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SYNTHESIS OF NEW PYRROLO-[3,4-*c*]ISOXAZOLE, PYRROLO[2,3-*d*]-[1,2,3]TRIAZOLE, TRIAZOLO[4,5-*c*]-PYRIDAZINE, AND DIPYRROLO-[3,2-*b*:3',4'-*d*]PYRAN DERIVATIVES

F. A. Amer[1], M. Hammouda[1], A.-A. S. El-Ahl[1], B. F. Abdel-Wahab[2]

New pyrrolo[3,4-c]isoxazole derivatives were synthesized from the key intermediates 4-cyano-pyrrolidin-3-ones in two steps. Pyrrolo[2,3-d][1,2,3]triazoles and triazolo[4,5-c]pyridazine were obtained from 2-arylhydrazono-4-cyano–1-(4'-methoxyphenyl)-3-oxopyrrolidines by refluxing with phenylhydrazine in either ethanol or glacial acetic acid. Aldol self-condensation of 1-aryl-4-cyano-pyrrolidin-3-ones afforded dipyrrolo-[3,2-b:3',4'-d]pyran derivatives.

Keywords: oxime, β-oxo nitriles, pyrrolidin-3-ones, aldol condensation

N-Arylpyrrolidin-3-one is a key starting material for the synthesis of a number of fused heterocycles, among them certain analogs of the anticancer drug *methotrexate* [1, 2]. Pyrrolidine derivatives which bear an alkyloxime substituent in position 4 and an aminoalkyl substituent in position 3 of the pyrrolidine ring were used to produce a series of fluoroquinolone antibacterials (e.g., *gemifloxacin*, *norfloxacin*) and also used as bax inhibitors [3–6]. Some of the 3-pyrrolidinone derivatives were used as inhibitors of HIV-1 replication [7]. We are reporting here the synthesis of some new fused heterocycles having a pyrrolidine moiety, such as pyrrolo[3,4-*c*]isoxazoles, pyrrolo[2,3-*d*][1,2,3]triazoles, triazolo[4,5-*c*]pyridazine, and dipyrrolo[3,2-*b*:3',4'-*d*]pyran derivatives.

The starting pyrrolidin-3-ones (considered as heterocyclic β-oxonitriles) **1a,b** were prepared from primary aromatic amines, acrylonitrile, and ethyl bromoacetate according to the methods reported [8–10]. We investigated their reaction with $NH_2OH \cdot HCl$ in refluxing ethanol containing sodium acetate. The reaction furnished the expected oxime derivatives [11, 12] **2a,b** (Scheme 1), but all attempts to cyclize these oximes into the pyrroloisoxazole derivatives **3a,b** were unsuccessful. We assumed that oximes 2a,b were present completely in the *Z*-form relative to the pyrrolidine ring, in which the OH group was oriented away from the cyano group. The *Z*-form of **2a,b** was stable under thermal, acidic, or basic conditions, therefore, the transformation of **2a,b** into **3a,b** proved to be difficult. We envisioned that if we introduce a bulky substituent in position 2 of the 3-pyrrolidinone **1a,b**, the geometry of the resulted oxime would be changed. Accordingly, we investigated the reaction of **1a** with aryldiazonium salts under mild basic conditions (ethanol and sodium acetate); the reaction

[1]Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt. [2]Applied Chemistry Department, National Research Center, Dokki, Giza, Egypt; e-mail: Beko_bfa@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1841-1848, December, 2007. Original article submitted February 08, 2007.

