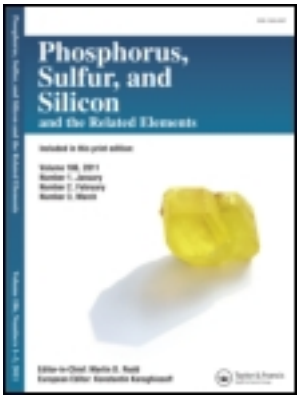

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Reactions of 5-Arylidene-2-thiohydantoins with Halogenated Compounds and Anthranilic Acid

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Reactions of 5-Arylidene-2-thiohydantoins with Halogenated Compounds and Anthranilic Acid

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*5-arylidene-2-thiohydantoins **1a–c** react with ethyl α-chloroacetate **2** and monochloroacetone to give the respective 2-imidazolinones **3a–c** and 2-acetonylmercaptohydantoins **9a–c**.*
*Compounds **3a–c** react with benzenediazonium chloride to afford hydrazones **5a–c**. The reaction of **1a–c** with ethylene bromide and with α,α-dichloroacetone gives the respective alkyl mercapto-derivatives **13a–c** and **14a–c**. The reaction of polyphosphoric acid with **3a–c**, **9a–c**, **13a–c** and **14a–c** yields the respective thiazolones **7a–c** , imidazothioles **10a–c**, imidazo-thiazoles **15a–c** and imidazothiazines **16a–c**. The mercapto-hydantoins **17a–d** react with anthranilic acid to give quinazolin-3,5-diones **19a,b** and/or **21a,b**. Structural elucidation for the new products are based on compatible elementary and spectroscopic evidences.*

Keywords 5-Arylidene-2-thiohydantoins; anthranilic acid; dihlogenated compounds; mono-; polyphosphoric acid

INTRODUCTION

The considerable biological and medicinal activities of thiazoles and imidazoquinazolines have stimulated recent interest in the synthesis of derivatives of these condensed heterocyclic ring systems.[1–6] As a part of our program directed towards the development of new simple procedures for the synthesis of fused azoles,[7–12] the reactions of 5-arylidene-2-thiohydantoins **1a–c** with monohalogenated and dihalogenated compounds, in addition to the reaction of products with anthranilic acid and polyphosphoric acid, were investigated.

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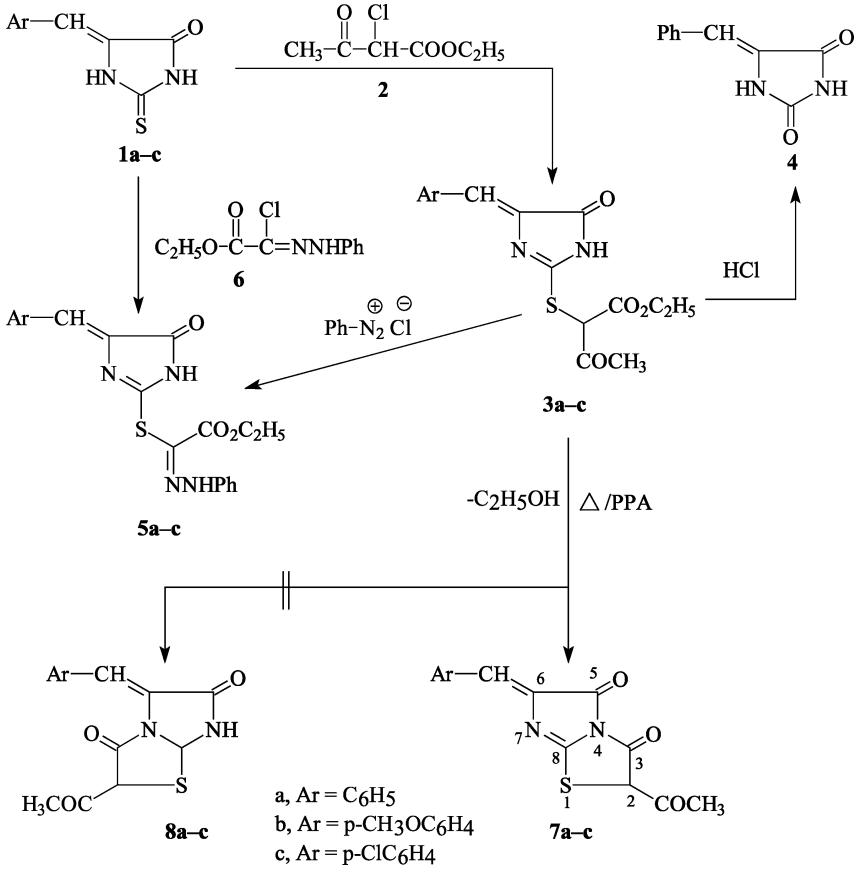
RESULTS AND DISCUSSION

It has been found that compounds **1a–c** reacted with ethyl α-chloroacetoacetate **2** in ethanol in the presence of sodium ethoxide at room temperature to yield products corresponding to the addition of one molecule of each of **1a–c** to one molecule of **2** followed by the loss of one molecule of HCl. The reaction products could be formulated as ethyl α-(4-arylidene-2-imidazolin-5-one-2-yl-thio)acetoacetates **3a–c** based on elemental analyses and spectral data. The IR spectra of **3a–c** showed the presence of absorption bands for one NH group and three carbonyl groups. ^{1}H-NMR spectrum of **3c** was found in good agreement with the assigned structure only (cf., Scheme 1 and Expecrimental section).

