Synthesis and Crystal Structure of Piperidinium 2-Aryl[1,2,4]triazolo[1,5-*a*]pyridinides and their Neutralization to 2-Aryl[1,2,4]triazolo[1,5-*a*]pyridines

Alí Hadi, Nazario Martín, Carlos Seoane* and José L. Soto

Departamento de Química Orgánica,
Facultad de Química, Universidad Complutense,
28040-Madrid, Spain

Armando Albert and Félix Cano

U.E.I. Cristalografía, Instituto Rocasolano, CSIC, Serrano 119,
28006-Madrid, Spain

Received February 10, 1992

A one step synthesis of novel piperidinium 2-aryl[1,2,4]triazolo[1,5-*a*]pyridinides **6** from 2'-benzoyl-2-cyanoacetohydrazide (**2**) and α-substituted cinnamonitriles **3** is described. The reaction takes place by *6-exo-dig* cyclization followed by an *5-exo-trig* process to afford salts **6**. The X-ray diffraction of compound **6a** reveal that the cation is strongly linked to the anion by hydrogen bonds and a characteristic partial stacking motive. 2-Aryl[1,2,4]triazolo[1,5-*a*]pyridines were obtained from salts **6** by treatment with hydrochloric acid.

J. Heterocyclic Chem., **29**, 1229 (1992).

The known preparative methods for the synthesis of [1,2,4]triazolo[1,5-*a*]pyridines involve: (a) Reaction of 1,2-diaminopyridine derivatives with compounds such as carboxylic acids and esters [1], 1,3-diketones [2] and acetylene derivatives [3]. (b) Cyclization of 2*N*-substituted aminopyridines [4]. (c) Reaction of 1-aminopyridinium salts with nitriles [5]. (d) From 3-cyanomethyl[1,2,4]triazole derivatives by reaction with ketomethylene compounds [6]. (e) Ring transformation of triazolo[4,3-*a*]pyridines and 2-thioxopyrones [7]. (f) Reaction of *N*-amino-α-pyridones with amides [8]. One step intramolecular synthesis of the title compounds are unusual [9] and most of these consist in intermolecular multistep processes in low overall yield.

In this paper we report the approach through the intramolecular nucleophilic substitution at a benzamide-type carbonyl group. Structural and X-ray studies of the novel piperidinium 2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinides **6** and the corresponding neutral [1,2,4]triazolo[1,5-*a*]pyridines **7** were also carried out.

Thus, by reaction of cyanoacetohydrazide (**1**) (Scheme) with benzoyl chloride at 0°, the corresponding benzoyl derivative **2** was obtained in good yield. Reaction of this compound **2** with α-substituted cinnamonitriles **3** and piperidine in alcoholic solution led to the *6-exo-dig* cyclization [10] of the intermediate **4** to yield the *N*-benzoylamino-3,4-dihydro-2-pyridones **5**. The subsequent 5-*exo-trig* cyclization by attack of the primary amino group to the low reactivity amide carbonyl group led to the [1,2,4]triazolo[1,5-*a*]pyridones that were isolated as the piperidinium salts due to the high acidity of the ring proton [11], in moderate to good yields.

Although the reaction to obtain **6** is of general scope, it is influenced by the nature of the substituent present on the aromatic ring coming from the cinnamonitrile. Thus, the reaction of **2** with ethyl *p*-nitrobenzylidene cyanoacetate **3** (R = CO_2Et, Ar = *p*-$NO_2C_6H_4$) and methyl *p*-nitrobenzylidene cyanoacetate **3** (R = CO_2Me, Ar = *p*-$NO_2C_6H_4$) using the standard procedure were met with futility. This fact could be accounted for by the stronger deactivating effect of the nitro group which leads to the retro-Michael reaction in the intermediate **4** [12].

Compound **6a** crystallizes as a salt with a piperidinium cation, and a delocalized fused heterocyclic anion. The main geometrical features of compound **6a** are presented in Table 1. The perspective drawing of **6a** appears in Figure 1 with the atomic labeling used in the crystallographic study.

All bond distances within the fused rings system present the expected values, but C2-C3, that is longer and N7-C8 which is shorter. The planarity of the fused system is somehow distorted in the pyridine ring where N4 is 0.012(2) Å away from the least squares plane. The triazolo ring presents angular distortions that lower the values at

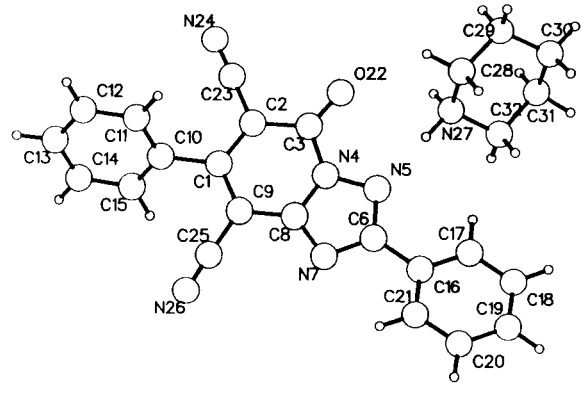
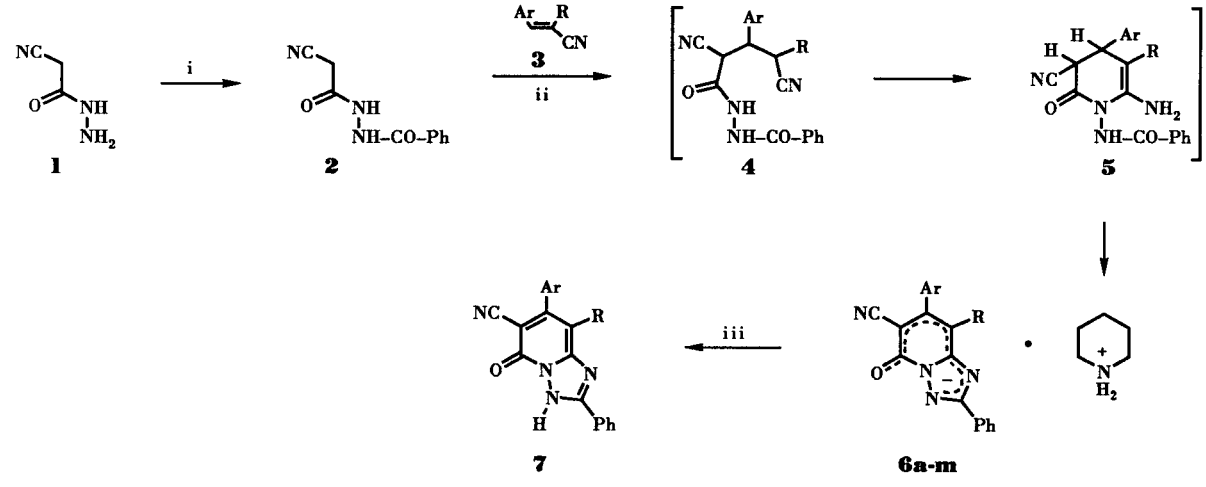