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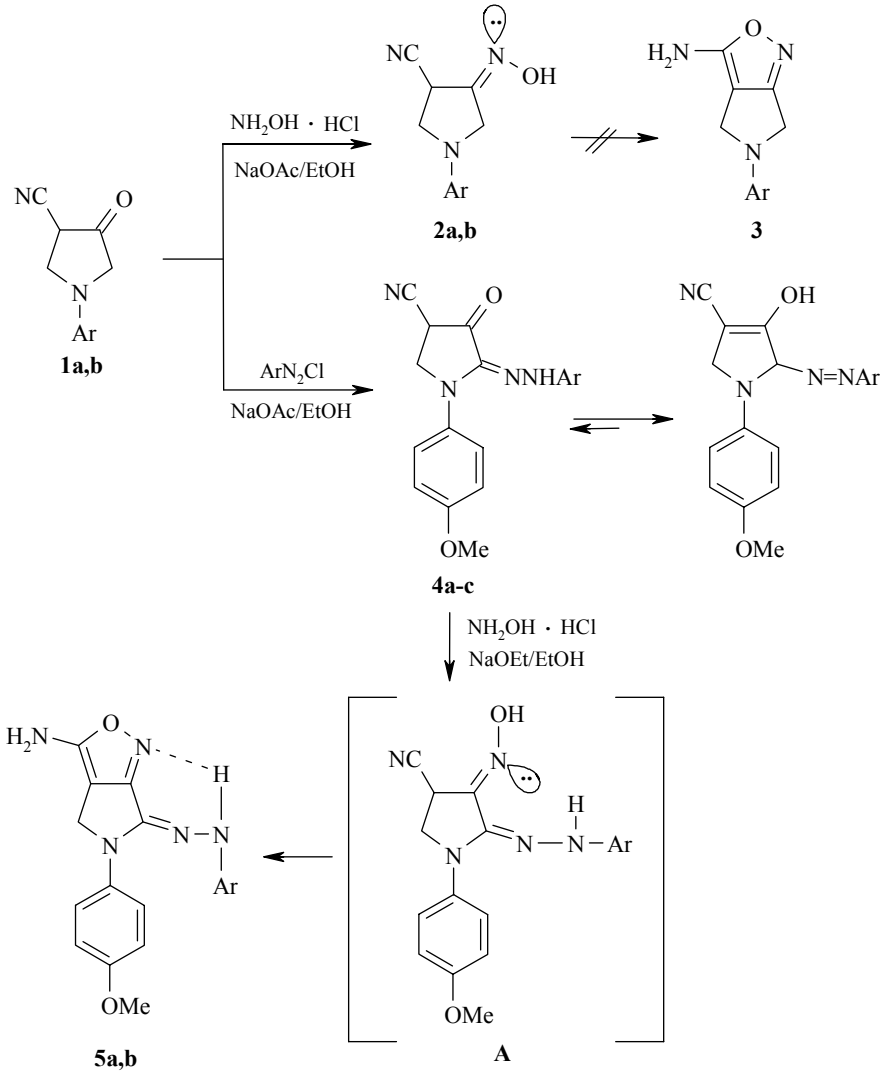
furnished the arylazopyrrolidine derivatives, **4a–c**. The treatment of compounds **4a,c** with hydroxylamine hydrochloride in ethanolic sodium ethoxide afforded the pyrroloisoxazole derivatives **5a,b**. The formation of the pyrroloisoxazoles **5a,b** from the reaction of **4b,c** with hydroxylamine hydrochloride proceeded *via* the oxime intermediate **A** which was presumably present in the *E*-form due to the steric interaction of the hydroxyl group with the bulky arylazo group in position 2 of the pyrroline ring (Scheme 1).

Scheme 1



1,2 **a** Ar = 4-$MeOC_6H_4$, **b** Ar = 4-MeC_6H_4; 4 **a** Ar = 4-MeC_6H_4, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-ClC_6H_4; 5 **a** Ar = 4-$MeOC_6H_4$, **b** Ar = 3-ClC_6H_4

