J. Fac. Pharm. Istanbul
29, 1 (1993)

İstanbul Ecz. Fak. Mec.
29, 1 (1993)

SYNTHESIS AND CHARACTERIZATION OF NEW 2-(ARYLIDENEHYDRAZONO)-4- METHYL-5-(ARYLAZO) THIAZOLINES

G. ÇAPAN, N. ERGENÇ, E. İLHAN and B. DOLATABADİ*

SUMMARY

Seven new thiazole derivatives have been synthesized from the reaction of α -oxo-α-methyl-N-(phenyl/substituted) ethanehydrazonoyl chlorides (A) (1, 2), obtained from the reaction of diazonium salts of aniline, 4-iodoaniline, 4-bromoaniline, 4-toluidine and benzocaine with chloroacetone, and thiosemicarbazones of 4-methylbenzaldehyde, 4-fluorobenzaldehyde, and furfural. The structure of the end products were determined using analytical and spectral methods. Fungicidal, insecticidal, and plant growth regulating activity tests are being carried out at Sittingbourne Research Centre, UK.

ÖZET

Tiazol türevlerinin biolojik bakımdan aktif olmalarından yola çıkılarak yedi yeni sübstitüe tiazol türevi sentezlenmiştir. Bu amaçla anilin, 4-iyodoanilin, 4-bromoanilin, 4- toluidin ve benzokainin diazonyum tuzları, monokloraseton ile kenetlenerek α-okso-α- metil-N-ariletanhidrazonoil klorürler (A) (1, 2) hazırlanmış; bu maddeler 4- florobenzaldehid-, 4-metilbenzaldehid- ve furfural-tiyosemikarbazonlar ile susuz CH_3COONa beraberliğinde 1-5 saat ısıtılarak siklize edilmiştir. Turuncu-kırmızı renkli ham ürünler

(*) Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Istanbul, Beyazıt 34452, İstanbul, Turkey.

etanolden billurlandırılarak saflaştırılmış (**1-7**); elementel analiz sonuçları ile kimyasal ve spektral verilerine dayanılarak yapıları kanıtlanmıştır. Maddeler fungisidal ve insektisidal etkileri ile bitkilerde büyüme düzenleyicisi özelliklerini araştırmak üzere Sittingbourne Research Centre, İngiltere'ye gönderilmiştir.

Key words: α-hydrazonoyl halides, thiosemicarbazones, thiazoles, tautomerism.

INTRODUCTION

Reaction of thiosemicarbazones and α - halo ketones furnish thiazoles (3-6). Thus when α-hydrazonoyl halides are used in place of the latter the reaction should lead to 2, 4, 5-trisubstituted thiazoles or thiazolines (7). Studies on the thiazole nucleus show that its derivatives demonstrate antiinflammatory (8), immunomodulating (9) and fungicidal (10) activity.

With a view to establish the structure of tautomeric thiazoles and to investigate their fungicidal, insecticidal and plant growth regulant activity a number of novel 2-(arylidenehydrazono)-4-methyl-5-(arylazo) thiazolines have been synthesized.