Figure 1. A view [16] of the molecular structure of salt **6a**, showing the atomic numbering.

Scheme



i = PhCOCl, 0°C; ii = piperidine, EtOH; iii = HCl 10%, EtOH, rt

Compound	R	Ar
6a	CN	C_6H_5
6b	CN	*p*-$CH_3C_6H_4$
6c	CN	*p*-$CH_3OC_6H_4$
6d	CN	*p*-ClC_6H_4
6e	CN	*p*-$NO_2C_6H_4$
6f	CO_2Me	C_6H_5
6g	CO_2Me	*p*-$CH_3C_6H_4$
6h	CO_2Me	*p*-$CH_3OC_6H_4$
6i	CO_2Me	*p*-ClC_6H_4
6j	CO_2Et	C_6H_5
6k	CO_2Et	*p*-$CH_3C_6H_5$
6l	CO_2Et	*p*-$CH_3OC_6H_4$
6m	CO_2Et	*p*-ClC_6H_4

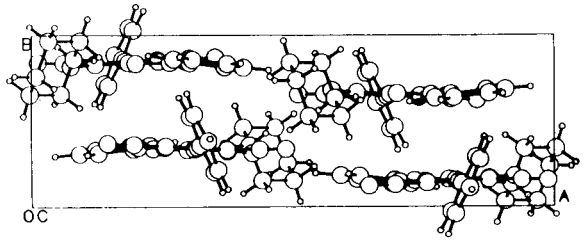


Figure 2. The crystal packing projected along the b axis [16] showing the intermolecular interactions.

N5 and N7, while the piperidine ring has a lower than usual value at C2-C3-N4 and higher at C2 and N4 (see Table 1).

The two phenyl rings are situated one almost coplanar and the other quite perpendicular to the fused system. The cation ring, puckered as a chair, is strongly linked to the anion moiety *via* a strong hydrogen bond, H27-N5 and a weaker one, H27-022; this hydrogen atom has also a much weaker contact to N24, but that might suggest some bifurcation [13]. Besides these hydrogen interactions, the aromatic rings show two of their fundamental ways of organization [14], presenting a partial stacking motive between a phenyl ring and two pyridine rings of other molecules, with a separation between planes of about 3.3 Å, some 0.9 Å of slip and around 30° of twist from coincidence in projection (see Figure 2).

Several attempts were performed to obtain the neutral [1,2,4]triazolo[1,5-*a*]pyridones **7**. Thus, when the reaction of 2′-benzoyl-2-cyanoacetohydrazide (**2**) with benzylidenemalononitrile **3a** (Ar = C_6H_5, R = CN) was carried out in the absence of piperidine, no evidence of formation of neutral compound **7** was observed. Compound **5a** (Ar = C_6H_5, R = CN) was obtained in 46% yield as the only isolated compound as a mixture of diastereomers due to the presence of the two chiral carbons in the ring (Scheme). This fact could be evidence that the driving force in the formation of the bicyclic system is the fromation of the salt, resulting in a very stable anion due to the charge delocalization in the two fused heterocyclic rings However, the neutral compounds **7** could be finally obtained from

Table 1

Geometrical Characteristics of Salt **6a** (Å, °)

a. Bond distance

Atomic item	Value	Range	Atomic item	Value	Range
C1-C2	1.403(3)	1.37-1.44(2)	C6-C16	1.466(2)	
C1-C9	1.389(2)	1.31-1.41(3)	N7-N8	1.330(2)	1.36-1.42(1)
C1-C10	1.487(2)		C8-C9	1.418.2	1.35-1.41(2)
C2-C3	1.440(2)	1.35-1.42(2)	C9-C25	1.422(3)	
C2-C23	1.418(2)		C23-N24	1.417(2)	
C3-N4	1.406(2)	1.36-1.41(2)	C25-N26	1.144(3)	
C3-O22	1.216(2)		N27-C28	1.487(3)	
N4-N5	1.371(2)	1.35-1.40(2)	N27-C32	1.485(3)	
N4-C8	1.362(2)	1.37-1.44(2)	C28-C29	1.506(5)	
N5-C6	1.332 (2)	1.31-1.43(3)	C29-C30	1.514(4)	
C6-N7	1.363(2)	1.29-1.37(2)	C30-C31	1.506(5)	
			C31-C32	1.509(4)	