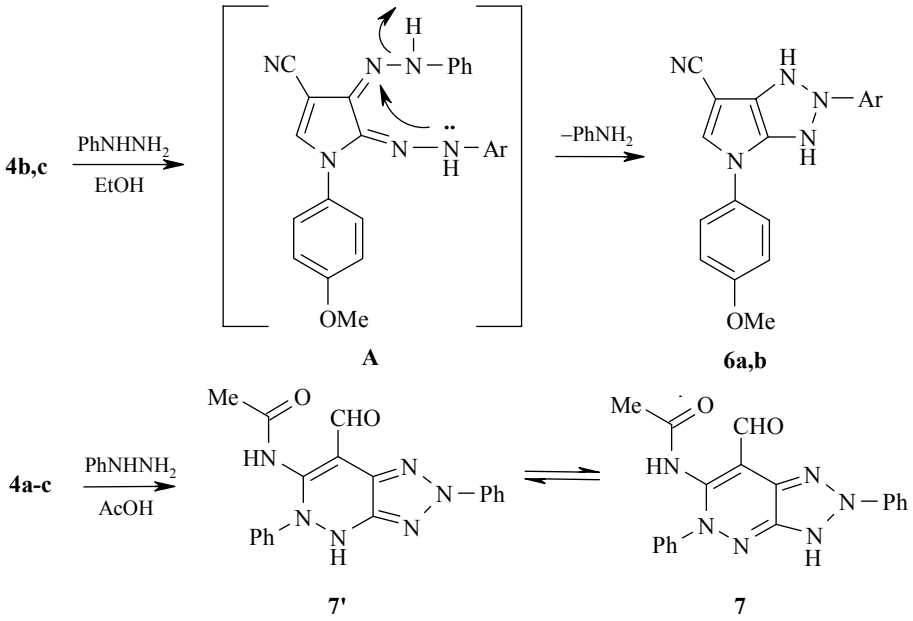
The ^{1}H NMR spectrum of **5a** showed a broad singlet (2H) at 5.77 ppm attributed to the methylene group of the pyrrolidine ring. Also two singlets for three protons at 9.02 and 8.19 ppm were present, attributed to NH_2 and NH groups, respectively. Physical and spectra data are given in Tables 1-3.

The reaction of compound **4b,c** with phenylhydrazine in ethanol afforded the pyrrolotriazole derivatives **6a,b**. However, on conducting the reaction in glacial acetic acid under refluxing conditions the arylazo derivatives **4a-c** underwent ring transformation into the triazolopyridazine derivative **7** (Scheme 2).

TABLE 1. Characteristics of the Synthesized Compounds **2** and **4–8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Color
		C	H	N			
2a	$C_{12}H_{13}N_3O_2$	62.32 / 62.39	5.66 / 5.76	18.17 / 18.23	234-235	73	Colorless
2b	$C_{12}H_{13}N_3O$	66.96 / 67.08	6.09 / 6.16	19.52 / 19.48	247-248	72	Colorless
4a	$C_{19}H_{18}N_4O_2$	68.24 / 68.42	5.43 / 4.62	16.76 / 16.75	176-177	57	Red
4b	$C_{19}H_{18}N_4O_3$	65.13 / 65.24	5.18 / 5.07	15.99 / 16.03	230-231	73	Scarlet red
4c	$C_{18}H_{15}ClN_4O_2$	60.93 / 61.02	4.26 / 4.33	15.79 / 15.77	267-268	77	Orange
5a	$C_{19}H_{19}N_5O_3$	62.45 / 62.56	5.24 / 5.32	19.17 / 19.07	228-229	62	Pale yellow
5b	$C_{18}H_{16}ClN_5O_2$	58.46 / 58.59	4.36 / 4.43	18.94 / 18.86	148-149	58	Pale yellow
6a	$C_{19}H_{17}N_5O_2$	65.69 / 65.81	4.93 / 5.02	20.16 / 20.09	264-266	49	Colorless
6b	$C_{18}H_{14}ClN_5O$	61.45 / 61.39	4.01 / 3.96	19.91 / 19.79	>315	48	Yellow
7	$C_{19}H_{16}N_6O_2$	63.32 / 63.76	4.47 / 4.64	23.32 / 23.40	115-117	42	Colorless
8a	$C_{24}H_{24}N_4O_4$	66.65 / 66.33	5.59 / 5.70	12.96 / 13.12	230-232	56	Pale yellow
8b	$C_{24}H_{24}N_4O_2$	71.98 / 71.78	6.04 / 6.22	13.99 / 13.83	>310	48	Pale yellow

