Diazo-, Azo-, and Azidoazoles. VII. Imidazo[1,2-*b*]- *versus* Imidazo[2,1-*c*]benzo-*as*-triazines

Sergio Castillón and Enrique Meléndez

Departamento de Química Orgánica, Facultad de Ciencias, Zaragoza, Spain

and Jaume Vilarrasa*

Departamento de Química Orgánica, Facultad de Química, Barcelona-28, Spain

Received June 29, 1981

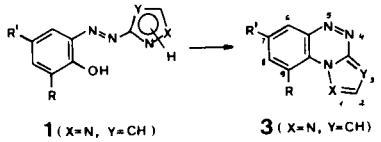
Treatment of 3-aminobenzo-*as*-triazines with bromoacetaldehyde ethylene acetal give linear tricyclic imidazobenzo-*as*-triazines, where 3-amino-7-methylbenzo-*as*-triazine 1-oxide yields the angular isomer. The structures of these compounds have been established by comparing their nmr spectra to those of pyrazolo [5,1-*c*]- and *s*-triazolo[5,1-*c*]benzo-*as*-triazines obtained form the appropriate azo derivatives by intramolecular cyclization.

J. Heterocyclic Chem., **19**, 61 (1982).

In a former paper (1), the intramolecular cyclization of 2-hydroxynaphthalene-1-azoazoles to naphtho[2,1-*e*]azolo-*as*-triazines (and related isomers) was studied in detail in order to elucidate the real structure of the tetracyclic compounds obtained, gain insight into a plausible mechanism for that sort of cyclization, and determine the validity of the process as a general synthetic method.

Pursuing the extension of these studies to analogous compounds in the benzene series, we observed that, in refluxing acetic acid or ethylene glycol, 2-hydroxyphenyl-1-azo derivatives of pyrazole (**1**) and *s*-triazole (**2**) listed below gave the expected pyrazolo[5,1-*c*]benzo-*as*-triazines

Scheme 1



1 (X=N, Y=CH)
2 (X=Y=N)

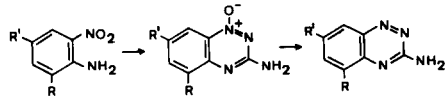
3 (X=N, Y=CH)
4 (X=Y=N)

a: R=H, R'=Me **b**: R=H, R'=OMe **c**: R=R'=Me

(**3**) and *s*-triazolo[5,1-*c*]benzo-*as*-triazines (**4**) (2), although more drastic cyclization conditions than those used in their naphthalenic counterparts had to be employed. Spectroscopic data (see Table I of ^{1}H-nmr spectra of the products) agree perfectly with the structures **3** and **4**, and can be satisfactorily compared with previously reported data of related compounds, *viz.*, 3(and 4)-substituted pyrazolo [5,1-*c*]benzo-*as*-triazines (3), 1(and 7)-substituted imidazo[5,1-*c*]benzo-*as*-triazines (4), and *s*-triazolobenzo-*as*-triazines (5).

By contrast, the application of the same synthetic scheme to similar imidazole derivatives (see Scheme I, but X = CH and Y = N) was unsuccessful, since the coupling reaction of 2-diazoimidazole with substituted phenols, both in basic and neutral media, did not take place (6). Thus, as a better route to these imidazobenzo-*as*-triazines, we envisaged a more formal synthetic sequence (7) such as that outlined in Scheme II, which proceeds through the formation of the corresponding 3-aminobenzo-*as*-triazines (**6**), obtained by reduction with sodium dithionite of their 1-*N*-oxides (**5**) (8) that arise in turn from the reaction of *o*-nitroanilines with cyanamide.

