SYNTHESIS AND POTENTIOMETRIC TITRATIONS OF SOME NEW 4-(BENZYLIDENEAMINO)-4,5-DIHYDRO-1*H*-1,2,4-TRIAZOL-5-ONE DERIVATIVES IN NON-AQUEOUS MEDIA

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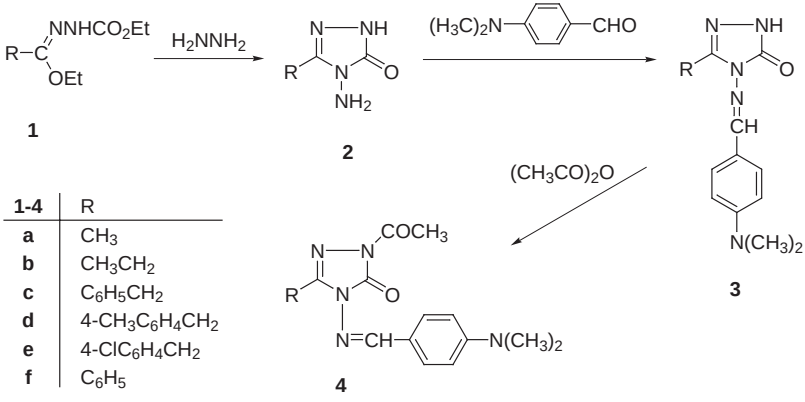
The synthesis of 3-alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) from the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 4-(dimethylamino)benzaldehyde is described. The newly synthesized **3** type compounds were titrated potentiometrically with tetrabutylammonium hydroxide in three non-aqueous solvents, including acetonitrile, isopropyl alcohol and *N*,*N*-dimethylformamide. The half-neutralization potential values and the corresponding pK_a values were determined for all cases. Thus, the effects of solvents and molecular structure upon acidity were investigated. In addition, *N*-acetyl derivatives of **3** type compounds were also obtained. The new synthesized compounds in the study were fully characterized.

Keywords: 4,5-Dihydro-1*H*-1,2,4-triazol-5-ones; Schiff bases; Acetylation; Acidity; Acidity constants; Potentiometric titration.

Several articles, involving the synthesis of some *N*-arylidenamino-1,2,4-triazole and *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, have been published up to date[1–10]. Also, the reactions of some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives with acetic anhydride were investigated[11–13]. In addition, antibacterial activities of some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been reported[10,13–17]. On the other hand, a number of studies involving the determination of pK_a values of some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives in non-aqueous solvents has been revealed[18–21]. In this study, a series of 3-alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) was synthesized from the reactions of

3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) with 4-(dimethylamino)benzaldehyde. The synthesized compounds **3** were titrated potentiometrically with tetrabutylammonium hydroxide in three non-aqueous solvents, acetonitrile, isopropyl alcohol and *N*,*N*-dimethylformamide to determine the pK_a values. For each new compound **3a**–**3f**, the potential of half neutralization (HNP) and the corresponding pK_a values were determined in the three mentioned non-aqueous solvents. The data obtained from the potentiometric titrations were interpreted, and the effect of substituent, in C-3 position and solvent effects were studied[18–21]. Determination of pK_a values of active constituents of certain pharmaceutical preparations is important, because their distribution, transport behavior, bonding to receptors, and contributions to metabolic behavior depend on the ionization constant[22–24]. Furthermore, the reactions of compounds **3** with acetic anhydride affording compounds **4** were investigated (Scheme 1).



1-4	R
a	CH_3
b	CH_3CH_2
c	$C_6H_5CH_2$
d	4-$CH_3C_6H_4CH_2$
e	4-$ClC_6H_4CH_2$
f	C_6H_5

SCHEME 1

EXPERIMENTAL

Melting points were taken on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra (wavenumbers in cm^{-1}) were registered on a Perkin–Elmer 1600 FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide on a Varian Mercury Apparatus at 200 MHz with TMS as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. UV absorption spectra (λ_{max} in nm) were measured in 10-mm quartz cells between 200 and 400 nm using a Shimadzu UV-1201 spectrophotometer. For potentiometric titrations, a Jenway 3040 ion analyser pH meter equipped with an Ingold pH electrode was used. Before potentiometric titrations, the pH meter was calibrated according to the instructions of the manufacturer. During the titrations, the titrant was added in increments of 0.05 ml after each stable reading, and the corresponding mV values were recorded.

