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REACTIONS OF 2,3-DIOXOPYRROLO-[2,1-*a*]ISOQUINOLINES WITH AMMONIA AND ALIPHATIC AMINES

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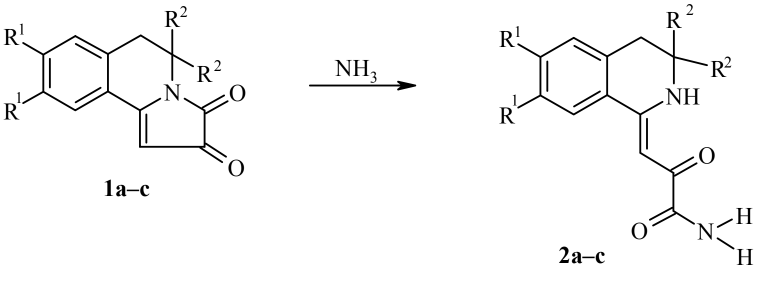
2,3-Dioxopyrrolo[2,1-a]isoquinolines, with either a tertiary amide substituent at position 1 or no substituent, react with ammonia and aliphatic amines with ring opening to form the corresponding enamino keto amides.

Keywords: amides of (3,3-dialkylisoquinolinidene-1)pyruvic and 2-oxobutandioic acids, ammonia, 5,5-dialkyl-2,3-dioxopyrrolo[2,1-*a*]isoquinolines, methylamine, ethylamine.

Derivatives of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline [1-4] have promise as reagents in the chemistry of alkaloids and their analogs [5,6].

The reactions of these compounds with N-nucleophiles have not been studied satisfactorily up to the present. The ease of opening of the pyrrole ring may be explained by angular tension which probably arises because all four carbon atoms are sp^2-hybridized which presupposes 120° angles which are not possible in a five-membered ring. We have shown previously that the reaction of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with hydrazine occurs with opening of the pyrrole ring [7]. The objective of the current work was to investigate the reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with ammonia and the simplest aliphatic amines.

The study showed compounds **1a-c** react readily with ammonia, methylamine, and ethylamine. The reactions were carried out by bubbling gaseous ammonia or an amine through a solution of the corresponding carbonyl compound in benzene at 20°C. The amides **3a-d** reacted analogously. The products of the reactions are the keto amides **2a-c** and **4a-h** (Table 1). The process is readily monitored by the decoloration of the solutions (the starting materials **1a-c** and **3a-d** are bright red in color). With a sufficiently strong gas flow the reactions are completed in 5 min.



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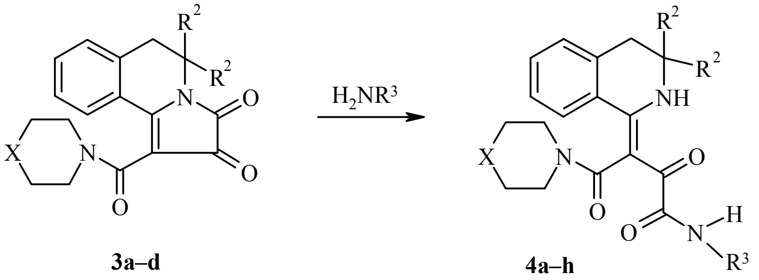

3a–d **4a–h**

As is seen in Table 1, the yields in all cases are practically quantitative.

The ^{1}H NMR spectra (Table 2) reflect the characteristics of the structures of amides **2** and **4**. In contrast to the spectra of the starting materials, in the spectra of the amides **2a-c** and **4a-h** there are singlets for the NH group of the ring (11.6-12.67 ppm), the basic nature of which is confirmed by a shift to weaker field on addition of CF_3COOH. Turning our attention to the fact in the primary amide group the protons of the NH_2 group (compounds **2a-c, 4a,c,h)** appear as two singlets, which indicates that they are not equivalent. It is possible that in this case one carbonyl group contributes to the formation of two H-chelate structures: with NH of the heterocycle and the NH of the amide. The formation of such chelates should favor restriction of rotation about the double bond in the amide group [8].

TABLE 1. Characteristics of the Compounds Synthesized

Compound*	R^3	X	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	Yield, %
2a	—	—	$C_{14}H_{16}N_2O_2$	68.7 / 68.8	6.5 / 6.6	11.6 / 11.5	213-215	91
2b	—	—	$C_{16}H_{18}N_2O_2$	71.0 / 71.1	6.6 / 6.7	11.4 / 10.4	222-223	94
2c	—	—	$C_{16}H_{20}N_2O_4$	63.0 / 63.1	6.5 / 6.6	9.3 / 9.2	229-231	89
4a	H	—	$C_{19}H_{23}N_3O_3$	68.7 / 66.8	6.7 / 6.8	11.4 / 12.3	166-167	95
4b	Me	—	$C_{20}H_{25}N_3O_3$	67.5 / 67.6	7.0 / 7.1	11.8 / 11.8	177-179	87
4c	H	CH_2	$C_{20}H_{25}N_3O_3$	68.4 / 67.6	7.0 / 7.1	11.7 / 11.8	141-142	86
4d	Me	CH_2	$C_{21}H_{27}N_3O_3$	68.2 / 68.3	7.3 / 7.4	11.5 / 11.4	146-148	90
4e	Et	CH_2	$C_{22}H_{29}N_3O_3$	68.7 / 68.9	7.6 / 7.6	10.9 / 11.0	142-143	88
4f	Me	$(CH_2)_2$	$C_{22}H_{29}N_3O_3$	68.7 / 68.9	7.5 / 7.6	11.1 / 11.0	159-160	85
4g	Et	$(CH_2)_2$	$C_{23}H_{31}N_3O_3$	69.4 / 69.5	7.8 / 7.9	10.6 / 10.6	164-166	77
4h	H	O	$C_{21}H_{25}N_3O_4$	65.7 / 65.8	6.5 / 6.6	10.9 / 11.0	169-171	81

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* **2a**,**b** **4a-h** R^1 = H, **2c** R^1 = MeO; **2a**,**c**, **4a-g** R^2–R^2 = Me_2, **2b**, **4h** R^2–R^2 = $(CH_2)_4$.

