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SYNTHESIS AND PROPERTIES OF ENAMINOKETOHYDRAZIDES OF THE 1,2,3,4-TETRAHYDROISOQUINOLINE SERIES

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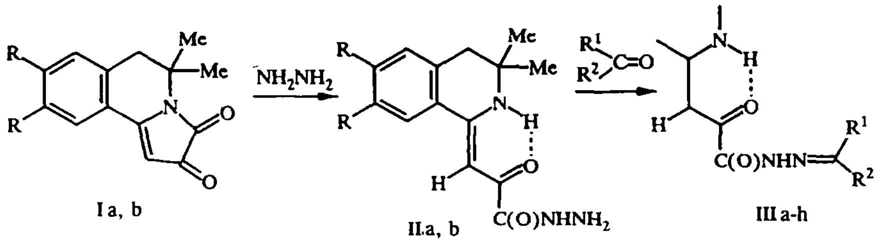
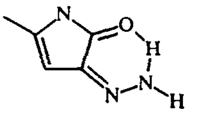
It has been established that the reaction of 2,3-dioxopyrrolo[2,1-a]isoquinolines with hydrazine occurs at the lactam carbonyl with fission of the pyrroledione ring and the formation of enaminoketohydrazides, the structure of which was confirmed by x-ray crystallographic and spectral data on these compounds and their derivatives (hydrazones).

Condensed dioxopyrrolines of the isoquinoline series are promising reactants in the chemistry of alkaloids and their analogs [1-7]. Reactions of these compounds with N-nucleophiles has been little studied up to the present time. It is known that the direction of the reaction of dioxopyrrolines with N-nucleophiles is determined both by the structure of the dicarbonyl compound and by the nature of the nucleophile [8]. The experimental conditions (temperature, solvent, reactant ratio, etc.) undoubtedly play a role in these reactions. Depending on these factors the nucleophilic attack may be directed to the ketone group [9-11] or the lactone carbonyl with fission of the pyrroledione ring [12]. In addition, reaction at the electron-deficient double bond is possible with the formation of an addition product at position 5 of the pyrrole ring [13]. The aim of the present work was to investigate the direction of the reaction of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with hydrazine hydrate.

The reaction of compounds (Ia, b) with a 10- to 15-fold excess of hydrazine hydrate by boiling in isopropanol is complete after 1-2 min. The process is easily checked by the decolorization of the solution [substances (Ia, b) are bright red]. The resulting reaction product separated as a precipitate. The substances obtained (IIa, b) react readily with various carbonyl compounds. Aromatic aldehydes give the N-substituted hydrazones (IIIa-f), and cyclohexanone and isatin the N-substituted hydrazones (IIIg, h).





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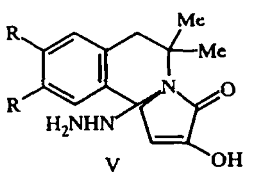

V

The characteristics of all the compounds obtained are given in Tables 1 and 2. According to the data in review [8] the product of the reaction being investigated may possess one of three structures, viz. (II), (IV), or (V). The PMR spectra of sub-