b. Angles

Atomic item	Value	Range	Atomic item	Value	Range
C9-C1-C10	121.1(2)		C6-N7-C8	103.0(1)	102-108(2)
C2-C1-C10	119.2(1)		N4-C8-N7	109.9(1)	105-112(2)
C2-C1-C9	119.7(2)	118-124(2)	N7-C8-C9	130.5(1)	126-135(2)
C1-C2-C23	120.1(1)		N4-C8-C9	119.5(1)	117-123(2)
C1-C2-C3	124.3(2)	118-122(1)	C1-C9-C8	118.3(2)	115-123(2)
C3-C2-C23	115.5(1)		C8-C9-C25	117.5(1)	
C2-C3-O22	127.5(2)		C1-C9-C25	124.1(1)	
C2-C3-N4	111.4(1)	116-121(1)	C2-C23-N24	179.0(2)	
N4-C3-O22	121.0(1)		C9-C25-N26	177.0(2)	
C3-N4-C8	126.7(2)	117-124(2)	C28-N27-C32	113.1(2)	
C3-N4-N5	123.7(1)	130-138(2)	N27-C28-C29	110.5(2)	
N5-N4-C8	109.6(1)	104-109(2)	C28-C29-C30	112.0(3)	
N4-N5-C6	102.1(1)	104-108(1)	C29-C30-C31	109.9(2)	
N5-C6-C16	122.3(1)		C30-C31-C32	111.0(3)	
N5-C6-N7	115.3(1)	111-116(1)	N27-C32-C31	110.8(2)	
N7-C6-C16	122.4(1)				

c. Torsion angles

Atomic item	Value	Atomic item	Value
N5-C6-C16-C17	-10.0(2)	N27-C28-C29-C30	-54.3(3)
C2-C1-C10-C11	-62.4(2)	C28-C29-C30-C31	56.0(3)
C28-N27-C32-C31	-55.4(3)	C29-C30-C31-C32	-56.4(3)
C32-N27-C28-C29	54.2(3)	C30-C31-C32-N27	56.2(3)

the piperidinium salt **6** by treatment with hydrochloric acid (Scheme). The acid conditions used did not affect the other functional groups present in the molecule and the procedure to synthesize compounds **7** proved to be of wide scope.

EXPERIMENTAL

Melting points were determined in capillary tubes in a Electrothermal 9200 apparatus and are uncorrected. The ^1H nmr and ^{13}C nmr spectra were recorded at 300 MHz and 75 MHz respectively on a Varian VXR 300s spectrometer. All nmr spectra were recorded as dimethyl sulfoxide solutions, chemical shifts being given as δ values with respect to tetramethylsilane as the internal standard. The ir spectra were measured with a Perkin-Elmer 781 instrument as potassium bromide pellets. Mass spectra were obtained with a Varian MAT 711 machine. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by tlc performed on silica gel plates (Merck 60-F) and using chloroform-methanol or toluene-ethyl acetate as the eluant.

Cyanoacetohydrazide, malononitrile, and piperidine were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. Benzylidenemalononitrile was also a commer-

cial product, but the remaining arylidenemalononitriles were prepared from aromatic aldehydes and malononitrile following the standard procedure [15].

X-Ray Crystallography.

The crystallographic analysis is summarized in Table 2. The final atomic co-ordinates together with the list of thermal components, hydrogen parameters, and bonds distances and angles have been deposited at the Fachinformationszentrum Karlsruhe.

Table 2

Crystal-analysis Parameters at Room Temperature

Crystal Data	
Formula	$C_{25}H_{18}N_6O$
Crystal habit	Prismatic, colorless
Crystal size (mm)	0.30 x 0.2 x 0.17
Symmetry	Monoclinic, $P2_1/n$
Unit cell determination	Least-squares fit from 76 reflections (θ <45)
Unit cell dimensions	21.528(1), 6.7755(2), 15.425(1) Å 90.0, 108.591(5), 90.0°
Packing V(Å^3), z	2132.5(2), 4
Dc (g.cm^{-3}), M, F(000)	1.3195, 422.488, 888
μ(cm^{-1})	6.391
Experimental Data	
Technique	Four circle diffractometer: Phillips PW 1000 Bisecting geometry Graphite oriented monochromator: Cu-Kα $\infty/2\theta$ scans, scan width 1.40 Detector apertures 1.0 x 1.0
Total measurements	Up to 65° in θ
Number of reflections:	
Measured	3596
Observed	2975 (3σ (I) criterion)
Standard reflections:	
	2 reflections every 90 minutes No variation
Solution and Refinement	
Solution	Direct methods
Refinement	L.S. on Fobs
Parameters	
Number of variables	377
Degrees of freedom	2598
Ratio of freedom	7.9
H atoms	Fourier synthesis
w-Scheme	Empirical as to give no trends in $\langle w\Delta^2F\rangle$ vs. $\langle F_0\rangle$ and $\langle \sin\theta/\lambda\rangle$ (5)
Final ΔF peaks	0.15 e Å
Final R and Rw	4.3, 5.1
Computer and programs	VAX 6410, SIR88 [17], XRAY80 [18], PARST [19]
Scattering factors	International Tables for X-Ray Crystallography [20]
Anomalous dispersion	International Tables for X-Ray Crystallography [20]

2'-Benzoyl-2-cyanoacetohydrazide (**2**).

To a stirred solution of 2-cyanoacetohydrazide (**1**) (1.98 g, 18.8 mmoles) in 3 ml of water at 0°, benzoyl chloride (4.34 g, 28.2 mmoles) from a dropping funnel and a solution of potassium carbonate (1.29 g) in 1.5 ml of water were added. After 20 minutes a precipitate was formed. It was collected by filtration and recrystallized from ethanol to yield white crystals (67% yield), mp 178-180°; ir: 3200 (NH), 2250 (CN), 1680 (C=O), 1620 (C=O) cm^{-1}; ^{1}H nmr: 3.84 (2H, s, CH_2), 7.69 (5H, m, ArH), 10.40 (1H, bs, NH), and 10.55 (1H, bs, NH).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.68. Found: C, 59.31; H, 4.25; N, 20.82.

6-Amino-1-benzoylamino-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (**5a**).