Chemicals were purchased from Fluka and Merck. After purification, isopropyl alcohol was used to prepare 0.05 M tetrabutylammonium hydroxide (TBAH). For all potentiometric titrations, 0.05 M TBAH in isopropyl alcohol was used.

The starting compounds **2a**–**2f** were prepared from the corresponding ethyl *N*-(ethoxycarbonyl)hydrazonates **1a**–**1f** with hydrazine hydrate[12,25].

Preparation of 3-Alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**). General Procedure

3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**2**) (0.01 mol) was dissolved in acetic acid (15 ml) and treated with 4-(dimethylamino)benzaldehyde (1.49 g, 0.01 mol). The mixture was refluxed for 1 h and then evaporated at 50–55 °C *in vacuo*. Several recrystallizations of the residue from an appropriate solvent gave pure compounds **3**.

4-[4-(Dimethylamino)benzylideneamino]-3-methyl-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3a**). Colorless crystals, yield 83%. M.p. 118 °C (EtOH–toluene, 1 : 3). For $C_{12}H_{15}N_5O$ (245.3) calculated: 58.76% C, 6.16% H, 28.55% N; found: 59.01% C, 6.08% H, 28.40% N. ^{1}H NMR (DMSO-d_6): 2.24 (s, 3 H, CH_3); 2.99 (s, 6 H, 2 CH_3); 6.76 (d, *J* = 7.3, 2 H, Ar-H); 7.65 (d, *J* = 7.6, 2 H, Ar-H); 9.42 (s, 1 H, CH); 11.73 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 11.12, 39.75 (2 C) (aliphatic carbons); 111.49 (2 C), 120.17, 129.13 (2 C), 155.32 (aromatic carbons); 144.03 (triazole C 3); 151.36 (N=CH); 152.24 (triazole C 5). IR (KBr): 3 205 (NH), 1 700 (C=O), 1 615, 1 610 (C=N), 815 (1,4-disubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 351 (10 680).

4-[4-(Dimethylamino)benzylideneamino]-3-ethyl-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3b**). Colorless crystals, yield 72%. M.p. 134 °C (EtOH–H_2O, 1 : 3). For $C_{13}H_{17}N_5O$ (259.3) calculated: 60.21% C, 6.61% H, 27.01% N; found: 60.02% C, 6.68% H, 26.80% N. ^{1}H NMR (DMSO-d_6): 1.22 (t, 3 H, CH_3); 2.62 (q, 2 H, CH_2); 3.00 (s, 6 H, 2 CH_3); 6.76 (d, *J* = 7.0, 2 H, Ar-H); 7.62 (d, *J* = 7.0, 2 H, Ar-H); 9.43 (s, 1 H, CH); 11.77 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 10.02, 18.60, 39.59 (2 C) (aliphatic carbons); 111.54 (2 C), 120.31, 129.12 (2 C), 155.25 (aromatic carbons); 147.88 (triazole C 3); 151.58 (N=CH); 152.28 (triazole C 5). IR (KBr): 3 203 (NH), 1 695 (C=O), 1 620, 1 605 (C=N), 815 (1,4-disubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 351 (16 570), 210 (8 610).

3-Benzyl-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3c**). Colorless crystals, yield 68%. M.p. 141 °C (EtOH–toluene, 1 : 3). For $C_{18}H_{19}N_5O$ (321.4) calculated: 67.27% C, 5.96% H, 21.79% N; found: 66.90% C, 6.00% H, 21.53% N. ^{1}H NMR (DMSO-d_6): 3.00 (s, 6 H, 2 CH_3); 4.01 (s, 2 H, CH_2); 6.76 (d, *J* = 8.2, 2 H, Ar-H); 7.24–7.32 (m, 5 H, Ar-H); 7.60 (d, *J* = 8.2, 2 H, Ar-H); 9.40 (s, 1 H, CH); 11.90 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 31.07, 39.57 (2 C) (aliphatic carbons); 111.52 (2 C), 120.31, 126.59, 128.32 (2 C), 128.71 (2 C), 129.13 (2 C), 136.00, 155.25 (aromatic carbons); 146.10 (triazole C 3); 151.58 (N=CH); 152.18 (triazole C 5). IR (KBr): 3 202 (NH), 1 705 (C=O), 1 620, 1 600 (C=N), 825 (1,4-disubstituted benzenoid ring), 740, 710 (monosubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 348 (17 850), 212 (8 380).

