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A NEW METHOD FOR THE SYNTHESIS OF 4-AMINO-3,5- DIMETHYLPYRAZOLES AND RELATED COMPOUNDS

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SUMMARY

Previously synthesized azopyrazoles were reduced with hydrazine hydrate without a catalyst. This reaction is an attractive alternate for the reduction of the azo functional group to obtain a new primary amine. In this study, we used a new modified method for the synthesis of some 4-aminopyrazole derivatives. 4-amino-3,5-dimethylpyrazole **(I)**, 4-amino-3,5-dimethyl-1-phenylpyrazole **(II)** 4-amino-3,5-dimethyl-1-(2-hydroxyethyl)pyrazole **(III)** and 4-amino-1,3,5-trimethylpyrazole **(V)** were obtained with high yield. 4-amino-1-(2-acetyloxy)ethyl-3,5-dimethylpyrazole **(IV)** and its intermediate azo compound, 4-(4-ethoxycarbonylphenylazo)-3,5-dimethyl-1-(2-acetyloxyethyl)pyrazole **(B)**, were synthesized as original compounds and their structures were elucidated using UV, IR, ^{1}H-NMR and mass spectroscopic methods. The mentioned method is more cheaper and provides higher yield than our previous method for the synthesis of 4-aminopyrazole derivatives.

ÖZET

Daha önce tarafımızdan sentezlenen bazı azopirazoller hidrazin hidrat ile katalizörsüz olarak redüklenmiştir. Bu reaksiyon azo fonksiyonel gruplarından yeni primer aminlerin redüksiyon ile elde edilmesi için ilgi çekici bir alternatiftir. Bu çalışmada modifiye edilen yeni bir sentez metodu kullanılarak bazı 4-aminopirazol türevleri sentezlenmiştir. 4-amino-3,5-dimetilpirazol **(I)**, 4-amino-3,5-dimetil-1-fenilpirazol **(II)** 4-amino-3,5-dimetil-1-(2-hidroksietil)pirazol **(III)**, 4-amino-1-(2-asetiloksi)etil-3,5-dimetilpirazol **(IV)** ve 4-amino-1,3,5-trimetilpirazol **(V)** yüksek

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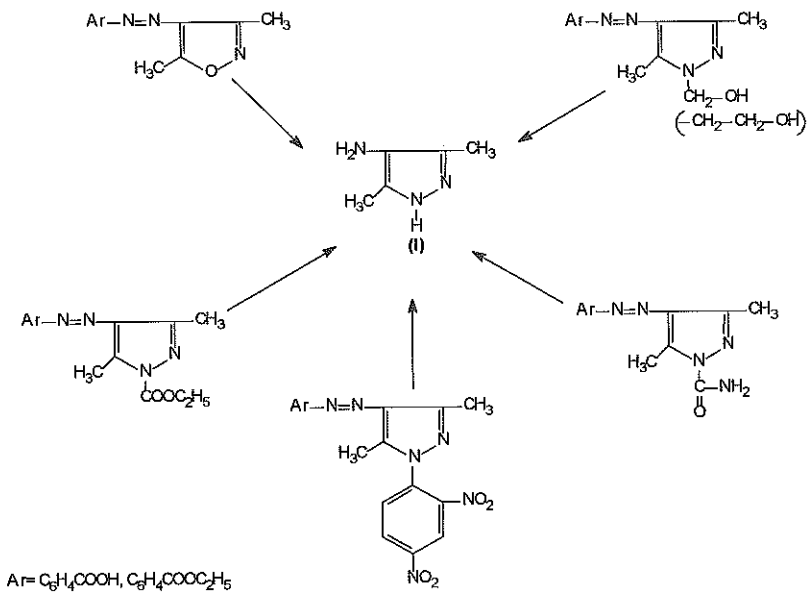
verimle kazanılmıştır. Bu bileşiklerden 4-amino-1-(2-asetiloksi)etil-3,5-dimetilpirazol **(IV)** ve ilgili azo bileşiği olan 4-(4-etoksikarbonilfenilazo)-3,5-dimetil-1-(2-asetiloksietil)pirazol **(B)** orijinal bileşiklerdir ve yapıları UV, IR, ^{1}H-NMR ve kütle spektroskopisi ile aydınlatılmıştır. Bu metod 4-aminopirazol türevlerinin sentezi için daha önce kullandığımız yöntemden daha ucuz ve yüksek verimli bir metoddur.

