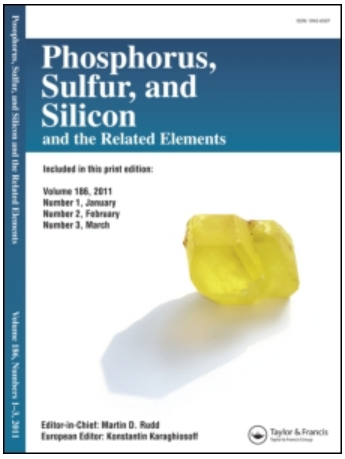



**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# γ-BROMOACETOACETANILIDES IN HETEROCYCLIC SYNTHESIS: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2,3-DIHYDROTHIAZOLE, PYRIDIN-2-ONE, 1,2,3-TRIAZINE, OXAZOLO[3,4-b]PYRIDINE AND PYRAZOLO[3,4-b]PYRIDINE DERIVATIVES

Rafat M. Mohareb[a]; Nadia I. Abdel-sayed[b]; Sherif M. Sherif[a]
[a] Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt [b] Chemistry Department, College for Girls, Ain Shams University, Heliopolis, Cairo, A. R. Egypt

**To cite this Article** Mohareb, Rafat M. , Abdel-sayed, Nadia I. and Sherif, Sherif M.(1991) 'γ-BROMOACETOACETANILIDES IN HETEROCYCLIC SYNTHESIS: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2,3-DIHYDROTHIAZOLE, PYRIDIN-2-ONE, 1,2,3-TRIAZINE, OXAZOLO[3,4-b]PYRIDINE AND PYRAZOLO[3,4-b]PYRIDINE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 63: 1, 119 — 129
**To link to this Article: DOI:** 10.1080/10426509108029435
**URL:** http://dx.doi.org/10.1080/10426509108029435

*Phosphorus, Sulfur, and Silicon*, 1991, Vol. 63, pp. 119–129
Reprints available directly from the publisher
Photocopying permitted by license only



# γ-BROMOACETOACETANILIDES IN HETEROCYCLIC SYNTHESIS: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2,3-DIHYDROTHIAZOLE, PYRIDIN-2-ONE, 1,2,3-TRIAZINE, OXAZOLO[3,4-b]PYRIDINE AND PYRAZOLO[3,4-b]PYRIDINE DERIVATIVES

RAFAT M. MOHAREB,*[a] NADIA I. ABDEL-SAYED[b] and SHERIF M. SHERIF[a]

[a]*Chemistry Department, Faculty of Science, Cairo University, Giza, A.R. Egypt;*
[b]*Chemistry Department, College for Girls, Ain Shams University, Heliopolis, Cairo, A.R. Egypt*

*(Received March 15, 1991; in final form May 21, 1991)*

The active methylene reagents **1a–d** reacted with phenyl isothiocyanate in basic DMF at room temperature to yield the non-isolable 1:1 adducts **2a–d**. In-situ cyclization of the latter with γ-bromoacetoacetanilides afforded the 2,3-dihydrothiazoles **3a–h**. The reactivity of **3a** towards a variety of chemical reagents has been undertaken. Thus, on smooth alkaline hydrolysis, with benzaldehyde and with benzenediazonium chloride, the thiazole derivatives **4**, **5**, **7** and **9** were obtained. With acetylacetone, malononitrile, ethyl cyanoacetate and cinnamonitriles it gave the corresponding thiazol-4-yl-pyridine derivatives **10**, **11**, **12**, and **13** respectively. **13** Reacted with hydroxylamine hydrochloride and phenyl hydrazine to give the corresponding fused ring systems **15** and **17** respectively.

*Key words:* Thiazole; pyridine; triazine; thiazolylpyridine.

