Synthesis, Acidity Constants and Tau to meric Structure of 7-Arylhydrazono[1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines in Ground and Excited States

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7-Arylhydrazono[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **4** were syn the sized from the re actions of 4-amino-5-phenyl-4H-[1,2,4]triazole-3-thiol **2** and 2-(2-naphthyl)-2-oxoethanehydrazonoyl bro mides **1** and their acid dis so ci a tion con stants pK and pK*, in the ground and ex cited states, re spec tively, were determined. Both pK and pK* con stants were cor re lated by Hammett equa tion. The pK and the spec tral data pre sented indicate that the title com pounds ex ist pre dom in antly in the hydrazone tau to meric form.

INTRODUCTION

Many de riv a tives of the [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine ring sys tem have at tracted con sider able at ten tion of many research groups be cause of their di verse and in ter estingbiological and phar macological activities.¹⁻³ How ever, the arylazo de riv a tives of such a ring sys tem have been hitherto un re ported, al though the arylazo group ing is known to be im por tant in pro moting anti-neoplastic ac tivity.⁴ In view of the im portant biological activities dis placed by [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines and azo groups, it was consid ered worth while to syn the size a series of the title compounds 4(Scheme I) and de ter mine their acid dis so ci a tion con stants pK and pK* in the ground and ex cited states, respec tively. Such arylazo com pounds are of in ter est to us due to the fol low ing. On the one hand, some of them might be use ful as potential pre cursors to novel pho to graphic cou plers





X = Br or CI; Ph = C_6H_5 ; R = 2-naphthyl

Ar = ZC₆H₄ ; Z : a, 4-MeO; b, 4-Me; c, 3-Me; d, H; e, 4-Cl; f, 3-Cl; g, 3-NO2; h, 4-MeCO; i, 4-EtOCO; j, 4-NO2 and/or la ser production.⁵ On the other hand, as they can exhibit azo-hydrazone tau tom erism, we aimed to elu ci date their ac tual tau to meric structure in both ground and excited states.

RESULTS AND DISCUSSION

The re quired hith erto un re ported N-aryl 2-(2- naphthyl)-2-oxoethanehydrazonoyl bro mides **1a-c, f-j** were pre pared by the cou pling of dimethyl 2-naphthoylmethylsulfonium bro mide with the ap pro pri ate diazotized an i lines in eth a nol in the pres ence of so dium ac e tate trihydrate. Their struc tures were sub stan ti ated by their spec tra (MS, IR and ¹H NMR) and el e men tal anal y ses (Ta ble 1 and 4). The other bro mides **1d** and **1e** were pre pared as pre vi ously re ported. ¹⁸

Reaction of 4-amino-5-phenyl-4H-1,2,4-triazole-3thiol **2** with 2-Aryl-2-oxoethanehydrazonoyl bro mides **1a-g** in eth a nol in the pres ence of so dium ethoxide af forded the respec tive thiohydrazonate es ters **3a-g**, re spec tively (Scheme I). Similar eactions of **2** with **1h-j** un der the same con ditions, di rectly af forded, how ever, the re spec tive 7-arylhydrazono-3,6-diaryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **4h-j**, proba bly via*in situ* dehydrative cyclization of the ini tially formed thiohydrazonates **3h-j** (Scheme I). The con ver sion of **3a-g** into the re spec tive triazolothiadiazines **4a-g** was af fected by their treat ment with ace tic acid. The struc tures of the products **4a-j** and their thiohydrazonate pre cur sors **3a-j** were estab lished on the ba sis of their el e men tal anal y sis and specral data (MS, ¹H NMR, IR and UV) (Ta bles 1-4).