2'-Benzoyl-2-cyanoacetohydrazide (**1**) (4 mmoles) and benzylidenemalononitrile (**2**) (7 mmoles) were suspended in *ca.* 10 ml of dry ethanol. The mixture was refluxed until the tlc showed the absence of starting material (30 hours). The solid that precipitated was collected by filtration and washed with acetone and ethanol to give pure **5a** as a mixture of diastereomers (46% yield), mp 250-252° (ethanol); ir: 3420, 3320, 3020, 2820, 2260, 2200, 1720, 1690, 1645, 1590, 1300, 1260, 1200 cm^{-1}; ^{1}H nmr: δ 4.20 (1H, m, CH), 5.10 and 5.40 (1H, 2 x dd, CH), 7.10-8.10 (12H, m, ArH, NH_2), 11.05 (1H, m, NH); ms: m/z (relative intensity) 357 (M^+, 35), 284 (10), 256 (15), 213 (18), 154 (42), 127 (30), 105 (100), 77 (35).

Anal. Calcd. for $C_{20}H_{15}N_5O_2$: C, 67.23; H, 4.20; N, 19.60. Found: C, 67.24; H, 4.07; N, 19.42.

Piperidinium 7-Aryl-6-cyano-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]-pyridinides 8-Substituted **6**. General Procedure.

A suspension of 2'-benzoyl-2-cyanoacetohydrazide (**2**) (0.42 g, 4 mmoles) and the corresponding α-substituted cinnamonitrile **3** (4 mmoles) in *ca.* 15 ml of dry ethanol and the equimolar amount of piperidine (4 mmoles) was refluxed for a variable time (7-34 hours) until tlc showed no starting material left. The precipitate that separated was collected by filtration. The mother liquors were concentrated to half of volume and after cooling, a second crop of solid was obtained. In other cases (compounds **6a-e**) the mother liquors were evaporated to dryness and a second crop was collected by adding ethyl acetate and ethyl ether. Further purification was accomplished by recrystallization in the appropriate solvent.

Piperidinium 6,8-Dicyano-5-oxo-2,7-diphenyl[1,2,4]triazolo[1,5-*a*]-pyridine (**6a**).

This compound was obtained in 50% yield, mp >300° (from ethanol); ir: 3080, 3050, 2960, 2215, 2210, 1680, 1620, 1320 cm^{-1}; ^{1}H nmr: δ 1.45 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 7.54 (7H, m, ArH), 8.21 (3H, m, ArH); ^{13}C nmr: δ 21.82 (γ-CH_2 piperidinium), 22.43 (β-CH_2 piperidinium), 44.01 (α-CH_2 piperidinium), 77.60, 83.36 (6-C, 8-C), 117.23, 118.61 (2 x CN), 127.03 (2 x C, ArH), 128.59 (2 x C, ArH), 128.84 (2 x C, ArH), 129.03 (2 x C, ArH), 129.64, 130.20, 130.87, 136.18 (C, ArH), 153.82, 155.20, 156.57 (7-C, 8a-C, 2-C), 162.33 (C=O).

Anal. Calcd. for $C_{25}H_{22}N_6O$: C, 71.07; H, 5.25; N, 19.89. Found: C, 70.88; H, 5.43; N, 19.62.

Piperidinium 6,8-Dicyano-7-(*p*-methylphenyl)-5-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridinide (**6b**).

This compound was obtained in 80% yield, mp 297-299° (from ethanol); ir: 3100, 3020, 2990, 2240, 1690, 1650, 1360 cm^{-1}; ^1H nmr: δ 1.42 (2H, m, CH_2 piperidine), 1.59 (4H, m, 2 x CH_2 piperidine), 2.42 (3H, s, CH_3), 3.01 (4H, m, 2 x CH_2 piperidine), 7.3-7.7 (7H, m, ArH), 8.20 (2H, m, ArH).

Anal. Calcd. for $C_{26}H_{24}N_6O$: C, 71.56; H, 5.50; N, 19.27. Found: C, 71.42; H, 5.60; N, 19.15.

Piperidinium 6,8-Dicyano-7-(*p*-methoxyphenyl)-6-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridinide (**6c**).

This compound was obtained in 46% yield, mp 273-275° (from ethanol); ir: 3090, 3020, 2990, 2240, 1680, 1630, 1360 cm^{-1}; ^1H nmr: δ 1.44 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 3.86 (3H, s, CH_3O), 7.11 (2H, d, ArH), 7.45-7.60 (5H, m, ArH), 8.19 (2H, m, ArH); ^{13}C nmr: δ 21.76 (γ-CH_2, piperidinium), 22.38 (β-CH_2, piperidinium), 43.95 (α-CH_2, piperidinium), 55.42 (CH_3O), 77.47, 83.38 (6-C, 8-C), 117.40, 118.77 (2 x CN), 113.89 (2 x C, ArH), 126.97 (2 x C, ArH), 128.93 (2 x C, ArH9, 130.37 (2 x C, ArH), 128.17, 130.08, 130.89, 154.93, 156.58, 157.27, 160.24 and 162.22 (C=O).

Anal. Calcd. for $C_{26}H_{24}N_6O_2$: C, 69.02; H, 5.31; N, 18.58; Found: C, 68.86; H, 5.45; N, 18.83.

Piperidinium 7-(*p*-Chlorophenyl)-6,8-dicyano-5-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridinide (**6d**).

