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*Original Scientific Paper*

# Synthesis of Some New Thienylazetidinones and Thiazolidinones Containing Pyrazolines

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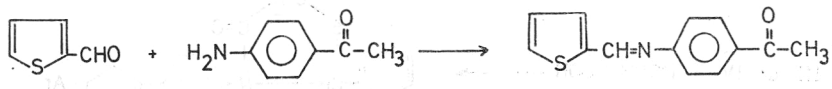
Condensation of thiophene-2-carboxaldehyde with 4-aminoacetophenone gave a quantitative yield of 4-(thienylideneamino)-acetophenone(I). Condensation of I with aromatic aldehydes yielded the corresponding 4-(4-substituted-phenyl)-4'-(2-thienyleneamino)-chalcone(II). Interaction of II with hydrazines gave 3-(4-2'-thienylideneamino)phenylpyrazolines (III, IV). Cyclocondensation of chloroacetyl chloride (or mercaptoacetic acid) on III or IV gave 3-chloro-1-(4-phenylpyrazolin-3'-yl)-4-(2''-thienyl)azetidin-2-ones (V, VI) and 3-(4-phenylpyrazolin-3'-yl)-2-(2''-thienyl)thiazolidin-4--ones (VII, VIII), respectively

In a previous publication[1] it has been shown that the cyclocondensation reaction of chloroacetyl chloride (and thioglycolic acid) on thienylidene anils gives azetidinones (and thiazolidinones). In view of the antibiotic activity of the azetidinone moiety, the antimicrobial activity of the thiazolidinone nucleus and the use of many heterocyclic sulphur compounds in the treatment of bilharziasis[2–5]. The present investigation deals with the synthesis of azetidinones (and thiazolidinones) containing a pyrazoline moiety in the para position to the phenyl ring hoping that the new compounds would be of medicinal value as schistosomidical agents.

Thus, thiophene-2-carboxaldehyde condensed easily with 4-aminoacetophenone in absolute ethanol[6] gave a quantitative yield of 4-(thienylideneamino)acetophenone(I).

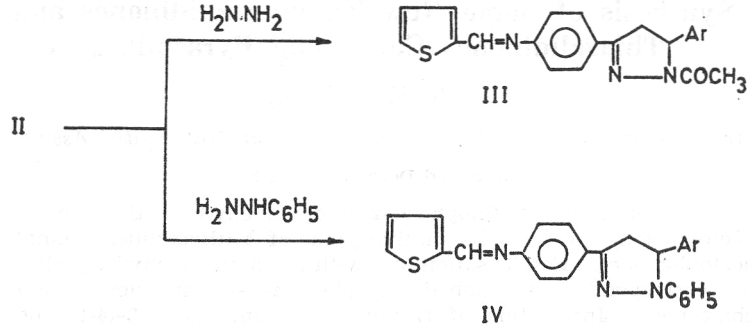


I

Condensation of I with aromatic aldehydes proceeded smoothly either in dry ethanol in the presence of piperidine as a base or via the Claisen-Schmidt procedure[7] (by stirring in the presence of aqueous alkali at room temperature 15—25 °C) which gave the corresponding 4-(4-substituted-phenyl)-4'-(2-thienylideneamino)chalcone(II).