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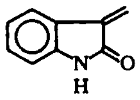
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			R	R¹ and R²	IR spectrum, ν, cm⁻¹	mp, °C	Yield, %
		C	H	N					
IIa	$C_{14}H_{17}N_3O_2$	64,7 64,8	6,5 6,6	16,3 16,2	H	–	1600, 1650 (C–O); 3190, 3300, 3320 (NH)	177...178	82
IIb	$C_{16}H_{21}N_3O_4$	60,1 60,2	6,5 6,6	13,2 13,2	OCH_3	–	1610, 1670 (C–O); 3180, 3280, 3310 (NH)	183...184	90
IIIa	$C_{21}H_{21}N_3O_2$	72,5 72,6	6,0 6,1	12,2 12,1	H	H and C_6H_5	1600, 1670 (C–O); 3080, 3200 (NH)	169...170	87
IIIb	$C_{23}H_{25}N_3O_4$	67,5 67,8	6,1 6,2	10,2 10,3	OCH_3	H and C_6H_5	1600, 1670 (C–O); 3100, 3250 (NH)	216...217	85
IIIc	$C_{21}H_{20}N_4O_4$	64,2 64,3	5,1 5,1	14,4 14,3	H	H and *p*-$C_6H_4NO_2$	1600, 1690 (C–O); 3120, 3310 (NH)	223...225	83
IIId	$C_{23}H_{24}N_4O_6$	61,0 61,1	5,3 5,4	12,4 12,4	OCH_3	H and *p*-$C_6H_4NO_2$	1600, 1700 (C–O); 3100, 3290 (NH)	221...223	88
IIIe	$C_{21}H_{21}N_3O_4$	67,7 67,9	5,6 5,7	11,2 11,3	H	H and 3,4-$C_6H_3(OH)_2$	1600, 1670 (C–O); 3070, 3250, 3280 (NH, OH)	254...255	78
IIIf	$C_{22}H_{23}N_3O_4$	67,1 67,2	5,7 5,9	10,6 10,7	H	H and C_6H_3-4-OH-3-OCH_3	1600, 1680 (C–O); 3080, 3240, 3270 (NH, OH)	182...184	63
IIIg	$C_{20}H_{25}N_3O_2$	70,7 70,8	7,3 7,4	12,5 12,4	H	$(CH_2)_5$	1600, 1680 (C–O); 3100, 3340 (NH)	175...176	58
IIIh	$C_{22}H_{20}N_4O_3$	67,9 68,0	5,1 5,2	14,5 14,4	H		1600, 1710, 1730 (C–O); 3130, 3200, 3310 (NH)	197...199	61

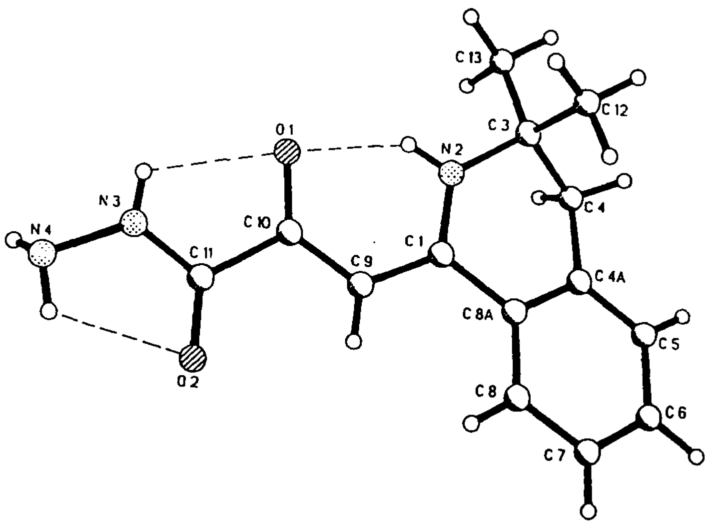


Fig. 1. Structure of the (IIa) molecule.

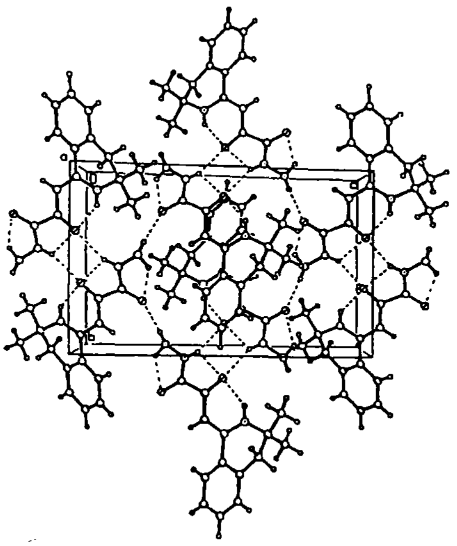


Fig. 2. Packing of the (IIa) molecule in the crystal.