This compound was obtained in 60% yield, mp 265-267° (from ethanol); ir: 3120, 3040, 2990, 2240, 1690, 1640, 1360 cm^{-1}; ^1H nmr: δ 1.49 (2H, m, CH_2 piperidine), 1.57 (4H, 2 x CH_2 piperidine), 2.96 (4H, m, 2 x CH_2 piperidine), 7.4-7.6 (7H, m, ArH), 8.14 (2H, m, ArH); ^{13}C nmr: δ 21.79 (γ-CH_2, piperidinium), 22.40 (β-CH_2, piperidinium), 43.97 (α-CH_2, piperidinium), 77.59, 83.28 (6-C, 8-C), 117.06, 118.74 (2 x CN), 127.01 (2 x C, ArH9, 128.71 (2 x C, ArH), 128.99 (2 x C, ArH), 130.79 (2 x C, ArH), 130.18, 131.69, 134.46, 135.03 (C, ArH), 153.67, 157.88, 156.39 (7-C, 8a-C, 2-C), 162.32 (C=O).

Anal. Calcd. for $C_{25}H_{21}N_6OCl$: C, 65.72; H, 4.60; N, 18.40; Found: C, 66.00; H, 4.50; N, 18.39.

Piperidinium 6,8-Dicyano-7-(*p*-nitrophenyl)-6-oxo-2-phenyl[1,2,4]-triazolo[1,5-*a*]pyridinide (**6e**).

This compound was obtained in 56% yield, mp 251-253° (from ethanol); ir: 3100, 2995, 2240, 1660, 1580, 1550, 1460, 1380, cm^{-1}; ^1H nmr: δ 1.56 (2H, m, CH_2 piperidine), 1.64 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 7.53 (3H, m, ArH), 7.88 (2H, d, ArH), 8.20 (3H, m, ArH), 8.41 (1H, d, ArH); ^{13}C nmr: δ 21.77 (γ-CH_2, piperidinium), 22.38 (β-CH_2, piperidinium), 43.96 (α-CH_2, piperidinium), 77.49, 82.99 (6-C, 8-C), 116.74, 118.18 (2 x CN), 123.76 (2 x C, ArH), 127.01 (2 x C, ArH), 128.98 (2 x C, ArH), 130.54 (2 x C, ArH), 130.20, 130.72, 142.69, 148.22 (C, ArH), 152.90, 153.54, 156.23 (7-C, 8a-C, 2-C), 162.40 (C=O).

Anal. Calcd. for $C_{25}H_{21}N_7O_3$: C, 64.24; H, 4.50; N, 20.99. Found: C, 63.98; H, 4.80; N, 21.10.

Piperidinium 6-Cyano-8-methoxycarbonyl-5-oxo-2,7-diphenyl-[1,2,4]triazolo[1,5-*a*]pyridinide (**6f**).

This compound was obtained in 63% yield, mp 252-254° (from ethanol); ir: 3080, 2990, 2220, 1710, 1640, 1550, 1500, 1390 cm^{-1}; ^1H nmr: δ 1.55 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 3.41 (3H, s, CH_3O), 7.28-7.31 (2H, m, ArH), 7.41-7.52 (6H, m, ArH), 8.16-8.19 (2H, m, ArH).

Anal. Calcd. for $C_{26}H_{25}N_5O_3 \cdot H_2O$: C, 65.96; H, 5.71; N, 14.80; Found: C, 65.92; H, 5.90; N, 14.71.

Piperidinium 6-Cyano-7-(*p*-methylphenyl)-8-methoxycarbonyl-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6g**).

This compound was obtained in 44% yield, mp 222-224° (from ethanol); ir: 3060, 2990, 2220, 1720, 1630, 1560, 1500, 1450, 1380 cm^{-1}; ^1H nmr: δ 1.55 (2H, m, CH_2 piperidene), 1.63 (4H, m, 2 x CH_2 piperidine), 2.37 (3H, s, CH_3), 3.01 (4H, m, 2 x CH_2 piperidine), 3.45 (3H, s, CH_3O), 7.17-7.52 (7H, m, ArH), 8.16 (2H, m, ArH), 8.23 (2H, bs, NH_2).

Anal. Calcd. for $C_{27}H_{27}N_5O_3 \cdot H_2O$: C, 66.52; H, 5.95; N, 14.37; Found: C, 66.64; H, 5.96; N, 14.51.

Piperidinium 6-Cyano-8-methoxycarbonyl-7-(*p*-methoxyphenyl)-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6h**).

This compound was obtained in 47% yield, mp 249-251° (from ethanol); ir: 3030, 2990, 2220, 1705, 1630, 1560, 1530, 1500, 1460, 1390 cm^{-1}; ^1H nmr: δ 1.56 (2H, m, CH_2 piperidine), 1.64 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 3.36 (3H, s, CH_3O), 3.48 (3H, s, CH_3O), 7.51 (3H, m, ArH), 7.77 (2H, m, ArH), 8.13-8.30 (6H, m, ArH, NH_2); ^{13}C nmr: δ 21.62 (γ-CH_2, piperidinium), 22.24 (β-CH_2, piperidinium), 43.84 (α-CH_2, piperidinium), 51.21 (CH_3O), 55.18 (CH_3O), 81.50, 99.86 (6-C, 8-C), 119.67 (CN), 113.27 (2 x C, ArH), 126.76 (2 x C, ArH), 128.67 (2 x C, ArH), 129.40 (2 x C, ArH), 130.42, 130.63, 131.31, 149.35 (C, ArH), 152.64, 156.78, 159.01 (7-C, 8a-C, 2-C), 161.75 (CO-N), 165.81 (CO-O).

Anal. Calcd. for $C_{27}H_{27}N_5O_4$: C, 66.80; H, 5.57; N, 14.43. Found: C, 66.61; H, 5.77; N, 14.31.

Piperidinium 7-(*p*-Chlorophenyl)-6-cyano-8-methoxycarbonyl-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6i**).