II

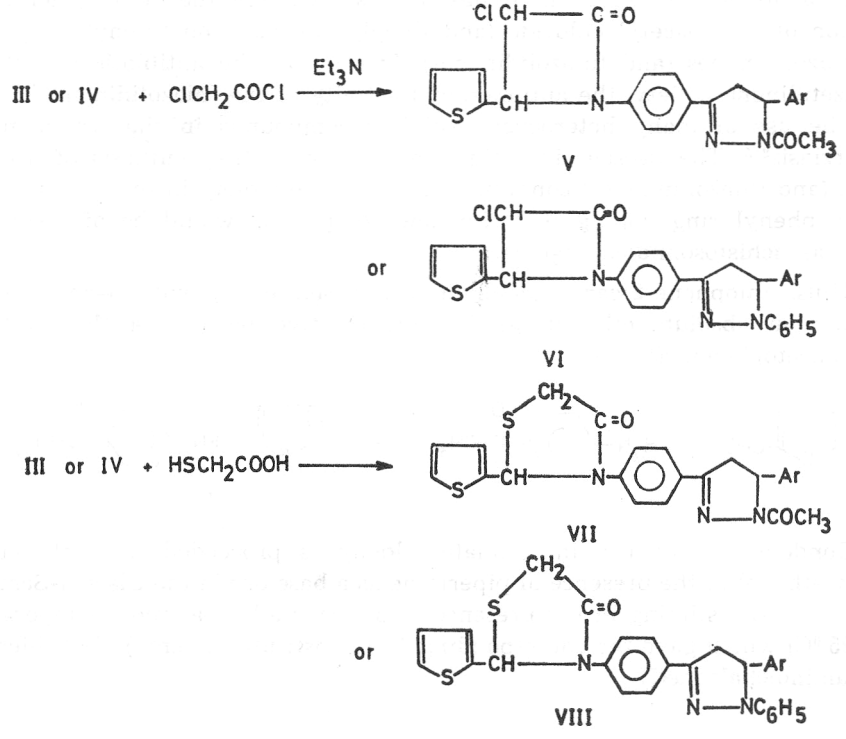
The presence of $\alpha,\beta$-unsaturated ketonic group in compound II resulted in an interaction with hydrazine hydrate in dry ethanol in the presence of glacial acetic acid[8] which gave *N*-monoacetylpyrazoline derivatives III. Moreover, the interaction of II with phenylhydrazine proceeded in dry ethanol in the presence of piperidine gave *N*-phenylpyrazoline derivatives IV.



III

IV

Furthermore, the cyclocondensation reaction of chloroacetyl chloride (or mercaptoacetic acid) with azomethine group[9,10] in compounds III and IV in dry dioxane gave 3-chloro-1-(4-phenylpyrazolin-3'-yl)-4-(2''-thienyl)azetidin-2--ones(V, VI) and 3-(4-phenylpyrazolin-3'-yl)-2-(2''-thienyl)thiazolidin-4-ones (VII, VIII), respectively.



V

VI

VII

VIII

The structure of compounds I—VIII has been confirmed by microanalytical data and IR analysis. The IR spectra[11] of (I) showed absorption bands at 1640 $cm^{-1}$ (C=N) and 1720 $cm^{-1}$ (C=O). Besides those, compound II exhibited an absorption at 1610—1590 $cm^{-1}$ (C=C). The absence of C=O absorption band the presence of a band at 1620—1615 $cm^{-1}$ (C=N cyclic) were characteristics of compounds III and IV. A band at 1760 $cm^{-1}$ (monocyclic $\beta$-lactam) for compounds V and VI and a band at 1700—1690 $cm^{-1}$ (thiazolidinone C=O) for compounds VII and VIII besides the absence of the band corresponding to C=N were in agreement with the proposed structures.

## EXPERIMENTAL

The infrared absorption spectra were determined with a Unicam SP 200 G spectrophotometer using the KBr wafer technique. All the melting points were uncorrected.

### *4-(Thienylideneamino)acetophenone(I)*

Equimolar rations of thiophene-2-carboxaldehyde and 4-aminoacetophenone were dissolved in absolute ethanol with a reflux for 3 hours. The reaction mixture was concentrated and the formed precipitate was filtered off, collected and crystallized from ethanol into pale yellow crystals, m. p. 83—84 °C,

*Anal.* $C_{13}H_{11}NOS$ calc'd.: C 68.12; H 4.80; N 6.11; S 13.97%
found: C 68.20; H 4.85; N 6.17; S 14.11%

### *4-(4-Substituted-phenyl)-4'-(2-thienylideneamino)chalcone(II)*

a) To a solution of I(0.01 mol) and aromatic aldehydes (0.01 mol) in absolute ethanol, two drops of piperidine were added. The reaction mixture was refluxed for 2 hours, concentrated, cooled, filtered, and the chalcones thus obtained were crystallized from ethanol.

b) Sodium hydroxide solution (0.55 mol/20 ml $H_2O$) was added to ethanol (15 ml) in a 100 ml flask provided with a mechanical stirrer.. The reaction flask was immersed in an ice bath, 4-(thienylideneamino)acetophenone I (0.01 mol) was added, followed by the appropriate aromatic aldehyde (0.01 mol) while stirring at 15—25 °C for 3 hours. The reaction mixture was left at room temperature for another half an hour, then, overnight in a refrigerator, filtered off, washed with cold water until the washings become neutral to litmus, and then washed three times with cold ethanol.