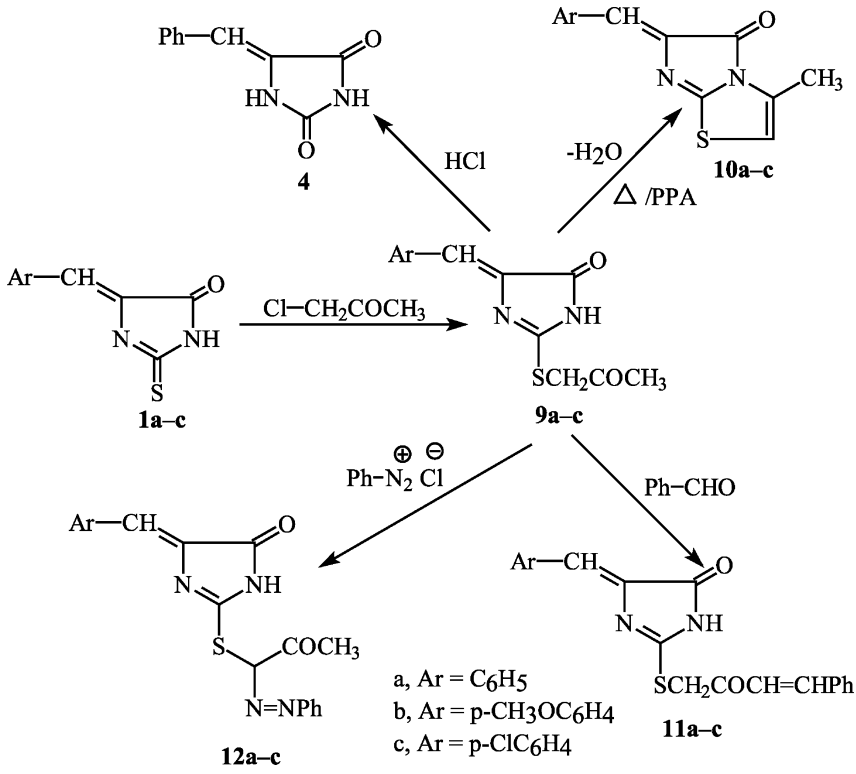


SCHEME 1

Furthermore, treatment of **3a** with ethanol-hydrochloric acid mixture resulted in the formation of 5-benzylidene hydantoin (**4**).[13]

Compounds **3a–c** coupled with benzenediazonium chloride in ethanol in the presence of sodium acetate in a Japp-Klingemann reaction to give ethyl 1-(4-arylidene-2-imidazolin-5-one-2-yl-thio)glyoxalate 1-phenylhydrazones **5a–c**. The structures of **5a–c** were supported by elemental analysis and spectral data (cf., Experimental section). Moreover, compounds **5a–c** also were synthesized by an alternative route via the reaction of **1a–c** with ethyl 1-chloroglyoxalate 1-phenylhydrazone (**6**) (from benzene diazonium chloride and ethyl α-chloroacetoacetate, cf., Scheme 1).

When compounds **3a–c** were heated with polyphosphoric acid, 2-acetyl-6-arylidene-imidazo[2, 1-*b*] thiazol-3,5-diones **7a–c**, and not their isomeric forms compounds **8a–c**, were obtained (cf., Scheme 2). The structure of **7a–c** was considered more probable to represent



SCHEME 2

the cyclization products on the basis that the hydrogen atom attached to the nitrogen atom at position-3 (—CO—NH) in 5-substituted-2-alkylmercaptohydantoins,[14,15] which is the only active site. Compounds **7a–c** gave the correct elemental analysis and spectral data.

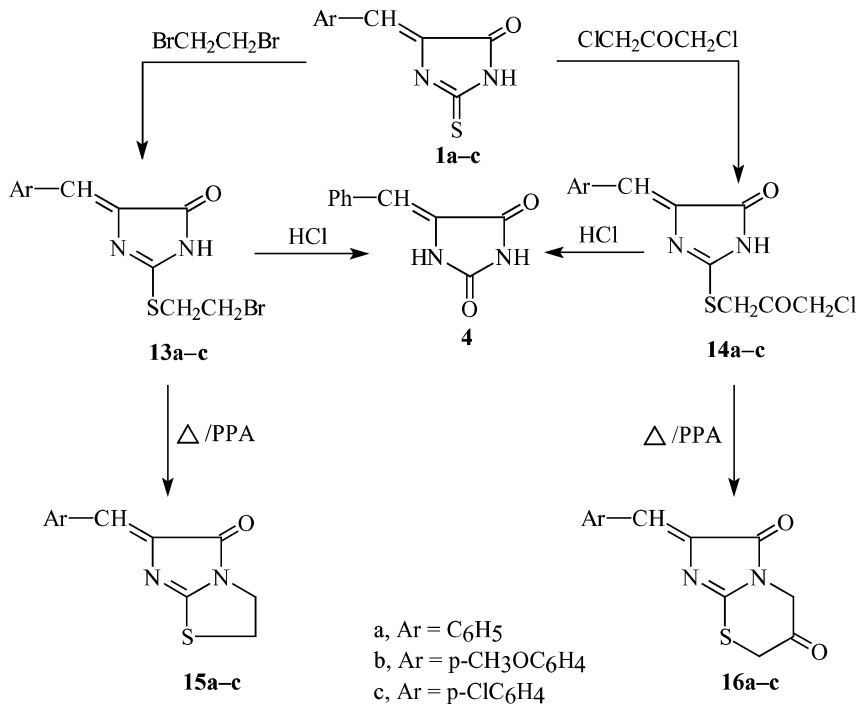
Similarly, 5-arylidene-2-thiohydantoins **1a–c** reacted with monochloroacetone under the same experimental conditions to yield 2-acetonylmercaptohydantoin derivatives **9a–c**. Compounds **9a–c** gave the correct elemental analysis and spectral data. In addition, **9a** was hydrolysed with ethanol-concentrated hydrochloric acid mixture to give 5-benzylidene hydantoin (**4**).[13]

Compounds **9a–c** were converted into imidazo[2,1-*b*]thiazole derivatives **10a–c**, via elimination of water in each case, by heating with polyphosphoric acid (cf., Scheme 2). Products **10a–c** gave the correct elemental analyses and spectral data (cf., Experimental section).