This compound was obtained in 40% yield, mp 216-218° (from ethanol); ir: 3080, 2990, 2220, 1710, 1630, 1550, 1500, 1450, 1390 cm^{-1}; ^1H nmr: δ 1.55 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 3.47 (3H, s, CH_3O), 7.31 (2H, d, ArH), 7.50 (5H, m, ArH), 8.17 (2H, m, ArH); ^{13}C nmr: δ 21.63 (γ-CH_2, piperidinium), 22.24 (β-CH_2, piperidinium, 43.85 (α-CH_2, piperidinium), 51.19 (CH_3O), 81.61, 99.28 (6-C, 8-C), 119.27 (CN), 126.82 (2 x C, ArH), 127.93 (2 x C, ArH), 128.70 (2 x C, ArH), 129.92 (2 x C, ArH), 129.68, 131.23, 132.63, 137.51 (C, ArH), 149.18, 152.72, 156.58 (7-C, 8a-C, 2-C), 161.88 (CO-N), 165.22 (CO-O).

Anal. Calcd. for $C_{26}H_{24}N_5O_3Cl \cdot H_2O$: C, 61.74; H, 5.12; N, 13.79. Found: C, 61.64; H, 4.94; N, 13.59.

Piperidinium 6-Cyano-8-ethoxycarbonyl-5-oxo-2,7-diphenyl-[1,2,4]triazolo[1,5-*a*]pyridinide (**6j**).

This compound was obtained in 74% yield, mp 258-259° (from ethanol); ir: 3100, 3000, 2220, 1710, 1640, 1560, 1460, 1390 cm^{-1}; ^1H nmr: δ 0.85 (3H, t, CH_3), 1.55 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 3.01 (4H, m, 2 x CH_2 piperidine), 3.90 (2H, q, CH_2O), 7.25-7.60 (8H, m, ArH), 8.20 (2H, d, ArH); ^{13}C nmr: δ 13.63 (CH_3), 21.76 (γ-CH_2, piperidinium), 22.36 (β-CH_2, piperidinium), 43.99 (α-CH_2, piperidinium), 59.71 (CH_2O), 81.28, 100.13 (6-C, 8-C), 119.58 (CN), 126.89 (2 x C, ArH), 127.91 (2 x C, ArH), 128.21 (2 x C, ArH), 128.78 (2 x C, ArH), 127.95, 129.70, 131.50, 138.74 (C, ArH), 149.72, 152.84, 156.84 (7-C, 8a-C, 2-C), 161.94 (CO-N), 165.03 (CO-O).

Anal. Calcd. for $C_{27}H_{27}N_5O_3$: C, 69.08; H, 5.76; N, 14.93; Found: C, 68.94; H, 5.82; N, 14.96.

Piperidinium 6-Cyano-8-ethoxycarbonyl-7-(*p*-methylphenyl)-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6k**).

This compound was obtained in 49% yield, mp 233-235° (from ethanol); ir: 3060, 3000, 2220, 1700, 1630, 1550, 1510, 1460, 1380, cm^{-1}; ^1H nmr: δ 0.85 (3H, t, CH_3), 1.55 (2H, m, CH_2 piperidine), 1.63 (4H, m, 2 x CH_2 piperidine), 2.38 (3H, s, CH_3), 3.01 (4H, m, 2 x CH_2 piperidine), 3.90 (2H, q, CH_2O), 7.20 (4H, q, ArH), 7.50 (3H, m, ArH), 8.18 (2H, d, ArH); ^{13}C nmr: δ 13.65 (CH_3), 20.95 (CH_3), 21.72 (γ-CH_2, piperidinium), 22.34 (β-CH_2, piperidinium), 43.98 (α-CH_2, piperidinium), 59.80 (CH_2O), 81.30, 100.05 (6-C, 8-C), 119.67 (CN), 126.83 (2 x C, ArH), 128.11 (2 x C, ArH), 128.39 (2 x C, ArH), 128.70 (2 x C, ArH), 129.57, 131.56, 135.76, 137.16 (C, ArH), 149.60, 152.80, 156.80 (7-C, 8a-C, 2-C), 161.90 (CO-N), 165.15 (CO-O).

Anal. Calcd. for $C_{28}H_{29}N_5O_3$: C, 69.57; H, 6.00; N, 14.49; Found: C, 69.37; H, 6.16; N, 14.33.

Piperidinium 6-Cyano-8-ethoxycarbonyl-7-(*p*-methoxyphenyl)-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6l**).

This compound was obtained in 45% yield, mp 230-232° (from ethanol); ir: 3060, 2980, 2220, 1700, 1630, 1550, 1510, 1450, 1380 cm^{-1}; ^1H nmr: δ 0.86 (3H, t, CH_3), 1.53 (2H, m, CH_2 piperidine), 1.64 (4H, m, 2 x CH_2 piperidine), 3.00 (4H, m, 2 x CH_2 piperidine), 3.82 (3H, s, CH_3O), 3.92 (2H, q, CH_2O), 7.08 (4H, q, ArH), 7.40-7.55 (3H, m, ArH), 8.15 (2H, d, ArH), 8.22 (2H, bs, NH_2), ^{13}C nmr: δ 13.82 (CH_3), 21.76 (γ-CH_2, piperidinium), 22.38 (β-CH_2, piperidinium), 43.98 (α-CH_2, piperidinium), 55.31 (CH_3O), 59.76 (CH_2O), 81.34, 100.30 (6-C, 8-C), 119.83 (CN), 113.38 (2 x C, ArH), 126.87 (2 x C, ArH), 128.77 (2 x C, ArH), 129.56 (2 x C, ArH), 129.66, 130.82, 131.56, 149.30 (c, ArH), 152.84, 156.87, 159.23 (7-C, 8a-C, 2-C), 161.84 (CO-N), 165.31 (CO-O).

Anal. Calcd. for $C_{28}H_{29}N_5O_4$: C, 67.33; H, 5.81; N, 14.03; Found: C, 67.19; H, 5.80; N, 13.99.

Piperidinium 7-(*p*-Chlorophenyl)-6-cyano-8-ethoxycarbonyl-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridinide (**6m**).