stances (IIa, b) (Table 2) enable structure (IV) to be excluded but allow no conclusion to be drawn between structures (II) and (V). The structure of compounds (IIa, b) may be confirmed most reliably by an x-ray structural investigation and this was carried out by us for compound (IIa). According to the x-ray data the molecule of this compound has a structure of general form shown in Fig. 1. Short intramolecular contacts exist in the molecule at $N_{(2)}-O_{(1)}$ 2.678(8) Å, $H_{(2N)}-O_{(1)}$ 1.95(5) Å, angle N–H...O 140(5)°; $N_{(3)}-O_{(1)}$ 2.662(8) Å, $H_{(3N)}-O_{(1)}$ 2.34(6) Å, angle N–H...O 102(5)°; $N_{(4)}-O_{(2)}$ 2.775(8) Å, $H_{(4NB)}-O_{(2)}$ 2.34(6) Å, angle N–H...O 110(5)° which may be considered either as weak H bonds or as electrostatic interactions between heteroatoms. As a result of intermolecular hydrogen bonds (Fig. 2) the molecules in the crystal are linked into centrosymmetric dimeric associates $N_{(3)}-H_{(3N)}...O_{(1)}$ [3 — x, 2 — y, 1 — z] [N...O 2.919(8) Å, H...O 2.10(6) Å, angle N–H...O 155(5)°], linked in its turn by weak H bonds $N_{(4)}-H_{(4NA)}...O(2)$ [3 — x, 0.5 + y, 1.5 — z] [N...O 3.246(8) Å, angle N–H...O 174(5)°] into a three-dimensional structural pattern. The coordinates and thermal parameters of atoms, bond lengths, and valence angles are given in Tables 3-5.

The IR and PMR spectra of compound (IIb) were analogous to those of substance (IIa) (Tables 1, 2). Consequently it may be considered that both compounds have the structure of enaminoketohydrazides.

TABLE 2. PMR Spectra of Compounds Synthesized

Compound	1-CH=, s	3-$(CH_3)_2$, s	4-CH_2, s	Ar, m	HC=N, s	2NH, s	Other signals
IIa	6,37	1,24	2,88	7,11...7,83	—	9,55, 10,23	4,46 br.s. (NH_2)
IIb	6,32	1,27	2,90	*	—	9,51, 11,46	4,41 br.s. (NH_2), 3,83 s ($2CH_3O$)
IIIa	6,50	1,26	2,92	7,35...7,79	8,50	11,69, 11,77	—
IIIb	6,40	1,20	2,80	6,87...7,67	8,50	11,75 br.	3,80 s ($2CH_3O$)
IIIc	6,50	1,27	2,94	7,36...8,30	8,60	11,72, 12,07	—
IIId	6,50	1,30	2,80	6,63...8,47	8,70	10,80, 11,60	3,90 s ($2CH_3O$)
IIIe	6,50	1,25	2,92	6,78...7,87	8,31	11,54, 11,68	9,23 and 9,35 s (2OH—Ar)
IIIf	6,50	1,23	2,88	6,73...7,91	8,42	11,58, 11,77	3,82 s (CH_3O); 9,27 s (OH—Ar)
IIIg	6,72	1,31	2,85	7,10...7,92	—	10,14, 11,61	1,65 br.s $(CH_2)_3$-C; 2,32 m $2CH_2$—C=N
IIIh	6,55	1,29	2,94	6,97...7,84	—	11,48, 11,53	10,82 (NHCO)

*6.89 s (5-H); 7.27 s (8-H).

It is noteworthy that in the PMR spectra of freshly prepared solutions of substances (IIa, b) in DMSO-D_6 containing water, signals were observed only for the H-chelated NH group and signals of the free (nonchelated) NH_2 group were not detected. The latter (at 4.46 and 4.41 ppm respectively) appeared in the spectra after keeping the sample for approximately 2 h in the ampul. The maximum integrated intensity of these signals was developed after 4-6 h. The described phenomenon reflects the process of rupture of hydrogen bonds (−O...H−N) in the chelate by the action of water.