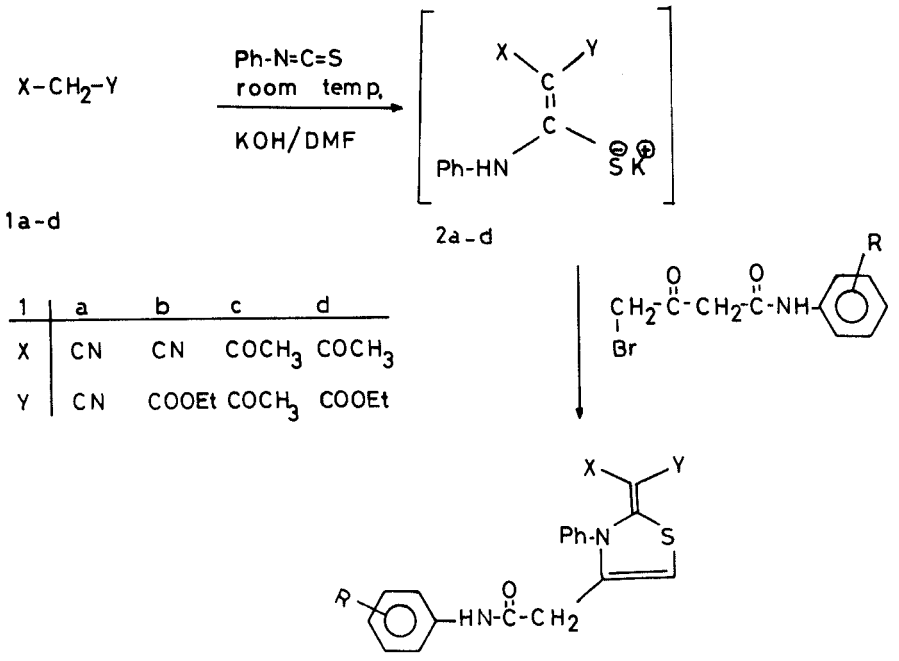


## INTRODUCTION

In the last few years we were involved in a programme aiming to developing convenient synthetic routes for polyfunctionally substituted heterocycles utilizing readily obtainable α-haloacetophenones,[1] α-haloketoximes,[2] α-ketohydrazidoyl bromides[3] and β-ketoanilides[4] as starting materials. In conjunction of our work, we wish now to make use of the Hantzsch reaction[5–8] for the synthesis of thiazoles, 2,3-dihydrothiazoles and thiazolidines to evaluate the synthetic potentialities of α-halo-β-ketoanilides in heterocyclic synthesis. The work has resulted in the development of convenient approaches for the synthesis of 2,3-dihydrothiazole, pyridin-2-one, 1,2,4-triazine, oxazolo[3,4-b]pyridine derivatives which have been shown to exhibit antiprotozoal,[9] antiviral,[10] bactericidal[11] and fungicidal properties.[12]

## RESULTS AND DISCUSSION

Thus in our laboratories, the base promoted reaction of the active methylene compounds **1a–d** with equimolar amounts of phenyl isothiocyanate in dry DMF at room temperature afforded the nonisolable intermediates **2a–d**. The latter undergoes in situ cyclization on treatment with γ-bromoacetoacetanilides[13] to yield exclusively the corresponding 2,3-dihydrothiazole derivatives **3a–h** in good yields (Chart 1). The identity of the product in each case was established on the basis of




| 1 | a | b | c | d |
|---|---|---|---|---|
| X | CN | CN | $COCH_3$ | $COCH_3$ |
| Y | CN | COOEt | $COCH_3$ | COOEt |

3a-h

| 3 | a | b | c | d | e | f | g | h |
|---|---|---|---|---|---|---|---|---|
| X | CN | CN | CN | CN | $COCH_3$ | $COCH_3$ | $COCH_3$ | $COCH_3$ |
| Y | CN | CN | COOEt | COOEt | $COCH_3$ | $COCH_3$ | COOEt | COOEt |
| R | H | p-$CH_3$ | H | p-$CH_3$ | H | p-$CH_3$ | H | p-$CH_3$ |

CHART 1

analytical and spectral data. Thus, e.g. the Ms spectrum of **3a** revealed a molecular formula $C_{20}H_{14}N_4OS$ ($M^+/e$ = 358). Its I.r. spectrum revealed two CN bands at $\bar{\nu}$ = 2220, 2210 $cm^{-1}$ and only one carbonyl function at $\bar{\nu}$ = 1680 $cm^{-1}$. Moreover, its $H^1$-n.m.r. spectrum showed a singlet signal (1H) at $\delta$ = 6.74 ppm characteristic of the 2,3-dihydrothiazole 5-H and only one broad signal (1H) at $\delta$ = 9.35 ppm for the NH group ($D_2O$ exchangeable). The formation of **3a** proceeds via loss of a KBr and a water molecule.

Next, we moved to investigate the chemical behaviour of **3a** towards a variety of chemical reagents and its use as a precursor for a variety of heterocyclic and fused heterocyclic ring systems (Chart 2). Thus, the smooth base catalysed hydrolysis of **3a** afforded the corresponding 4-carboxymethyleno-2,3-dihydrothiazole derivative **4**, which could be titrated against sodium hydrogen carbonate solution, implying that it contains a carboxylic group.

