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SYNTHESIS OF MONOOXIMES OF 3,3-DIALKYL-3,4-DIHYDRO-1-ISOQUINOLYL ARYL KETONES AND DIKETONES

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1-Aroylmethyl-3,3-dialkyl-3,4-dihydroisoquinolines were synthesized by the Ritter reaction. The nitrosylation of these isoquinoline derivatives proceeds smoothly at the β-enamine carbon atom to give monooximes of 3,3-dialkyl-3,4-dihydro-1-isoquinolyl aryl diketones. Loss of an acetyl group occurs in the nitrosylation of 1-(α-acetylbenzyl)-3,3-dimethyl-3,4-dihydroisoquinoline.

Keywords: aroylacetonitriles, isoquinoline, oximes, nitrosylation, Ritter reaction.

The discovery of the role of nitric oxide in the human organism [1, 2] has led to a search for organic compounds with potential as NO donors. Oximes of 3,4-dihydro-1-isoquinolyl alkyl ketones and esters of (3,4-dihydro-1-isoquinolyl)oximinoacetic acids possess antiarrhythmic, antiaggregating, and hypotensive activity [3-6]. The hypotensive activity of these esters might be related to the release of NO under physiological conditions. These compounds may be obtained as the result of nitrosylation of the corresponding enamines by sodium nitrite in acetic acid [7] or trimethylchlorosilane–alkyl nitrite [8] in chloroform.

We attempted to introduce an aroylmethyl group at position 1 in the isoquinoline system to enhance the lipophilicity of the oxime molecules. At first glance, this would appear to be readily accomplished by acylation of 1,3,3-trimethyl-3,4-dihydroisoquinoline using a suitable aroyl chloride. Enamines are acylated either at the nitrogen atom or at the β-carbon atom depending on the reagent, reaction conditions, and enamine structure [9-12]. The *gem*-dimethyl groups at position 3 of the isoquinoline system do give rise to steric hindrance for the reaction at the nitrogen atom [13], while 1-methyl-3,4-dihydroisoquinolines are acylated exclusively at the β-carbon atom [14]. However, the acylation of 1,3,3-trimethyl-3,4-dihydroisoquinoline by *p*-methoxybenzoyl chloride proved impossible since mixtures of mono- and diaroyl derivatives are formed, and isolation of individual products is difficult.

In the present work, a method is proposed for the preparation of 1-aroylmethyl-3,3-dialkyl-3,4-dihydroisoquinolines **1a-d** directly by the Ritter reaction [15] between aroylacetonitriles **2** and dialkylbenzylcarbinols **3** (see Scheme 1).

Isoquinolines **1a-d** are smoothly nitrosylated at the enamine carbon atom upon the action of $NaNO_2$ in acetic acid or ethanol and the addition of hydrochloric acid to give oximes **4a-d**.

The physical characteristics of these products are given in Table 1.

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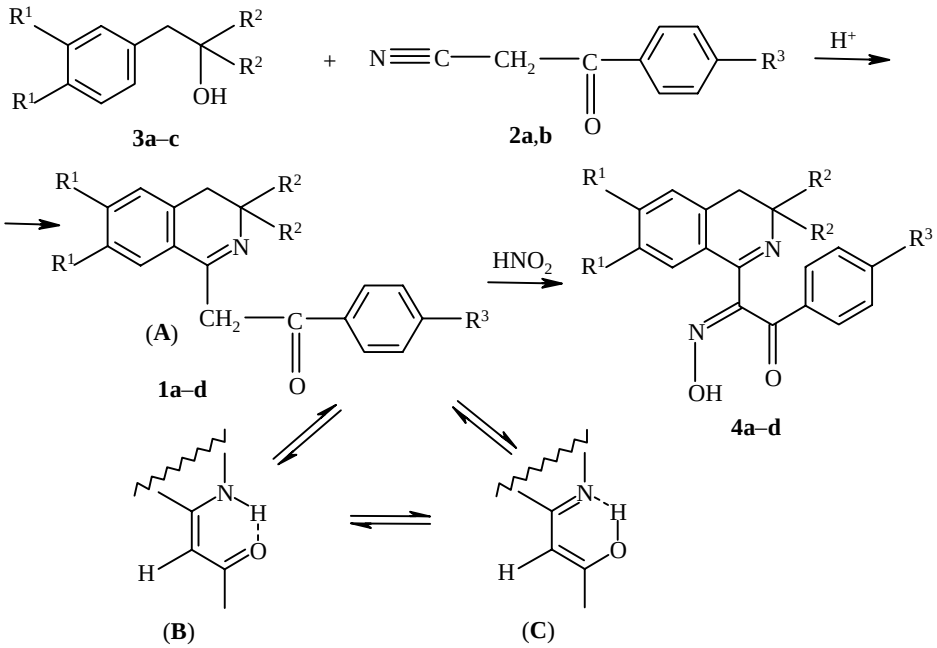
Scheme 1