This compound was obtained in 45% yield, mp 236-238° (from ethanol); ir: 3080, 3000, 2220, 1700, 1640, 1560, 1420 cm^{-1}, ^1H nmr: δ 0.90 (3H, t, CH_3), 1.55 (2H, m, CH_2 piperidine), 1.64 (4H, m, 2 x CH_2 piperidine), 3.02 (4H, m, 2 x CH_2 piperidine), 3.92 (2H, q, CH_2O), 7.30-7.60 (7H, m, ArH), 8.17 (2H, dd, ArH); ^{13}C nmr: δ 13.80 (CH_3), 21.51 (γ-CH_2, piperidinium), 22.12 (β-CH_2, piperidinium), 43.76 (α-CH_2, piperidinium), 59.50 (CH_2O), 81.20, 99.52 (6-C, 8-C), 119.18 (CN), 126.65 (2 x C, ArH), 127.72 (2 x C, ArH), 128.52 (2 x C, ArH), 129.86 (2 x C, ArH), 129.46, 131.24, 132.50, 137.56 (C, ArH), 148.66, 152.67, 156.41 (7-C, 8a-C, 2-C), 161.73 (CO-N), 164.46 (CO-O).

Anal. Calcd. for $C_{27}H_{26}N_5O_3Cl$: C, 64.22; H, 5.15; N, 13.87. Found: C, 64.02; H, 5.13; N, 13.69.

7-Aryl-6-cyano-5-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridines 8-Substituted **7**. General Procedure.

To a solution of 0.2 mmole of the corresponding salt **6** in 10-20 ml of ethanol, a solution of 10% hydrochloric acid (15-20 ml) was added. After stirring, the reaction mixture was left at room temperature for 24 hours and the solid precipitated was collected by filtration and washed with plenty of water (neutral *p*H). Further purification was accomplished by recrystallization in acetonitrile.

6,8-Dicyano-5-oxo-2,7-diphenyl[1,2,4]triazolo[1,5-*a*]pyridine (**7a**).

This compound was obtained by following the general procedure in 70% yield, mp >380°; ir: 3200-2600, 2230, 1660, 1600, 1520, 1460, 1420, 1380, 1280 cm^{-1}; ^1H nmr: 7.52 (8H, br. s, ArH), 8.20 (2H, m, ArH); ^{13}C nmr: 77.29, 83.87 (6-C, 8-C), 117.07, 118.48 (2 x CN), 127.12 (2 x C, ArH), 128.63 (2 x C, ArH), 128.85 (2 x C, ArH), 129.07 (2 x C, ArH), 129.71, 130.20, 130.38, 136.10 (C, ArH), 153.45, 155.46, 156.37 (7-C, 8a-C, 2-C), 161.65 (C=O).

Anal. Calcd. for $C_{20}H_{11}N_5O$: C, 71.22; H, 3.26; N, 20.77. Found: C, 70.96; H, 3.27; N, 20.70.

6,8-Dicyano-7-(*p*-methoxyphenyl)-6-oxo-2-phenyl[1,2,4]triazolo-[1,5-*a*]pyridine (**7c**).

This compound was obtained in 78% yield, mp 361-363°; ir: 3200-2600, 2230, 1660, 1610, 1580, 1520, 1460, 1420, 1380 cm^{-1}; ^1H nmr: 3.86 (3H, s, CH_3O), 7.11 (2H, m, ArH), 7.51 (5H, m, ArH), 8.18 (2H, d, ArH).

Anal. Calcd. for $C_{21}H_{13}N_5O_2$: C, 68.66; H, 3.54; N, 19.07. Found: C, 68.30; H, 3.49; N, 19.05.

6,8-Dicyano-7-(*p*-nitrophenyl)-6-oxo-2-phenyl[1,2,4]triazolo[1,5-*a*]-pyridine (**7e**).

This compound was obtained in 82% yield, mp >380°; ir: 3200-2600, 2220, 1650, 1620, 1540, 1460, 1420, 1380 cm^{-1}; ^1H nmr: 7.54 (3H, m, ArH), 7.88 (2H, d, ArH), 8.20 (2H, m, ArH), 8.42 (2H, d, ArH).

Anal. Calcd. for $C_{20}H_{10}N_6O_3$: C, 62.83; H, 2.62; N, 21.99. Found: C, 62.58; H, 2.59; N, 21.78.

6-Cyano-8-methoxycarbonyl-7-(*p*-methoxyphenyl)-5-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine (**7h**).

This compound was obtained in 71% yield, mp 328-330°; ir: 3300-2600, 2220, 1700, 1650, 1600, 1540, 1500, 1450, 1430, 1410, 1370 cm^{-1}; ^1H nmr: 3.55 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 7.04 (2H, m, ArH), 7.25 (2H, d, ArH), 7.63 (3H, m, ArH), 8.17 (2H, m, ArH).

Anal. Calcd. for $C_{22}H_{16}N_4O_4$: C, 66.00; H, 4.00; N, 14.00. Found: C, 65.83; H, 3.99; N, 13.81.

7-(*p*-Chlorophenyl)-6-cyano-8-methoxycarbonyl-5-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine (**7i**).

This compound was obtained in 78% yield, mp 345-347°; ir: 3300-2600, 2220, 1710, 1660, 1610, 1590, 1550, 1510, 1450, 1430, 1390 cm^{-1}; ^1H nmr: 3.56 (3H, s, CH_3O), 7.35 (2H, d, ArH), 7.56 (5H, m, ArH), 8.17 (2H, m, ArH).

Anal. Calcd. for $C_{21}H_{13}N_4O_3Cl$: C, 62.30; H, 3.21; N, 13.84. Found: C, 62.12; H, 3.17; N, 13.66.

6-Cyano-8-ethoxycarbonyl-5-oxo-2,7-diphenyl[1,2,4]triazolo[1,5-*a*]-pyridine (**7j**).