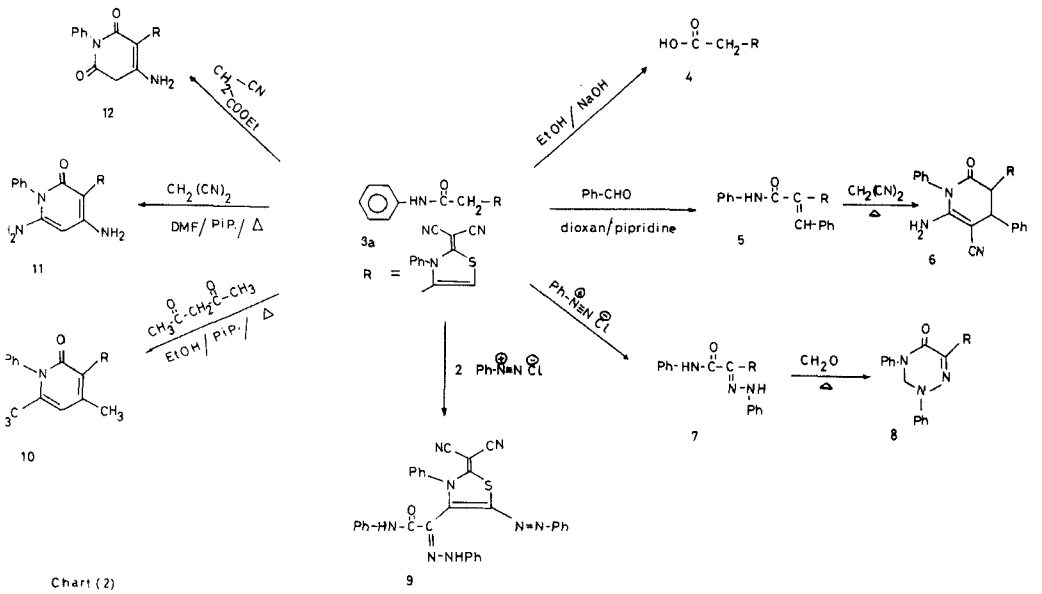


CHART 2

Condensation of **3a** with equimolar amount of benzaldehyde in refluxing dioxane-piperidine solution furnished the corresponding benzylidene derivative **5** (Chart 2). The latter cyclized to the corresponding pyridin-2-one derivative **6** on refluxing with malononitrile in ethanolic-piperidine solution. Formation of **6** is assumed to proceed via anticipated Michael addition of malononitrile to the benzylidene moiety in **5** followed by in-situ cyclization. Both elemental and spectral data of **5** and **6** are consistent with the assigned structures (cf. Tables I and II). Coupling of **3a** with equimolar amount of benzenediazonium chloride in cold ethanolic sodium acetate solution afforded the corresponding phenylhydrazone **7**. The other possible coupling reaction of the thiazole **5-H** was excluded based on the spectral data. Thus, the $^1$H-n.m.r. spectrum of the reaction product revealed the absence of the $CH_2$ singlet signal and the presence of a singlet (1H) at $\delta$ = 6.86 ppm characteristic for the 2,3-dihydrothiazole **5-H**. Refluxing **7** with ethanolic formaldehyde solution effected cyclization to yield the corresponding 1,2,4-triazine derivative **8**, a synthetic route well documented for the synthesis of as-triazine ring systems.[14] On the other hand, coupling of **3a** with two equivalents of benzenediazonium chloride afforded the corresponding 5-phenylazo-4-phenylazomethano-2,3-dihydrothiazole derivative **9**. To our knowledge, the formation of a 5-(arylazo)-2,3-dihydrothiazole derivative has not yet been reported in literature.[15–17] Thus, the preparation of **9** is presumed to be the first example so far.

When **3a** was treated with acetylacetone in ethanol in the presence of a catalytic amount of piperidine, the corresponding 3-(2′,3′-dihydrothiazol-4′-yl)-pyridin-2-one derivative **10** was obtained.

Also, the pyridin-2-one derivative **11** was isolated when **3a** was reacted with malononitrile in refluxing DMF in the presence of a catalytic amount of piperidine. Similarly, treatment of **3a** with ethyl cyanoacetate under the same experimental conditions afforded the corresponding 4-amino-3-(thiazol-4′-yl)-pyridin-2,6-dione

derivative **12**. The structures assigned to the products **11** and **12** are based on analytical and spectral data (cf. Tables I and II).

Compound **12** condensed with equimolar amount of benzaldehyde in refluxing ethanol containing a catalytic amount of piperidine to give the corresponding 5-benzylidene-pyridin-2,6-dione derivative **13** (Chart 3). Alternatively, the reaction of **3a** with benzylidenemalononitrile or ethyl benzylidenecyanoacetate under the same conditions furnished a single product which is identical in all respects with **13** (m.p., mixed m.p. and I.r. spectrum).

Treatment of **13** with hydroxylamine hydrochloride in refluxing ethanolic-potassium hydroxide solution for **1h** afforded a single product of molecular formula $C_{30}H_{18}N_6O_2S$. Two possible isomeric structures were proposed, **14** and **15**. The oxazolo[3,4-b]pyridin-2-one derivative structure **15** is assigned for the reaction product based on its synthesis through another reaction route. Thus, reaction of **12** with hydroxylamine hydrochloride afforded the oxime **16**. The latter reacts with benzaldehyde to afford the same product **15** (identical m.p. and mixed m.p.). The formation of **15** from **13** is assumed to proceed via oxidation of the expected reaction product under the reaction conditions. Similar oxidations have been previously reported by us[18] and by another group.[19] These findings promoted us to investigate the reaction of **13** with other amine derivatives. Thus, with phenyl hydrazine in refluxing ethanol, the pyrazolo[3,4-b]-pyridin-6-one derivative **17** is formed not the



TABLE I

Physical and analytical data of the newly prepared compounds

| Compd. (colour) | solvent | m.p. (°C) | yield (%) | Mol.formula (M.wt.) | Analysis (Calcd./Found) % C | H | N |
|---|---|---|---|---|---|---|---|
| 3a (yellow) | EtOH | 214 | 79 | $C_{20}H_{14}N_4OS$ (358.40) ($M^+$/e=358) | 67.02<br>67.00 | 3.93<br>3.78 | 15.63<br>15.19 |
| 3b (orange) | AcOH | 240 | 82 | $C_{21}H_{16}N_4OS$ (372.43) | 67.72<br>67.65 | 4.32<br>4.00 | 15.04<br>14.69 |
| 3c (pale yellow) | EtOH | 185 | 80 | $C_{22}H_{19}N_3O_3S$ (405.45) ($M^+$=405) | 65.17<br>64.82 | 4.71<br>4.50 | 10.36<br>10.00 |
| 3d (yellow) | EtOH | 212 | 68 | $C_{23}H_{21}N_3O_3S$ (419.48) | 65.85<br>65.59 | 5.04<br>4.61 | 10.02<br>9.82 |
| 3e (yellow) | EtOH | 140 | 75 | $C_{22}H_{20}N_2O_3S$ (392.45) ($M^+$/e=392) | 67.33<br>67.00 | 5.13<br>4.82 | 7.13<br>7.00 |
| 3f (yellow) | EtOH | 209 | 88 | $C_{23}H_{22}N_2O_3S$ (406.48) | 67.96<br>67.69 | 5.45<br>5.02 | 6.89<br>6.63 |
| 3g (orange) | EtOH | 140 | 82 | $C_{23}H_{22}N_2O_4S$ (422.48) | 65.38<br>65.00 | 5.24<br>4.96 | 6.63<br>6.44 |