Scheme 2



6 **a** Ar = 4-$MeOC_6H_4$, **b** Ar = 4-ClC_6H_4

TABLE 2 Spectroscopic Characteristics of Compounds **4–8**

Com-pound	IR spectrum ν, cm^{-1} (group)	Mass spectrum, *m/z* (I_{rel}, %)
4a	1658 (C=O); 2220 (C≡N); 3257 (enolic OH)	335 [M^++1] (70); 334 [M^+] (100); 305 (15); 290 (56); 157 (10); 108 (8); 77 (45)
4b	1634 (C=O); 2221 (C≡N); 3200 (enolic OH)	351 [M^++1] (35); 350 [M^+] (100); 292 (45); 244 (18); 157 (8); 108 (7); 77 (50)
4c	1642 (C=O); 2222 (C≡N); 3294 (enolic OH)	357 [M^++2] (22); 356 [M^++1] (73); 355 [M^+] (100); 157 (6); 108 (7); 77 (55)
5a	1609 (C=N); 3462-3172 (NH_2 and NH)	367 [M^++2] (77); 366 [M^++1] (100); 335 (13); 150 (6); 135 (5.5)
5b	1606 (C=N); 3408-3172 (NH_2 and NH)	372 [M^++2] (66); 370 [M^+] (100); 337 36); 135(12); 77 (58)
6a	2225 (C≡N); 3278 (NH)	349 [M^++2] (24); 348 [M^++1] (100); 333 (41); 149 (22); 135 (7); 133 (62)
6b	2227 (C≡N); 3287(NH)	354 [M^++2] (24); 353 [M^++1] (100); 317 (41); 149 (22); 135 (7); 133 (62)
7	1647 (amidic C=O); 1735 (aldehydic C=O); 3284 (amidic NH)	360 [M^+] (100); 317 (17); 241 (10); 206 (15); 77 (48)
8a	2225 (C≡N); 3258-3102 (NH_2, OH)	433 [M^++1] (1); 432 [M^+] (1.4); 401 (10); 382 (4.2); 370 (3); 217 (0.7); 119 (100); 91 (96)
8b	2225 (C≡N); 3281-3181 (NH_2, OH)	401 [M^++1] (1); 400 [M^+] (1.4); 383 (3); 382 (4.2); 366 (3); 217 (0.7); 119 (100); 91 (96)

The ^{1}H NMR spectrum of compound **6b** showed a multiplet at 7.88-6.92 ppm corresponding to eight aromatic protons overlapped with one proton singlet corresponding to the pyrrole ring hydrogen; the two NH groups were observed as two singlets at 9.37 and 9.28 ppm. The ^{1}H NMR spectrum of **7** displayed one proton singlet at 9.58 ppm corresponding to an aldehydic proton and lacked any absorption peak corresponding to the methoxy group, indicating the removal of *p*-anisidine part of the molecule (a starting material) during the reaction. Upon starting with different arylazo derivatives, the same triazolopyridazine was obtained, indicating the removal of the arylazo group during the reaction. The proposed mechanism for the formation of compound **7** is depicted in Scheme 3. The reaction is thought to proceed *via* the formation of pyrrolotriazole intermediate **B**, which in the further reaction with another molecule of phenylhydrazine, followed by ring opening and recyclization, afforded the intermediate **C**. Tautomerization of **C** would give the intermediate **D**, which underwent acetylation by acetic acid to give intermediate **E**. Hydrolysis of the imine ion **E** by traces of water in the reaction medium furnished compound **7** (Scheme 3).

The structures of the triazole derivatives **6a,b** and **7** were also confirmed by ^{13}C NMR spectrum and mass-spectral data which revealed the molecular ion peaks for **6a** and **7** at *m/z* 347 and 360, respectively. Also the ^{1}H NMR spectrum of compound **7** showed it to be present as a tautomeric mixture (Tables 1-3).