The structure of the compounds obtained is in agreement with their IR spectra (Table 1). The spectra of hydrazides (IIa, b) contained absorption bands of a conjugated H-chelated carbonyl (1600 and 1610 cm^{-1}), a carbonyl of a hydrazide group (1650 and 1670 cm^{-1}), the H-chelated NH group of an isoquinoline ring (3190 and 3180 cm^{-1}), and also of an NH group of the hydrazide fragment [the band at 3300 and 3200 cm^{-1} in the spectrum of substance (IIa) and 3280 and 3310 cm^{-1} in the spectrum of hydrazide (IIb)]. Bands for the NH_2 group were absent, unlike the spectra of the initial hydrazides (IIa, b), from the IR spectra of the hydrazones (IIIa-h), but the picture of an H-chelated fragment was retained in the spectrum. Bands for the functional groups of radicals R^1 and R^2 also appeared in the IR spectra, viz. the OH groups of phenols (IIId, e) and the C(O)NH fragment of isatin [hydrazone (IIIh)]. The signals of the protons of the mentioned functional groups and also of the cyclohexane fragment [hydrazone (IIIg)] were observed in the PMR spectra of the appropriate hydrazones (Table 2).

The structures of substances (IIa) and (IIIa) were also confirmed by their mass spectra. For example, peaks were observed in the mass spectrum of hydrazide (IIa), in addition to the molecular ion peak at *m/z* 259, corresponding to the fission of the $C(O)NHNH_2$ group (100%, *m/z* 200) with subsequent fission of the isoquinoline carbonyl (*m/z* 172) and then CH_3 and CH_2 groups from the molecule. A similar picture was also observed in the mass spectrum of the corresponding hydrazone (IIIa) in which there was a peak for the molecular ion of *m/z* 347 (55%) and the same base peak (100%) of *m/z* 200, corresponding to fission of the hydrazide fragment C(O)NHN=CHPh.

The hydrazinolysis reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines may have one more direction, i.e., the formation of a hydrazone at the ketone group of the obtained enaminoketohydrazides (IIa, b). The fact that a hydrazone of such a type [7] is not formed under the present conditions may be explained by the reduced electrophilicity of the ketone carbonyl due to conjugation with the enamine group. In addition the hydrazide formed during the reaction precipitates as a solid which may hinder subsequent reaction.

TABLE 3. Coordinates of Atoms ($\times 10^4$, for H $\times$ 10^3) and Their Isotropic (equivalent, for nonhydrogen atoms) Temperature Parameters ($\times 10^3$, for H $\times$ 10^2) in the Structure of (IIa)

Atom	x	y	z	U, Å^2
$O_{(1)}$	13862(4)	8569(4)	5023(2)	48(1)
$O_{(2)}$	15238(5)	7681(4)	7182(2)	52(2)
$N_{(2)}$	12366(6)	6376(6)	4243(3)	40(2)
$N_{(3)}$	15716(6)	9545(5)	6388(3)	45(2)
$N_{(4)}$	16672(7)	10226(7)	7073(4)	55(2)
$C_{(1)}$	12894(6)	5662(6)	4963(3)	35(2)
$C_{(3)}$	11397(6)	5805(6)	3477(3)	39(2)
$C_{(4)}$	10394(7)	4709(7)	3793(4)	44(2)
$C_{(4A)}$	11241(7)	3684(6)	4408(3)	40(2)
$C_{(5)}$	10818(8)	2297(8)	4462(4)	57(3)
$C_{(6)}$	11586(9)	1411(8)	5064(5)	66(3)
$C_{(7)}$	12792(8)	1880(7)	5639(5)	54(3)
$C_{(8)}$	13228(7)	3262(7)	5607(4)	45(2)
$C_{(8A)}$	12466(6)	4176(6)	5000(3)	37(2)
$C_{(9)}$	13783(7)	6327(6)	5659(4)	38(2)
$C_{(10)}$	14183(6)	7736(6)	5650(3)	35(2)
$C_{(11)}$	15108(6)	8310(6)	6480(4)	38(2)
$C_{(12)}$	12350(8)	5170(10)	2862(5)	58(3)
$C_{(13)}$	10493(9)	7037(9)	3054(5)	60(3)
$H_{(2N)}$	1257(6)	728(6)	429(4)	5(2)
$H_{(3N)}$	1572(7)	990(7)	587(4)	6(2)
$H_{(4NA)}$	1605(6)	1091(6)	730(3)	4(2)
$H_{(4NB)}$	1691(6)	956(6)	746(4)	5(2)
$H_{(4A)}$	992(7)	413(7)	328(4)	7(2)
$H_{(4B)}$	961(6)	523(6)	404(3)	4(2)
$H_{(5)}$	993(6)	205(6)	409(4)	5(2)
$H_{(6)}$	1129(7)	45(7)	505(4)	7(2)
$H_{(7)}$	1331(7)	129(7)	601(4)	6(2)
$H_{(8)}$	1407(6)	358(6)	596(3)	5(2)
$H_{(9)}$	1410(6)	578(6)	612(3)	4(2)
$H_{(12A)}$	1305(9)	430(9)	307(5)	12(3)
$H_{(12B)}$	1168(7)	486(7)	236(4)	7(2)
$H_{(12C)}$	1300(6)	588(6)	271(3)	4(4)
$H_{(13A)}$	1120(7)	782(8)	285(4)	8(2)
$H_{(13B)}$	977(6)	666(6)	261(4)	4(2)
$H_{(13C)}$	985(7)	739(7)	344(4)	7(2)

