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REACTION OF 2,3-DIOXOPYRROLO-[2,1-*a*]ISOQUINOLINES WITH AROMATIC AND SECONDARY ALIPHATIC AMINES

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It has been found that 2,3-dioxopyrrolo[2,1-a]isoquinolines react with aromatic amines in glacial acetic acid and with heteroaromatic and secondary aliphatic amines in the absence of acid with opening of the pyrroledione ring to give 1,2,3,4-tetrahydroisoquinoline enamino ketoamides.

Keywords: aromatic and heteroaromatic amines, 5,5-dialkyl-2,3-dioxopyrrolo[2,1-*a*]isoquinolines, 1,2,3,4-tetrahydroisoquinoline enamino ketoamides, acid catalysis.

We have previously shown that the reaction of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with hydrazine hydrate [1], ammonia, and lower aliphatic amines [2] takes place readily and is accompanied by opening of the pyrroledione ring. The ease with which the reaction occurs can be explained by the high nucleophilicity of the reagents. With the aim of establishing a link between the structure of the nucleophile and the reactivity we have studied the reaction of pyrrolo[2,1-*a*]isoquinolines with aromatic, heterocyclic, and secondary aliphatic amines.

The investigation has shown that the reaction does not occur by simply refluxing compounds **1a-c** with aromatic amines in alcohol or benzene (monitoring by TLC). At the same time, heating in glacial acetic acid (i.e. under acid catalysis conditions) opening of the dioxopyrroline ring occurs to give the N-arylideneaminoketoamides **2a-g**. The reaction conditions depend of the nature of the substituent in the aromatic ring. In the case of the less reactive nitroanilines (compounds **2d,e,g**) refluxing is required but in all of the remaining examples a temperature of 60-70°C gives an optimum yield. Nitrogen-containing heterocyclic amines like α- and γ-aminopyridines, and 2-aminothiazole react with compounds **1a,b** similarly with opening of the ring but with simple refluxing in alcohol or benzene in the absence of acetic acid to give the amides **2h-j**. It is likely that the basic nitrogen atom in the ring itself has catalytic activity.

Study of the reaction of compounds **1a-c** with secondary aliphatic amines (pyrrolidine, piperidine, morpholine) has shown that they occur just as readily as with ammonia and primary aliphatic amines to give the enaminoketoamides **3a-d**. Compounds **3b,c** (respectively X = CH_2 and X = O) have been prepared previously by a counter synthesis from the enaminoketoester **4** [3]. The presence of an enaminocarbonyl fragment in the structure of substance **3** is confirmed by annelation of the pyrroledione ring using oxalyl chloride (compound **5**) (Scheme 1).

Characteristics of compounds **2, 3, 5** are given in Table 1. By contrast with those of the starting material, the ^{1}H NMR spectra of amides **2** and **3** (Table 2) show singlet signals for the ring NH protons (10.49-11.77 ppm), the basic nature of which is confirmed by a shift to lower field upon addition of CF_3COOH. The spectra of the amides **2** show amide group NH singlets (9.13-10.75 ppm) and also multiplets for the

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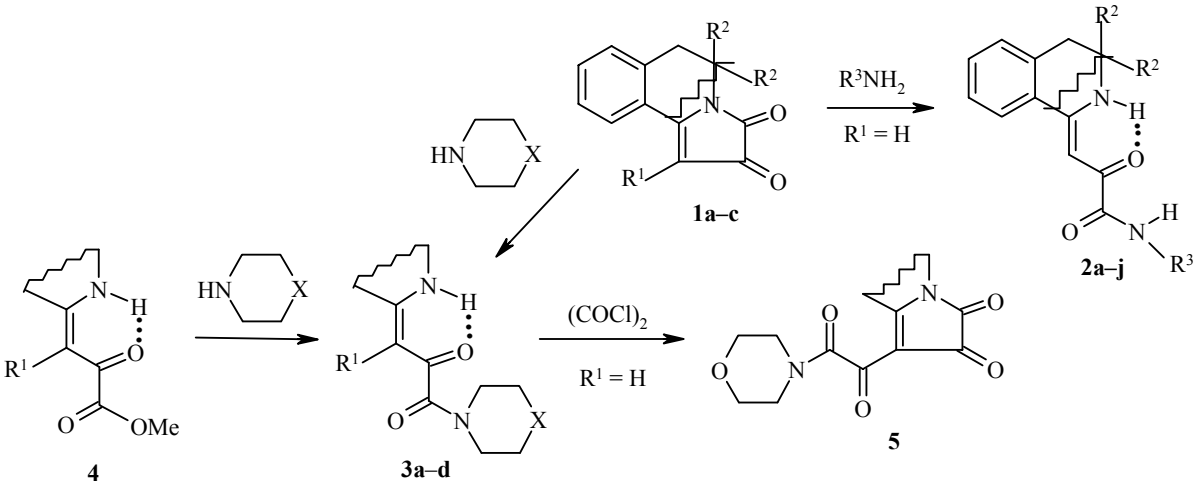
Scheme 1