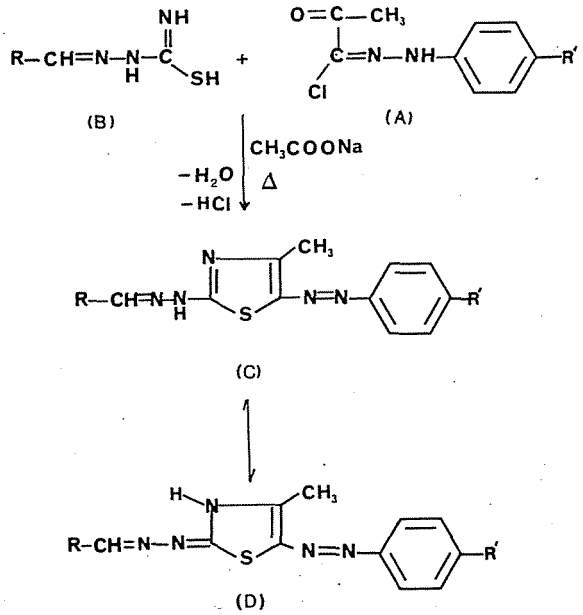
RESULTS and DISCUSSION

The reaction between α-oxo-α-methyl-N- (phenyl/substituted phenyl) ethanehydrazonoyl chlorides (A) and thiosemicarbazones of 4-fluoro-, 4-methylbenzaldehyde and furfural (B) proceeds smoothly in ethanolic medium to afford deeply colored end products (**1-7**) (Scheme 1 and Table 1).

It is believed that the first stage of the reaction involves formation of a C-S bond as a molecule of HCl is eliminated. Then ring closure takes place with the enolic form of (A) and a molecule of water is lost (11).

Analytical and spectral data (UV, IR, ^{1}H-NMR, MS) (Table 2) of **1-7** obtained as described above provided proof for the formation of the desired 2, 4, 5-trisubstituted thiazoles/thiazolines. UV spectra showed absorption maxima cited for similar structures (7). Running the spectra in $CHCl_3$ (**1** and **5**) caused a hypsochromic shift only in the maxima observed at 456.4 (443 nm) and 450.0 nm (439 nm). When 0.05N HCl was used as the solvent no shift was observed, whereas 0.05 N NaOH caused a drastic bathochromic shift moving the above cited maxima of **1** and **5** to 531 and 576 nm, respectively.

Supportive evidence was obtained from the IR spectra which did not show the C=O stretching vibrations (1680 cm^{-1}) of the starting substances (A) (2). Although **5-7**



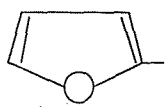
Scheme 1

showed C=O absorptions of the ester group at about 1705-1680 cm^{-1} the appearance and the position of this band allowed certain assignment. The N-H and C=N stretching vibrations were also observed in the expected regions (Table 2).

As previously reported (7), **1-7** may exist in two tautomeric forms -either as 2-arylidenehydrazinothiazole (C) or 2-arylidenehydrazono-4-thiazoline (D) depending upon the position of the mobile hydrogen. The ^{1}H-NMR spectra of **1** and **2** (DMSO-d_6) showed this hydrogen at 10.62 (D_2O exchange) and 10.56 ppm, respectively. The spectra of **5-7** ($CDCl_3$) showed the same hydrogen at about 7.48-7.51 ppm. These values were in accordance with the values reported for (D) (7) and thus we concluded that **5-7** were in that form in $CDCl_3$. The ^{1}H-NMR spectrum of **6** recorded in DMSO-d_6 showed the NH resonance at 10.78 ppm which is very near the NH resonances of **1** and **2.** Although values around 11 ppm were given for the absorption position of the NH of (C) ($CDCl_3$) solvent difference did not allow certain assignment. All the other protons resonated in the expected regions and integrated to give exact proton numbers.

MS of **2** (El), 5 and **7** (CI-CH_4) showed molecular (M^+) or quasi-molecular (MH^+) ions which confirmed their molecular weights (Table 2). The fragmentation pattern observed in spectra taken by both techniques were in accordance with those reported for similar stuctures (7). All the compounds are being tested for fungicidal, insecticidal and plant growth regulant activity at Sittingbourne Research Centre, UK.