The products from method (a) and (b) have the same m. p. and no depression in mixed m. p's and have the same IR spectra. The results are listed in Table I.

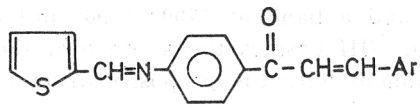
### *3-(4-2'-thienylideneamino)phenylpyrazolines(III,IV)*

a) *Formation of* N-*monoacetylpyrazolines(III).* To a solution of chalcone II (1 g) in ethanol (30 ml), hydrazine hydrate (98%, 4 ml) was first added, then 5 ml gl. acetic acid and the reaction mixture was refluxed for 5 hours, cooled and concentrated in vacuo. The residue was washed with dry ether and crystallized from ethanol to give the corresponding *N*-monoacetylpyrazolines III.

b) *Formation of* N-*phenylpyrazolines(IV).* To a solution of chalcone II (1 g) in ethanol (30 ml) it was added phenylhydrazine (0.01 mol) in ethanol (10 ml) and two drops of piperidine. The reaction mixture was refluxed for 5 h, and then cooled and filtered. The products were washed with dry ether and crystallized from ethanol-benzene. The physical data of compounds III and IV are given in Table II

TABLE I

*4-(4-Substituted-phenyl)-4'-(2-thienylideneamino)chalcone(II)*



| Compound | Ar | m. p. (°C) | Yield (%) | M. F. M. Wt. | Analysis† (Calc./Found) % | |
|---|---|---|---|---|---|---|
| | | | | | N | S |
| IIa | 4-$CH_3$—$C_6H_4$ | 160—61 | 80 | $C_{21}H_{17}NOS$ 331 | 4.22 4.34 | 9.66 9.51 |
| b | 4-Cl—$C_6H_4$ | 178—79 | 83 | $C_{20}H_{14}NOSCl$ 351.5 | 3.98 4.06 | 9.10 9.00 |
| c | 4-$NO_2C_6H_4$ | 212—13 | 81 | $C_{20}H_{14}N_2O_3S$ 362 | 7.73 7.85 | 8.83 8.77 |
| d | 4-$N(CH_3)_2$—$C_6H_4$ | 113—14 | 75 | $C_{22}H_{20}N_2OS$ 360 | 7.77 7.91 | 8.88 9.01 |
| e | 4-OH—$C_6H_4$ | 202—3 | 65 | $C_{20}H_{15}NO_2S$ 333 | 4.20 4.41 | 9.60 9.51 |
| f | $C_6H_5$— | 186—87 | 70 | $C_{20}H_{15}NOS$ 317 | 4.41 4.50 | 10.09 10.22 |

† Satisfactory analyses for C and H were also obtained.

*3-Chloro-1-(4-phenylpyrazolin-3'-yl)-4-(2''-thienyl)azetidin-2-ones(V,VI)*

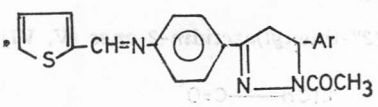
To a well stirred solution of III or IV (0.01 mol) and triethylamine (0.02 mol) in dry dioxane (50 ml) monochloroacetyl chloride (0.02 mol) was added dropwise at room temperature, the reaction mixture was stirred for 5 h and left at room temperature for 5 days. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was concentrated to a minimum volume and poured into cold water. The solid crystallized from ethanol. The results are listed in Table III.

*3-(4-Phenylpyrazolin-3'-yl)-2-(2''-thienyl)thiazolidin-4-ones(VII,VIII)*

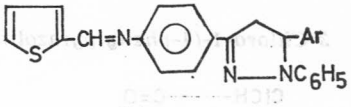
A mixture of III or IV (0.01 mol) and mercaptoacetic acid (0.01 mol) in dry benzene (100 ml) was refluxed using a water separator until the theoretical amount of water has been collected. After most of benzene had been removed under reduced pressure, the residue was dissolved in ether and seeded. In some cases the thiazolidinone separated out from benzene directly. The results are given in Table IV.

