Mar. Üniv. Ecz. Der.,
2 (1), 1—6 (1986)

J. Pharm. Univ. Mar.,
2 (1), 1—6 (1986)

2,4-DİHİDRO-3H-1,2,4-TRİAZOL-3-TİON VE 2,3-DİHİDRO-1,3,4-TİYADİAZOL TÜREVLERİNİN SENTEZİ

SYNTHESIS OF 2,4-DIHYDRO-3H-1,2,4-TRIAZOLE-3-THIONE AND 2,3-DIHDRO-1,3,4-THIADIAZOLE DERIVATIVES

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SUMMARY

In this study, new azopyrazole substituted 2,4-dihydro-4-ethyl-3H-1,2,4-triazole-3-thione and 2,3-dihydro-2-ethylimino-1,3,4-thiadiazole were synthesized using 1-phenyl-3,5-dimethyl-4-(p-hidrazinocarbonilphenylazo) pyrazole as a starting material. Furthermore, the azo groups of substances were reduced with hydrazine hydrate.

The structure of these substances were elucidated using UV, IR, NMR (for substances 2, 3 and 4) and Mass (for substances 3 and 4) spectral methods besides elementary analysis.

ÖZET

Bu çalışmada, başlangıç maddesi olarak 1-fenil-3,5-dimetil-4-(p-hidrazinokarbonilfenilazo)pirazol kullanılarak yeni azopirazol substitue 2,4-dihidro-4-etil-3H-1,2,4-triazol-3-tion ve 2,3-dihidro-2-etilimino-1,3,4,-tiyadiazol yapısında bileşiklerin sentezi yapılmıştır. Ayrıca maddelerin azo grubu hidrazin hidrat ile redüklenmiştir. Maddelerin yapıları elemanter analiz ve UV, IR, NMR (madde 2, 3 ve 4) ve Mass (madde 3 ve 4) spektroskopik yöntemlerden yararlanılarak aydınlatılmıştır.

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INTRODUCTION

Various azopyrazole (1-4), 1,2,4-triazole and 1,3,4-thiadiazole (5-7) derivatives have been reported to possess hypoglycemic activity. This paper describes the synthesis and spectroscopic analysis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives having an azopyrazole moiety in the 5 position.

Preliminary pharmacological testing on rabbits revealed that the compound **3** possess potent hypoglycemic activity.

EXPERIMENTAL PART

Melting points were taken on apparatus Buchi (Flawil/Schweiz) and are uncorrected. UV spectra were obtained with a 25 Model Beckman recording spectrophotometer. IR spectra were recorded on a Perkin-Elmer 577 Spectrophotometer in KBr. NMR spectra were recorded on a Varian T-60 instrument using TMS as an internal standard. Mass spectra were recorded on a Varian 44S spectrometer.

N^1-[p-(1-phenyl-3,5-dimethyl-4-pyrazolylazo)benzoyl]-N^4-ethylthiosemicarbazide (**2**)

To a solution of 3.34 g **1** in ethanol was aded 1 ml ethylisothiocyanate. The reaction mixture was refluxed for 3 h. The formed crystalline product was filtered, washed with petroleum ether and recrystallized from ethanol. Compound **2** formed orange crystals, m.p. 196°C, yield 88 %. IR: 3220 (NH), 1670 (C=0), 1225 cm^{-1} (C=S). ^{1}H-NMR: δ (ppm), 1.11 (t, 3H, CH_3), 2.53, 2.70 (s. 6H, two CH_3), 3.30-3.70 (q, 2H, CH_2), 7.63 (s, 5H, C_6H_5), 7.88 (d, 2H, Ar-H), 8,18 (d, 2H, Ar-H), 9.36 (s, 1H, N-NH), 10.41 (s. 1H, CONH). Anal: Calculated for $C_{21}H_{23}N_7OS$ (421): C, 59.83; H, 5.49; N, 23.26. Found: C, 59.43; H, 5.79; N, 22.95.

2,4-Dihydro-5-[p-(1-phenyl-3,5-dimethyl-4-pyrazolylazo)phenyl]-4-ethyl-3H-1,2,4-triazole-3-thione (**3**)

To the **2** of 2.10 g was added 15 ml 2N NaOH and the mixture refluxed for 2 h. The formed solid product was dissolved in water and acidified with HCl. The solid product, so separated, was washed with water and recrystalized from ethanol. Compound **3** formed

orange crystals, m.p. 221-3°C yield 79 %. IR: 3100 (NH), 1270 (C—N), 1145 cm^{-1} (C=S). ^{1}H-NMR: δ (ppm), 1.40 (t, 3H, CH_3), 2.63, 2.70 (s, 6H, two CH_3), 4.26 (q, 2H, CH_2), 7.43 (s. 5H, C_6H_5), 7.66 (d, 2H, Ar-H), 7.96 (d, 2H, Ar-H). Mass: M^+m/e 403, other fragmentation m/e 302, 199, 171, 103 and 77 (base peak). Anal. Calculated for $C_{21}H_{21}N_7S$ (403): C, 62.53; H. 5.24; N, 24.31. Found C, 62.40; H, 5.37; N, 24.18.