4-[4-(Dimethylamino)benzylideneamino]-3-(4-methylbenzyl)-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3d**). Colorless crystals, yield 78%. M.p. 116 °C (EtOH). For $C_{19}H_{21}N_5O$ (355.4) calculated: 68.04% C, 6.31% H, 20.88% N; found: 67.85% C, 6.53% H, 20.61% N. ^{1}H NMR (DMSO-d_6): 2.24 (s, 3 H, CH_3); 3.00 (s, 6 H, 2 CH_3); 3.95 (s, 2 H, CH_2); 6.75 (d, *J* = 8.8, 2 H, Ar-H); 7.25–7.31 (m, 4 H, Ar-H); 7.60 (d, *J* = 8.8, 2 H, Ar-H); 9.38 (s, 1 H, CH); 11.90 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 20.51, 30.66, 39.58 (2 C) (aliphatic carbons); 111.54 (2 C), 120.20,

128.57 (2 C), 128.88 (2 C), 129.12 (2 C), 132.75, 135.63, 154.87 (aromatic carbons); 146.19 (triazole C 3); 151.35 (N=CH); 152.26 (triazole C 5). IR (KBr): 3 210 (NH), 1 715 (C=O), 1 620, 1 615 (C=N), 820 (1,4-disubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 349 (17 900), 210 (5 500).

3-(4-Chlorobenzyl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3e**). Colorless crystals, yield 74%. M.p. 121 °C (EtOH–toluene, 1 : 3). For $C_{18}H_{18}ClN_5O$ (355.8) calculated: 60.76% C, 5.10% H, 19.68% N; found: 60.57% C, 4.97% H, 19.40% N. ^{1}H NMR (DMSO-d_6): 2.99 (s, 6 H, 2 CH_3); 4.02 (s, 2 H, CH_2); 6.76 (d, *J* = 7.6, 2 H, Ar-H); 7.35 (s, 4 H, Ar-H); 7.54 (d, *J* = 8.2, 2 H, Ar-H); 9.41 (s, 1 H, CH); 11.91 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 30.42, 39.77 (2 C) (aliphatic carbons); 111.52 (2 C), 120.13, 128.24 (2 C), 129.16 (2 C), 130.65 (2 C), 131.26, 134.83, 154.95 (aromatic carbons); 145.69 (triazole C 3); 151.35 (N=CH); 152.26 (triazole C 5). IR (KBr): 3 200 (NH), 1 700 (C=O), 1 620, 1 598 (C=N), 820 (1,4-disubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 334 (33 330), 217 (14 280).

4-[4-(Dimethylamino)benzylideneamino]-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3f**). Colorless crystals, yield 60%. M.p. 114 °C (EtOH–H_2O, 1 : 3). For $C_{17}H_{17}N_5O$ (307.4) calculated: 66.43% C, 5.57% H, 22.79% N; found: 66.55% C, 5.43% H, 22.50% N. ^{1}H NMR (DMSO-d_6): 3.00 (s, 6 H, 2 CH_3); 6.78 (d, *J* = 7.0, 2 H, Ar-H); 7.51–7.66 (m, 5 H, Ar-H); 7.93 (d, *J* = 6.4, 2 H, Ar-H); 9.30 (s, 1 H, CH); 12.31 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 39.55 (2 C) (aliphatic carbons); 111.57 (2 C), 119.90, 126.86, 127.60 (2 C), 128.40 (2 C), 129.44 (2 C), 144.24, 158.59 (aromatic carbons); 145.69 (triazole C 3); 151.53 (N=CH); 152.46 (triazole C 5). IR (KBr): 3 200 (NH), 1 710 (C=O), 1 620, 1 600 (C=N), 825 (1,4-disubstituted benzenoid ring), 745, 700 (monosubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 350 (28 760), 221 (22 200).