EXPERIMENTAL

The PMR spectra were drawn on a Tesla BS 587A (80 MHz) instrument in DMSO-D_6, internal standard was HMDS. The IR spectra were taken on a UR 20 instrument in Nujol. The mass spectra of substances (IIa) and (IIIa) were drawn on a MAT 311 instrument (70 eV, EI). A check on the course of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV 254 plates in the system acetone–ethanol–chloroform, 1:3:6, visualizing with iodine vapor.

The synthesis of the initial compounds (Ia, b) was described in [3, 5]. All substances were recrystallized from isopropyl alcohol.

Crystals of substances (IIa) ($C_{14}H_{17}N_3O_2$) were monoclinic of space group $P2_{1/c}$, at 20°C: a = 9.122(2), b = 9.533(2), c = 15.629(2) Å, β = 99.48(2)°, V = 1340.6(5) Å^3, Z = 4, d_{calc} = 1.285 g/cm^3. The parameters of the unit cell and the intensity of 2448 reflections were measured on a Siemens P3/PC automatic four-circle diffractometer (20°C, MoKα, graphite monochromator, $\theta/2\theta$ scanning, θ_{max} = 25°). The structure was solved by the direct method and refined by a full-matrix least squares method in an anisotropic approach for nonhydrogen atoms. The hydrogen atoms, located by a difference Fourier synthesis were refined in an isotropic approach. The final divergence factors were R = 0.055 and R_w = 0.057 from 1101 independent reflections with $I > 3\sigma$ (I). All calculations were carried out on an IBM PC/AT 486 using the SHELXTLPLUS program.

TABLE 4. Bond Lengths (d) in the Structure of (IIa)

Bond	d, Å	Bond	d, Å
$O_{(1)}$—$C_{(10)}$	1,258(7)	$C_{(3)}$—$C_{(13)}$	1,522(10)
$O_{(2)}$—$C_{(11)}$	1,239(7)	$C_{(4)}$—$C_{(4A)}$	1,494(8)
$N_{(2)}$—$C_{(1)}$	1,336(7)	$C_{(4A)}$—$C_{(5)}$	1,383(10)
$N_{(2)}$—$C_{(3)}$	1,471(7)	$C_{(4A)}$—$C_{(8A)}$	1,408(7)
$N_{(3)}$—$N_{(4)}$	1,422(7)	$C_{(5)}$—$C_{(6)}$	1,368(10)
$N_{(3)}$—$C_{(11)}$	1,320(8)	$C_{(6)}$—$C_{(7)}$	1,376(10)
$C_{(1)}$—$C_{(8A)}$	1,473(8)	$C_{(7)}$—$C_{(8)}$	1,380(10)
$C_{(1)}$—$C_{(9)}$	1,397(7)	$C_{(8)}$—$C_{(8A)}$	1,388(8)
$C_{(3)}$—$C_{(4)}$	1,523(9)	$C_{(9)}$—$C_{(10)}$	1,393(8)
$C_{(3)}$—$C_{(12)}$	1,524(10)	$C_{(10)}$—$C_{(11)}$	1,528(7)