aromatic protons, the integrated intensities of which correspond to the sum of the protons of the amide aromatic substituent plus the four protons of the isoquinoline ring. There are also signals corresponding to the substituents, e.g. a singlet methyl group signal on the aromatic ring at 2.32 ppm (compound **2b**), a singlet for the methoxy group on the aromatic nucleus (3.78 pm in compound **2c**), and multiplets for the protons of the pyrrolidine (compound **3a**) or morpholine fragments (compounds **3d, 5**).

TABLE 1. Characteristics of the Compounds Synthesized

Compound	R^3*	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
2a	C_6H_5	$C_{20}H_{20}N_2O_2$	74.8 / 74.9	6.4 / 6.3	8.8 / 8.7	159-160	51
2b	*p*-MeC_6H_4	$C_{21}H_{22}N_2O_2$	75.2 / 75.4	6.5 / 6.6	8.4 / 8.4	143-145	55
2c	*p*-$MeOC_6H_4$	$C_{16}H_{20}N_2O_4$	69.8 / 70.0	6.7 / 6.8	8.5 / 8.6	154-156	45
2d	*p*-$O_2NC_6H_4$	$C_{20}H_{19}N_3O_4$	65.6 / 65.7	5.1 / 5.2	11.6 / 11.5	179-181	60
2e	*m*-$O_2NC_6H_4$	$C_{20}H_{19}N_3O_4$	65.5 / 65.7	5.1 / 5.2	11.6 / 11.5	155-157	56
2f	Ph	$C_{22}H_{22}N_2O_2$	76.2 / 76.3	6.3 / 6.4	8.0 / 8.1	70-72	47
2g	*p*-$O_2NC_6H_4$	$C_{22}H_{21}N_3O_4$	67.4 / 67.5	5.3 / 5.4	10.8 / 10.7	191-193	72
2h	2-Pyridyl	$C_{19}H_{19}N_3O_2$	70.8 / 71.0	5.9 / 6.0	13.2 / 13.1	101-103	58
2i	4-Pyridyl	$C_{19}H_{19}N_3O_2$	70.8 / 71.0	5.9 / 6.0	12.9 / 13.1	197-199	63
2j	2-Thiazolyl	$C_{17}H_{17}N_3SO_2$	62.2 / 62.4	5.1 / 5.2	12.9 / 12.8	166-167	55
3a	—	$C_{18}H_{22}N_2O_2$	72.4 / 72.5	7.3 / 7.4	9.3 / 9.4	83-85	52
3d	—	$C_{23}H_{29}N_3O_5$	64.4 / 64.6	6.7 / 6.8	9.6 / 9.8	94-95	47
5	—	$C_{20}H_{20}N_2O_5$	65.1 / 65.2	5.4 / 5.5	7.6 / 7.6	199-200	67

* **1c, 3d** R^1 = 1-morpholinocarbonyl, remainder R^1 = H; **2f,g** $R^2 + R^2 = (CH_2)_4$, remainder R^2 = Me; **3d** X = O.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm						
	3-$(CH_3)_2$, s or 3-$(CH_2)_4$, m	4-CH_2, s	1-HC=, s	Aromatic protons, m	NH amide, s	NH ring, s	Other protons
2a	1.32	2.83	6.68	7.03-7.82 (9H)	9.25	11.52	—
2b	1.31	2.82	6.67	6.91-7.84 (8H)	9.20	11.46	2.32 (s, CH_3-Ar)
2c	1.30	2.85	6.10	6.83-7.62 (8H)	9.13	10.49	3.78 (s, OCH_3)
2d	1.32	2.83	6.62	7.10-8.13 (8H)	9.60	11.50	—
2e	1.30	2.82	6.68	7.10-8.50 (8H)	9.52	11.54	—
2f	1.22-1.72	2.85	6.68	6.68-7.61 (8H)	9.22	11.68	—
2g	1.28-1.92	2.90	6.62	7.07-8.11 (8H)	9.65	11.72	—
2h	1.28	2.82	6.64	7.11-8.21 (8H)	9.70	11.50	—
2i	1.33	2.85	6.65	7.12-8.40 (8H)	9.43	11.60	—
2j	1.30	2.83	6.60	6.80-7.76 (6H)	10.75	11.50	—
3a	1.32	2.78	6.32	7.0-7.68 (4H)	—	10.80	1.25-1.40 (m, $2CH_2$-C); 1.70-2.50 (m, $2CH_2$-N)
3d	1.40	2.80	—	7.0-7.44 (4H)	—	11.20	3.39-3.65 (16H, m, $2N(CH_2)_2O$)
5	1.50	2.95	—	7.13-8.52 (4H)	—	—	3.26-3.74 (8H, m, $N(CH_2)_2O$)