Preparation of 1-Acetyl-3-alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**). General Procedure

The corresponding compound **3** (0.01 mol) was refluxed with acetic anhydride (15 ml) for 0.5 h. After addition of absolute ethanol (50 ml), the mixture was refluxed for 1 h. Evaporation of the resulting solution at 40–45 °C *in vacuo* and several recrystallizations of the residue from an appropriate solvent gave pure compounds **4**.

1-Acetyl-3-benzyl-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1H-1,2,4-triazol-5-ones (**4c**). Colorless crystals, yield 83%. M.p. 151 °C (benzene–petroleum ether, 1 : 3). For $C_{20}H_{21}N_5O_2$ (363.4) calculated: 66.10% C, 5.82% H, 19.27% N; found: 65.86% C, 5.65% H, 19.50% N. ^{1}H NMR (DMSO-d_6): 2.49 (s, 3 H, $COCH_3$); 3.00 (s, 6 H, 2 CH_3); 4.01 (s, 2 H, CH_2); 6.76 (d, *J* = 7.6, 2 H, Ar-H); 7.30–7.35 (m, 5 H, Ar-H); 7.60 (d, *J* = 8.9, 2 H, Ar-H); 9.40 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6): 23.47, 31.15, 39.35 (2 C) (aliphatic carbons); 111.52 (2 C), 120.18, 126.58, 128.93 (2 C), 129.13 (2 C), 129.57, 134.67, 135.86, 154.87 (aromatic carbons); 146.04 (triazole C 3); 151.36 (N=CH); 152.24 (triazole C 5); 166.10 (C=O). IR (KBr): 1 770, 1 710 (C=O), 1 615, 1 600 (C=N), 825 (1,4-disubstituted benzenoid ring), 750, 700 (monosubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 352 (15 540), 209 (8 690).

1-Acetyl-4-[4-(dimethylamino)benzylideneamino]-3-(4-methylbenzyl)-4,5-dihydro-1H-1,2,4-triazol-5-ones (**4d**). Colorless crystals, yield 84%. M.p. 149 °C (benzene–petroleum ether, 1 : 3). For $C_{21}H_{23}N_5O_2$ (377.5) calculated: 66.83% C, 6.14% H, 18.55% N; found: 66.80% C, 6.02% H, 18.42% N. ^{1}H NMR (DMSO-d_6): 2.26 (s, 3 H, CH_3); 2.50 (s, 3 H, $COCH_3$); 3.02 (s, 6 H, 2 CH_3); 4.03 (s, 2 H, CH_2); 6.78 (d, *J* = 8.9, 2 H, Ar-H); 7.15–7.27 (m, 4 H, Ar-H); 7.63 (d, *J* = 8.6, 2 H, Ar-H); 9.22 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6): 20.57, 23.50, 30.68, 39.35 (2 C) (aliphatic car-

bons); 111.54 (2 C), 119.48, 128.93 (2 C), 129.00 (2 C), 129.61 (2 C), 131.55, 136.02, 157.51 (aromatic carbons); 146.25 (triazole C 3), 151.52 (N=CH); 151.62 (triazole C 5), 166.02 (C=O). IR (KBr): 1 775, 1 705 (C=O), 1 625, 1 600 (C=N), 828 (1,4-disubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 353 (11 350), 210 (6 720).

1-Acetyl-4-[4-(dimethylamino)benzylideneamino]-3-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-ones (**4f**). Colorless crystals, yield 93%. M.p. 175 °C (benzene–petroleum ether, 1 : 3). For $C_{19}H_{19}N_5O_2$ (349.4) calculated: 65.32% C, 5.48% H, 20.04% N; found: 65.61% C, 5.55% H, 19.80% N. ^{1}H NMR (DMSO-d_6): 2.59 (s, 3 H, $COCH_3$); 3.02 (s, 6 H, 2 CH_3); 6.79 (d, J = 7.2, 2 H, Ar-H); 7.20–7.95 (m, 7 H, Ar-H); 9.14 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6): 23.75, 39.57 (2 C) (aliphatic carbons); 111.78 (2 C), 119.39, 125.70, 128.57 (2 C), 128.78 (2 C), 130.05 (2 C), 131.34, 161.41 (aromatic carbons); 146.08 (triazole C 3), 151.45 (N=CH); 153.02 (triazole C 5), 166.46 (C=O). IR (KBr): 1 760, 1 720 (C=O), 1 625, 1 595 (C=N), 815 (1,4-disubstituted benzenoid ring), 735, 695 (monosubstituted benzenoid ring). UV (ethanol), λ_{max} (ε): 355 (25 970), 221 (16 000).