TABLE 5. Valence Angles (ω) in the Structure of (IIa)

Angle	ω, deg	Angle	ω, deg
$C_{(1)}$—$N_{(2)}$—$C_{(3)}$	125,6(5)	$C_{(4A)}$—$C_{(5)}$—$C_{(6)}$	121,1(6)
$N_{(4)}$—$N_{(3)}$—$C_{(11)}$	122,8(5)	$C_{(5)}$—$C_{(6)}$—$C_{(7)}$	120,8(7)
$N_{(2)}$—$C_{(1)}$—$C_{(8A)}$	117,5(5)	$C_{(6)}$—$C_{(7)}$—$C_{(8)}$	119,4(6)
$N_{(2)}$—$C_{(1)}$—$C_{(9)}$	120,5(5)	$C_{(7)}$—$C_{(8)}$—$C_{(8A)}$	120,6(6)
$C_{(8A)}$—$C_{(1)}$—$C_{(9)}$	122,0(5)	$C_{(1)}$—$C_{(8A)}$—$C_{(4A)}$	118,8(5)
$N_{(2)}$—$C_{(3)}$—$C_{(4)}$	107,6(4)	$C_{(1)}$—$C_{(8A)}$—$C_{(8)}$	121,6(5)
$N_{(2)}$—$C_{(3)}$—$C_{(12)}$	109,4(5)	$C_{(4A)}$—$C_{(8A)}$—$C_{(8)}$	119,6(5)
$C_{(4)}$—$C_{(3)}$—$C_{(12)}$	111,5(6)	$C_{(1)}$—$C_{(9)}$—$C_{(10)}$	123,3(5)
$N_{(2)}$—$C_{(3)}$—$C_{(13)}$	106,1(5)	$O_{(1)}$—$C_{(10)}$—$C_{(9)}$	126,1(5)
$C_{(4)}$—$C_{(3)}$—$C_{(13)}$	111,1(5)	$O_{(1)}$—$C_{(10)}$—$C_{(11)}$	117,4(5)
$C_{(12)}$—$C_{(3)}$—$C_{(13)}$	110,9(6)	$C_{(9)}$—$C_{(10)}$—$C_{(11)}$	116,4(5)
$C_{(3)}$—$C_{(4)}$—$C_{(4A)}$	112,5(5)	$O_{(2)}$—$C_{(11)}$—$N_{(3)}$	123,2(5)
$C_{(4)}$—$C_{(4A)}$—$C_{(5)}$	123,0(5)	$O_{(2)}$—$C_{(11)}$—$C_{(10)}$	122,6(5)
$C_{(4)}$—$C_{(4A)}$—$C_{(8A)}$	118,3(5)	$N_{(3)}$—$C_{(11)}$—$C_{(10)}$	114,2(5)
$C_{(5)}$—$C_{(4A)}$—$C_{(8A)}$	118,5(5)		

(3,3-Dimethyl-6,7-R_2-1,2,3,4-tetrahydro-1-isoquinolinidene)pyruvic Acid Hydrazides (IIb). A mixture of compound (Ia, b) (10 mmole) and 70% hydrazine hydrate (4.5 ml, 100 mmole) in isopropanol (10 ml) was boiled for 1-2 min. The bright red solution became decolorized and a precipitate formed. The mixture was cooled to 20°C, the solid filtered off, dried, and recrystallized.

N-[(3,3-Dimethyl-6,7-R_2-1,2,3,4-tetrahydro-1-isoquinolinidene)pyruvoyl]hydrazones (IIIa-h). The appropriate aldehyde or ketone (10 mmole) was added to a boiling solution of compound (IIa, b) (10 mmole) in absolute benzene or alcohol (30 ml). The mixture was boiled for 15-20 min. After the end of the reaction (check by TLC) the reaction mixture was cooled to 20°C, the precipitated solid filtered off, dried, and recrystallized.

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