c**.

11a, m.p. 273 °C, yield 78 %. No depression was observed when admixed with an authentic sample[13].

11b, m.p. 288 °C, yield 75 %. $C_{17}H_{12}N_4O_2S$(336.30)Calcd. C 60.7 H 3.57 N 16.7 S 9.5; Found C 60.8 H 3.6 N 16.7 S 9.5.

11c, m.p. > 300 °C, yield 75 %. $C_{16}H_9N_4O_2SCl$(356.77)Calcd. C 53.9 H 2.52 N 15.7 S 9.0 Cl 10.0; Found C 53.7 H 2.6 N 15.6 S 9.0 Cl 9.9.

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[Ph 593]

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Neue Untersuchung über Inhaltsstoffe der Kreuzdornrinde, 2. Mitt.[1]

Isolierung und Charakterisierung der blau fluoreszierenden Leitstoffe aus der Rinde von Rhamnus catharticus L.[2]

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Eingegangen am 31. März 1982

Aus der Rinde von Rhamnus catharticus L. wurden die Naphthalidprimveroside 6-Methoxysorinin **(1b)** und Sorinin **(2b)** als Heptaacetylderivate isoliert und charakterisiert. Die Strukturen wurden vorwiegend mit spektroskopischen Methoden ermittelt. **1b** und **2b** fungieren in der Ph. Eur. II als Leitstoffe der Kreuzdornrinde bei der dc-Prüfung der offizinellen Rhamnus-Drogen: sie sind verantwortlich für die blaue Fluoreszenz der Zone mit Rf = 0,25.

New Investigation of the Constituents of Rhamni cathartici Cortex, II: Isolation and Characterization of the Blue Fluorescing Leading Substances from the Cortex of Rhamnus catharticus

The naphthalide primverosides 6-methoxysorinin **(1b)** and sorinin **(2b)** were isolated as heptaacetates from the stem bark of Rhamnus catharticus L. (purging buckthorn). Their structures were established mainly by spectroscopic methods. These glycosides are leading substances in Ph. Eur. II for Rhamni cathartici cortex in the TLC analysis of Frangulae and Rhamni purshiani cortices: they are responsible for the blue fluorescence of the spot at Rf = 0.25.

Die Ph. Eur. II prüft bei Frangulae cortex und Rhamni purshiani cortex auf Verfälschung oder Verunreinigung durch Rhamni cathartici cortex mit Hilfe der Dünnschicht-Chromatographie: Im langwelligen UV darf das Chromatogramm keine blau fluoreszierenden Zonen mit Rf 0,25[3] und 0,40[4] zeigen. Der Zone mit Rf 0,25 liegen zwei lactonische Naphthalindiglykoside zugrunde, deren Isolierung und Strukturaufklärung im folgenden beschrieben werden. Spektroskopische Daten natürlich vorkommender 1.8-Dihydroxynaphthalidglykoside liegen in der Literatur nicht vor.

Bei der DC des MeOH-Extraktes gelagerter Rinde von Rhamnus catharticus L. entsprechend der Monographie „Frangulae cortex" nach Ph. Eur. II ergeben die im

0365-6233/83/0505-0399 $ 02.50/0