Table 1: Data of compounds **1-7**

Comp.	R[1)]	R'	Formula (MW)	Mp (°C)	Yield (%)	Analysis (calcd/found) C	H	N
1	C_6H_4F	H	$C_{17}H_{14}FN_5S$ (339.38)	255	86	60.15 59.71	4.15 4.25	20.63 21.20
2	"	I	$C_{17}H_{13}FIN_5S$ (465.27)	263	55	43.88 43.75	2.81 2.92	15.05 15.39
3	"	Br	$C_{17}H_{13}BrFN_5S$ (418.27)	270	58	48.81 48.88	3.13 3.18	16.74 17.58
4	"	CH_3	$C_{18}H_{16}FN_5S$ (353.41)	245-7	62	61.16 61.16	4.56 4.82	19.81 19.36
5	"	$CO_2C_2H_5$	$C_{20}H_{18}FN_5O_2S$ (411.44)	252	82	58.38 58.40	4.40 4.50	17.02 17.00
6	$C_6H_4CH_3$	$CO_2C_2H_5$	$C_{21}H_{21}N_5O_2S.\ 1/2H_2O$ (416.49)	237	65	60.55 60.40	5.32 5.30	16.81 16.80
7		CO_2C2H_5	$C_{18}H_{17}N_5O_3S$ (383.42)	262	58	56.23 56.30	4.71 4.50	18.21 18.20

[1)] The substituent is at 4- position (**1-6**)

Table 2: Spectral data of compounds **1, 2, 5-7**

Compound MS (m/z) (%)	UV γ^{EtOH} nm (log ε)		IR (KBr) (cm^{-1}) ν_{max}	^{1}H NMR (δppm) [1)2)3)]
1	456.4 (4.40) 314.2 (3.97) 253.2 (4.09)	3240 (N-H) 1600 (C=N)	10.62 (1H,s,NH), 8.69 (1H, s,=CH), 7.95 (2H,dd J= 8.80, 5.67 Hz,ar), 7.47 (6H,m,ar), 6.99 (1H,m.ar), 2.65 (3H,s,CH_3)	
2	457.8 (4.43) 320.0 (sh) 257.0 (4.18)	3180 (N-H) 1605 (C=N)	10.56 (1H,s,NH), 8,69 (1H,s,=CH), 7.93 (2H,dd J=8.75, 5.74 Hz,ar), 7.66 (2H,d J=8.55 Hz,ar), 7.36 (2H,t J=8.75 Hz,ar), 7.27 (2H,d J=8.55 Hz,ar), 2.59 (3H,s,CH_3)	465 (M^+) (55), 343, 325, 296, 274, 244 231, 218, 203 (100), 188, 147, 122, 108, 95, 76, 71, 42, 28
5	450.0 (4.42) 304.0 (3.98) 278.0 (3.98)	3240 (N-H) 1680 (C=O) 1600 (C=N)	8.60 (1H,s,=CH), 8.04 (2H,d J=8.97 Hz,ar), 7.87 (2H,dd J=8.69, 5.45 Hz,ar), 7.48 (1H,s,NH), 7.22 (2H,d J=8.97 Hz, ar), 7.13 (2H,tJ=8.69 Hz,ar), 4.38 (2H,q J=7.2 Hz, CH_2), 2.69 (3H,s,CH_3), 1.40 (3H,t J=7.3 Hz,CH_3)	440 ($M+C_2H_5$)$^+$, 412 (MH^+) (20), 393, 291, 272, 245, 221, 192, 176, 153, 141, 122 (100), 117, 99
6	450.4 (4.51) 314.8 (4.15) 278.0 (3.95)	3400 (N-H) 1705 (C=O) 1610 (C=N)	8.62 (1H,s,=CH), 8.05 (2H,d J=8.75 Hz, ar), 7.77 (2H, d J=8.04 Hz,ar), 7.51 (1H,s,NH), 7.27 (2H,d J=8.04 Hz ar), 7.22 (2H,d J=8.75 Hz,ar), 4.37 (2H,q J=7.2 Hz, CH_2) 2.70 (3H,s,CH_3), 2.43 (3H,s,CH_3), 1.40 (3H,t J=7.3 Hz,CH_3)	
7	456.8 (4.47) 320.2 (4.09) 280.0 (3.98)	3240 (N-H) 1705 (C=O) 1605 (C=N)	8.46 (1H,s,=CH), 8.04 (2H,d J=7.50 Hz,ar), 7.65 (1H,s, C5-H), 7.50 (1H,s,NH), 7.20 (2H,D J=7.50 Hz,ar), 6.98 1H,s,C3-H), 6.57 (1H,s,C4-H), 4.36 176, 166, 151, 117, 99, 94 (100) (2H,q J=7.0 Hz,	412 ($M+C_2H_5$)$^+$, 384 (MH^+) (10), 355, 338, 319, 291, 275, 257, 242, 221, 194, CH_2), 2.69 (3H,s,CH_3), 1.39 (3H,t J=7.0Hz,CH_3)

1) ^{1}H-NMR spectra of **1** and **2** and **5-7** were recorded in DMSO-d_6 and $CDCl_3$, respectively.