The dimerization of pyrrolidin-3-ones has been well established in the literature [13]. During our study on pyrrolidin-3-ones **1a,b**, we realized that these compounds have a great tendency towards aldol self-condensation in slightly acidic alcoholic solution. Thus, on being refluxed in ethanol containing a catalytic amount of hydrochloric acid **1a,b** furnished products **8a,b**, which are thought to be formed *via* the aldol self-condensation of intermediate **F** (Scheme 4). The structures of **8a,b** were based on spectral and analytical data. The ^{1}H NMR spectrum of **8a** displayed a doublet of doublets centered at 2.72 ppm (J = 18 and 8 Hz) assigned to H_a and H_b; an AB system at 3.28 and 3.52 ppm assigned to H_g and H_f (J = 8 Hz); a multiplet at 3.82-3.74 ppm corresponding to two protons (H_e and H_c). This multiplet is a doublet of doublets H_c overlapped with another doublet H_e as a part of another A_2B_2 system. Another signal of this A_2B_2 system was observed at 4.01 ppm (J = 10.1 Hz), which was assigned to H_d.

The aromatic protons of the two *p*-substituted benzene rings were observed as two indistinguishable A_2B_2 systems at 7.14, 6.91, 6.78 and 6.43 ppm with a coupling constant (J = 8 Hz). The hydroxy group was observed as a singlet at 3.67 ppm, while the amino group was observed as two broad singlets at 7.94 and 7.11 ppm. Also, two singlets (three protons each) were observed at 3.73 and 3.65 ppm assigned to the two methoxy groups.