At ten tion was then turned to the tau to meric struc ture of the prod ucts **4a-j** as they can ex ist in the tau to meric hydrazone form **4A** or the arylazoenamine form **4B** (Scheme I). Unfortunately, their IR spectra (Ta ble 2) which were re-

Compd. No.	v (KBr) cm ⁻¹ / m/e (%)				
1a	3290, 1650, 1615 /				
	384(4), 383(5), 239(14), 155(100), 127(75), 122(63), 95(11), 77(14), 65(7)				
1b	3270, 1655, 1615 /				
	367(3), 366(5), 323(23), 155(100), 127(55), 91(4), 77(20)				
1c	3270, 1655, 1615 /				
	367(15), 366(19), 156(16), 155(100), 127(87), 91(2), 77(15)				
1f	3242, 1654, 1527 /				
	383(2), 387(2), 155(100), 127(79), 99(13), 77(12)				
1g	3224, 1649, 1625 /				
	$399(3), 397(4), 353 (M^+ - NO_2)(16), 155(100), 127(83), 95(11), 77(13)$				
1h	3220, 1670, 1645, 1625 /				
	396(10), 395(3), 352(10), 351(34), 350(91), 154(4), 127(100), 119(20),				
2-	//(10)				
3 a	3375, 3300, 3000, 1708, 10147 406(20), 201(58), 255(45), 282(61), 262(62), 102(22), 180(70)				
	490(50), 591(50), 553(45), 263(01), 202(02), 195(52), 160(79), 155(04), 127(60), 102(87), 86(100), 77(26), 102(87), 86(100), 77(26), 102(87), 102				
3h	135(94), 127(00), 102(87), 80(100), 77(20)				
50	479(5) $478(4)$ $461(35)$ $422(75)$ $208(25)$ $191(1)$ $155(100)$ $127(75)$				
	103(44), 91(55), 77(32)				
3c	3210. 3186. 3043. 1700. 1616 /				
	479(5), 478(3), 461(35), 432(13), 343(17), 257(9), 191(1), 188(27), 171(7),				
	155(26), 126(25), 103(44), 91(100), 77(31).				
3d	3215, 3150, 1695, 1649 /				
	465(8), 464(10), 415(15), 414(18), 375(12), 251(18), 191(28), 180(37),				
	155(100), 127(91), 103(21), 91(14), 77(65)				
3e	3330, 3205, 3058, 1650, 1620 /				
	497(1.0), 449(3), 409(8), 361(4), 299(10), 270(41), 214(24), 155(100),				
	127(55), 105(8), 77(6)				
3f	3274, 3186, 3060, 1650, 1618 /				
	497(3), 449(9), 409(24), 388(8), 299(32), 270(100), 214(75), 167(18),				
	155(10), 108(11), 79(9)				
3g	3245, 3185, 1695, 1616 /				
	$404(191 - 190_2)(28), 432(21), 328(23), 299(19), 289(11), 281(18), 250(11), 232(12), 102(7), 188(35), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(48), 164(12), 152(90), 155(59), 177(10), 171(16), 171(16), 171(16), 171(16), 171(16), 171(16), 171(16), 152(90), 155(59), 152(59)$				
	220(13), 192(7), 188(25), 177(19), 171(48), 164(12), 153(80), 155(58), 127(04), 102(100), 01(22), 77(68)				
	12/(94), 105(100), 91(22), //(68)				

Table 1. IR and Mass Spectral Data of the New Compounds 1 and 3

corded in po tas sium bro mide were not of too much help to decide which is the ac tual tau to meric form of the com pounds in ques tion. This prob lem was solved by ex am in ing both the ¹H NMR and UV spec tra of **4a-j** and cor re la tion of their acid ity con stants by Hammett equa tion.

The ¹H NMR spec tra of **4a-j** in deuterated chlo ro form re vealed, in each case, the pres ence of only one NH pro ton sig nal near δ 10.34-10.91 (Ta ble 3). The ap pear ance of only the lat ter sig nal in the re gion δ 10.0-12.0 in di cates that the stud ied com pounds **4a-j** ex ist pre dom i nantly in the hydrazone form **4A**. This is be cause the ¹H NMR spec tra of compounds that ex ist as an equi lib rium mix ture of hydrazone and azo tautomers were re ported to show in each case two exchange able singlets at δ 10.12 and δ 11.50 cor re spond ing together to one pro ton as sign able to the NH pro ton res o nances of the hydrazone and arylazoenamine forms, re spec tively.⁷