2) Spectra of **6** ($CDCl_3$) shows a more intense H_2O peak at 1.60 ppm which confirms the presence of water in the molecule.

3) C3-H, C4-H, C5-H of the furyl residue (**7**) appear as distorted singlets.

EXPERIMENTAL

Chloroacetone, aromatic amines, aldehydes and thiosemicarbazide were commercially available. M.p.'s were determined on a Büchi apparatus (Büchi-Flawil/Schweiz) and are uncorrected. Elemental analyses were performed either at Sittingbourne Research Centre, UK or on a Carlo Erba 1106 instrument. UV, IR (KBr), ^{1}H-NMR, EI and CI (CH_4) mass spectra were taken on 2100 S Shimadzu, Perkin-Elmer 577 Grating, Bruker AC 200 (200 MHz) instruments or provided by Pennsylvania State University, USA and Sittingbourne Research Centre, UK, respectively.

General procedure for the synthesis of 1-7

To a solution of 0.005 mol aldehyde thiosemicarbazone (B) in 70 ml of EtOH, 0.005 mol of α-oxo-α-methyl-N- (phenyl/substituted phenyl) ethanehydrazonoyl chloride (A) and 0.41 g of anhydrous CH_3COONa were added. The mixture was refluxed on a water bath for 1-5h (**1-5, 7** 5h and **6** 1h), then cooled and left stand overnight, filtered and washed with H_2O. The crude products thus obtained were recrystallized from EtOH to give reddish-brown (**1-4**) or orange colored (**5-7**) crystalline substances.

Acknowledgement. We are indebted to Mr. Roy Davis, Sittingbourne Research Centre, UK, for the elemental analyses and mass spectra.

REFERENCES

1. Dubenko, R. G., Gorbenko, E. F., *Zh. Org. Khim.*, **4,** 634 (1968).-*C.A.*, **69,** 2620a (1968).
2. Ergenç, N., Özçekiç, H., *J. Fac. Pharm. İstanbul*, **17,** 1 (1981).-*C.A.*, **97,** 162481n (1982).
3. Bulka, E., Rohde, H. G., Beyer, H., *Ber*, **98,** 259 (1965).
4. Bulka, E., Dinse, H. D., *Z. Chem.*, **5,** 376 (1965).-*C.A.*, **64,** 3514h (1966).
5. Bilinsky, S., Bielak, L., *Ann. Univ. Marie Curie Sklodowska*, **23,** 107 (1968).-*C.A.* **72,** 21634m (1970).
6. Singh, S. P., Seghal, S., Sharma, P. K., *Indian J. Chem.*, **29B,** 533 (1990).
7. Ergenç, N., Özçekiç, H., *Pharmazie*, **43,** 832 (1988).
8. Brown, K., Kater, D. P., Cavalla, J. F., Green, D., Neuberry, R. A., Wilson, A. B., *J. Med. Chem.*, **17,** 1177 (1974).
9. Schorlemmer, H. U., Dickneite, G., Blumbach, J., Dürckheimer, W., Sedlacek, H. H., *Arzneim.-Forsch/Drug Res.* **39,** 1085 (1989).
10. Abdel-Lateef, M. F. A., Stec, M., Eckstein, Z., *Acta Pytopathol.* **8,** 269 (1973).-*C.A.* **81,** 115750j (1974).
11. Adams, R., Organic Reactions, **6,** p. 373, John Wiley and Sons Inc., New York (1951).