Compounds **9a–c** reacted with benzaldehyde in ethanolic sodium ethoxide solution to give cinnamoylmethylmercapto derivatives **11a–c** (cf., Scheme 2). The IR spectra of **11a–c** showed the presence of one NH group, two C=O groups, and C=N. In addition, the ^{1}H-NMR spectrum of **11a** in DMSO- $\underline{d}_6$ revealed signals for one exchangeable NH, $-CH_2$, —COCH, and two ylidinic CH together with aromatic protons (cf., Experimental section). On the other hand, **9a–c** coupled with benzenediazonium chloride to afford the azo derivatives **12a–c**, which gave the correct elemental analyses and spectral data (cf., Experimental section).

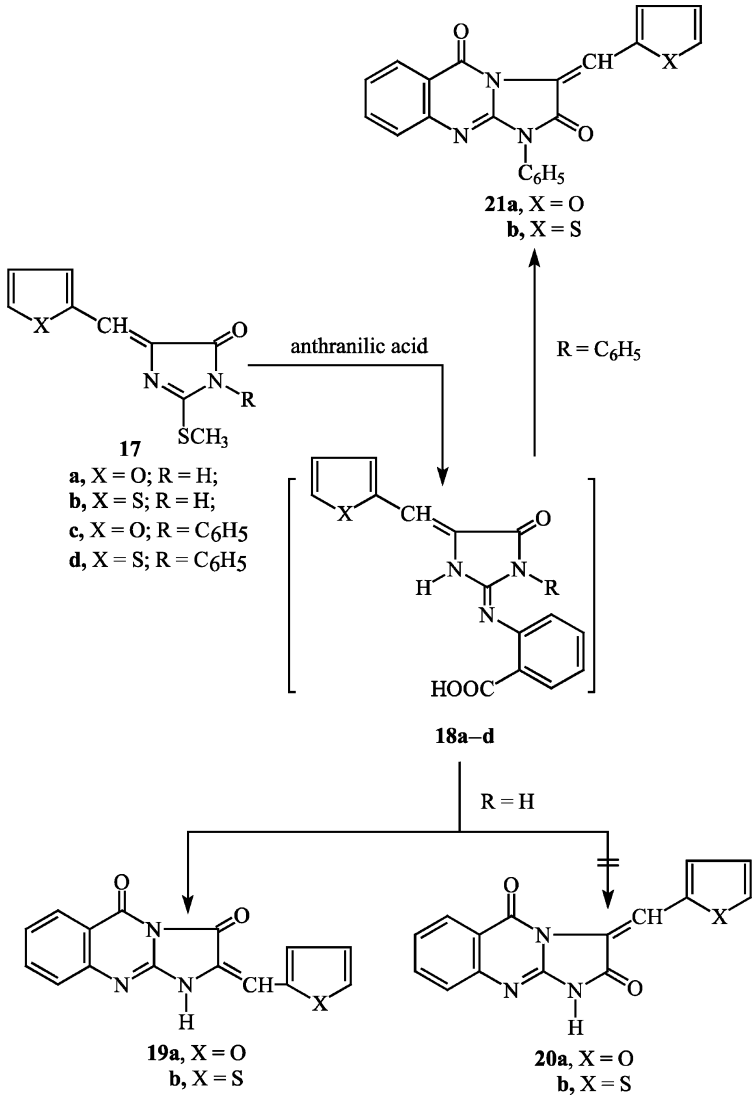
The work also was extended to study the behaviour of 5-arylidene-2-thiohydantoins **1a–c** towards dihalogenated compounds. Thus, when a mixture of equimolar amounts of each of **1a–c** and ethylene bromide and/or α,α-dichloroacetone in ethanol containing an equimolar amount of sodium ethoxide was stirred at room temperature, the alkylmercapto derivatives **13a–c** and **14a–c** were obtained, respectively, based on elemental analysis and spectral data. Moreover, when **13a** and/or (**14a**) were treated with ethanol-concentrated hydrochloric acid mixture, 5-benzylidene hydantoin (**4**)[13] was obtained in each case. Compounds **13a–c** and **14a–c** were cyclized via the elimination of HBr and HCl, respectively, by heating with polyphosphoric acid to give imidazo[2,1-*b*]thiazole derivatives **15a–c** and imidazo[2,1-*b*]thiazine derivatives **16a–c** respectively (cf., Scheme 3).