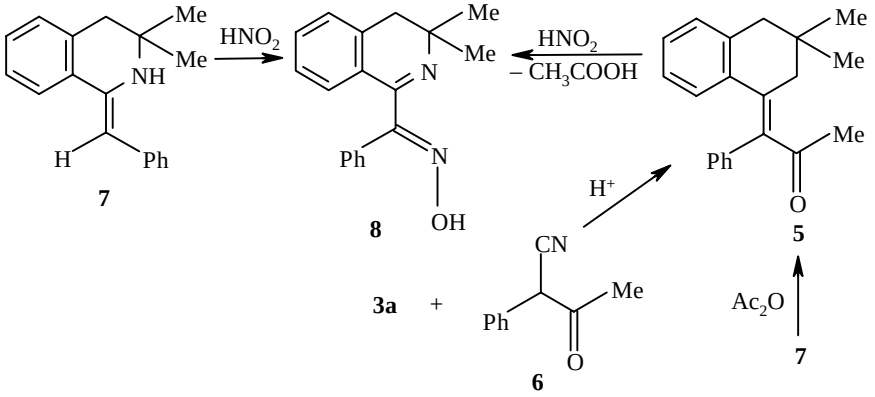
1, 4 a $R^1 = R^3 = H$, $R^2 = Me$; **b** $R^1 = H$, $R^2 = Me$, $R^3 = OMe$; **c** $R^1 = H$, $R^2 + R^2 = (CH_2)_5$, $R^3 = OMe$; **d** $R^1 = R^2 = Me$, $R^3 = H$. **2a** $R^3 = H$; **b** $R^3 = Me$. **3a** $R^1 = H$, $R^2 = Me$; **b** $R^1 = H$, $R^2 + R^2 = (CH_2)_5$; c $R^1 = R^2 = Me$

TABLE 1. Physical Characteristics of Synthesized Compounds

Compound	Empirical Formula	Found, % / Calculated, %			mp, °C (crystallization solvent)	Yield, % (method)
		C	H	N		
1a	$C_{19}H_{19}NO$	82.90 / 82.28	7.36 / 6.90	4.79 / 5.05	139-141 (2-propanol)	52
1b	$C_{20}H_{21}NO_2$	78.51 / 78.74	6.79 / 6.88	4.67 / 4.56	Oil	90
1c	$C_{23}H_{25}NO_2$	79.84 / 79.51	7.43 / 7.25	4.20 / 4.03	Oil	69
1d	$C_{21}H_{23}NO$	82.29 / 82.58	7.41 / 7.59	4.61 / 4.58	165-166 (hexane)	54
4a	$C_{19}H_{18}N_2O_2$	74.39 / 74.49	6.05 / 5.92	8.92 / 9.32	196-197 (ethanol)	62
4b	$C_{20}H_{20}N_2O_3$	71.60 / 71.41	6.24 / 5.99	8.37 / 8.32	148–149 (ethanol + H_2O)	65
4c	$C_{23}H_{24}N_2O_3$	73.74 / 73.38	6.37 / 6.43	7.69 / 7.44	213-215 (ethanol)	68
4d	$C_{21}H_{22}N_2O_2$	75.55 / 75.42	6.77 / 6.63	8.09 / 8.38	163-166 (MeOH + H_2O)	36
5	$C_{20}H_{21}NO$	82.80 / 82.48	7.48 / 7.26	5.12 / 4.81	155-157 (hexane)	40(A) 48(B)
8	$C_{18}H_{18}N_2O$	77.51 / 77.67	6.31 / 6.52	10.17 / 10.06	201-203 (MeOH + H_2O)	61

A study of the nitrosylation of esters of 1-alkyl-1-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolyliden)acetic acids by sodium nitrite in acetic acid showed the loss of the alkyl group as an alcohol and formation of α-oximino derivatives [16]. Hence, we investigated the nitrosylation of 1-(α-acetylbenzyl)-3,3-dimethyl-3,4-dihydroisoquinoline **6** [17] using the Ritter reaction [15] or by acetylation of 1-benzyl-3,3-dimethyl-3,4-dihydroisoquinoline **7**.