Key words: 4-Aminopyrazoles, azopyrazoles, hydrazine hydrate, reduction

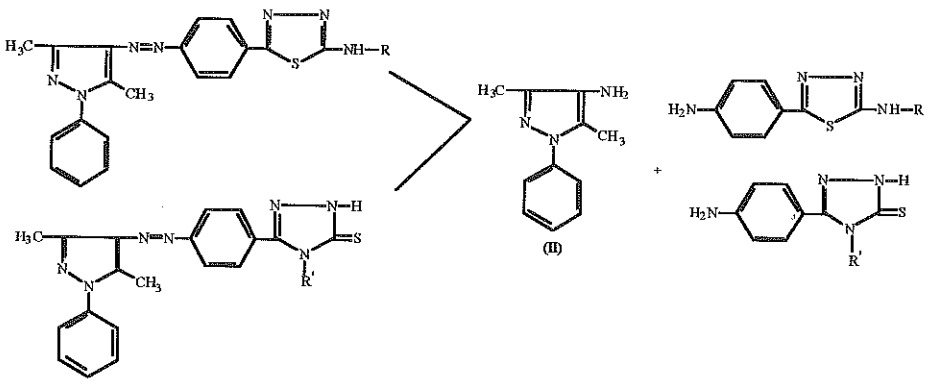
INTRODUCTION

Aromatic amines are widely used as intermediates for dyes, photographic materials, pharmaceutical and agricultural chemicals and as antioxidants. They are generally prepared by the reduction of aromatic nitro or azo compounds using a vast array of reagents in solution phase reactions [1]. Hydrazine hydrate has been extensively used for reduction purposes in the presence of heterogeneous catalysts such as activated zinc-copper , Zn-C, Fe-C, Pd-C, Pt-C, Raney Ni, $FeCl_3.6H_2O$-activated carbon, Fe(III) oxides, Fe(III)-MgO, graphite and clays. The reduction is usually conducted in refluxing alcoholic solvents or dioxane. The reduction of azo compounds had also been performed with hydrazine hydrate in presence of Raney Ni (2,3). In our laboratory, we have been using hydrazine hydrate without a catalyst for the reduction of azopyrazoles in recent years (4-10). Thus several aminopyrazoles have been obtained using this method as shown in schemes 1 and 2.



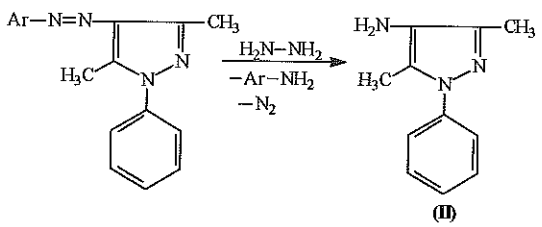
Scheme 1. Synthesis of 4-amino-3,5-dimethylpyrazole **(I)**

In this communication, we wish to report a simple reduction of azo compounds to the corresponding amino derivatives as depicted in schemes 1 and 2 by using lower amounts of hydrazine hydrate without a catalyst. By this method aminopyrazoles could be obtained with a higher yield.



R= CH_3, C_2H_5, CH_2=CH-CH_2 (CH_2-CH_2-CH_3), C_4H_9, C_6H_{11}, C_6H_5, CH_2-CH_2-C_6H_5

R'= CH_3, C_2H_5, CH_2=CH-CH_2 (CH_2-CH_2-CH_3), C_4H_9, C_6H_{11}, C_6H_5, CH_2-CH_2-C_6H_5, C_6H_4(p-Br), C_6H_4(p-Cl)



Ar= C_6H_4COOH, $C_6H_4COOC_2H_5$

Scheme 2. Synthesis of 4-amino-1-pheny1-3,5-dimethylpyrazole **(II)**

RESULTS AND DISCUSSION

4-Aminopyrazoles (**I-V**) were prepared by the reduction of azo compounds which were synthesized in four steps starting from appropriate amine compounds following the reported procedure (5,11). The synthetic pathway followed for the preparation of the target molecules **I-V** is presented in scheme 3.