TABLE I (*Continued*)

| Compd. (colour) | solvent | m.p. (°C) | yield (%) | Mol.formula (M.wt.) | Analysis (Calcd./Found) % C | H | N |
|---|---|---|---|---|---|---|---|
| 3h (orange) | EtOH | 199 | 78 | $C_{24}H_{24}N_2O_4S$ (436.50) | 66.03 65.88 | 5.53 5.39 | 6.41 6.35 |
| 4 (yellow) | DMF | >300 | 64 | $C_{14}H_9N_3O_2S$ (283.29) | 59.35 59.21 | 3.19 3.00 | 14.83 14.61 |
| 5 (orange) | DMF | >300 | 69 | $C_{27}H_{18}N_4OS$ (446.51) | 72.62 72.49 | 4.06 4.00 | 12.54 12.46 |
| 6 (orange) | DMF | >300 | 62 | $C_{30}H_{20}N_6OS$ (512.57) | 70.29 70.13 | 3.92 3.77 | 16.39 16.31 |
| 7 (orange) | DMF | >300 | 79 | $C_{26}H_{18}N_6OS$ (462.51) | 67.52 67.39 | 3.92 3.85 | 18.16 17.86 |
| 8 (yellow) | DMF | >300 | 66 | $C_{27}H_{18}N_6OS$ (474.52) | 68.34 68.19 | 3.82 3.66 | 17.71 17.70 |
| 9 (yellow) | EtOH | 186 | 75 | $C_{32}H_{22}N_8OS$ (566.62) ($M^+$/e=566) | 67.83 67.75 | 3.90 3.77 | 19.77 19.58 |
| 10 (yellow) | DMF | >300 | 71 | $C_{25}H_{18}N_4OS$ (422.48) | 71.07 70.85 | 4.29 4.00 | 13.26 12.95 |
| 11 (orange) | EtOH | 266 | 83 | $C_{23}H_{16}N_6OS$ (424.46) | 65.08 64.85 | 3.79 3.51 | 19.79 19.61 |
| 12 (orange) | EtOH | 231 | 78 | $C_{23}H_{15}N_5O_2S$ (425.45) | 64.93 64.85 | 3.55 3.39 | 16.46 16.37 |
| 13 (orange) | AcOH | 283 | 72[a] 57[b] | $C_{30}H_{19}N_5O_2S$ (513.55) | 70.16 70.00 | 3.72 3.69 | 13.63 13.60 |
| 15 (orange) | DMF | >300 | 69[c] 73[d] | $C_{30}H_{18}N_6O_2S$ (526.55) | 68.43 68.35 | 3.44 3.02 | 15.96 15.89 |
| 16 (yellow) | dioxane | >300 | 81 | $C_{23}H_{16}N_6O_2S$ (440.25) | 62.70 62.30 | 3.66 3.31 | 19.10 18.87 |
| 17 (orange) | DMF | >300 | 69[e] 70[f] 83[g] | $C_{36}H_{23}N_7OS$ (601.66) | 71.86 71.75 | 3.85 3.81 | 16.29 16.00 |
| 19 (yellow) | EtOH | 221 | 82 | $C_{29}H_{21}N_7OS$ (515.31) | 67.54 67.31 | 4.10 4.32 | 19.03 18.72 |

a) yield from 3a; b) yield from 12; c) yield from 13; d) yield from 16; e) yield from 13; f) yield from 17; g) yield from 19.

TABLE II

I.r. and $^1$H-n.m.r. data of the newly prepared compounds

| Compd. No. | I.r $\bar{\nu}$cm$^{-1}$ selected bands | $^1$H-n.m.r ($\delta$ ppm) |
|---|---|---|
| 3a | 3450-3300 (NH), 3050 (CH aromatic), 2890 ($CH_2$, 2220, 2210 (2 CN), 1680 (CO), 1630 (C=C). | 4.52 (s, 2H, $CH_2$), 6.74 (s,1H, thiazole 5-H), 7.36-7.58 (m, 10H, aromatic protons), 9.35 (s, br, 1H, NH). |
| 3b | 3450-3330 (NH), 3050 (CH aromatic), 2980, 2890 ($CH_2$, $CH_3$), 2220, 2210 (2 CN), 1680 (CO), 1630 (C=C). | 1.41 (s, 3H, $CH_3$), 4.55 (s, 2H, $CH_2$), 6.89 (s, 1H, thiazole 5-H), 7.28-7.49 (s, 9H, aromatic protons), 9.41 (s, br, 1H,NH). |
| 3c | 3450-3250 (NH), 3040 (CH aromatic), 2980, 2895 ($CH_2$, $CH_3$), 2220 (CN), 1710, 1680 (2 CO), 1630 (C=C). | 1.63 (t, 3H, J=8.1 Hz, $CH_3$), 4.22 (s, 2H, $CH_2$), 4.45 (q, 2H, J=6.0 Hz, $CH_2$), 6.91 (s, 1H, thiazole 5-H), 7.32-7.75 (m, 10H, aromatic protons), 10.59 (s, br, 1H, NH). |
| 3d | 3450-3350 (NH), 3050 (CH aromatic), 2980, 2890 ($CH_2$, $CH_3$), 2220 (CN), 1710, 1690 (2 CO), 1630 (C=C). | 1.51 (s, 3H, $CH_3$), 1.64 (t,3H, J=8.3 Hz, $CH_3$), 4.29 (s, 2H, $CH_2$), 4.44 (q, 2H, J=6.2 Hz, $CH_2$), 6.84 (s, 1H, thiazole 5-H), 7.31-7.55 (m, 9H, aromatic protons), 10.81 (s, br, 1H,NH). |
| 3e | 3450-3330 (NH), 3040 (CH aromatic), 2980, 2895 ($CH_2$, $CH_3$), 1710, 1690, 1680 (3 CO), 1630 (C=C). | 1.62, 2.32 (2s, 6H, $2CH_3$),4.29 (s, 2H, $CH_2$), 6.81 (s, 1H,thiazole 5-H), 7.28-7.38 (m, 10H, aromatic protons), 10.31 (s,br, 1H, NH). |
| 3f | 3450-3350 (NH), 3040 (CH aromatic), 2980,2890 ($CH_2$, $CH_3$), 1710, 1700, 1680 (3 CO), 1630 (C=C). | 1.69,2.22,2.38 (3s, 9H, $3CH_3$), 4.23 (s, 2H, $CH_2$), 6.79 (s,1H, thiazole 5-H), 7.31-7.42 (m,9H, aromtaic protons), 9.91 (s,br, 1H, NH). |
| 3g | 3400-3350 (NH), 3050 (CH aromatic), 2980, 2895 ($CH_2$, $CH_3$), 1720, 1700, 1680 (3 CO), 1630 (C=C). | 1.52 (s, 3H, $CH_3$), 1.69 (t, 3H, J=8.0 Hz, $CH_3$), 4.25 (s, 2H, $CH_2$), 4.50 (q, 2H, J=6.1 Hz, $CH_2$), 6.88 (s, 1H, thiazole 5-H), 7.36-7.61 (m, 10H, aromatic protons), 10.58 (s, br, 1H, NH). |
| 3h | 3450-3350 (NH), 3050 (CH aromatic), 2985,2890 ($CH_2$, $CH_3$), 1720,1710,1680 (3 CO) 1630 (C=C). | 1.59, 1.63 (2s, 6H, $2CH_3$), 1.68 (t, 3H, J=8.2 Hz, $CH_3$), 4.22 (s, 2H, $CH_2$), 4.65 (q, 2H, J=6.3 Hz, $CH_2$), 6.82 (s, 1H, thiazole 5-H), 7.30-7.52 (m, 9H, aromatic protons), 10.21 (s, br, 1H, NH). |