Scheme 2



Loss of the acetyl group occurs under the nitrosylation conditions to give an oxime. Nitrosylation of **7** also gave oxime.

Three tautomeric forms (**A**, **B**, and **C**, see Scheme 1) may be presented for isoquinolines **1a-d**. Form **A** may be excluded since there are vinyl proton signals at 6.20-6.23 ppm in the ^{1}H NMR spectra of these compounds (Table 2). The selection between enamine (**B**) and enol (**C**) forms was made using the literature data for form **B** with an intramolecular O···H hydrogen bond of (3,3-dimethyl-3,4-dihydro-1-isoquinolyl)acetic acids [18] unsubstituted in the α-position, which exist in enamine form **B** with an intramolecular hydrogen bond (the NH group signals in the ^{1}H NMR spectrum in $CDCl_3$ is found at 8.88-8.90 ppm) and form **B** of benzoyl derivatives of heterocyclic ketene aminals [19] (the NH group signals in the ^{1}H NMR spectrum in $CDCl_3$ is at 10.19-12.59 ppm). The position of the NH groups in the ^{1}H NMR spectra of **1a-d** at 11.66-11.85 ppm indicates that structure **B** also obtains in our case. Analogously, form **B** with intramolecular hydrogen bonding is also found for 1-(4',4'-dimethyl-2',6'-cyclohexadion-1'-yl)-3,4-dihydroisoquinolines studied by IR and UV spectroscopy and X-ray diffraction structural analysis [20]. The IR band for the NH group in **1a-d** does not appear above 3000 cm^{-1} either in vaseline mull or CH_2Cl_2 solution due to strong intramolecular hydrogen bonding, while the carbonyl band is found at 1590-1620 cm^{-1}. Similar behavior is encountered for **5**. The formation of an intramolecular hydrogen bond is clearly possible only for *Z*-configuration of **1a-d**, which is indicated by the downfield shift in the olefin proton signals in the ^{1}H NMR spectra (Table 2) [21].

The ^{1}H NMR spectra of oximes **4a-d** have broad singlets for the oxime group at 9.56-14.10 ppm and two sets of signals for all the protons appear in the spectrum of **4a** taken at 250 MHz. The signal intensity ratio is 5:6. This finding suggests the existence of *Z*- and *E*-isomers relative to the C=N bond. The singlets for the N-OH group are found at 11.85 and 12.33 ppm. It proved impossible to assign these signals to a specific form at this stage of the investigation. Products **4a-d** were isolated as a single compound, presumably the *Z*-isomer.

The IR spectra of **1b,c, 4b**,**c** also have strong bands for the methoxy groups $\nu_{asC–O–C}$ at 1235-1265 cm^{-1} and $\nu_{sC–O–C}$ at 1030-1040 cm^{-1} (Table 2).