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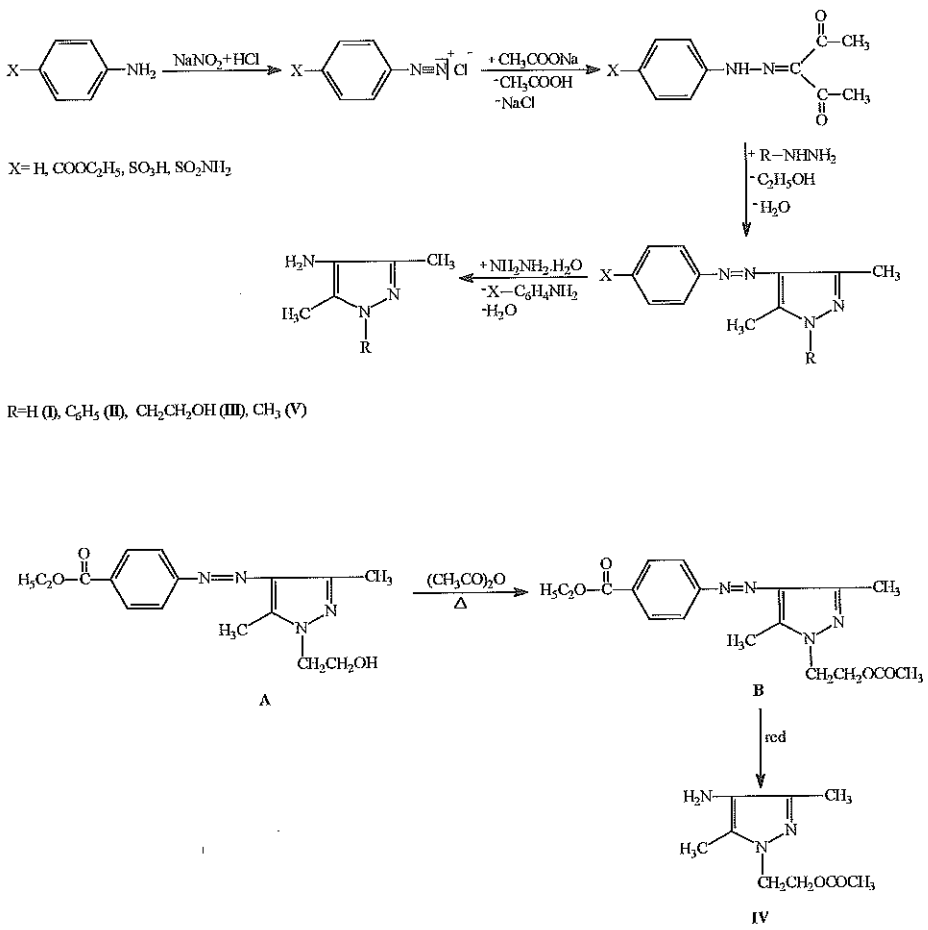

Scheme 3. Synthesis pathway followed for the preparation of the target compounds **I-V**

4-Amino-3,5-dimethylpyrazole **(I)** was synthesized by the reduction of 4-nitro-3,5-dimethylpyrazole by Morgan and co-workers (12,13). However we had prepared this amine compound reducing azo derivatives by hydrazine hydrate with higher yield (5,11). In case of the the compounds containing ester functional group in the aromatic ring, 4-aminobenzoic acid hydrazide was obtained instead of ethyl 4-aminobenzoate. The C-N bond at 1- position of the pyrazole ring of compound having 2-hydroxyethyl residue was also reduced with hydrazine hydrate beside the azo group. Thus 4-amino-3,5-dimethylpyrazole **(I)** was obtained. We now report that this compound can be obtained in higher yield employing lower amounts of hydrazine hydrate which also afforded selectivity for the reduction of the azo group.