Scheme 3

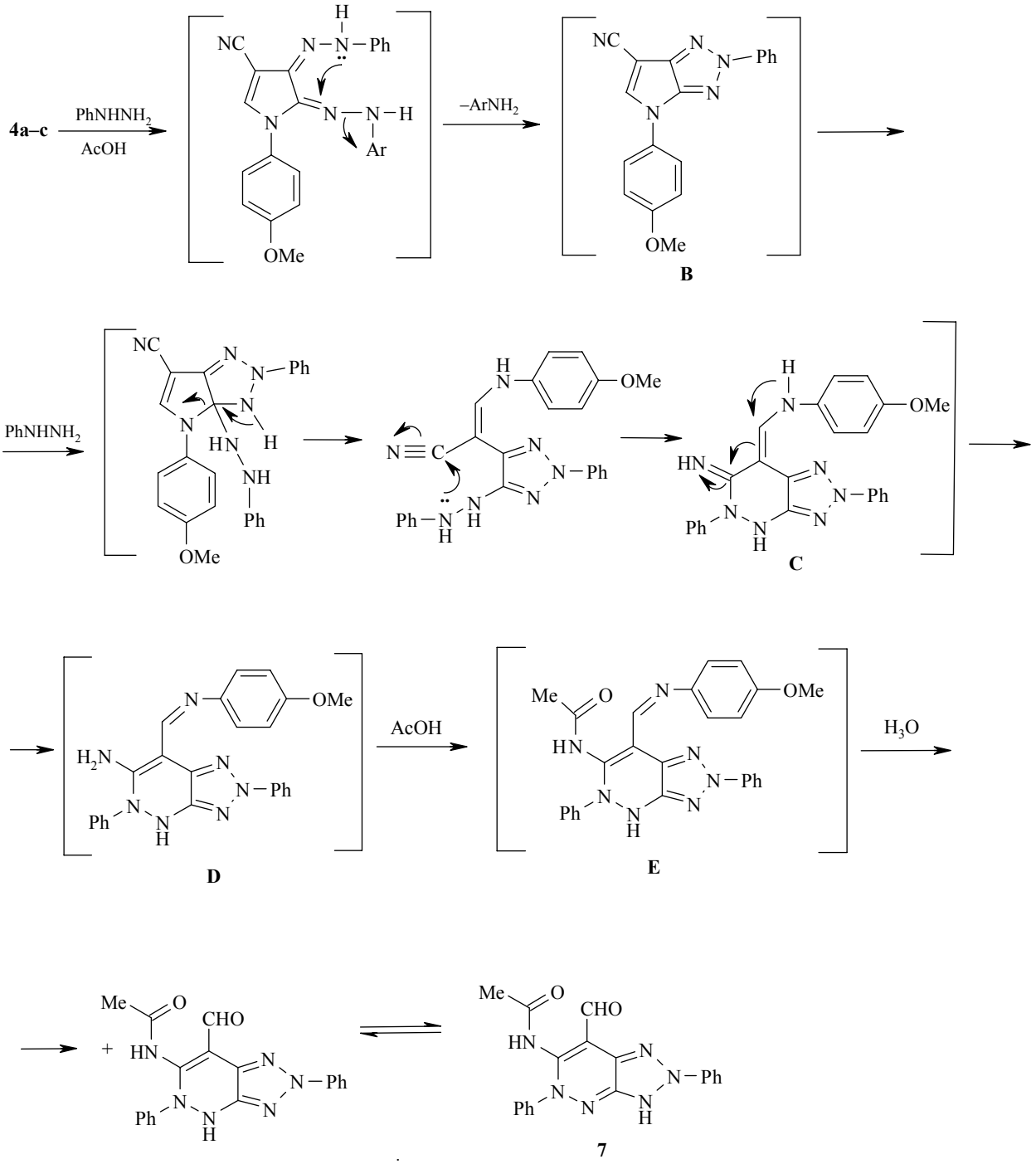
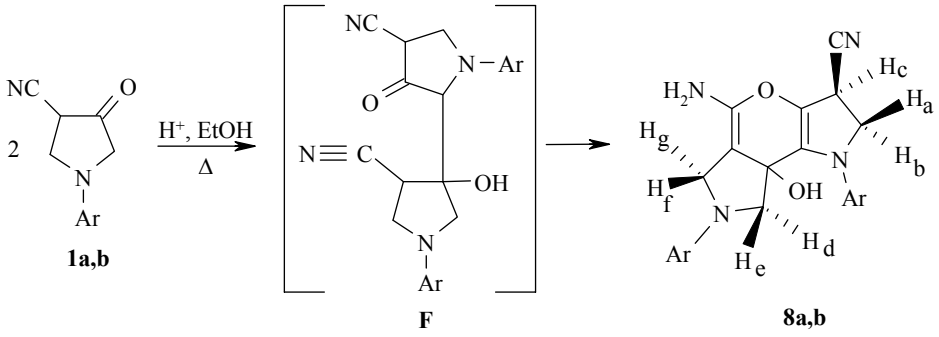