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	C–$(CH_2)_n$–C, m	N$(CH_2)_2$, m, and O$(CH_2)_2$, m	Aromatic protons	NH, amide, s	NH, ring, s	Other protons
2a	1.30	2.97	—	—	7.30-7.83, m	7.45, 7.68	11.6	7.50, s (HC=)
2b	1.63-1.80	3.03	—	—	7.35-7.82, m	7.40, 7.70	11.8	7.50, s (HC=)
2c	1.23	2.85	—	—	6.67 s, 7.13 s	7.48, 7.53	12.67	3.73, s, and 3.75, s, ($2CH_3O$); 6.37, s (HC=)
4a	1.45	2.97	0.9-1.82 (4H)	2.80-3.20 (4H)	7.29-7.68, m	7.36, 7.57	12.20	—
4b	1.43	3.02	0.95-1.80 (4H)	2.75-3.20 (4H)	7.25-7.70, m	8.05	12.25	—
4c	1.42	2.98	1.0-1.75 (6H)	2.80-3.15 (4H)	7.32-7.73, m	7.47, 7.70	12.35	—
4d	1.44	3.02	1.1-1.68 (6H)	2.65-3.20 (4H)	7.33-7.80, m	8.0	12.35	2.65, s (CH_3N)
4e	1.42	3.0	0.95-1.70 (6H)	2.70-3.23 (4H)	7.35-7.75, m	8.05	12.30	1.02, t ($C\underline{H}_3CH_2$), 2.93, q ($CH_3C\underline{H}_2$)
4f	1.50	3.10	1.0-1.72 (8H)	2.70-3.40 (4H)	7.30-7.73, m	8.10	12.40	2.63, s (CH_3N)
4g	1.45	3.13	0.9-1.65 (8H)	2.60-3.45 (4H)	7.28-7.72, m	8.10	12.40	1.0, t ($C\underline{H}_3CH_2$), 2.90, q ($CH_3C\underline{H}_2$)
4h	1.31-1.95	3.05	—	2.65-3.50 (8H)	7.15-7.65, m	7.39, 7.59	12.35	—

In the IR spectra of amides **2a-c** in chloroform solution (0.01 mol/l) there are absorption bands in the region of 3220 (ring NH) and 3410 (amide NH_2) together with a broad band of the associated carbonyl of the amide groups (1600) and the conjugated ketone carbonyl (1700 cm^{-1}).

The IR spectra of compounds which contain both primary and tertiary amide groups (compounds **4a,c,h**) contain absorption bands of the ring NH (3160) and amide NH groups (3360), two amide carbonyl groups (1600-1610) and a ketone carbonyl (1665 cm^{-1}). The spectra of the secondary amides **4b, d-g** have absorption bands for the amide NH (3300) and C=O groups (1610) and also for the ring NH (3200) and the ketone carbonyl (1660 cm^{-1}).

The structure of the compounds obtained is confirmed by the mass spectra. For example the mass spectrum of amide **2a** has, apart from the molecular ion peak at 244* (10.1%), peaks corresponding to loss of the amide group (100%, 200). The mass spectra of amides **2b,c** are analogous. In the mass spectra of amides **4** low intensity molecular ion peaks are observed, for example, 3.1% (341) and 1.9% (383) respectively for the diamides **4a** and **4f** respectively. Analysis of the mass spectra of these compounds shows that the first step after ionization is the loss of the lighter amide fragment C(O)NHR^3. For example, for amide **4a** the intensity of the peak corresponding to the loss of this group is 45.15% (297) and for amides **4f** and **4g** the intensities are 100 and 88,4% respectively (for both 325). In the mass spectra of all the diamides **4** the most intense peaks correspond to successive losses of the fragment C(O)NHR^3, followed by the amino group found in the composition of the tertiary amide (96.5-100%, 228).

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d$_6$ spectra containing HMDS as internal standard were recorded with a Bruker DRX 500 (500 MHz) spectrometer. IR spectra were recorded on a Specord-80 spectrometer. Mass spectra were recorded with a MAT-311 spectrometer (70 eV, EI). The purity of the compounds synthesized was determined by TLC on Silufol UV-254 strips with 1:3:6 acetone–ethanol–chloroform as eluent, and development with iodine vapor.

All of the compounds synthesized were recrystallized from isopropanol.

The synthesis of the starting materials **1a-c** and **3a-d** was described in [2, 9].

Amides of [3,3-(R^2)$_2$-6,7-(R^1)$_2$-1,2,3,4-Tetrahydroisoquinolinidene-1]pyruvic Acids (2a-c) and the Diamides of 3[3,3-(R^2)$_2$-1,2,3,4-Tetrahydroisoquinolinidene-1]-2-oxobutandioic Acids (4a-h) (General Method). Gaseous ammonia or the corresponding amine was bubbled through a solution of the corresponding dioxopyrroline **1a-c** or **3a-h** (10 mmol) in benzene (50-100 ml). The difficult to dissolve amides **2b,d** dissolved on boiling and in these cases the syntheses were carried out at 50-60°C. The reactions were carried out at 20° for all the other substances. When the solution was decolorized the solvent was evaporated in vacuum, the crystalline residue was filtered off, dried, and recrystallized.

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* Here and later the values of *m/z* are given for the ion peaks.

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