The elec tronic ab sorp tion spec tra of the com pounds **4a-j** in dioxane (Ta ble 2) are also com pat i ble with the hydrazone form **4A**. As shown in Ta ble 2, each com pound ex hib its in dioxane two bands in the re gions 270-350 and 350-440 nm. Such an ab sorp tion pat tern is sim i lar to that of typ i cal hy drazones.⁸ Fur ther more the spec tral data of the unsubstituted derivative **4d**, taken as a rep re sen ta tive ex am ple of the se ries stud ied, in differ ent sol vents (Ta ble 2) show small shifts in λ_{max} . Such small shifts in λ_{max} of **4d** in differ ent sol vents are due to sol vent-solute in ter ac tion and are con sis tent with the as signed tau to meric form **4A**. In agree ment with this con clusion is the ob ser va tion that the spec tra of arylhydrazones de-

Table 2. Electronic Absorption and IR Spectral Data of the Compounds **4a-j**

Compd. No.	λ_{max} (Dioxane) (Log ϵ)	∨ (cm ⁻¹) NH, C=N, C=O
4a 4b 4c 4d ⁺ 4e 4f 4g 4h	408 (3.86), 300 (4.29) 392 (3.88), 305 (4.23) 398 (4.02), 312 (4.26) 394 (4.13), 310 (4.35) 390 (4.06), 304 (4.23) 389 (4.01), 302 (4.22) 379 (4.16), 307 (4.36) 397 (4.40), 319 (4.42)	NH, C=N, C=O 3150, 1602 3190, 1612 3170, 1614 3120, 1608 3150, 1609 3100, 1620 3110, 1620 3147, 1618, 1670
4i 4j	393 (4.31), 318 (4.38) 406 (4.51), 325 (4.29)	3159, 1610, 1706 3160, 1610

⁺ Solvent: λ_{max} (Log ε) Ethanol: 400 (4.11), 305 (4.32); Chloroform: 395 (4.06), 316 (4.26); Acetic acid: 389 (3.69), 310 (4.01); Cyclohexane: 401 (3.80), 305 (4.07); Pyridine: 404 (3.90), 331 (4.02); Ether: 396 (3.90), 307 (sh) (4.23).

rived from the re ac tion of qui nones with N-alkyl-N- arylhydrazines, un like those of o-hydroxy and p-hydroxy-azo com pounds, are largely in dependent of the sol vent po larity.⁹

Re cently, it has been shown that LFER cor re la tion of the acid ity con stants of a se ries of com pounds that can ex ist in the azo and/or the hydrazone tau to meric forms can be used to iden tify their ac tual tau to meric form(s).¹⁰ Ac cord ingly, in the pres ent work, the acid ity con stants, pK's, of the se ries 4a-j were determined by spec tropho to metric method in 80% (v/v) dioxane-water mix ture at 27 °C and ionic strength of 0.1. In acid me dium each of the com pounds un der study shows a maximum (band A) in the region 350-450 nm, whereas in al kaline me dium it ex hib its an other max i mum (band-B) in the re gion 450-590 nm. As the pH in creases, the height of the for mer band-A de creases and si mul ta neously that of the sec ond band-B in creases and the spec tra show, in each case, one isobestic point in di cat ing the pres ence of at least two spe cies in equi lib rium. This spec tral be hav iour is characteristic of a simple one-stage protolytic equilibrium. In each case, plots of absorbance val ues at ei ther one of the two char ac ter is tic wave lengths ex hibit sig moid curves with in flec tion point at a given pH value that cor re sponds to the appar ent pK value of the com pound un der study. From the pHabsorbance data the respective acidity constants in the ground state were cal cu lated and the re sults are sum ma rized in Table 5.