Work is extended further to investigate the behavior of 5-ylidene-2-methylmercapto hydantoin derivatives **17a**,**b** towards the action of anthranilic acid for the synthesis of some new imidazo[2,1-*b*] quinazolines containing 2-furyl and 2-thianyl moieties required for biological activity studies. Thus, it was found that compounds **17a**,**b** reacted with anthranilic acid to afford products corresponding to the addition of one molecule of each of **17a**,**b** to one molecule of anthranilic acid with the



SCHEME 3

elimination of one molecule of methane thiol and one molecule of water. The reaction products were formulated as 2-ylidene imidazo[2,1-*b*]-quinazoline-3,5-diones **19a**,**b** or their isomeric forms **20a**,**b** (cf., Scheme 4). The structure of **19a**,**b** was considered more probable to represent the cyclization products based on the report that the hydrogen atom attached to N-3 is the only active site on 5-arylidene-2-alkylmercapto-hydantoins,[14,15] and hence it facilitates the loss of water, which is necessary for the cyclization step. This fact was supported from previous results from this laboratory for other 5-arylidene-2-thiohydantoin derivatives.[17] On the other hand, **17c**,**d** reacted with anthranilic acid to give 1-phenyl-3-ylidene-imidazo[2,1-*b*] quinazoline-2, 5-diones **21a**,**b**. The formation of **19a**,**b** and **21a**,**b** is assumed to proceed via the condensation of the amino group of anthranilic acid with the methylmercapto derivatives **17a–d** and with the elimination of methane thiol to give nonisolable intermediates **18a–d**, respectively, which cyclize readily with the loss of water under the applied reaction conditions to give the final isolable products **19a**,**b** and **21a**,**b**, respectivey (cf., Scheme 4).



SCHEME 4

EXPERIMENTAL

All melting point are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer in KBr discs. The ^{1}H-NMR spectra were recorded on a varian EM 390-90 MHz spectrometer using deuterated DMSO-d_6 as a solvent and TMS as an internal standard.

Chemical shifts are exposed as δ ppm units. Microanalytical data were obtained by the Microanalytical Centre at the Faculty of Sciences, Cairo University.

Reactions of 5-Arylidene-2-thiohydantoins 1a–c with Ethyl α-Chloro-acetoacetate 2

A solution of each of **1a–c** (0.01 mole) in ethanol (50 mL) containing sodium ethoxide (prepared from 0.25 g, 0.011g atom sodium) was treated with ethyl α-chloroacetoacetate **2** (0.01 mole). The reaction mixture was stirred for 3 h and left overnight at room temperature. The solid obtained was filtered off, washed with water, and then crystallized from ethanol to give yellow crystals of ethyl α-(4-arylidene-2-imidazolin-5-one-2-yl-thio)acetoacetate **3a–c**.

3a, m.p. 178°C, yield 72%, elemental analysis for $C_{16}H_{16}N_2O_4S$, Calcd. C, 57.83; H, 4.82; N, 8.43; S, 9.64; found: C, 57.62; H, 5.14; N, 8.20; S, 9.51; IR (cm^{-1}: 3360 (NH), 1735, 1720, 1690 (3 C=O) and 1640 (C=N).

3b, m.p. 195-6°C, yield 73%, elemental analysis for $C_{17}H_{18}N_2O_5S$, Calcd. C, 56.35; H, 4.97; N, 7.73; S, 8.84; found: C, 56.11; H, 5.23; N, 7.90; S, 8.62; IR (cm^{-1}): 3380 (NH), 1735, 1725, 1700 (3 C=O) and 1640 (C=N).

3c, m.p. 210°C, yield 78%, elemental analysis for $C_{16}H_{15}N_2O_4SCl$, Calcd. C, 52.39; H, 4.09; N, 7.64; S, 8.73; Cl, 9.69; found: C, 52.60; H, 4.31; N, 7.52; S, 8.94; Cl, 9.41; IR (cm^{-1}: 3390 (NH), 1730, 720, 1700 (3 C=O) and 1645 (C=N); and ^{1}H-NMR (δ ppm): 1.9 (t, 3H, $\underline{CH_2}$ CH_3), 2.8 (s, 3H, $COCH_3$), 4.1 (q, 2H, $\underline{CH_2}CH_3$), 4.5 (s, 1H, S-CH), 6.4 (s, 1H, Ar-CH=), 7.2–7.5 (m, 4H, Ar-$\underline{H}$) and 9.1 (s, 1H, NH, exchangeable with D_2O).

Action of Conc. Hydrochloric Acid on 3a

A mixture of **3a** (1 g), ethanol (20 mL), and concentrated hydrochloric acid (8 mL) was refluxed for 2 h. A solid product was obtained. On cooling, the solid was filtered off and crystallized from ethanol to give 5-benzylidene hydantoin **(4)**, [m.p. 220° C, yield 65%], showing no depression in its melting point when admixed with an authentic sample.[13]

Preparation of Ethyl 1-[4-Arylidene-2-imidazolin-5-one-2-yl-thio]-glyoxalate 1-Phenylhydrazones 5a–c

Method (A): From 3a–c with Diazonium Salts

Compounds **3a–c** (0.01 mole) were suspended in 50 mL of ethanol containing 3 g of sodium acetate. The mixture was cooled in an ice bath,

treated with an equimolar amount with benzenediazonium chloride, and left for 1 h and then poured onto cold water. The precipitate formed was collected, dried, and crystallized from ethanol as reddish-brown crystals of **5a–c**.

Method (B): From 1a–c with Ethyl 1-Chloroglyoxalate 1-Phenyl-hydrazone 6

A solution of 5-benzylidene-2-thiohydantoins **1a–c** (0.01 mole) in ethanol (50 mL) containing sodium ethoxide (0.011 mole) was treated with ethyl 1-chloroglyoxalate 1-phenylhydrazone (**6**) (from benzenediazonium chloride, and ethyl α-chloroacetoacetate). The reaction mixture was stirred at room temperature for 3 h and left overnight at room temperature. The solid that was obtained was filtered off and washed with water and then crystallized from ethanol to give **5a–c** (showing no depression in melting points when admixed with samples **5a–c**, prepared as described above).