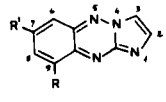
Scheme II



5a-c **6a-c**

The treatment of **6a** with bromoacetaldehyde ethylene acetal in ethylene glycol at 120° for 24 hours or in refluxing ethylene glycol for 3 hours gave a product of M^+ 184, analyzed as $C_{10}H_8N_4$, as the only tricyclic compound. Likewise **6b** and **6c** afforded products of M^+ 200 and M^+ 198, respectively. The comparison of the ^{1}H-nmr spectra of these products (see Table II) with those of compounds **3** and **4** indicates that we are not dealing with the angular compounds, imidazo[2,1-*c*]benzo-*as*-triazines, but with the linear imidazo[1,2-*b*]benzo-*as*-trazines (**7a-c**). In fact, the protons H-6, H-8 and H-9 lie at higher fields in **7a-c** than

Figure



7a-c

in corresponding **3a-c** and **4a-c**, according to the apparent quinonoid character of the linear structures. It is also noteworthy that the methyl groups of compounds **3c** and **4c** located at position 9 appear in dimethyl sulfoxide at 2.95 and 3.00 ppm, respectively, *i.e.*, 0.45 and 0.40 ppm downfield relative to the methyl groups located at position 7, whereas in **7c** Me-9 lies at 2.55 ppm in the same solvent, *i.e.*, only 0.13 ppm downfield with respect to Me-7, and

Table I

^{1}H-NMR Spectra of Compounds **3** and **4** (a)

		H-2	H-3	H-6	H-8	H-9	R-7	R-9	J_{23}	J_{68}	J_{89}
3a	Deuteriochloroform	8.18	7.38	8.36	7.71	8.28	2.60		2.5	2.7	8.7
	DMSO-d_6	8.33	7.50	8.30	7.86	8.18	2.59		2.5	2.0	8.6
3b	Deuteriochloroform	8.08	7.30	7.86	7.45	8.29	3.98		2.5	2.7	9.3
	DMSO-d_6	8.35	7.54	8.08	7.72	8.36	4.02		2.5	2.6	8.6
3c	Deuteriochloroform	8.13	7.32	8.22	7.50		2.46	2.98	2.5		
	DMSO-d_6	8.33	7.50	8.18	7.65		2.50	2.95	2.5		
	TFA	8.88	8.06	8.22	8.14		2.75	3.31	2.8		
4a	Deuteriochloroform	8.71		8.62	7.98	8.42	2.70			2.7	8.7
	DMSO-d_6	8.81		8.46	7.93	8.25	2.62			2.0	8.6
4b	Deuteriochloroform	8.60		8.10	7.70	8.37	4.05			2.7	9.3
	DMSO-d_6	8.96		8.23	7.88	8.43	4.07			2.6	8.6
4c	Deuteriochloroform (b)	8.87		8.42	7.86		2.51	2.94			
	DMSO-d_6	8.84		8.35	7.83		2.60	3.00			
	TFA	9.38		8.73	8.23		2.82	3.25			

(a) δ in ppm (mean values of four scans, mostly), J in Hz. (b) Plus a TFA drop.

Table II

^{1}H-NMR Spectra of Compounds **7a** to **7c**

		H-2	H-3	H-6	H-8	H-9	R-7	R-9	J_{23}	J_{68}	J_{89}
7a	Deuteriochloroform	8.31	8.53	7.66	7.53	7.97	2.54		1.4	2.6	9.3
	DMSO-d_6	8.50	8.65	7.66	7.56	7.86	2.55		1.3		
7b	Deuteriochloroform	8.20	8.35	7.00	7.33	7.87	4.00		1.4	2.6	10.0
7c	Deuteriochloroform	8.28	8.51	7.42	7.30		2.46	2.70	1.4		
	DMSO-d_6	8.46	8.57	7.35	7.27		2.42	2.55	1.3		

Table III

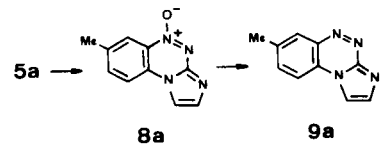
^{1}H-NMR Spectra of Imidazo[2,1-*c*]benzo-*as*-triazines **8a** and **9a**