TABLE II (*Continued*)

| Comd. No. | I.r $\bar{\nu}$cm$^{-1}$ selected bands | $^1$H-n.m.r ($\delta$ ppm) |
|---|---|---|
| 4 | 3620-3450 (OH), 3050 (CH aromatic), 2900 ($CH_2$), 2225 2210 (2 CN), 1700 (CO),1630 (C=C). | 4.43 (s, 2H, $CH_2$), 6.89 (s, 1H, thiazole 5-H), 7.30-7.35 (m, 5H, aromatic protons), 11.44 (s, 1H, COOH). |
| 5 | 3450-3350 (NH), 3050 (CH aromatic), 2220, 2210 (2CN) 1690 (CO), 1630 (C=C). | 6.89 (s, 1H, thiazole 5-H), 7.30 7.38 (m, 16H, ylidene CH and aromatic protons), 10.23 (s,br,1H,NH). |
| 6 | 3445-3300 ($NH_2$), 3050 (CH aromatic), 2225,2215,2200 (3 CN), 1690 (CO), 1650 (C=C). | 4.21 (d, 1H, pyridine 3-H), 4.45 (s, 2H, $NH_2$), 5.28 (d, 1H, pyridine 4-H), 6.87 (s, 1H, thiazole 5-H), 7.29-7.38 (m,15H,aromatic protons). |
| 7 | 3450-3320 (2 NH), 3050 (CH aromatic), 2220, 2200 (2CN), 1680 (CO), 1630 (C=C). | 6.86 (s, 1H, thiazole 5-H), 7.31-7.39 (m, 15H, aromatic protons), 10.12, 10.45 (2s,br,2H, 2NH). |
| 8 | 3040 (CH aromatic), 2900 ($CH_2$), 2220, 2200 (2 CN), 1700 (CO), 1630 (C=C). | 5.51 (s, 2H, $CH_2$), 6.89 (s, 1H, thiazole 5-H), 7.28-7.37 (m,15H, aromatic protons). |
| 9 | 3450-3320 (2 NH), 3040 (CH aromatic), 2220,2210 (2 CN), 1690 (CO), 1630 (C=C). | 7.31-7.42 (m, 20H, aromatic protons) 10.21,10.51 (2S,br,2H, 2NH). |
| 10 | 3100 (CH aromatic), 2950, 2880 ($CH_3$), 2220, 2200 (2 CN) 1700 (CO), 1630 (C=C). | 2.41, 2.53 (2s, 6H, $2CH_3$), 6.85 (s, 1H, thiazole 5-H), 7.31-7.92 (m, 11H, pyridine 5-H and aromatic protons). |
| 11 | 3450-3320 (2 $NH_2$), 3100 (CH aromatic), 2220, 2210 (2 CN), 1700 (CO), 1630 (C=C). | 4.45, 5.01 (2s, 4H, 2 $NH_2$), 6.90 (s, 1H, thiazole 5-H), 7.31-7.63 (m, 11H, pyridine 5-H and aromatic protons). |
| 12 | 3450-3300 (2 $NH_2$), 3040 (CH aromatic), 2220, 2210 (2 CN), 1700,1690 (2 CO),1630 (C=C) | 3.51 (s, 2H, $CH_2$), 5.29 (s, 2H,$NH_2$), 6.81 (s, 1H, thiazole 5-H), 7.29-7.38 (m, 10H, aromatic protons). |
| 13 | 3450-3300 ($NH_2$), 3050 (CH aromatic), 2220,2200 (2 CN), 1700, 1690 (2 CO), 1640 (C=C). | 5.43 (s, 2H, $NH_2$), 6.87 (s, 1H,thiazole 5-H), 7.31-7.49 (m, 16H, ylidene and aromatic protons). |
| 15 | 3480-3340 ($NH_2$), 3050 (CH aromatic), 2220, 2210 (2 CN), 1700 (CO), 1630 (C=C). | 4.45 (s, 2H, $NH_2$), 6.89 (s, 1H, thiazole 5-H), 7.30-7.38 (m, 15H, aromatic protons). |
| 16 | 3580-3330 (OH, $NH_2$), 3050 (CH aromatic), 2225,2220 (2 CN), 1700 (C=O), 1660 (C=N). | 3.81 (s, 2H, $CH_2$), 5.31 (s, 2H,$NH_2$), 6.90 (s, 1H, thiazole 5-H), 7.30-7.37 (m, 10H, aromatic protons), 10.21 (s, br, 1H, OH). |