2,3-Dihydro-2-ethylimino-5-[p-(1-phenyl-3,5-dimethyl-4-pyrazolylazo)phenyl]-1,3,4-thiadiazole (**4**)

To the **2** of 2,10 g was added 4 ml concd. H_2SO_4 in small portions. The mixture was shaken vigorously to form a homogeneous solution and set aside (30 min). It was then poured in ice water and neutralized with Na_2CO_3. The solid product was filtered, washed with water and recrystallized from ethanol. Compound **4** formed orange crystals, m.p. 206-7°C, yield 85 %. IR: 3315 (NH), 1669 cm^{-1} (C=N). ^{1}H-NMR: δ (ppm), 1.03 (t, 3H, CH_3), 2.56, 2.63 (s. 6H, two CH_3), 3.15 (m, 2H, CH_2), 6.43 (t, NH), 7.58 (s, 5H, C_6H_5), 7.83 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H), 10.33 (s, NH). Mass: M^+m/e 403, other fragmentation m/e 360, 334, 301, 302, 303 (base peak), 275, 199, 171, 118, 77. Anal. Calculated for $C_{21}H_{23}N_7OS.H_2O$ (421): C, 59.83; H. 5.49; N, 23.26. Found C, 60.25; H, 5.95; N, 22.79.

General procedure for the synthesis of compounds **6** and **7**

A mixture of the azo compound (0.0025 mol), hydrazine hydrate (of 99 %) and ethanol (30 ml) was stirred for 30 min. at 70°C. Excess ethanol was removed by distillation. When the water was added to the solution, white crystalline product was obtained and recrystallized from dilute ethanol. The mother liquor as extracted with chloroform. After distillation of chloroform, the remaining oily product (**5**) was converted to diazonium salt and coupled with acetylacetone. So compound **8** was produced. mp. 118-9°C (8).

2,4-dihydro-5-(p-aminophenyl)-4-ethyl-3H-1,2,4-triazole-3-thione (**6**)

m.p. 246-8°C lit. m.p. 246-8°C (6), yield 59 %. IR: 3460, 3350, 1614 (NH_2), 3090 cm^{-1} (NH).

2,3-dihydro-2-ethylimino-5-(p-aminophenyl)-1,3,4-thiadiazole (**7**)

m.p. 170°C, yield 54 %. IR: 3338, 1624 (NH_2), 1655 cm^{-1} (C=N).

Anal. Calculated for $C_{10}H_{12}N_4S.H_2O$ (238): C, 50.4; H, 5.92; N, 23.5. Found C, 49.6; H, 6.53; N, 22.9.