TABLE II

*3-(4-2'-Thienylideneamino)phenylpyrazolines (III, IV)*




III



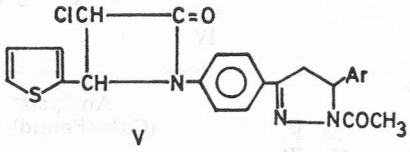

IV

| Compound | Ar | m. p. (°C) | Yield (%) | M. F. M. Wt. | Analysis† (Calc./Found) % | |
|---|---|---|---|---|---|---|
| | | | | | N | S |
| IIIa | 4-$CH_3$—$C_6H_4$ | 132—3 | 55 | $C_{23}H_{21}N_3OS$ 387 | 10.85 10.88 | 8.26 8.38 |
| b | 4-Cl—$C_6H_4$ | 207—8 | 40 | $C_{22}H_{18}N_3OSCl$ 407.5 | 10.30 10.38 | 7.85 7.92 |
| c | 4-$NO_2$—$C_6H_4$ | 156—7 | 50 | $C_{22}H_{18}N_4O_3S$ 416 | 12.98 13.05 | 7.69 7.71 |
| d | 4-$N(CH_3)_2$—$C_6H_4$ | 135—6 | 45 | $C_{24}H_{24}N_4OS$ 416 | 13.46 13.51 | 7.69 7.59 |
| e | 4-OH—$C_6H_4$ | 139—40 | 41 | $C_{22}H_{19}N_3O_2S$ 389 | 10.79 10.59 | 8.22 8.25 |
| f | $C_6H_5$— | 216—17 | 52 | $C_{22}H_{19}N_3OS$ 373 | 11.26 11.27 | 8.57 8.57 |
| IVa | 4-$CH_3$—$C_6H_4$ | 145—6 | 44 | $C_{27}H_{23}N_3S$ 421 | 9.97 10.03 | 7.60 7.53 |
| b | 4-Cl—$C_6H_4$ | 140—2 | 39 | $C_{26}H_{20}N_3SCl$ 441.5 | 9.51 9.62 | 7.24 7.33 |
| c | 4-$NO_2$—$C_6H_4$ | 190—2 | 58 | $C_{26}H_{20}N_4O_2S$ 450 | 12.00 12.11 | 7.11 7.17 |
| d | 4-$N(CH_3)_2$—$C_6H_4$ | 119—20 | 35 | $C_{28}H_{26}N_4S$ 450 | 12.44 12.34 | 7.11 7.22 |
| e | 4-OH—$C_6H_4$ | 122—24 | 42 | $C_{26}H_{21}N_3OS$ 423 | 9.92 9.80 | 7.56 7.44 |
| f | $C_6H_5$— | 162—4 | 54 | $C_{26}H_{21}N_3S$ 407 | 10.31 10.27 | 7.86 8.00 |

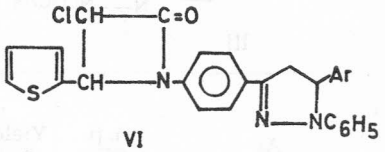
† Satisfactory analyses for C and H were also obtained.