TABLE II (*Continued*)

| Compd. No. | I.r $\bar{\nu}_{cm^{-1}}$ selected bands | $^1$H-n.m.r ($\delta$ ppm) |
|---|---|---|
| 17 | 3450-3300 ($NH_2$), 3040 (CH aromatic), 2220,2210 (2 CN), 1700 (CO), 1640 (C=C). | 4.46 (s, 2H, $NH_2$), 6.81 (s, 1H,thiazole 5-H), 7.30-7.41 (m, 20H, aromatic protons). |
| 19 | 3450-3300 ($NH_2$, NH), 3045 (CH aromatic), 2225,2220 (2 CN), 1700 (C=O), 1650 (C=N). | 3.69 (s, 2H, $CH_2$), 5.23 (s,2H,$NH_2$), 6.87 (s, 1H, thiazole 5-H), 7.33-7.39 (m,15H,aromatic protons), 8.37 (s,br, 1H, NH). |

isomeric structure **18**. The formation of **17** as the reaction product is established also via its synthesis from **12**. Thus, **12** reacted with phenyl hydrazine to afford the hydrazone derivative **19**, the latter reacted with benzaldehyde to afford the same product **17** (identical m.p. and mixed m.p.). Again, the reaction of **15** with aniline in refluxing acetic acid in the presence of ammonium acetate afforded a single product which is identical in all respects with **17** (m.p., mixed m.p. and I.r. spectrum). A reasonable mechanism for the formation of **17** from **15** can be illustrated by considering N—O bond ring cleavage followed by aniline reaction to produce the non-isolable phenylhydrazo intermediate **20** and in-situ recyclization via water elimination (c.f. Chart 3).



## EXPERIMENTAL

All melting points are uncorrected. I.r. spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. $^1$H-n.m.r. spectra were recorded on a Varian EM-390 MHZ spectrometer with DMSO as solvent and TMS as internal reference. Chemical shifts are expressed as $\delta$ units (ppm). Ms spectra were recorded on Varian MAT CH-7 spectrometer at 70 eV. Analytical data were obtained from the Microanalytical Data centre at Cairo University, Egypt.

*General procedure for the synthesis of the 2,3-dihydrothiazole derivatives* **3a–h**. To a cold suspension of finely ground potassium hydroxide (0.025 mol) in DMF (30 ml) the active methylene compound **1a–d** (0.025 mol) was added and subsequently phenyl isothiocyanate (0.025 mol). The whole mixture was then stirred at room temperature for 24 h and treated with the appropriate p-substituted-$\gamma$-bromoacetoacetanilide (0.025 mol) and left at room temperature for an additional 12 h. The reaction mixture was then triturated with cold water (60 ml) and neutralized with dilute hydrochloric acid. The resulting precipitated solid was collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

*[2-(Dicyanomethylene(-2,3-dihydro-3-phenyl-1,3-thiazol-4-yl]-acetic acid* (**4**). A suspension of **3a** (0.01 mol) in ethanol (30 ml) containing sodium hydroxide (0.01 mol) was refluxed for 30 min. The mixture was acidified with dilute hydrochloric acid (till pH = 8) and then triturated with cold water. The solid product, so formed was filtered off and crystallized from the proper solvent.

*4-(Benzalacetanilido-α-yl)-2-(dicyanomethylene)-2,3-dihydro-3-phenyl-1,3-thiazole* (**5**). Equimolecular amounts of **3a** and benzaldehyde (0.01 mol) in dioxane (30 ml) containing a catalytic amount of piperidine (3 drops) were refluxed for 3 h. The solid product which precipitated on standing and dilution with cold water was collected by filtration and crystallized from the proper solvent.

*6-Amino-2-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-1,4-diphenyl-5-cyano-pyridin-2-one* (**6**). A suspension of **3a** (0.005 mol) was refluxed with malononitrile (0.005 mol) in ethanol (20 ml) catalyzed with a few drops of piperidine for 2 h. The reaction mixture was poured onto water and