5a, m.p. 230°C, yield 60%, elemental analysis for $C_{20}H_{18}N_4O_3S$, Calcd. C, 60.91; H, 4.57; N, 14.21; S, 8.12; found: C, 60.67; H, 4.25; N, 14.57; S, 8.00; IR (cm^{-1}: 3380, 3260 (2NH), 1730, 1715 (2 C=O) and 1640 (C=N)[1] H-NMR (δ ppm): 1.7 (t, 3H, CH_2 $\underline{CH_3}$), 4.1 (q, 2H, $\underline{CH_2}CH_3$), 6.2 (s, 1H, Ar-$\underline{CH}$=), 7.2–7.5 (m, 10H, Ar-$\underline{H}$) and 9.8, 11.3 (2s, 2H, 2 NH, exchangeable with D_2O).

5b, m.p. 260°C, yield 62%, elemental analysis for $C_{21}H_{20}N_4O_4S$, Calcd. C, 59.43; H, 4.72; N, 13.21; S, 7.55; found: C, 59.23; H, 4.51; N, 13.05; S, 7.81; IR (cm^{-1}: 3400, 3310 (2NH), 1735, 1720 (2 C=O) and 1635 (C=N).

5c, m.p. 294–295°C, yield 70%, elemental analysis for $C_{20}H_{17}N_4O_3SCl$, Calcd. C, 56.01; H, 3.97; N, 13.06; S, 7.47; Cl, 8.28; found: C, 56.20; H, 4.21; N, 12.84; S, 7.70; Cl, 8.52; IR (cm^{-1}: 3390, 3280 (2NH), 1735, 1720 (2 C=O) and 1640 (C=N).

Preparation of 2-Acetyl-6-arylidene imidazo[2,1-b]-thiazol-3,5-diones 7a–c

A mixture of each of **3a–c** (1 g) and polyphosphoric acid (prepared from 4 g of phosphorus pentoxide and 4 mL of 85% phosphoric acid) was heated on the water bath for 1 h and then in an oil bath (125–130°C) for 30 min. After cooling, the reaction mixture was poured onto ice-cold water and neutralized with potassium carbonate solution. The solid thus obtained was crystallized from ethanol to give deep yellow crystals identified as **7a–c**.

7a, m.p. 235° C, yield 72%, elemental analysis for $C_{14}H_{10}N_2O_3S$, Calcd. C, 58.74; H, 3.49; N, 9.69; S, 11.19; Found: C, 58.56; H, 3.70;

N, 9.61; S, 11.50; IR (cm^{-1}: 1690, 1710, 1720 (3 C=O) and 1635 (C=N) and ^{1}H-NMR (δ ppm): 2.8 (s, 3H, CH_3), 4.4 (s, 1H, SC H), 6.3 (s, 1H, Ar-CH =) and 7.2–7.5 (m, 5H, Ar-H).

7b, m.p. 250°C, yield 70%, elemental analysis for $C_{15}H_{12}N_2O_4S$, Calcd. C, 56.96; H, 3.79; N, 8.86; S, 10.13; Found: C, 56.71; H, 3.64; N, 8.56; S, 9.95; IR (cm^{-1}): 1700, 1715, 1720 (3 C=O) and 1640 (C=N).

7c, m.p. 280°C, yield 75%, elemental analysis for $C_{14}H_9N_2O_3SCl$, Calcd. C, 52.42; H, 2.81; N, 8.74; S, 9.98; Cl, 11.07; found: C, 52.24; H, 3.10; N, 8.53; S, 10.20; Cl, 11.32; IR (cm^{-1}: 1695, 1720, 1725 (3 C=O) and 1645 (C=N).

Reaction of 1a–c with Monochloroacetone

A solution of each of **1a–c** (0.01 mole) in ethanol (50 mL) containing sodium ethoxide (prepared from 0.25 g, 0.011 g atom sodium) were treated with monochloroacetone (0.01 mole). The reaction mixture was stirred for 2 h and was worked up as in of the preparations of **3a–c**. The reaction products were crystallized from ethanol to give yellow crystals of 2-acetonylmercaptohydantoin derivatives **9a–c**.

9a, m.p. 170° C, yield 82%, elemental analysis for $C_{13}H_{12}N_2O_2S$, Calcd. C, 60.00; H, 4.62; N, 10.77; S, 12.31; Found: C, 60.21; H, 4.50; N, 10.93; S, 12.50; IR (cm^{-1}: 3370 (NH), 2950 (saturated CH), 1720, 19695 (2 C=O) and 1640 (C=N) and ^{1} H-NMR (δ ppm): 2.6 (t, 3H, CH_3), 4.1 (s, 2H, S- CH_2), 6.5 (s, 1H, Ar-CH=), 7.2–7.4 (m, 5H, Ar-H) and 8.3 (s, 1H, NH, exchangeable with D_2O).

9b, m.p. 185°C, yield 78%, elemental analysis for $C_{14}H_{14}N_2O_3S$, Calcd. C, 57.93; H, 4.83; N, 9.66; S, 11.03; Found: C, 57.75; H, 4.63; N, 9.46; S, 11.30; IR (cm^{-1}: 3380 (NH), 2960 (saturated CH), 1720, 19695 (2 C=O) and 1645 (C=N).

9c, m.p. 205–206°C, yield 85%, elemental analysis for $C_{13}H_{11}N_2O_2SCl$, Calcd. C, 52.97; H, 3.74; N, 9.51; S, 10.87; Cl, 12.05; Found: C, 53.10; H, 3.82; N, 9.35; S, 10.66; Cl, 12.22; IR (cm^{-1}: 3340 (NH), 2970 (saturated CH), 1725, 1700 (2 C=O) and 1640 (C=N).