RESULTS AND DISCUSSION

Several studies of potentiometric titrations of some 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives with tetrabutylammonium hydroxide (TBAH) in non-aqueous solvents such as isopropyl alcohol, methyl alcohol, *tert*-butyl alcohol and acetone were found in literature; they give[19–21] the pK_a values for the compounds ranging from 9.79 to 16.05.

In this study, six new 3-alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**) and three new 1-acetyl-3-alkyl(aryl)-4-[4-(dimethylamino)benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**4**) were synthesized. Compounds **3** were titrated potentiometrically with TBAH in non-aqueous solvents such as isopropyl alcohol, *N*,*N*-dimethylformamide and acetonitrile of relative dielectric permittivity 19.4, 37 and 36, respectively. From the titration curves, the HNP values and the corresponding pK_a values were obtained.

As an example, the potentiometric titration curves for 0.001 M 4-[4-(dimethylamino)benzylideneamino]-3-(4-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3d**) solutions titrated with 0.05 M TBAH in isopropyl alcohol, *N*,*N*-dimethylformamide and acetonitrile are given in Fig. 1. As it is clearly seen, a typical S-shaped titration curve was obtained.

The half-neutralization potentials (HNP) and the corresponding pK_a values for compounds **3a**–**3f**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *N*,*N*-dimethylformamide and acetonitrile are given in Table I.

As it is well known, the acidity of a compound depends on some factors. The two most important factors are the solvent effect and molecular structure[19–21,26–31]. Table I shows that the HNP values and corresponding pK_a

TABLE I
The half-neutralization potentials (HNP) and the corresponding pK_a values of compounds **3a**–**3f** in isopropyl alcohol, *N*,*N*-dimethylformamide and acetonitrile

Compound	Isopropyl alcohol		*N*,*N*-Dimethyl formamide		Acetonitrile	
	HNP, mV	pK_a	HNP, mV	pK_a	HNP, mV	pK_a
3a	–402	14.05	–462	15.31	–570	17.72
3b	–352	13.39	–446	15.22	–449	15.22
3c	–398	14.33	–492	15.79	–512	16.47
3d	–388	14.18	–369	12.44	–376	13.86
3e	–430	14.22	–537	17.63	–511	16.72
3f	–342	13.01	–472	15.54	–485	15.76

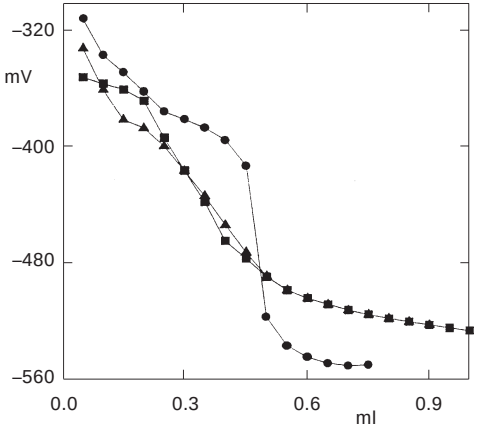


FIG. 1
Potentiometric titration curves of 10^{-3} M 4-[4-(dimethylamino)benzylideneamino]-3-(4-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3d**) solutions titrated with 0.05 M TBAH in isopropyl alcohol (▲), *N*,*N*-dimethylformamide (❑) and acetonitrile (●) at 25 °C

values obtained from potentiometric titrations depend on the non-aqueous solvents used. The results obtained illustrate that acetonitrile is the best solvent. As can be observed in Fig. 1, for example, the potential jump of compound **3d** in the end-point is very large for acetonitrile ranging from –413 to –517 mV.

In addition, Table I shows that the molecular structure of titrated compounds affects the HNP and corresponding pK_a values depending on the substituents at C-3 in the same solvent.

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