		H-1	H-2	H-6	H-8	H-9	Me	J_{12}	J_{68}	J_{89}
8a	Deuteriochloroform	8.57	7.81	8.26	7.88	8.35	2.51	1.3	2.6	8.6
9a	Deuteriochloroform	8.11	8.03	8.40	7.71	7.91	2.61	1.5	2.2	8.2
	DMSO-d_6	8.79	8.07	8.31	7.83	8.33	2.58	1.3	2.6	8.6

similar differences are observed in deuteriochloroform. In other words, the great downfield shift undergone by Me-9 of **3c** and **4c**, mainly attributed to the proximity of the azole ring (9), does not occur in compound **7c**, which is another good reason for taking into account the linear instead of the angular structure.

Finally, in order to get an additional simple proof of the structure of these compounds, we tried to prepare one of such angular tricyclic compounds and compare it with its thought linear isomer. After unsuccessful attempts using bromoacetaldehyde dimethyl acetal and catalytic amounts of acid, and/or changing the range of temperatures, we found a suitable route from the 3 amino-1-*N*-oxide derivatives. Thus, compound **5a**, heated with bromoacetaldehyde ethylene acetal in ethylene glycol at 120°, gave the *N*-oxide **8a** together with a small amount of the reduced product (**9a**). Treatment of the mixture with sodium dithionite afforded exclusively **9a** in good yield (10). The ^{1}H-nmr spectra of these compounds (see Table III) agree

Scheme III



with those of **3a** and **4a**, the chemical shifts of H-6, H-8, and H-9 being very similar in the four cases. Furthermore, the chemical shifts of H-1 and H-2 of **9a** in dimethyl sulfoxide are very close to the respective values for naphtho[2,1-*e*]imidazo[2,1-*c*]-*as*-triazine (1), in which an angular arrangement of the rings occurs.

In summary, we believe that three useful conclusions can be derived from our present work. First, the formation of the imidazole ring, in benzo-*as*-triazines **6a-c**, takes place on N-2 of the triazine yielding the linear isomer, even though the cyclization product on N-4 (the angular one) seems to possess a greater aromatic character (11).

Secondly, the ^{1}H-nmr spectroscopy allows one to readily distinguish between linear and angular isomers, since the benzene protons corresponding to the first ones appear at quite higher fields. Finally, it should be recalled the role of the *N*-oxide substituent acting as an easily removable group that directs the cyclization with bromoacetadehyde ethylene acetal towards one of two possible sites (12). We are now interested in extending the application of these results to the synthesis of related polyazaaromatic systems.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed at the "Instituto de Química Bio-orgánica", C.S.I.C., Barcelona. Magnetic resonance spectra were obtained on Perkin-Elmer R-12B or R-24 spectrometers. Infrared, electronic, and mass spectra were recorded on Perkin-Elmer 283, Perkin-Elmer-Hitachi 200, and Hewlett-Packard 5930A instruments, respectively.

Azo Derivatives.

Azo derivatives **1a-c** and **2a-c** were prepared by a common method (1) and used in the next step without further purification.

Pyrazolo[5,1-*c*]benzo-*as*-triazines (**3a-c**).

Crude azo derivatives **1a-c** (10-20 mmoles) were heated either in refluxing acetic acid for 2-3 days or in refluxing ethylene glycol for one day. In the first case, the solutions obtained were evaporated to dryness and the residues mixed with silica gel and extracted in a Soxhlet apparatus with benzene. These benzene solutions were first washed with 10% aqueous sodium hydroxide, then with water, and finally dried over anhydrous sodium sulfate. Evaporation of the solvent gave crude yellow solids, which were recrystallized in ethanol affording **3a-c** with 69%, 35%, and 40% yields respectively (based upon the starting amine).