Action of Conc. Hydrochloric Acid on 9a

A mixture of **9a** (1 g), ethanol (20 mL), and conc. hydrochloric acid (8 mL) was refluxed for 2 h. The solid product obtained on cooling was filtered off and crystallized from ethanol to give 5-benzylidene-hydantoin (**4**) (m.p. 220°C), yield 65% (showing no depression in melting point when admixed with authentic sample).[13]

Preparation of 6-Arylidene-3-methyl-imidazo[2,1-b]thiazol-5-one Derivatives 10a–c

A mixture of each of **9a–c** (1 g) and polyphosphoric acid (prepared from 4 g of phosphorus pentoxide and 4 mL of 85% phosphoric acid) was heated on the water bath for 1 h and then in an oil bath (125–130°C) for 30 min. The reaction mixture was worked up as in the preparations of **7a–c**. The solid obtained was crystallized from ethanol to give deep yellow crystals identified as **10a–c**.

10a, m.p. 150°C, yield 65%, elemental analysis for $C_{13}H_{10}N_2OS$, Calcd. C, 64.46; H, 4.13; N, 11.57; S, 13.22; found: C, 64.25; H, 4.40; N, 11.42; S, 13.50; IR (cm^{-1}: 2960 (saturated CH), 1720 (C=O) and 1635 (C=N) and ^{1}H-NMR (δ ppm): 2.3 (t, 3H, C$\underline{H}_3$), 6.3, 6.7 (2s, 2H, 2C$\underline{H}$=) and 7.2–7.5 (m, 5H, Ar-H).

10b, m.p. 165°C, yield 72%, elemental analysis for $C_{14}H_{12}N_2O_2S$, Calcd. C, 61.76; H, 4.41; N, 10.29; S, 11.76; Found: C, 61.53; H, 4.70; N, 10.62; S, 12.00; IR (cm^{-1}: 2970 (saturated CH), 1725 (C=O) and 1640 (C=N).

10c, m.p. 175°C, yield 75%, elemental analysis for $C_{13}H_9N_2OSCl$, Calcd. C, 56.42; H, 3.25; N, 10.13; S, 11.57; Cl, 12.84; found: C, 56.70; H, 3.12; N, 9.96; S, 11.73; Cl, 12.50; IR (cm^{-1}): 2980 (saturated CH), 1720 (C=O) and 1645 (C=N).

Action of Benzaldehyde on 9a–c

A solution of each of **9a–c** (0.01 mole) in ethanol (50 mL) containing sodium ethoxide (prepared from 0.25 g, 0.011 g atom sodium) was treated with benzaldehyde (1.1 mole). The reaction mixture was stirred for 3 h and left overnight at room temperature. The solid obtained was filtered off, washed with water, and then crystallized from acetic acid to give brown crystals of cinnamoyl methylmercapto derivatives **11a–c**.

11a, m.p. 280–281°C, yield 70%, elemental analysis for $C_{20}H_16N_2$-O_2S, Calcd. C, 68.97; H, 4.59; N, 8.05; S, 9.19; found: C, 68.66; H, 4.80; N, 8.31; S, 9.50; IR (cm^{-1}: 3360 (NH), 1715, 1690 (2 C=O) and 1640 (C=N) and ^{1} H-NMR (δ ppm): 4.8 (s, 2H, C$\underline{H}_2$), 6.4 (s, 1H, Ar-CH=), 6.6, 6.8 (2d, 2H, COC$\underline{H}$=C$\underline{H}$Ph), 7.2–7.6 (m, 10H, Ar-H) and 9.1 (s, 1H, NH, exchangeable with D_2O).

11b, m.p. > 300°C, yield 72%, elemental analysis for $C_{21}H_{18}N_2O_3S$, Calcd. C, 66.66; H, 4.76; N, 7.41; S, 8.47; found: C, 66.46; H, 4.58; N, 7.70; S, .23; IR (cm^{-1}: 3380 (NH), 1720, 1685 (2 C=O) and 1635 (C=N).

11c, m.p. > 300°C, yield 78%, elemental analysis for C_{20} $H_{15}N_2O_2$-SCl, Calcd. 62.74; H, 3.92; N, 7.32; S, 8.36; Cl, 9.28; Found: C, 62.53;

H, 4.11; N, 7.50; S, 8.13; Cl, 9.65; IR (cm^{-1}): 3410 (NH), 1725, 1690 (2 C=O) and 1645 (C=N).

Action of Benzenediazonium Chloride on 9a–c

A cold solution of benzenediazonium chloride (0.01 mole) (prepared from the equivalent amount of the aniline, HCl and $NaNO_2$) gradually was added to a cold solution of **9a–c** (0.01 mole) dissolved in pyridine (25 mL) for 30 min at 0–5°C. The reaction mixture was stirred in the ice box for 2 h. The solid product that was formed was collected by filtration, washed with water, and then crystallized from ethanol to give red crystals of **12a–c**.

12a, m.p. 280°C, yield 60%, elemental analysis for $C_{19}H_{16}N_4O_2S$, Calcd. C, 62.64; H, 4.39; N, 15.38; S, 8.79; found: C, 62.23; H, 4.15; N, 15.50; S, 8.46; IR (cm^{-1}: 3370 (NH), 1720, 1680 (2 C=O) and 1635 (C=N) and ^{1}H-NMR (δ ppm): 2.7 (s, 3H, COC $\underline{H}_3$), 5.1 (s, 1H, C$\underline{H}$), 6.3 (s, 1H, Ar-CH=), 7.2–7.6 (m, 10H, Ar-H) and 9.5 (s, 1H, NH, exchangeable with D $_2$O).