Several azo compounds were reduced by hydrazine hydrate to obtain compound **I**, but this amine compound was obtained in higher yield using aniline as the starting material. The other pyrazole amines **II** and **V** were generally prepared by the reduction of 4-nitro or nitrosopyrazole derivatives (15,16). The amine compound **III** was synthesized by the reduction of the azo derivatives with Pd/C (14). In this study, these amine compounds **II, III** and **V** were obtained by the reduction of azo derivatives with lower amounts of hydrazine hydrate. When aniline was used as an initial material to produce 4-amino-1-(2-hydroxyethyl)-3,5-dimethylpyrazole **(III)** the reduction was not succesfull. So this reaction was carried out with the compound having an ester group and using lower amount of hydrazine hydrate for reduction. Consequently, 4-amino-1-(2-hydroxyethyl)-3,5-dimethylpyrazole **(III)** was obtained together with ethyl 4-amino benzoate. 4-amino-1-(2-acetyloxyethyl)-3,5-dimethylpyrazole **(IV)** and its intermediate azo compound (B) were synthesized for the first time in this study. For this purpose, acetylacetone was coupled with diazonium salt of ethyl 4-aminobenzoate and then reacted with 2-hydroxyethyl hydrazine to obtain the azo derivative. Then the azo derivative was acetylated and reduced with hydrazine hydrate and 4-amino-1-(2-acetyloxyethyl)-3,5-dimethylpyrazole **(IV)** was obtained. When 4-amino-1-(2-hydroxyethyl)-3,5-dimethylpyrazole **(III)** was directly treated with acetic anhydride, the amino group was acetylated instead of the hydroxyl group. For that reason hydroxyl group was acetylated before the reduction of azo compound with hydrazine hydrate. The amine compounds **I, II, III** and **V** are not novel but the spectral characterization of **I, III** and **V** was made for the first time in this study. The UV spectra of **I, III, IV** and **V** showed strong bands at 237-243 nm which corresponds to aminopyrazole. In the IR spectra of **I, III, V** the NH_2 bands were observed in the 3163-3343 cm^{-1} region. The ^{1}H-NMR spectra of **I, III, IV** and **V** displayed the NH_2 resonance at about 2.60-3.30 ppm. Pyrazole methyl protons were detected at 2.10 ppm as a singlet for compound **I**. The same protons were observed as two different singlets at 2.15 and 2.27 ppm (for 5-methyl and 3-methyl) for compound **III**. 5-methyl and 3-methyl protons of compound **IV** resonated at 2.34 and 2.46 ppm . In addition the methyl protons of the acetyloxy group were observed as a singlet at 1.89 ppm and methylene protons were dedected as triplets at 4.15 and 4.30 ppm. In addition compound **IV** showed the molecular ion peak as $(M+1)^+$ at m/z 198 in the electron spray ionization (ES) mass spectrum. The electron impact (EI) mass spectrum of **V** showed the molecular ion peak as $(M-H)^+$ at m/z 124 which confirmed its molecular weight. Some important fragments are shown in scheme 4.

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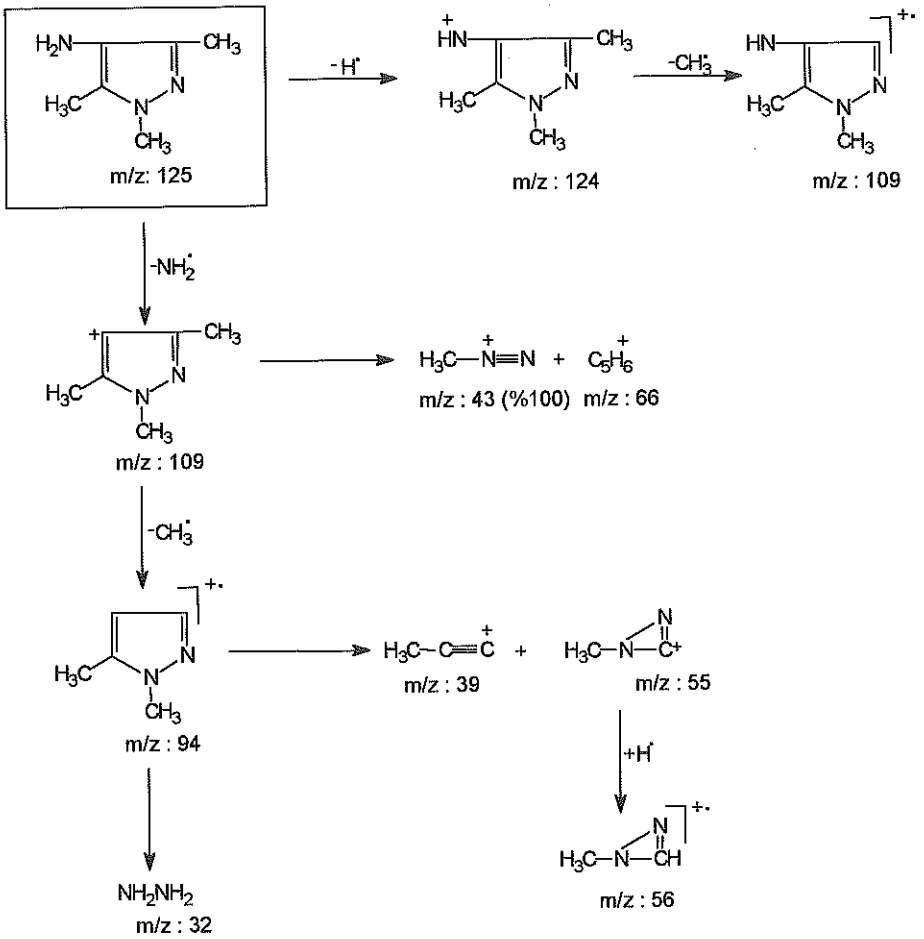