This compound was obtained in 68% yield, mp 331-333°; ir: 3300-2600, 2220, 1700, 1650, 1600, 1590, 1540, 1500, 1450, 1420, 1400 cm^{-1}; ^1H nmr: 0.77 (3H, t, CH_3), 3.89 (2H, q, CH_2O), 7.30-7.60 (8H, m, ArH), 8.19 (2H, m, ArH).

Anal. Calcd. for $C_{22}H_{16}N_4O_3$: C, 68.75; H, 4.17; N, 14.58. Found: C, 68.46; H, 4.11; N, 14.56.

6-Cyano-8-ethoxycarbonyl-7-(*p*-methylphenyl)-5-oxo-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine (**7k**).

This compound was obtained in 74% yield, mp 363-365°; ir: 3300-2600, 2220, 1700, 1650, 1600, 1590, 1540, 1500, 1450, 1400, 1370 cm^{-1}; ^1H nmr: 0.82 (3H, t, CH_3), 2.39 (3H, s, CH_3), 3.92 (2H, q, CH_2O), 7.20-7.60 (7H, m, ArH), 8.15 (2H, m, ArH).

Anal. Calcd. for $C_{23}H_{18}N_4O_3$: C, 69.35; H, 4.52; N, 14.07. Found: C, 68.99; H, 4.45; N, 14.00.

Acknowledgements.

Support of this work by a grant from the Comisión Interministerial de Ciencia y Tecnología of Spain (PB-89-0495 and PB-87-0291) is gratefully acknowledged. One of the authors (A. H.) is grateful to Ministerio de Asuntos Exteriores of Spain for a research fellowship.

REFERENCES AND NOTES

[1] T. Irikura and S. Suzne, German Patent 2,905,823 Kyorin Pharmaceutical Co. Ltd., (1980); *Chem. Abstr.*, **94**, 121541 (1981); French Patent 2,450,259 (1980); *Chem. Abstr.*, **97**, 72373 (1982); Japanese Patent 8163983 Kanebo Ltd., (1981); *Chem. Abstr.*, **95**, 203964 (1981).

[2] K. Kubo, N. Itoh, I. Sohzu, Y. Isomura and H. Honma, Japanese Patent 7905996 Yamamoudu Pharmaceutical Co. Ltd., (1979); *Chem. Abstr.*, **91**, 57007 (1979).

[3] K. Gewald, A. Schnbert and G. Martin, *J. Prakt. Chem.*, **317**, 561 (1975).

[4] L. S. Davis and G. Jones, *J. Chem. Soc., (C)*, 690 (1970); H. Berner and H. Reinshagen, *Monatsh. Chem.*, **106**, 1059 (1975).

[5] K. Suzne, Japanese Patent 7939094 Kyorin Pharmaceutical Co. Ltd., (1979); *Chem. Abstr.*, **91**, 91646 (1979); R. E. Banks and S. M. Hitchen, *J. Fluorine Chem.*, **15**, 179 (1980); *Chem Abstr.*, **93**, 95180 (1980); *ibid.*, **20**, 373 (1982); *Chem Abstr.*, **97**, 109934 (1982); O. Toshihike, H. Massaki, T. Vasunobu and Y. Emike, *Chem. Pharm. Bull.*, **14**, 506 (1966).

[6] V. A. Chuiguk and K. V. Fedotov, *Ukr. Khim. Zh.*, **46**, 1306 (1980); *Chem. Abstr.*, **94**, 208680 (1981).

[7] K. Potts and C. R. Surapeni, *J. Heterocyclic Chem.*, **7**, 1019 (1970); P. Molina, M. Alajarin and A. Soler, *An. Quim.*, **76C**, 207 (1980).

[8] R. C. Phadke and D. W. Rangnekar, *Synthesis*, 860 (1986).

[9] G. P. Ellis, Synthesis of Fused Heterocycles, Wiley Interscience, Chichester, New York, 1987.

[10] The original Baldwin nomenclature for classifying cyclizations is used here. See: J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

[11] N. Martín, M. Quinteiro, C. Seoane, J. L. Soto, I. Fonseca, F. Florencio and J. Sanz, *J. Org. Chem.*, **55**, 2259 (1990); M. J. Callejo, P. Lafuente, N. Martín-León, M. Quinteiro, C. Seoane and J. L. Soto, *J. Chem. Soc., Perkin Trans 1*, 1687 (1990).

[12] A similar behaviour in related molecules is known, N. Martín-León, M. Quinteiro, C. Seoane and J. L. Soto, *Liebigs Ann. Chem.*, 101 (1990).

[13] A. Rich and N. Davidson, Structural Chemistry and Molecular Biology, V. H. Freeman and Co., San Francisco, 1968.

[14] R. Gautam, Crystal Engineering, Elsevier Amsterdam, 1989.

[15] B. Corson and R. Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928); A. C. Cope and K. E. Hoyle, *ibid.*, **63**, 733 (1941).

[16] W. D. S. Motherwell, PLUTO, A Program for Plotting Crystal and Molecular Structures, Cambridge University, England, 1978.

[17] G. Cascarano, C. Giacovazzo, Dip, Geomineralogico, University of Bari; M. G. Burla, G. Polidori, Dip. Scienze de la Terra, University of Perugia; M. Camalli, R. Spagna, Inst. Strutt. Chimica C.N.R., Roma; D. Viterbo, Dip. Chimica, University della Calabria Consenza, SIR88, 1988.

[18] J. M. Stewart, F. A. Kundell and J. C. Baldwin, The X-Ray 76 Computer Science Center, University of Maryland, College Park, Maryland, USA.

[19] M. Nardelli, *M. Comut. Chem.*, PARST, **7**, 95 (1983).

[20] International Tables for X-Ray Crystallography, Vol **IV**, Birmingham Press, (1974).

[21] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-56028, the names of the authors, and the journal citation.