12b, m.p. 230°C, yield 68%, elemental analysis for $C_{20}H_{18}N_4O_3S$, Calcd. C, 60.91; H, 4.57; N, 14.21; S, 8.12; found: C, 61.20; H, 4.35; N, 14.00; S, 8.40; IR (cm^{-1}: 3380 (NH), 1725, 1690 (2 C=O) and 1640 (C=N).

12c, m.p. 298°C, yield 71%, elemental analysis for $C_{19}H_{15}N_4O_2SCl$, Calcd. C, 57.21; H, 3.76; N, 14.05; S, 8.03; Cl, 8.91; found: C, 57.50; H, 3.46; N, 14.03; S, 7.79; Cl, 9.20; IR (cm^{-1}: 3390 (NH), 1725, 1695 (2 C=O) and 1640 (C=N).

Reaction of 1a–c with Ethylenebromide and/or α,α'-Dichloroacetone

A solution of each of **1a–c** (0.01 mole) in ethanol (50 mL) containing sodium ethoxide (prepared from 0.25 g, 0.011 g atom sodium) was treated with each of ethylene bromide and/or α,α'-dichloroacetone (0.01 mole). The reaction mixture was stirred for 5 h and worked up as was the preparations of **3a–c**. The reaction products were crystallized from ethanol to give yellow crystals of alkylmercapto derivatives **13a–c** and/or brown crystals of alkylmercapto derivatives **14a–c** (cf. Table I).

Action of Conc. Hydrochloric Acid on Each of 13a and 14a: Preparation of 2-Alkyl Mercaptohydantoin Derivatives 13a–c and 14a–c

A solution of **13a** and/or **14a** (1 g), ethanol (20 mL) and conc. hydrochloric acid (8 mL) was refluxed for 2 h. The solid product

TABLE I 2-Alkylmercaptohydantoin Derivatives 13a–c and 14a–c

Comp.	M.P. (°C)	Yield (%)	Mol. formula	% Analysis calcd./found C	H	N	S	Cl	Br	IR $(cm)^{-1}$
13a*	190	64	$C_{12}H_{11}N_2OSBr$	46.30	3.53	9.00	10.29	—	25.72	3380 (NH), 2960 (saturated CH),
				46.53	3.70	9.31	10.05	—	25.56	1715 (C=O) and 1635 (C=N)
13b	205	63	$C_{13}H_{13}N_2O_2SBr$	48.00	4.00	8.61	9.85	—	24.62	3400 (NH), 2970 (saturated CH),
				48.24	4.11	8.46	9.62	—	24.90	1720 (C=O) and 1640 (C=N)
13c	225	70	$C_{12}H_{10}N_2OSClBr$	41.68	2.89	8.12	9.26	10.27	23.15	3410 (NH), 2970 (saturated CH),
				41.80	2.63	8.06	9.50	10.15	23.41	1725 (C=O) and 1640 (C=N)
14a**	190	75	$C_{13}H_{11}N_2O_2SCl$	52.97	3.74	9.50	10.86	12.05	—	3370 (NH), 2960 (saturated CH),
				52.65	3.54	9.80	10.61	12.30	—	1725, 1715 (C=O) and 1640 (C=N)
14b	210–11	72	$C_{14}H_{13}N_2O_3SCl$	51.77	4.00	8.63	9.86	10.94	—	3385 (NH), 2970 (saturated CH),
				51.91	4.30	8.46	9.65	11.20	—	1715, 1720 (2 C=O) and 1635 (C=N)
14c	240	77	$C_{13}H_{10}N_2O_2SCl_2$	47.41	3.03	8.51	9.72	21.58	—	4050 (NH), 2950 (saturated CH),
				47.70	3.21	8.23	9.54	21.26	—	1725, 1710 (2 C=O) and 1645 (C=N)

^{1}H-NMR (δ ppm): *4.1, 4.4 (2t, 4H, SC$\underline{H}_2$-C$\underline{H}_2$Br), 6.2 (s, 1H, Ar-C$\underline{H}$=), 7.2–7.5 (m, 5H, Ar-$\underline{H}$) and 8.7 (s, 1H, N$\underline{H}$, exchangeable with D_2O).

**4.3, 5.4 (2s, 4H, SC$\underline{H}_2$-COC$\underline{H}_2$Cl), 6.2 (s, 1H, Ar-C$\underline{H}$=), 7.2–7.5 (m, 5H, Ar-$\underline{H}$) and 9.1 (s, 1H, N$\underline{H}$, exchangeable with D_2O).

obtained on cooling was filtered off and crystallized from ethanol to give 5-benzylidenehydantoin **(4)** [m.p. 220°C (yield 65%)] showing no depression in melting point when admixed with an authentic sample.[13]

Action of Polyphosphoric Acid on 13a–c and 14a–c: Preparation of Imidazo[2,1-b]thiazole Derivatives 15a–c and Imidazo-[2,1-b]thiazine Derivatives 16a–c

A mixture of each of **13a–c** and/or **14a–c** (1 g) and polyphosphoric acid (prepared from 4 g of phosphorus pentoxide and 4 mL of 85% phosphoric acid) was heated on the water bath for 1 h and then in an oil bath (125–130°C) for 30 min. The reaction mixture was worked up as was the preparations of **7a–c**. The solid obtained was crystallized from ethanol to give deep yellow crystals identified as imidazo[2,1-b]thiazole derivatives **15a–c** and/or deep brown crystals of imidazo[2,1- b]thiazine derivatives **16a–c** (cf. Table II).