The IR spectra of the ketoamides **2** and **3** show broadened bands at 3030-3050 (ring NH) and 1610-1620 cm^{-1} (ketone carbonyl) which correspond to an H-chelated form. The secondary amide group in the spectra of compounds **2** appears as bands at 1690-1700 (C=O) and 3330-3350 cm^{-1} (NH). The tertiary amide carbonyl group in compound **3** gives an absorption band at 1630 cm^{-1}. In compound **5** the ketoamide fragment gives absorption bands at 1630 (tertiary amide C=O group) and 1650 cm^{-1} (ketone C=O). The dioxopyrroline group fragment absorbs at 1705 and 1740 cm^{-1} (lactam and ketone carbonyls respectively).

The mass spectra of the amides **2** show weak molecular ion peaks (e.g. 2% (*m/z* 312) for compound **2h** and 1.3% (*m/z* 327) for compound **2j**). Generally, the most intense peak (100%) for the amides **2** is the peak corresponding to fission of the amide group (*m/z* 200).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Tesla BS-567A instrument (100 MHz) using $CDCl_3$ solvent and HMDS internal standard (δ 0.05 ppm). IR spectra were recorded on a Specord M-80 and mass spectra on an MAT-311 instrument (70 eV, EI method).

Checking of the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates using the system acetone–ethanol–chloroform (1:3:6) and were revealed using a 0.5% solution of chloranil in benzene.

The compounds prepared were recrystallized from benzene (**2c**), hexane (**2h**), petroleum ether (**3a**), or isopropanol (all of the remainder).

The synthesis of the starting compounds **1a-c** has been described in [4, 5].

3-[3,3-Dimethyl-(R^2)$_2$-1,2,3,4-tetrahydroisoquinolinyl-1-iden]-2-oxopropanoic Acid N-R^3-Amides 2a-j (General Method).

A. **Compounds 2a-g** (R^3 = Ar). The corresponding aniline (12 mmol) was added to a solution of the corresponding dioxopyrroline **1a,b** (10 mmol) in glacial acetic acid (30 ml). For the preparation of the amides **2d,e,g** the mixture was refluxed for 1.5 h and for the rest it was heated for 1 h at 60-70°C (monitored by TLC). The product was cooled to 20°C and diluted with water (100 ml).The precipitate was filtered off, carefully washed on the filter with 25% aqueous ammonia solution, and then with water, dried, and recrystallized.

B. **Compounds 2h-j** (R^3 = Het). The corresponding hetarylamine (12 mmol) was added to the corresponding dioxopyrroline **1a,b** (10 mmol) in isopropanol (for compounds **2h,i**) or benzene (compound **2j**) (50 ml) and refluxed for 1 h. The product was cooled to 20°C, diluted with water (100 ml) (compounds **2h,i**) or hexane (compound **2j**) and the precipitate was filtered off, dried, and recrystallized.

3-R^1-3-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolinyl-1-iden)-2-oxopropanoic Acids Amides 3a-d. The corresponding secondary amine (15 mmol) was added to the corresponding dioxopyrroline (10 mmol) in ethanol (15 ml). Upon heating to 60-70°C the solution immediately decolorized. It was diluted with water (100 ml) and the precipitate was filtered off, dried, and recrystallized. The yields of amides **3b,c** were 48 and 50%. Using the counter synthesis from compound **4** the yields were 56 and 52% [3].

1-(N-Morpholinooxalyl)-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (5). A mixture of the enamine **3d** (3.68 g, 10 mmol) and triethylamine (2.80 ml, 20 mmol) in ether (150 ml) was added to oxalyl chloride (0.86 ml, 10 mmol) in absolute ether (50 ml) at 0-5°C. The reaction mixture was taken to 20°C and left at this temperature for a further 30 min. The precipitate was filtered off, washed with water, dried, and recrystallized.

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