As shown in the latter Table 5, the acid ity constants of **4** are influenced by the substituents present in the phenyl group, being increased by electron with drawing substituent and decreased by electron do nating groups. Correlation of the pK_a data with the Hammett substituent constants \overline{Q}_x and \overline{Q}_x^- resulted in the following equations:

$$pK = 10.88 - 3.03 \, \mathbb{Q}_x; r = 0.967; s = \pm 0.10 \tag{1}$$

Compd. m/e (%) No. 477(15), 476(22), 449(31), 416(14), 310(19), 342(39), 282(46), 273(15), 266(33), **4**a 153(53), 134(28), 127(57), 122(70), 103(78), 77(100) 4b 461(34), 460(22), 433(390), 400(11), 343(26), 258(18), 153(36), 126(12), 91(100), 77(42) 4c 461(5), 460(34), 431(17), 342(32), 257(20), 188(27), 153(40), 139(14), 127(46), 103(72), 91(100), 77(47) 4d 447(30), 446(22), 418(13), 342(24), 244(9), 188(20), 153(33), 139 (8), 127(39), 103(70), 92(12), 77(100) 4e 481(22), 480(38), 453(21), 420(20), 342(20), 286(16), 277(13), 238(15), 196(15), 188(37), 171(26), 153(63), 127(55), 111(41), 103(100), 99(26), 77(55) 4f 481(48), 480(20), 343(36), 238(14), 188(37), 154(65), 153(100), 127(68), 125(23), 111(46), 103(88), 99(26), 77(84) 4g 492(61), 491(56), 464(50), 432(16), 431(14), 355(12), 341(18), 311(13), 288(14), 196(16), 188(62), 171(24), 153(76), 139(15), 127(62), 103(100), 91(13), 77(47) 4h 489(81), 488(44), 343(36), 328(16), 296(21), 286(20), 188(54), 165(21), 153(82), 137(20), 127(70), 119(66), 103(100), 91(37), 77(70) 4i 520(10), 519(22), 459(17), 342(29), 297(25), 264(17), 228(11), 196(14), 188(34), 171(26), 165(20), 153(83), 149(28), 127(87), 103(100), 92(18), 77(92) 4j 492(27), 491(26), 328(26), 312(26), 298(15), 188(36), 171(68), 153(100), 139(25), 127(60), 103(93), 91(18), 77(36)

Table 3. Characteristic Mass Spectral Data of the New Products 4a-j

Compd. No.	δ (multiplicity, number of protons) ⁺
la	3.7 (s, 3H), 7.2-8.25 (m, 11H), 8.92 (s, 1H)
1b	2.25 (s, 3H), 6.7-8.1 (m, 11H), 8.7 (s, 1H)
1c	2.31 (s, 3H), 7.0-8.4 (m, 11H), 8.65 (s, 1H)
1f	7.07-8.08 (m, 11H), 8.62 (s, 1H)
1g	6.76-8.16 (m, 11H), 8.56 (s, 1H)
1h	2.55 (s, 3H), 7.19-8.65 (m, 11H), 8.87 (s, 1H)
3a	3.69 (s, 3H), 6.22 (s, 2H), 6.7-8.4 (m, 16H), 10.8 (s, 1H)
3b	2.20 (s, 3H), 5.97 (s, 2H), 7.0-8.5 (m, 16H), 10.7 (s, 1H)
3c	2.40 (s, 3H), 6.41 (s, 2H), 6.92-8.11 (m, 16H), 11.14 (s, 1H)
3d	5.96 (s, 2H), 7.05-8.52 (m, 17H), 10.71 (s, 1H)
3e	5.94 (s, 2H), 7.19-8.49 (m, 16H), 10.80 (s, 1H)
3g	6.16 (s, 2H), 7.19-8.10 (m, 16H), 10.80 (s, 1H)
4a	3.36 (s, 3H), 6.99-8.10 (m, 16H), 10.34 (s, 1H)
4b	2.16 (s, 3H), 7.56-8.38 (m, 16H), 10.51 (s, 1H)
4c	2.14 (s, 3H), 7.72-8.43 (m, 16H), 10.59 (s, 1H)
4d	6.92-8.40 (m, 17H), 10.59 (s, 1H)
4e	7.08-8.41 (m, 16H), 10.69 (s, 1H)
4f	7.9-8.43 (m, 16H), 10.70 (s, 1H)
4g	7.47-8.44 (m, 16H), 10.95 (s, 1H)
4h	2.30 (s, 3H), 7.05-8.53 (m, 16H), 10.71 (s, 1H)
4i	1.72 (t, <i>J</i> = 7 Hz, 3H), 4.22 (q, <i>J</i> = 7 Hz, 2H), 7.14-8.43 (m, 16H), 10.91 (s,
	1H)
4j	7.19-8.12 (m, 16H), 11.17 (s, 1H)

Table 4. ¹H NMR Spectra Data of the Compounds 1, 3 and 4

⁺ in CDCl₃ or DMSO-d₆

$$pK = 10.89 - 2.35 \ Q_x^-; r = 0.985; s = \pm 0.06$$
 (2)

where r and s are the cor relation co efficient and the stan dard de viation, respectively. From the values of r and s, it is ob vious that the pK values are better cor related with the ex alted Hammett substituent con stant Q_x^- .