In the second case, the ethylene glycol solutions were diluted five times with water and extracted with methylene chloride. These extracts were washed with 10% aqueous sodium hydroxide, then with water, dried over sodium sulfate, and evaporated to dryness. Similar yields to the above mentioned ones were obtained after recrystallization in ethanol.

Compound **3a** had mp 169-171°; ir (potassium bromide): 3100 w, 3060 w, 1620 w, 1580 w, 1540 s, 1310 s, 1298 s, 1220 s, 1130 s, 818 s, 730 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 222 (4.43), 236 (4.44), 249 (4.35), 329 (3.81), 386 (3.59).

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.12; H, 4.57; N, 30.30.

Compound **3b** had mp 167-169°; ir (potassium bromide): 3115 w, 3040 w, 1615 w, 1585 w, 1535 s, 1500 s, 1370 s, 1248 s, 1230s, 1135 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 220 (4.37), 244 (4.53), 333 (3.76), 404 (3.60).

*Anal.*Calcd. for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.81; H, 4.20; N, 27.72.

Compound **3c** had mp 160-161°; ir (potassium bromide): 3135 w, 3100 w, 1580 w, 1525 w, 1440 s, 1305 s, 1255 s, 1085 s, 1030 s, 1010s, 685 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 222 (4.48), 238 (4.48), 340 (3.86), 360 (3.75).

Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.27. Found: C, 66.52; H, 5.24; N, 28.44.

Triazolo[5,1-*c*]benzo-*as*-triazines (**4a-c**).

Crude azo derivatives **2a-c** (10-20 mmoles) were heated in refluxing ethylene glycol for 20-24 hours. The solutions were left to cool, diluted with water and extracted with methylene chloride. These extracts were rinsed with aqueous sodium hydroxide, then with water, and finally dried over sodium sulfate. The solids obtained after evaporating the solutions were recrystallized in ethanol giving **4a** (68% from the amine), **4b** (50%), and **4c** (55%), respectively.

Compound **4a** had mp 230-231°; ir (potassium bromide): 3105 w, 1538 s, 1330 s, 1290 s, 1260 s, 1135 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 229 (4.51), 305 (3.99), 317 (3.98), 364 (3.62).

Anal. Calcd. for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.51; H, 3.75; N, 37.66.

Compound **4b** had mp 210-211°; ir (potassium bromide): 3120 w, 3040 w, 1615 s, 1580 w, 1538 s, 1520 s, 1325 s, 1320 s, 1225 s, 1135 s, 1010 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 216 (4.36), 240 (4.49), 307 (3.89), 319 (3.92), 3.88 (3.54).

Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.76; H, 3.44; N, 34.60.

Compound **4c** had mp 225-227°; ir (potassium bromide): 3110 w, 1585 s, 1518 s, 1405 s, 1333 s, 1312 s, 1270 s, 1235 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 216 (4.43), 2.28 (4.49), 251 (4.33), 324 (3.99), 360 (3.53).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.07; H, 4.74; N, 35.01.

Imidazo[1,2-*b*]benzo-*as*-triazine (**7a-c**).

Ten mmoles of 3-aminobenzo-*as*-triazines **6a-c**, prepared in two steps from the corresponding *o*-nitroanilines (7), were dissolved in the minimum volume required of ethylene glycol, 11 mmoles of bromoacetaldehyde ethylene acetal were added, and the solutions were refluxed for 3 hours. The reaction mixtures were left to cool, diluted five times with water, and extracted with methylene chloride. The products collected by evaporating the dried organic extracts were purified by column chromatography over aluminum oxide and eluted with methylene chloride giving **7a-c** with 27%, 35% and 25% respectively.

Compound **7a** had mp 191-193°; ir (potassium bromide): 3115 w, 3085 w, 1630 w, 1560 w, 1435 s, 1250 s, 1112 s, 870 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 218 (4.26), 252 (4.56), 381 (3.79), 454 (3.69); ms: M$^+$ 184.

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 64.99; H, 4.20; N, 30.30.