RESULTS and DISCUSSION

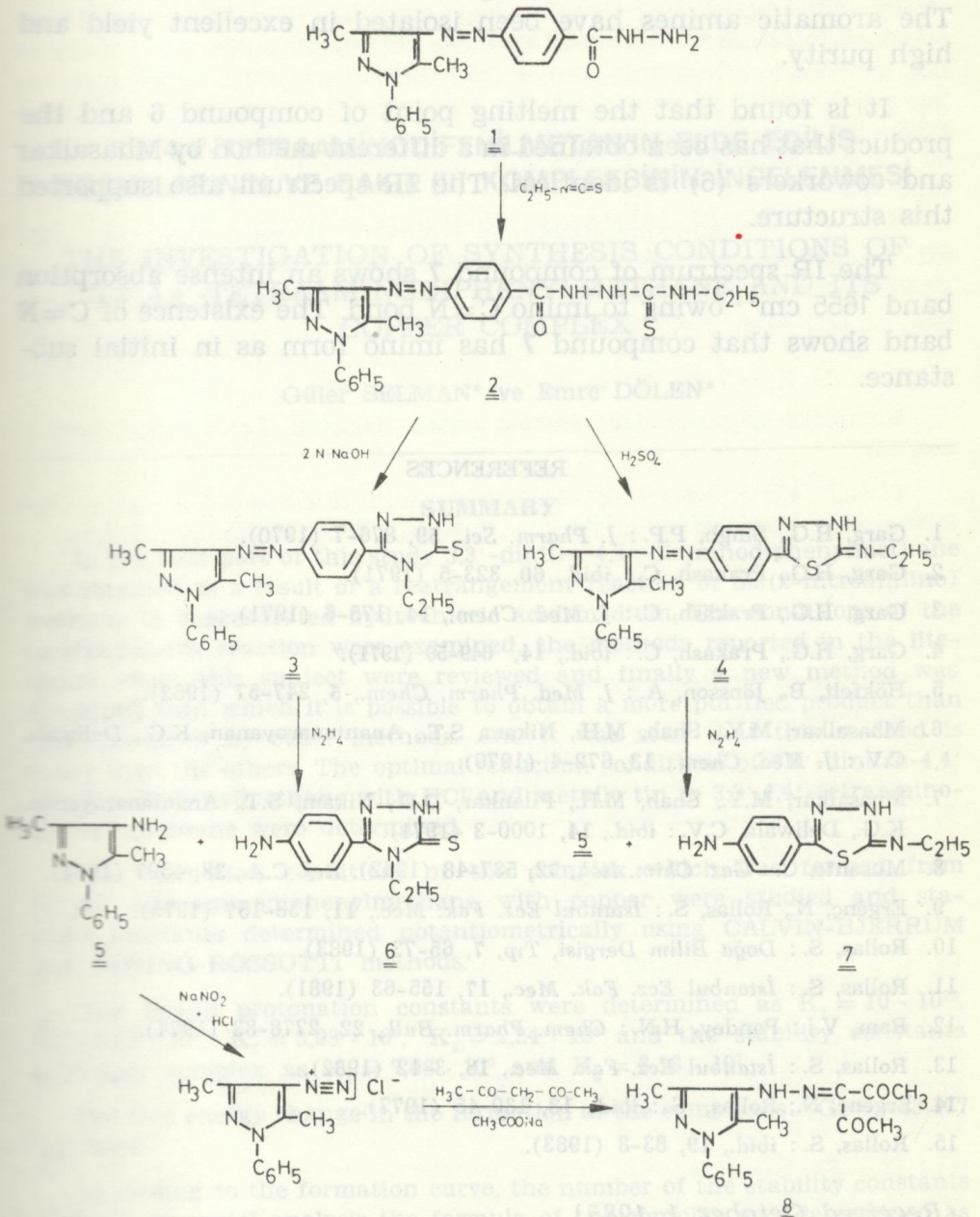
The synthesis of 2,4-dihydro-5-[p-(1-phenyl-3,5-dimethyl-4-pyrazolyazo)phenyl]-4-ethyl-3H-1,2,4-triazole-3-thione (**3**) and 2,3-dihydro-2-ethylimino-5-[p-(1-phenyl-3,5-dimethyl-4-pyrazolylazo) phenyl]-1,3,4-thiadiazole (**4**) prepared by the methods outlined in scheme.

Compound **2** was obtained by addition of ethylisothiocyanate to 1-phenyl-3,5-dimethyl-4-(p-hydrazinocarbonylphenylazo)pyrazole (**1**) (9, 10).

The cyclization of compound **2** with 2N-NaOH gave the sodium salt of compound **3**. The sodium salt of **3** was dissolved in water and acidified with dilute hydrochloric acid. So the compound **3** was obtained (11). The IR spectra of **3** showed NH band in the range of 3100 cm^{-1}. Furthermore, the presence of band in the range of 1145 cm^{-1} due to the C=S group and the absence of band in the region 2600-2550 cm^{-1} due to the SH group shows that the mercaptotriazole considered here is 2,4-dihydro-3H-1,2,4-triazole-3-thione in solid state. In the NMR spectrum, the finding of SH peak in the area of methyl protons instead of NH peak shows that the compound **3** is in the thiole form in solid state (12). In the mass spectrum of **3**, molecular ion peak is m/e 403 and base peak m/e 77.

The cyclization of compound **2** in concd. sulphuric acidic medium gave the compound **4**. The formation mechanism of **4** has been described in our previous paper (13). The IR spectrum of **4** shows an intense absorption band in the range of 3315 cm^{-1} due to the NH bond and 1669 cm^{-1} due to the C=N bond. But the NMR spectrum of **4** in DMSO exhibited two NH signals as a triplet at 6.43 ppm and a singlet at 10.33 ppm. These IR and NMR spectral data showed that the compound **4** predominantly exists in the imino form in solid state and exists in the amino$\rightleftharpoons$imino tautomeric equilibria in DMSO. In the mass spectrum of **4**, molecular ion peak is m/e 403 and base peak is m/e 303.

In our previous work, 4-aminopyrazole derivatives were prepared by reducing the azopyrazole derivatives with hydrazine



Scheme

hydrate without a catalyst in ethanol (9, 14, 15). This reductive cleavage reaction offers advantages over other reduction methods. The aromatic amines have been isolated in excellent yield and high purity.

It is found that the melting point of compound **6** and the product that has been obtained in a different method by Mhasalkar and coworkers (6) is identical. The IR spectrum also supported this structure.

The IR spectrum of compound **7** shows an intense absorption band 1655 cm^{-1} owing to imino C=N bond. The existence of C=N band shows that compound **7** has imino form as in initial substance.

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(Received October 1, 1985)