The observed linear correlation between pK and $\overline{g_x}^{-}$ indicates that among the possi ble tau to meric hydrazone and

Table 5. Acid Dissociation Constants of **4a-j** in Ground and Excited States

Compd.	pK	λ_{max}	λ_{max}	Δv _	pK*
No.		(a)	(b)	(cm^{-1})	
4a	11.55	405	500	4691	1.79
4b	11.30	402	496	4714	1.43
4c	11.22	400	499	4959	0.91
4d	11.14	400	504	5158	0.41
4 e	10.06	405	504	4850	-0.028
4f	9.68	390	505	5839	-2.46
4g	9.30	384	496	5880	-2.93
4h	8.94	397	526	6176	-3.91
4i	9.22	393	514	5990	-3.24
4i	8.02	410	576	7029	-6.60

(a) in acid medium; (b) in alkaline medium

azo forms **4A** and **4B**, respectively, the former tautomeric form predominantly exists in solution. This is because if **4** exists as equilibrium mix ture of say **4A** and **4B** (Scheme II), the effective acid dis sociation constant K will be given by the equation:

$$K = K_1 / (K_T + 1) = K_2 K_T / (1 + K_T)$$
(3)

where K_1 and K_2 are the acid dis so ci a tion constants of the hydrazone and azo tautomers, respectively, and K_T is the tau-

Scheme II



to meric equi lib rium con stant. Ac cord ing to this last equation a lin ear cor re la tion be tween pK and \mathbb{Q}_x^- would be ob served only if K_T is in de pend ent of the substituent and this will never be the case.¹¹ Fur ther more, the value of $\rho = 2.35$ seems to be in fa vor of the hydrazone tau to mer**4A** as it is in good agreement with those re ported for sim i lar hy dra zones and not arylazo derivtives.¹² If the azo form **4B** were the predom i nant tau to mer for the stud ied com pounds **4a-j**, the value of the reaction con stant ρ would have been not more than 0.75. This is be cause the transmissive fac tor for the bridge -C=C-N=N- in the azo form **4B** is ex pected to be 0.32 as the transmissive factors of the -C=C- and -N=N- bridges were re ported to be 0.47 and 0.69, re spec tively.¹³

To shed some light on the pre dom i nant tauomeric form of the products 4a-j in the excited state, we ex am ined the corre la tion of their acid ity con stants pK* in the sin glet ex cited state with the Hammett con stants \mathbf{Q}_x and \mathbf{Q}_x . At present there are three methods avail able for the determination of the acid dis so ci a tion con stant pK* of a sin glet ex cited state. These are: (a) mea sure ment of flu o res cence in ten sity as a func tion of pH; (b) measure ment of flu ores cence frequency of the acid and its con ju gate base; and (c) mea sure ment of ab sorp tion fre quency of both spe cies.¹⁴ As method-c is rather gen eral, it was adopted in the pres ent work to de ter mine the ex cited state pK* values for the reaction series 4a-jun der study. Accord ing to this method, which uti lizes the so-called Forster energy cycle, ¹⁵ the value of ΔpK , the difference between the val ues of the acid ity con stants pK* and pK of a given compound in the ex cited state and ground states, re spec tively, is usu ally eval u ated by the equation:

$$\Delta pK = pK^* - pK = 0.625 \ (\Delta v)/T$$
 (4)

where $\Delta \nu$ rep re sents the fre quency difference (in wave number) be tween the ab sorp tion λ_{max} of the neutral compound and its conjugate acid or base.^{14,16} The values of pK*, calculated for the reaction series **4a-j** using this equation are given in Table 5.