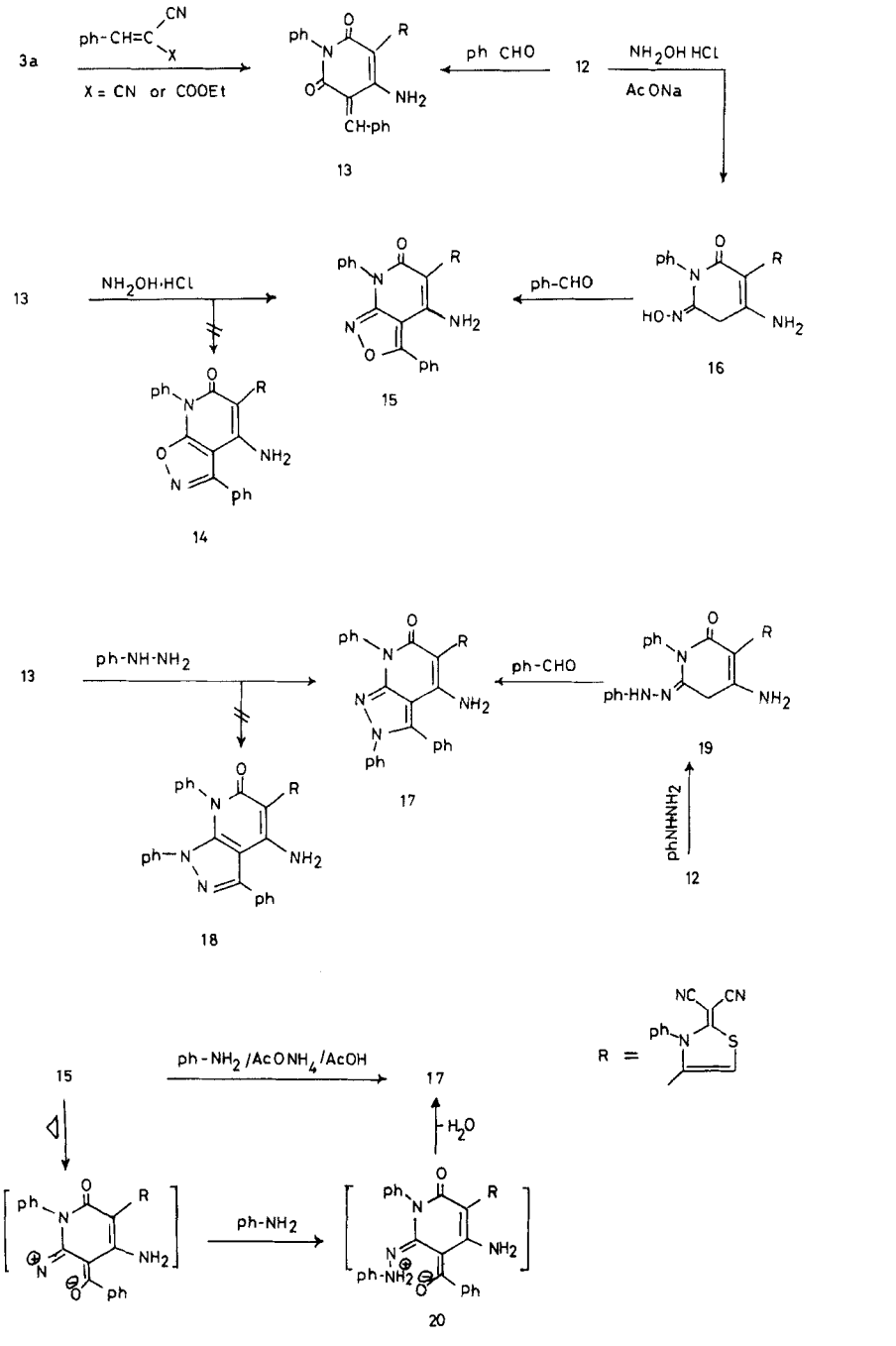



CHART 3

neutralized with dilute hydrochloric acid. The solid product which precipitated was collected by filtration and crystallized from the proper solvent.

*2,3-(Dihydro)-2-(dicyanomethylene)-1-phenyl-4-(phenylazo-acetanilido-α-yl)-1,3-thiazole* (**7**). To a stirred solution of **3a** (0.01 mol) in ethanol (50 ml) containing sodium acetate (5 g) benzenediazonium chloride [prepared by adding sodium nitrite (0.01 mol) to the equivalent amount of aniline in hydrochloric acid with cooling and stirring] was added dropwise while cooling and stirring. The reaction mixture was then left at room temperature for 2 h and the solid product so formed was collected by filtration, crystallized from the proper solvent.

*3-[2-(Dicyanomethylene)-2,3-dihydro-1-phenyl-1,3-thiazol-4-yl]-2,4-diphenyl-3H-1,2,4-triazin-2-one* (**8**). To a suspension of **7** (0.005 mol) in ethanol (20 ml), 4 ml of formaldehyde solution (40%) was added. The mixture was refluxed for 15 min. The solid product which precipitated on stand at room temperature was filtered off, washed with water and crystallized from the proper solvent.

*4-(Acetanilido-α-phenylazo-α-yl)-2-(dicyanomethylene-2,3-dihydro-3-phenyl-5-phenylazo-1,3-thiazole* (**9**). The same experimiental procedure mentioned above for the preparation of **7** has been followed except for using a two-fold amount of benzenediazonium chloride (0.02 mol).

*3-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-4,6-dimethyl-1-phenyl-pyridin-2-one* (**10**). To a solution of equimolar amounts (0.01 mol) of each of **3a** and acetylacetone in ethanol (30 ml), a catalytic amount of piperidine (3 drops) was added. The mixture was refluxed for 2 h and allowed to stand overnight at room temperature. The solid product which precipitated after dilution with water (20 ml) and neutralization with dilute hydrochloric acid was filtered off and crystallized from the proper solvent.

*4,6-Diamino-3-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-1-phenylpyridin-2-one* (**11**). To a solution of **3a** (0.01 mol) in DMF (30 mol) containing piperidine (3 drops), malononitrile (0.01 mol) was added. The mixture was boiled under reflux for 2 h, then left overnight at room temperature. The mixture was triturated with water (30 ml), the solid product so formed, was filtered off and crystallized from the proper solvent.

*4-Amino-3-[2'-dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-1-phenyl-pyridine-2,6-dione* (**12**). The same experimental procedure described above for the synthesis of **11** has been followed except for using ethyl cyanoacetate (0.01 mol) instead of malononitrile.

*4-Amino-5-benzal-3-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-1-phenylpyridin-2,6-dione* (**13**).

**Method (A):** To a mixture of **12** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (30 ml), piperidine (4 drops) was added. After boiling under reflux for 3 h, product **13** which separated on cooling, triturated with water and neutralized with few drops of dilute hydrochloric acid, was filtered off and crystallized from the proper solvent.