TABLE 3. ^{1}H NMR Spectrum of Compounds **4–8**

Com-pound	δ, ppm (*J*, Hz)
4a	2.51 (3H, s, CH_3); 3.62 (3H, s, OCH_3); 6.95 (2H, d, *J* = 7.8, Ar–H); 7.13 (2H, d, *J* = 7.6, Ar–H); 7.28 (2H, d, *J* = 7.8, Ar–H); 7.53 (2H, d, *J* = 7.6, Ar–H); 8.96 (1H, s, OH)
4b	3.68 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 6.94 (2H, d, *J* = 7.8, Ar–H); 7.11 (2H, d, *J* = 7.6, Ar–H); 7.29 (2H, d, *J* = 8.0, Ar–H); 7.54 (2H, d, *J* = 8.0, Ar–H); 8.94 (1H, s, OH)
4c	3.68 (3H, s, OCH_3); 6.94 (2H, d, *J* = 7.8, Ar–H); 7.13 (2H, d, *J* = 7. 6, Ar–H); 7.28 (2H, d, *J* = 7.8, Ar–H); 7.53 (2H, d, *J* = 7.6, Ar–H); 8.94 (1H, s, OH)
5a	3.82 (3H, s, OCH_3); 3.98 (3H, s, OCH_3); 5.77 (2H, s, CH_2); 6.93 (2H, d, *J* = 9.1, Ar–H); 7.04 (2H, d, *J* = 9.0, Ar–H); 7.61 (2H, d, *J* = 2.4, Ar–H); 7.64 (2H, d, *J* = 2.1, Ar–H); 8.19 (1H, s, NH); 9.02 (2H, s, NH_2)
5b	3.88 (3H, s, OCH_3); 5.83 (2H, s, CH_2); 6.91 (2H, d, *J* = 9.1, Ar–H); 7.02 (2H, d, *J* = 9.0, Ar–H); 7.59 (2H, d, *J* = 2.4, Ar–H); 7.64 (2H, d, *J* = 2.1, Ar–H); 8.20 (1H, s, NH); 9.03 (2H, s, NH_2)
6a	3.65 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 7.85-6.90 (9H, m, 8Ar–H and H-5); 9.26 (1H, s, NH); 9.37 (1H, s, NH)
6b	3.76 (3H, s, OCH_3); 7.88–6.92 (9H, m, 8Ar–H and H-5); 9.28 (1H, s, NH); 9.39 (1H, s, NH)
7	2.85 (3H, s, CH_3); 7.62–6.68 (10H, m, Ar–H); 7.95 (1H, s, NH of pyridazine ring); 8.91 (1H, s, amidic NH); 9.58 (s, 1H, CHO)
8a	2.72 (2H, dd, *J* = 18 and *J* = 8, H_a and H_b); 3.28 (1H, d, *J* = 8.1, H_f); 3.52 (1H, d, *J* = 8.1, H_g); 3.65 (3H, s, OCH_3); 3.67 (1H, s, OH); 3.73 (3H, s, OCH_3); 3.82-3.74 (2H, m, H_c and H_c); 4.01 (1H, d, *J* = 10.8, H_d); 6.43 (2H, d, *J* = 7.8, Ar–H); 6.78 (2H, d, *J* = 7.8, Ar–H); 6.91 (2H, d, *J* = 7.8, Ar–H); 7.14 (1H, s, NH); 7.16 (2H, d, *J* = 8.1, Ar–H); 7.94 (1H, s, NH)
8b	1.93 (3H, s, CH_3); 1.96 (3H, s, CH_3); 2.68 (2H, dd, *J* = 18 and *J* = 8, H_a and H_b); 3.26 (1H, d, *J* = 8.1, H_f); 3.51 (1H, d, *J* = 8.1, H_g); 3.68 (1H, s, OH); 3.82-3.75 (2H, m, H_c and H_c); 4.01 (1H, d, *J* = 10.8, H_d); 6.41 (2H, d, *J* = 7.8, Ar–H); 6.79 (2H, d, *J* = 7.8, Ar–H); 6.90 (2H, d, *J* = 7.8, Ar–H); 7.14 (1H, s, NH); 7.17 (2H, d, *J* = 8.1, Ar–H); 7.96 (1H, s, NH)

Scheme 4



1, 8 **a** Ar = 4-$OMeC_6H_4$, **b** Ar = 4-MeC_6H_4

The mass spectrum of compound 8b showed the molecular ion peak at *m/z* 400; this fitted exactly with the calculated mass. The IR spectra of compound 8a,b showed a weak absorption bands at 2225–2230 cm^{-1}, which showed the presence of a carbonitrile group. Physical and spectroscopic data are given in Tables 1–3.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Perkin Elmer 1650 and Pye-Unicam SP300 IR spectrophotometers. NMR spectra were recorded in deutrated DMSO with TMS as an internal standard using a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu and GCMS 5988-A HP spectrometers. Elemental analyses were carried out in the Microanalytical Laboratory of Cairo University, Giza, Egypt. Pyrrolidin-3-one derivatives **1a,b** were prepared according to the procedures reported [8-10], and hydroxylamine·HCl and phenylhydrazine were purchased from British Drug Houses (BDH). Acrylonitrile, ethyl bromoacetate, and primary aromatic amines were purchased from Aldrich Company. Sodium acetate trihydrate, sodium nitrite, and solvents were purchased from EI-Nasr Pharmaceutical Chemical Co. (ADWIC), Egypt.