Compound **7b** mp 211-213°; ir (potassium bromide): 3105 w, 3100 w, 1615 s, 1452 s, 1398 s, 1240 s, 1210 s, 1120 s, 810 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 224 (4.34), 253 (4.58), 398 (3.98), 440 (3.63); mx: M$^+$ 200.

Anal. Calcd. for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 60.07; H, 4.22; N, 28.15.

Compound **7c** had mp 170-172°; ir (potassium bromide): 3138 w, 1630 w, 1428 s, 1120 s, 870 s, cm^{-1}; uv: ν max nm (log ϵ) in ethanol 216 (4.35), 258 (4.67), 388 (3.86), 458 (3.69); ms: M$^+$ 198.

Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.27. Found: C, 66.42; H, 5.30; N, 28.14.

Reaction of **5a** with Bromoacetaldehyde Ethylene Acetal.

Bromoacetaldehyde ethylene acetal (3.34 g, 20 mmoles) was added to compound **5a** (1.74 g, 10 mmoles) dissolved in 100 ml of ethylene glycol, and the mixture was heated to 120° for 24 hours. The product was crystallized by adding 100 ml of water to the solution, the needless obtained being filtered off and dried *in vacuo*. A 50% yield of **8a** (M$^+$ 200), impurified by **9a** (15-20% of the mixture, as determined by nmr spectroscopy), was obtained.

Imidazo[2,1-*c*] benzo-*as*-triazine (**9a**).

Sodium dithionite (305 mg, 3.6 mmoles) dissolved in a few ml of water was added to the above **8a** and **9a** mixture in 200 ml of hot ethanol, and the resulting solution was refluxed for 2 hours. The flask was left to cool, the inorganic products were filtered off, and the solvent evaporated. Recrystallization in ethanol yielded 275 mg (85%) of **9a**, mp 224-226°; ir (potassium bromide): 3120 w, 3070 w, 1565 w, 1505 s, 1310 s, 1295 s, 1210 s, 1130 s, 1105 s, 795 s, 765 s, 750 s, cm^{-1}; ms: M$^+$ 184.

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.33, H, 4.63; N, 30.40.

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(2) No isomeric *s*-triazolo[3,4-*c*]benzo-*as*-triazines were obtained besides **4** (1) in the conditions employed.

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(6) Most of 2-diazoimidazole decomposes before coupling in all the cases.

(7a) J. Jiu and G. P. Mueller, *J. Org. Chem.*,**24**, 813 (1959); (b) J. C. Mason and G. Tennant, *J. Chem. Soc. (B)*, 911 (1970).

(8) Reduction with sodium dithionite in different conditions (5a) than those used here (7) gave the hydrazo derivative. The ready oxidation of the hydrazo to the azo group in these compounds, as has been demonstrated in the naphthalene series (S. Castillón, unpublished work), can account for the differences appeared in the literature.

(9) In tetracyclic compounds (1), the naphthalenic proton near the azole ring is shifted downfield, independently of the nature of the azole.

(10) Prolonged heating of the mixture of **5a** and the acetal, as well as of **8a**, in ethylene glycol led directly to the desired **9a**, although in worst yields.

(11) It may be thought that the kinetically favoured product is obtained, in the same way as the oxidation of 3-aminobenzo-*as*-triazine at room temperature gives almost exclusively the 2-*N*-oxide derivative (7b).

(12) The condensation of 3-hydrazinobenzo-*as*-triazine 1-oxide (5a) and of 3-hydrazinopyrido[2,3-*e*]-*as*-triazine 1-oxide (A. Messmer, G. Hajós, P. Benkó, and L. Pallos, *J. Heterocyclic Chem.*, **10**, 575 (1973)) with orthoesters affords angular triazolotriazine oxides too. See also A. R. Katritzky and J. M. Lagowski, "The Chemistry of Heterocyclic *N*-Oxides", Academic Press, London, 1971.