As shown, the val ues of pK^* , like those of pK of the ground state, are in flu enced by the substituent in the hydrazone moi ety. Cor re la tion of these pK^* data with the Hammett substituent con stants, \mathbb{Q}_x and \mathbb{Q}_x^- us ing the method of least squares gave the following linear equations:

$$pK^* = 0.407 - 6.76 \, \overline{q}_x; r = 0.939; s = \pm 0.14 \tag{5}$$

$$pK^* = 0.439 - 5.28 \ Q_x^-; r = 0.985; s = \pm 0.06$$
 (6)

Such data in di cate that pK^* are also better cor re lated with $\overline{0}_x$ con stants. Fur ther more, a sin gle glance at the p val-

ues ob tained shows that they are larger than the cor re sponding ground state values. These re sults em pha size the im portance of res o nance ef fects in ex cited states, which are, of course, ex pected since ionic res o nance struc tures make much larger con tri bu tion in the ex cited state than to ground state. In ad di tion, such lin ear cor re la tions in di cate that the stud ied com pounds ex ist pre dom i nantly in the ex cited state in one tau to meric form, namely the hydrazone tau to mer **A**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal ap para tus and they are un corrected. IR spec tra of all new compunds were re corded in KBr us ing Fou rier Trans form and Pye Unicam SP300 In fra red spec tro pho tometers. ¹H NMR spec tra were re corded in deutrated chlo ro form or dimethylsulfoxide us ing a Varian Gem ini 200 NMR spectrom e ter. Mass spec tra were re corded on a GCMS-Q P1000-EX Varian MAT 711 and SSQ 7000 spec trom e ters. The ul travi o let spec tra were re corded us ing a Perkin Elmer Lambda 40 spectrophotometer. El e men tal anal y ses were car ried out at the Microanalytical Cen ter of Cairo Uni ver sity, Giza, Egypt.

4-Amino-5-phenyl-4H-1,2,4-triazole-3-thiol **2** and Naryl 2-oxo-2-(2-naphthyl)ethanehydrazonoyl bro mides **1b**, **d**,**e**,**i**,**j** were pre pared as pre viously de scribed.^{17,18}

N-aryl 2-oxo-2-(2-naphthyl)ethanehydrazonoyl bro mides 1a,c and 1f-h

General Procedure

A sus pen sion of dimethyl (2-naphthoylmethyl) sul fonium bro mide (3.1 g, 0.01 mol) and so dium ac e tate trihydrate (1.3 g, 10 mmol) in eth a nol (100 mL) was cooled to $0.5 \,^{\circ}$ C in an ice-bath while be ing stirred. To the re sult ing cold mix ture was added the ap pro pri ate arenediazonium chlo ride, pre pared by diazotizing the re spec tive aryla mine (0.01 mol) in the usual way. Af ter the ad di tion was com pleted (20 min), the re ac tion mix ture was left in an ice-box for 3 h. The solid product that pre cip i tated was fil tered off, washed with wa ter and crys tal lized from the ap pro pri ate sol vent to give the re spective hydrazonoyl bro mide **1**. The com pounds pre pared are listed to gether with their phys i cal con stants in Ta ble 6.

3-(4-Amino-5-phenyl-1,2,4-triazolyl)thio hydrazonates, 3 Method A

To a mix ture of equimolar quantities of the ap propriate hydrazonoyl bromide **1** and triazolethiol **2** (10 mmol each) in dry ben zene (40 mL) was added triethylamine (1.4 mL, 10 mmol). The mix ture was stirred for 15 h at room temper a ture,