**Method (B):** To a suspension of **3a** (0.01 mol) in ethanol (30 ml) containing triethylamine (3 drops), benzylidenemalononitrile or ethyl benzylidenecyanoacetate (0.01 mol) was added. The mixture was refluxed for 3 h and then evaporated in vacuo. The residue was triturated with water and the resulting product was filtered off, crystallized from the proper solvent.

*6-Amino-5-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-3,7-diphenyl-oxazolo-[3,4-b]pyridin-4-one* (15). A mixture of **13** (0.005 mol), hydroxylamine hydrochloride (0.005 mol), ethanol (50 ml) and potassium hydroxide (0.005 mol) was refluxed for 1 h, evaporated in vacuo then poured onto ice/water mixture (50 ml). The solid product so formed was filtered off and crystallized from the proper solvent.

*4-Amino-3-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-6-oximo-1-phenyl-pyridin-2-one* (**16**). To a dry solid of **12** (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and fused sodium acetate (1 g) were added. The whole mixture was heated in an oil bath (150°C) for 1 h. The resulting product is triturated with water and the solid product was filtered off then crystallized from the proper solvent.

*Reaction of* **16** *with benzaldehyde to afford* **15**. To a mixture of **16** (0.01 mol) and benzaldehyde (0.01 mol) in DMF (30 ml), piperidine ($\frac{1}{2}$ ml) was added. The whole mixture is heated under reflux for 6 h. The solid product formed upon dilution with water was collected by filtration.

*6-Amino-5-[2'-dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-1,3,7-triphenyl-pyrazolo-[3,4-b]pyridin-4-one (17).*

**Method (A):** A mixture of 13 (0.005 mol), phenyl hydrazine (0.005 mol), ethanol (50 ml) and piperidine (4 drops) was refluxed for 2 h. The resulting mixture was concentrated, cooled, poured onto cold water and neutralized with dilute hydrochloric acid. The solid product was filtered off and crystallized from the proper solvent.

**Method (B):** A mixture of 15 (0.005 mol), aniline (0.005 mol), ammonium acetate (0.005 mol) and glacial acetic acid (30 ml) were refluxed for 2 h. The resulting mixture was then evaporated in vacuo, cooled and poured onto cold water. The solid product so formed was filtered off and crystallized from the proper solvent.

*4-Amino-3-[2'-(dicyanomethylene)-2',3'-dihydro-1'-phenyl-1',3'-thiazol-4'-yl]-6-phenylhydrazono-pyridin-2-one* (**19**). To a dry solid of 12 (0.01 mol), phenyl hydrazine (0.01 mol) was added. The whole mixture was heated in a boiling water bath for 6 h then poured into ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and crystallized from the proper solvent.

*Reaction of* **19** *with benzaldehyde to afford* **17**. The same experimental procedure described for the synthesis of **15** from **16** was carried out except for the use of **19** instead of **16**.

## ACKNOWLEDGEMENTS

The spectroscopic measurements were performed at City University London by Prof. S. A. Matlin. Thanks to the support of the International Organization for Chemical Sciences in Development (IOCD).



## REFERENCES

1. R. M. Mohareb, S. M. Sherif, H. Z. Shams and A. M. El-Torgoman, *Z. Naturforsch.*, **45b,** 1067 (1990).
2. R. M. Mohareb, A. Habashi, E. A. A. Hafez, S. M. Sherif, *Arch. Pharm., (Weinheim),* **320,** 776 (1987).
3. A. S. Shawali, M. Sami, S. M. Sherif, C. J. Parkanyi, *J. Heterocyclic Chem.,* **17,** 877 (1980).
4. A. Habashi, N. S. Ibrahim, S. M. Sherif, H. Z. Shams, R. M. Mohareb, *Heterocycles,* **24,** 2463 (1986).
5. A. Hantzsch, H. J. Weber, *Ber. Dtsch. Chem. Ges.*, **20,** 3118 (1887).
6. R. P. Rao, *J. Indian Chem. Soc.*, **38,** 787 (1961).
7. R. P. Rao, S. R. Singh, *J. Indian Chem. Soc.*, **50,** 492 (1973).
8. R. Laliberte, H. Warwick, G. Medawar, *Canadian J. Chem.*, **46,** 3643 (1968).
9. S. K. Mallick, A. R. Martin, R. G. Lingard, *J. Med. Chem.*, **14,** 528 (1971).
10. A. Andolsek, B. Stanovnik, M. Tisler, M. Likar, P. Schauer, *J. Med. Chem.*, **14,** 53 (1971).
11. P. N. Dhal, T. E. Achary, A. Nayak, *Indian J. Chem.*, **13,** 753 (1975).
12. S. R. Singh, *J. Indian Chem. Soc.*, **52,** 734 (1975).
13. M. I. Ali, M. A. Abou-State, N. M. Hassan, *Indian J. Chem., 4* (1973).
14. K. T. Potts, *Chem. Rev.*, **61,** 87 (1961).
15. G. R. Newkome, A. Nayak, *Adv. Heterocyclic Chem.*, **25,** 84 (1979).
16. F. C. Brown, *Chem. Rev.*, **16,** 463 (1961).
17. R. M. Mohareb, S. M. Sherif, F. A. M. Abdel-Aal, N. I. Abdel-Sayed, *Liebigs, Ann. Chem.*, 1143(1990).
18. N. S. Ibrahim, R. M. Mohareb, H. Z. Shams, *Z. Naturforsch.*, **43b,** 1351 (1988).
19. J. L. Soto, C. Seoane, P. Zammorano, F. Javier, *Synthesis,* 529 (1981).