Scheme 4. Synthesis pathway followed for the preparation of the target compounds **I-V**

In conclusion we achieved a simple reduction of azo compounds to the corresponding amino derivatives by using hydrazine hydrate without a catalyst.

EXPERIMENTAL

All chemicals were purchased from Aldrich, Fluka and Merck in this study. UV spectra were recorded on a Beckman DU 530 spectrophotometer. The IR spectra were recorded on Perkin Elmer X 98 as KBr discs (νcm^{-1}). ^{1}H-NMR spectra (DMSO-d_6) were run on Bruker AVANCE -DPX 400 (400MHz) instrument with TMS as internal standard (chemical shifts in δ, ppm and coupling constants J in Hz).

Mass spectra were recorded on Fisons Instruments VG Platform II mass spectrometer (70 eV) with Electron Impact method and Agilent 1100 MSD spectrometer in the electrospray mode in The Turkish Scientific and Technical Research Council (TUBİTAK) laboratory.

General procedure for the synthesis of 4-aminopyrazoles: 4-aminopyrazoles were prepared by the reduction of azo compounds which were synthesized in four steps starting from appropriate amine compounds as mentioned in synthesis methods below. The aryldiazonium salts of amines were coupled with acetylacetone in the presence of sodium acetate. The precipitated hydrazone was recrystallized from ethanol. A solution of hydrazone in glaciel acetic acid was refluxed with substituted hydrazine / hydrazine hydrate for 5 hours. The product was filtered and recrystallized from ethanol (5,11). A solution of the azo compound (3.2 mmol) in ethanol was reduced with hydrazine hydrate (0.5 ml) at 50°C. The mixture was diluated with distilled water and extracted with diethyl ether. Resulting extract was evaporated and recrystallized from ethanol.

Acetylation of 4-(4-ethoxycarbonylphenylazo)-3,5- dimethyl-1-(2 hydroxyethyl)pyrazole:
4-(4-Ethoxycarbonylphenylazo)-3,5-dimethyl-1-(2-hydroxyethyl)pyrazole (**A**) was obtained according to the general synthesis method. 2.5 mmol **A** was refluxed with 5 ml acetic anhydride for 45 min. The precipitate formed was filtered and recrystallized from ethanol.

4-Amino-3,5-dimethylpyrazole **(I)***:* 80% Yield, mp 209 °C (lit. mp 203-205 °C (12); UV λmax nm(log ε) 237 (5.51), IR(KBr) 3347, 3163 (N-H); 2882 (C-H) cm^{-1}. ^{1}H-NMR, δ ppm: 2.10 (s, 6H, pyrazole 3,5-dimethyl); 3.30 (s, 2H, NH_2); 11.40 (s, 1H, pyrazole NH).

4-Amino-3,5-dimethyl-1-phenylpyrazole **(II)***:* 27% Yield, mp 67 °C (lit. mp 62 °C) (5).

4-Amino-3,5-dimethyl-1-(2-hydroxyethyl)pyrazole **(III)***:* 78% Yield, mp 102 °C (lit. mp 99-101 °C [14]; UV λmax nm(log ε) 242 (4.25), IR(KBr) 3284 (O-H and N-H); 2882 (C-H), 1393 (O-H), 1052 (C-O) cm^{-1}. ^{1}H-NMR, δ ppm: 2.15 (s, 3H, pyrazole 5-methyl); 2.27 (s, 3H, pyrazole 3-methyl), 2.60 (s, 2H, NH_2); 3.85 (t, 2H, CH_2CH_2OH); 4.00-4.20 (m, 3H, CH_2CH_2OH and CH_2CH_2OH).