Compd.	Yield,	M.p.,°C	Molecular	Ana	Anal. Calcd./Found	
No.	%	(solvent)	formula	C,%	H,%	N,%
1a	85	145 (a)	$C_{19}H_{15}BrN_2O_2$	59.55	3.95	7.31
			(383.2)	59.1	3.7	7.3
1b	95	164 (a) ⁱ	C ₁₉ H ₁₅ BrN ₂ O	62.14	4.12	7.63
			(367.2)	62.4	4.0	7.6
1c	90	142 (a)	C ₁₉ H ₁₅ BrN ₂ O	62.14	4.12	7.63
			(367.2)	62.0	4.0	7.5
1d	75	150 (a) ⁱⁱ	C ₁₈ H ₁₃ BrN ₂ O (353.2)			
1e	95	209 (a) ⁱⁱⁱ	C ₁₈ H ₁₂ BrClN ₂ O (387.7)			
1f	90	198 (b)	C ₁₈ H ₁₂ BrClN ₂ O	55.77	3.12	7.23
			(387.7)	55.6	3.5	7.2
1g	90	220 (c)	C ₁₈ H ₁₂ BrN ₃ O ₃	54.29	3.04	10.55
0			(398.2)	54.2	3.0	10.5
1h	80	208 (b)	$C_{20}H_{15}BrN_2O_2$	60.78	3.83	7.09
			(395.3)	60.4	4.0	7.0
1i	95	184 (b) ^{iv}	$C_{21}H_{17}BrN_2O_3$ (425.3)			
1j	95	212 (b) ^v	$C_{18}H_{12}BrN_3O_3$ (398.2)			

Table 6. N-Aryl 2-(2-Naphthyl)-2-oxoethanehydrazonoyl bromides, 1a-j

Solvent of crystallization: (a) Ethanol; (b) Acetic acid; (c) Dioxane.

ⁱ Lit.^{18b} mp. 166-167 °C; ⁱⁱ Lit.^{18a} m.p. 149-150 °C; ⁱⁱⁱ Lit.^{18b} mp. 208-210 °C; ^{iv} Lit.^{18b} mp. 184-185 °C; ^v Lit.^{18b} mp. 211-213 °C.

then the sol vent was distilled under reduced pressure in a rota tory evap or a tor. The solid left was collected, washed with water and finally crystal lized from the appropriate sol vent to give the respective thiohydrazonate ester **3**. The compounds **3a-g** prepared, to gether their physical constants, are listed in Table 7. The products iso lated from sim i lar reactions of **2** with **1h-j**, proved to be the triazolothiadiazines **4h-j**, respectively (Table 8).

Method B

To an ethanolic so dium ethoxide so lu tion, pre pared from so dium metal (0.11 g, 0.005 g.atom) and ab so lute eth a-

Table 7. 3-(4-Amino-5-phenyl-1,2,4-triazolyl)thio hydrazonates, 3a-g
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Compd.	Yield,	M.p.,°C	Molecular	Anal. Calcd./Found		
No.	%	(solvent)	formula	C,%	Н,%	N,%
3a	80	198 (a)	$C_{27}H_{22}N_6O_2S$	65.57	4.48	16.99
3b	75	165 (a)	$C_{27}H_{22}N_6OS$	67.76	4.5	10.5 17.56
3c	75	167 (a)	(478.6) C ₂₇ H ₂₂ N ₆ OS	67.6 67.76	4.1 4.63	17.4 17.56
24	20	170 (-)	(478.6)	67.4	4.7	17.8
30	80	170 (a)	(464.5)	67.22 67.2	4.34 4.2	18.09
3e	75	190 (a)	$C_{26}H_{19}CIN_6OS$	62.58	3.84	16.84
3f	75	180 (b)	$C_{26}H_{19}ClN_6OS$	62.58	3.4 3.84	16.4 16.84
			(499.0)	62.2	4.0	16.8
3g	85	160 (b)	C ₂₆ H ₁₉ N ₇ O ₃ S (509.6)	61.1 59.9	3.76 3.4	19.24 19.3

Solvent of crystallization: (a) Ethanol; (b) Dioxane-water.