Preparation of 2-Ylidene Imidazo[2,1-b]quinazoline-3,5-diones 19a,b

A mixture of 0.01 mole of each of 5-ylidene-2-methylmercaptohydantoins **17a**,**b**[16] (0.01 mole) and anthranilic acid (0.01 mole) was heated in ethanol (50 mL). During the reaction, the odor of the evolved methanethiol easily could be detected. The heating was continued until the odor of CH_3SH ceased (for 5 h). The reaction mixture was left to cool at room temperature. The crystalline substances were separated and crystallized from acetic acid as brown crystals of **19a,b**.

19a, m.p. 220°C, yield 70%, elemental analysis for $C_{15}H_9N_3O_3$, Calcd. C, 64.52; H, 3.23; N, 15.05; found: C, 64.60; H, 3.52; N, 15.21; IR (cm^{-1}): 3330 (NH), 1725, 1690 (2 C=O) and 1645 (C=N).

19b, m.p. 280–281°C, yield 72%, elemental analysis for $C_{15}H_9N_3O_2S$, Calcd. C, 61.02; H, 3.05; N, 14.24; S, 10.85; found: C, 61.31; H, 3.20; N, 14.22; S, 11.00; IR (cm^{-1}: 3305 (NH), 1720, 1685 (2 C=O) and 1640 (C=N) and ^{1}H-NMR (δ ppm): 6.2 (s, 1H, Ar-CH=), 6.6–6.9 (m, 3H, thiophene H-3, H-4 and H-5), 7.2–7.5 (m, 4H, Ar-H) and 11.1 (s, 1H, NH, exchangeable with D_2O).

Preparation of 1-Phenyl-3-ylideneimidazo[2,1-b]quinazoline-2,5-diones 21a,b

A mixture of 0.01 mole of each of 5-ylidene-2-methylmercaptohydantoins **17c**,**d** (0.01 mole) and anthranilic acid (0.01 mole) was heated in ethanol (50 mL). During the reaction, the odor of the evolved

TABLE II Imidazo[2,1-b]thiazole Derivatives 15a–c and Imidazo[2,1-b]thiazine Derivatives 16a–c

Comp.	M.P. (°C)	Yield (%)	Mol.formula	% Analysis calcd./found C	H	N	S	Cl	IR $(cm)^{-1}$
15a	240	60	$C_{12}H_{10}N_2OS$	62.60	4.35	12.17	13.91	—	2950 (saturated CH), 1715 (C=O) and
				62.80	4.61	12.40	13.75	—	1630 (C=N)
15b*	290	63	$C_{13}H_{12}N_2O_2S$	60.00	4.62	10.76	12.31	—	2950 (saturated CH), 1725 (C=O) and
				60.21	4.80	10.56	12.64	—	1640 (C=N)
15c	>300	70	$C_{12}H_9N_2OSCl$	54.44	3.40	10.59	12.09	13.42	2970 (saturated CH), 1720 (C=O) and
				54.23	3.62	10.80	12.31	13.25	1640 (C=N)
16a	225	70	$C_{13}H_{10}N_2O_2S$	60.46	3.87	10.85	12.40	—	2950 (saturated CH), 1715, 1700 (2
				60.24	4.11	10.60	12.13	—	C=0) and 1635 (C=N)
16b**	250	70	$C_{14}H_{12}N_2O_3S$	58.33	4.16	9.72	11.12	—	2965 (saturated CH), 1720, 1700 (2
				58.50	4.42	9.49	10.87	—	C=0) and 1640 (C=N)
16c	>300	75	$C_{13}H_9N_2O_2SCl$	53.33	3.07	9.57	10.90	12.13	2960 (saturated CH), 1720, 1695 (2
				53.10	3.31	9.80	11.23	12.50	C=0) and 1645 (C=N)

^{1}H-NMR(δ ppm): *3.9(s, 3H, $OC\underline{H}_3$), 4.2, 4.6 (2t, 4H, $S\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}N$), 6.4 (s, 1H, AR-C<u>H</u>=) and 7.2–7.6 (m, 4H, AR-<u>H</u>).
**3.8 (s, 3H, $OC\underline{H}_3$), 4.2, 4.7 (2s, 2H, $2C\underline{H}_2$, 6.3 (s, 1H, AR-C<u>H</u>=) and 7.3–7.5 (m, 4H, AR-<u>H</u>).

methanethio easily could be detected. The reaction was worked up as previously described, and the solid obtained was crystallized from ethanol as brown crystals of **21a**,**b**.

21a, m.p. 296°C, yield 70%, elemental analysis for C_{21} $H_{13}N_3O_3$, Calcd. C, 70.98; H, 3.66; N, 11.83; Found: C, 70.76; H, 3.54; N, 14.00; IR (cm^{-1}): 1720, 1685 (2 C=O) and 1640 (C=N) and ^{1}H-NMR (δ ppm): 6.1 (s, 1H, CH=), 6.7–7.0 (m, 3H, thiophene H-3, H-4, and H-5) and 7.2–7.6 (m, 9H, Ar-H).

21b, m.p. 292°C, yield 72%, elemental analysis for $C_{21}H_{13}N_3O_2S$, Calcd. C, 67.92; H, 3.50; N, 11.32; S, 8.63; found: C, 68.10; H, 3.37; N, 11.14; S, 8.52; IR (cm^{-1}: 1715, 1690 (2 C=O) and 1635 (C=N).

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