4-(4-ethoxycarbonylphenylazo)-3,5-dimethyl-1-(2-acetyloxyethyl)pyrazole ***(B)****:* 60% Yield, mp 89°C; UV λmax nm 237; IR(KBr) 1710, 1740 (C=O); 1420, 1550 (C=C) cm^{-1}. ^{1}H-NMR, δ ppm: 1.27 (t, 3H, $-CH_3CH_2O-$); 1.90 (s, 3H, $-OCOCH_3$); 2.35 (s, 3H, pyrazole 3-methyl); 2.46 (s, 3H, pyrazole 5-methyl); 4.15 (t, 2H, $-N-CH_2CH_2-$); 4.26 (q, 2H, $-CH_3CH_2O$); 4.30 (t, 2H, $-CH_2CH_2O-$); 7.65 (d, 2H, J=8.58, ortho protons to

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azo); 7.98 (d, 2H, J=8.62, meta protons to azo). Mass (EI) m/z: 360.67(M^+), 358(100%), 209, 139, 87, 65, 43.

4-Amino-1-(2-acetyloxy)ethyl-3,5-dimethylpyrazole **(IV)**: 30% Yield, mp 60°C. UV λmax nm(log ε) 243(4.56). ^{1}H-NMR, δ ppm: 1.89 (s, 3H, -OCOCH$_3$), 2.34(s, 3H, pyrazole 5-methyl); 2.46 (s, 3H, pyrazole 3-methyl), 2.60 (s, 2H, NH$_2$); 3.90 (t, 2H, CH$_2$CH$_2$O-); 4.01(t, 2H, CH$_2$CH$_2$O-). Mass (ES) m/z: 198 (M^++1), 156 (100%), 139, 121, 112, 109, 96, 87.

4-Amino-1,3,5-trimethylpyrazole **(V)**: 66% Yield, mp 98 °C (lit. mp 100-101 °C [14]; UV λmax nm(log ε) 240 (4.28), IR(KBr) 3345, 3209 (N-H); 2941 (C-H) cm^{-1}. ^{1}H-NMR, δ ppm: 1.92 (s, 3H, pyrazole 5-methyl); 2.00 (s, 3H, pyrazole 3-methyl), 3.10 (s, 2H, NH$_2$). Mass (EI) m/z: 124(M^+-1), 109, 84, 66, 56, 55, 43(100%), 39.

REFERENCES

1. Mohapatra, S.K., Sonavane, S.U., Jayaram, R.V., Selvam, P., *Applied Catalysis B, Environmental,* **46**, 155-163 (2003).
2. Alonso, F., Radivoy, G., Yus, M., *Tetrahedron,* **56**, 8673-8678 (2000).
3. Vass, A., Dudas, J., Toth, J., Varma, R. S., *Tetrahedron Lett.*, **42**, 5347-5349 (2001).
4. Ergenç, N., Açıkkol, S., *J. Fac. Pharm. İstanbul.*, **8**, 101-108 (1972).
5. Ergenç,N., Rollas, S., *J. Fac. Pharm. İstanbul.*, **11**, 138-157 (1975).
6. Ergenç,N., Rollas, S., *J. Fac. Pharm. Istanbul.*, **11**, 177-182 (1975).
7. Ergenç,N., Rollas, S., *J. Fac. Pharm. Istanbul.*, **13**, 139-145 (1977).
8. Rollas, S., *J. Sci. And Tech., Univ. Mar.*,**1**, 59-68 (1985).
9. Rollas, S., *J. Sci. And Tech., Univ. Mar.*,**3**, 195-200 (1986).
10. Özger, Y., Rollas, S., *J. Sci. And Tech., Univ. Mar.*,**5**, 133-140 (1988).
11. Ergenç, N., Rollas, S., *J. Fac. Pharm. Istanbul*, **11**, 8-23 (1975).
12. Morgan, G.T., Reilly, J., *J. Chem. Soc.*, **105**, 435-443 (1914); CA , **8**, 1749 (1914).
13. Morgan, G.T., Ackerman, I., *J. Chem. Soc.*, **123**, 1308-1318 (1923); CA,**17**, 2580 (1923).
14. Bianchi, M., *Ann. Chim.*, **56**, 151-155 (1966); CA, **64**, 17571c (1966).
15. Tolf, B.R., Dahlbom, R., Akerson, A., Theorell H. *Biol. Princ. Natt. Prod.*, 265-277 (1984); CA, **101**, 125690k (1984).
16. Reilly, J., Mascweeney, D., *Prog. Roy. Irish. Acad.*, **29B**, 497-504 (1931); CA, **25**, 1523 (1931).

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