1-Aryl-4-cyanopyrrolidine-3 Oximes 2a,b. A mixture of compound **1a** or **1b** (2 mmol) in ethanol (20 ml), hydroxylamine·HCl (0.14 g, 2 mmol) and fused sodium acetate (0.16 g, 2 mmol) was refluxed for 2 h, then left to stand at room temperature. The product obtained was filtered off and recrystallized from ethanol.

2-Arylhydrazono-4-cyano-1-(4'-methoxyphenyl)-3-oxopyrrolidines 4a–c. To an ice-cooled mixture of compound **1a** (2.16 g, 1 mmol) and sodium acetate trihydrate (4.1 g, 5 mmol) in ethanol (50 ml) a solution of the appropriate diazonium salt (1 mmol) was added dropwise with stirring for 15 min. The stirring was continued further for 30 min, and the reaction mixture was allowed to stand overnight in ice. The solid product was collected by filtration and recrystallized from ethanol.

6-Amino-4-(4'-methoxyphenyl)-3-phenylhydrazono-3,5-dihydropyrrolo[3,4-c]isoxazoles 5a,b. Hydroxylamine·HCl (0.14 g, 2 mmol) and ethanolic sodium ethoxide (prepared from 0.5 g sodium metal and 15 ml of ethanol) were added to a suspension of **4b** or **4c** (2 mmol) in ethanol (20 ml). The reaction mixture was refluxed for 4 h and then evaporated *in vacuo*. The remaining solid product was dissolved in water and neutralized with diluted acetic acid. The resulting solid product was collected by filtration and recrystallized from ethanol.

2-Aryl-6-cyano-4-(4'-methoxyphenyl)-1,3-dihydropyrrolo[2,3-*d*][1,2,3]triazoles 6a,b. A mixture of **4b** or **4c** (2 mmol) and phenylhydrazine (0.32 g, 3 mmol) in ethanol (25 ml) was refluxed for 3 h. The crystals obtained after concentration were filtered off and recrystallized from ethanol.

3-Acetamido-4-formyl-2,6-diphenyl-1,2-dihydro-1,2,3-triazolo[4,5-*c*]pyridazine (7). A mixture of **4a**, **4b** or **4c** (2 mmol) and phenylhydrazine (0.27 g, 2.5 mmol) in glacial acetic acid (20 ml) was refluxed for 3 h. The solvent was evaporated *in vacuo* to dryness. The resulting solid product was purified with ethanol and then recrystallized from ethyl acetate. ^{13}C NMR spectrum, δ, ppm: 19.27, 20.67, 38.56, 38.87, 39.18, 39.48, 39.80, 40.11, 40.41, 111.72, 112.10, 118.42, 118.93, 128.73, 129.12, 148.83, 149.43, 169.13, 175.30.

5-Amino-1,7-diaryl-3-cyano-8a-hydroxy-2,3,8,8a-tetrahydro-6H-dipyrrolo[3,2-*b*:3',4'-*d*]-4-pyrans 8a,b. A mixture of **1a** or **1b** (2 mmol) in ethanol (15 ml) and traces of conc. HCl was refluxed for 4 h. Then the solid product formed during reflux was filtered off and recrystallized from DMF–H_2O (3:1). 8a: ^{13}C NMR spectrum, δ, ppm: 20.77, 38.57, 38.88, 39.50, 39.80, 40.12, 40.42, 45.22, 53.61, 55.40, 60.45, 84.48, 86.10, 112.05, 114.70, 114.83, 122.07, 125.60, 132.13, 141.40, 151.02, 157.12, 162.81, 186.58.

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