Compd.	Yield,	M.p.,°C	Molecular	Ana	Anal. Calcd./Found		
No.	%	(solvent)	formula	C,%	Н,%	N,%	
4a	60	280 (a)	C ₂₇ H ₂₀ N ₆ OS	68.05	4.23	17.63	
			(476.6)	68.0	4.0	17.6	
4b	65	264 (b)	$C_{27}H_{20}N_6S$	70.41	4.38	18.25	
			(460.6)	70.4	4.2	18.2	
4c	55	260 (a)	$C_{27}H_{20}N_6S$	70.41	4.38	18.25	
			(460.6)	69.5	4.1	18.5	
4d	70	270 (b)	$C_{26}H_{18}N_6S$	69.94	4.06	18.82	
			(446.5)	69.3	4.3	18.8	
4e	65	290 (c)	C ₂₆ H ₁₇ ClN ₆ S	64.93	3.56	17.47	
			(480.9)	65.0	3.5	17.5	
4f	60	300 (b)	C26H17ClN6S	64.93	3.56	17.47	
			(480.9)	64.3	3.5	17.3	
4g	75	308 (d)	$C_{26}H_{17}N_7O_2S$	63.53	3.49	19.95	
			(491.5)	63.5	3.4	20.0	
4h	75	268 (b)	C ₂₈ H ₂₀ N ₆ OS	68.84	4.13	17.20	
			(488.6)	68.5	4.3	17.2	
4i	80	250 (b)	$C_{29}H_{22}N_6O_2S$	67.11	4.27	16.19	
			(518.6)	66.8	4.6	15.8	
4j	85	305 (d)	$C_{26}H_{17}N_7O_2S$	63.53	3.49	19.95	
			(491.5)	63.2	3.4	19.8	

Table 8. 7-Arylazo-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines, 4a-j

Solvent of crystallization: (a) Ethanol; (b) Acetic acid; (c) Dioxane, (d) DMF.

nol (20 mL) was added the triazolethione 2 (0.96 g, 5 mmol). Af ter stir ring the mix ture for 15 min, the ap pro pri ate hydrazo noyl bro mide 1 (5 mmol) was added and stir ring con tin ued for 4-6 h. Dur ing this pe riod, the hydrazonoyl bro mide dissolved and new pre cip i tate was formed. The re ac tion mix ture was then left over night at room tem per a ture. The crude product that pre cip i tated was fil tered off, washed with wa ter and fi nally crystal lized from the ap pro pri ate sol vent. The iso lated prod ucts proved iden ti cal in all re spects with those ob tained above by Method A.

Here too the re ac tions of **2** with **1h-j**, when car ried out as above, af forded directly the triazolothiadiazine de riv a tives **4h-j**, re spec tively (Table 8).

7-Arylhydrazono[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines, 4a-g

A solution of the appropriate thiohydrazonate **3** (2 mmol) in ace tic acid (10 mL) was refluxed for 1 h and then cooled. The solid that pre cipi tated was collected by filtration, washed with water, dried and finally crystal lized from the appropriate sol vent to give the respective triazolothiadiazine derivative **4**. The compounds prepared to gether with their physical constants are given in Table 8.

pK Determination

The acid dis so ci a tion con stants of the com pounds 4a-j

were determined spec trophoto metrically in 80 vol% dioxanewa ter mix ture at 27 °C \pm 0.1 °C and ionic strength 0.1. An Orion 420A pH me ter fit ted with com bined glass elec trode type 518635 was em ployed for mea sure ment of pH val ues. The in stru ment was ac cu rate to \pm 0.01 pH unit. It was cal ibrated us ing two stan dard Beckman buffer so lu tions of pH 4.01 and 7.00. The pH me ter read ings (B) re corded in dioxanewater so lu tions were con verted to hy dro gen ion con cen tration [H⁺] by means of the widely used re la tion of van Uitert and Haas¹⁹ namely:

$$-\log [H^+] = B + \log U_H$$

where $\log U_{\rm H}$ is the correction factor for the solvent composition and ionic strength used for which B is read. The value was determined by recording the pH values for a series of solutions containing known amounts of hy drochloric acid and so dium chloride such that the ionic strength is 0.1 in 80 vol % dioxane-water at 27 °C. The value of log U_H was found to be -0.48.

The experimental procedure followed in the determination of pK constants and their cal cu la tions from the absorbance - pH data are as previously de scribed (8). The pK values obtained were reproducible to within \pm 0.02 pK unit. The results are sum marized in Table 5. Received June 3, 2000.

Key Words

Hydrazonoyl halides; 1,2,4-Triazole-3-thione; Thiohydrazonate esters; Forster cycle; Hammett equation; Tautomerism.

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