TABLE III

*3-Chloro-1-(4-phenylpyrazolin-3'-yl)-4-(2''-thienyl)azetidin-2-ones (V, VI)*




V



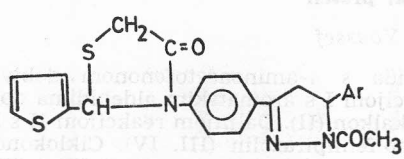

VI

| Compound | Ar | m. p. (°C) | Yield (%) | M. F. M. Wt. | Analysis† (Calc./Found) % | | |
|---|---|---|---|---|---|---|---|
| | | | | | N | S | Cl |
| Va | 4-$CH_3$—$C_6H_4$ | 182—3 | 25 | $S_{25}H_{22}N_3O_2SCl$ 463.5 | 9.06 9.12 | 6.90 7.05 | 7.65 7.72 |
| b | 4-$NO_2$—$C_6H_4$ | 144—5 | 25 | $C_{24}H_{19}N_4SCl$ 494.5 | 11.32 11.30 | 6.47 6.50 | 7.17 7.00 |
| c | 4-$N(CH_3)_2$—$C_6H_4$ | 164—5 dec. | 20 | $C_{26}H_{23}N_4O_2SCl$ 490.5 | 11.41 11.46 | 6.52 6.66 | 7.23 7.38 |
| VIa | 4-$CH_3$—$C_6H_4$ | 125—6 | 19 | $C_{29}H_{24}N_3OSCl$ 497.5 | 8.44 8.38 | 6.43 6.38 | 7.13 6.98 |
| b | 4-$NO_2$—$C_6H_4$ | 196—7 | 28 | $C_{28}H_{21}N_4O_3SCl$ 528.5 | 10.59 10.72 | 6.05 6.23 | 6.71 6.80 |
| c | 4-$N(CH_3)_2$—$C_6H_4$ | 138—9 | 21 | $C_{30}H_{27}N_4OSCl$ 526.5 | 10.63 10.75 | 6.07 6.27 | 6.74 6.61 |

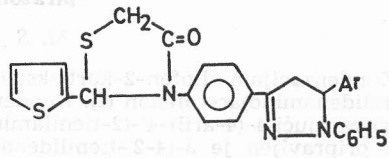
† Satisfactory analyses for C and H were also obtained.

TABLE IV

*3(p-Phenylpyrazolin-3'-yl)-2-(2"-thienyl)thiazolidin-4-ones (VII, VIII)*



VII



VIII

| Compound | Ar | m. p. (°C) | Yield (%) | M. F. M. Wt. | Analysis† (Calc./Found) % | |
|---|---|---|---|---|---|---|
| | | | | | N | S |
| VIIa | 4-$CH_3$—$C_6H_4$ | 127—30 | 60 | $C_{25}H_{23}N_3O_2S_2$ 461 | 9.11 9.14 | 13.88 13.69 |
| b | 4-$NO_2$—$C_6H_4$ | 155—8 | 65 | $C_{24}H_{20}N_4O_4S_2$ 492 | 11.38 11.31 | 13.00 14.04 |
| c | 4-$N(CH_3)_2$—$C_6H_4$ | 130—2 | 57 | $C_{26}H_{26}N_4O_2S_2$ 490 | 11.42 11.52 | 13.06 13.13 |
| VIIIa | 4-$CH_3$—$C_6H_4$ | 110—12 | 45 | $C_{29}H_{25}N_3OS_2$ 495 | 8.48 8.61 | 12.92 12.72 |
| b | 4-$NO_2$—$C_6H_4$ | 118—20 | 60 | $C_{28}H_{22}N_4O_3S_2$ 526 | 10.64 10.60 | 12.16 12.22 |
| c | 4-$N(CH_3)_2$—$C_6H_4$ | 105—6 | 42 | $C_{30}H_{28}N_4OS_2$ 524 | 10.68 10.52 | 12.21 12.39 |

† Satisfactory analyses for C and H were also obtained.

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## SAŽETAK

### Sinteza nekih novih tenilazetidinona i tiazolidinona koji sadržavaju pirazolinski prsten

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Kondenzacijom tiofen-2-karboksaldehida s 4-aminoacetofenonom dobiven je 4-(tienilidenamino)acetofenon (I). Kondenzacijom I s aromatskim aldehidima dobiveni su odgovarajući 4-(4-aril)-4'-(2-tienilamino)kalkon (II). Daljnjom reakcijom II s hidrazinom pripravljen je 3-(4-2'-tienilidenamino)fenilpirazolin (III, IV). Ciklokondenzacijom s kloroacetilkloridom (ili merkaptooctenom kiselinom) spojevi III i IV daju 3-kloro-1-(4-fenilpirazolin-3'-il)-4-(2''-tienil)azetidin-2-on (V, VI) i 3-(4-fenilpirazolin-3'-il)-2-(2''-tienil)tiazolidin-4-on (VII, VIII).


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