TABLE 2. Spectral Characteristics for Compounds **1, 4, 5,** and **8**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm, SSCC (*J*), Hz				
		3,3-Me_2/ 3,3-$(CH_2)_5$	4-CH_2 (2H, s)	H_{arom} in dihydroisoquinoline and H_{Ar}	N–OH (1H, br. s)	other protons
1a	1620, 1600 (sh.), 1565, 1340, 1285 (s), 1250, 1205, 1175, 1040, 890, 805	1.12 (6H, s)	2.82	7.88 (1H, d, 8-H_{arom}); 7.66-7.35 (8H, m, 5-, 6-, 7- H_{arom}, 5-H_{Ar})	—	6.20 (1H, s, CH=); 11.85 (1H, br. s, NH)
1b	3065, 3030, 1590, 1560, 1330, 1300, 1235, 1170, 1035, 875, 845	1.21 (6H, s)	2.70	7.23-7.02 (4H, m, 5-, 6-, 7- H_{arom}); 7.88 (2H, d, *J* = 9.03, 2-, 6-H_{Ar}); 6.82 (2H, d, *J* = 9.03, 3-, 5-H_{Ar})	—	3.67 (3H, s, OCH_3); 6.23 (1H, s, CH=); 11.66 (1H, br. s, NH)
1c	3020, 2850, 1590, 1555, 1335, 1300, 1260, 1215, 1170, 1040, 980	1.90-1.20 (10H, m)	2.63	7.95 (1H, m, 8-H_{arom}); 7.71-7.32 (3H, m, 5-, 6-, 7- H_{arom}); 8.17 (2H, d, *J* = 9.00, 2-, 6-H_{Ar}); 7.08 (2H, d, *J* = 9.00, 3-, 5-H_{Ar})	—	3.78 (3H, s, OCH_3); 6.20 (1H, s, CH=); 11.70 (1H, br. s, NH)
1d	1595, 1580, 1545, 1540 (sh.), 1340, 1330, 1305, 1270, 1240 (s), 1190, 1175, 1165 (s), 1135, 1085, 1070, 1040, 1130 (C), 1000, 975, 890, 865, 810	1.28 (6H, s)	2.74	7.49 (1H, s, 8-H_{arom}); 6.89 (1H, s, 5-H); 7.88-7.83 and 7.40-7.31 (2H and 3H, two m, 5-H_{Ar})	—	2. 23 (6H, s, Ar-CH_3); 6.22 (1H, s, CH=); 11.68 (1H, br. s, NH)
4a	3200 (br.), 1640, 1570, 1510, 1340, 1280, 1175, 1080, 1065, 1040, 1020, 1010, 965, 945	1.21 and 1.00 (6H, two s)	2.80 and 2.68 (2H, two s)	8.11 and 8.00 (1H, two d, 8-H_{arom}); 7.78-7.08 (8H, m, 5-, 6-, 7-H_{arom}, 5-H_{Ar})	11.85 and 12.33 (1H, two s)	—
4b	3130 (sh., br.), 1640, 1580, 1565, 1505, 1330 (s), 1260 (s), 1175, 1150 (s), 1130, 1110, 1040, 995, 960	1.21 (6H, s)	2.75	7.24-7.03 (4H, m, 5-, 6-, 7-, 8-H_{arom}); 7.97 (2H, d, *J* = 9.03, 2-, 6-H_{Ar}); 6.64 (2H, d, *J* = 9.03, 3-, 5-H_{Ar})	11.81	3.72 (3H, s, OCH_3)
4c	3200 (sh., br.), 1640 (s), 1585 (s), 1565, 1500, 1340, 1300, 1265 (s), 1230, 1205, 1170, 1160 (s), 1125, 1040, 1010, 980	1.89-1.24 (10H, m)	2.49	7.80-7.40 (4H, m, 5-, 6-, 7-, 8-H_{arom}); 8.15 (2H, d, *J* = 8.80, 2-, 6-H_{Ar}); 7.10 (2H, d, *J* = 8.80, 3-, 5-H_{Ar})	14.10	3.82 (3H, s, OCH_3)
4d	3140 (sh., br.), 1650, 1610, 1590, 1565, 1340, 1270, 1250, 1195, 1170, 1125, 1100, 1075, 1035 (s), 1005, 980, 965, 910, 890	1.20 (6H, s)	2.69	6.86 (1H, s, 8-H_{arom}); 6.81 (1H, C, 5-H_{arom}); 7.98-7.90 and 7.38-7.09 (2H and 3H, two m, 5-H_{Ar})	9.56	2.09 (3H, s, Ar-CH_3); 2.17 (3H, s, Ar-CH_3)
5	1580, 1540, 1275, 1225, 1160, 995, 980, 805, 785, 730, 705	1.35 (6H, s)	2.82	7.20, 6.71 and 6.51 (1H, 1H, 7H, three m, 4-H_{arom} and 5- H_{Ar})	—	1.80 (3H, s, CH_3CO); 12.80 (1H, s, NH)
8	3200 (br.), 1670, 1605, 1560, 1245, 1210, 1175, 1160, 1140, 1120, 1070, 980, 960, 930, 920	1.24 (6H, s)	2.73	7.87 (1H, s, 8-H_{arom}); 7.48-7.11 (8H, m, 5-, 6-, 7-H_{arom}, 5-H_{Ar})	12.70	—

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Tesla BS-587A spectrometer at 80 MHz in $CDCl_3$ and DMSO-d_6 (for **4a-c**) and on a Bruker WM-250 spectrometer for **4a** with HMDS as the internal standard. The IR spectra were taken on a UR-20 spectrometer for vaseline mulls or neat (**1b,d**). The mass spectrum of **4a** was taken on a Finnigan MAT mass spectrometer with direct sample inlet into the ion source and ionizing voltage 70 eV. The reaction course was monitored by thin-layer chromatography on Silufol plates with 9:1 chloroform–acetone as the eluent developed by 2% chloranil in toluene.

1-(Benzoylmethylidene)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (1a). A solution of benzoylacetonitrile **2a** (3.1 g, 21.4 mmol) and 2-methyl-1-phenyl-2-propanol (3.2 g, 21.3 mmol) in benzene (30 ml) was added over 10 min to conc. sulfuric acid (7 ml) at 20-50°C with vigorous stirring. The solution was stirred for 2 h at 25°C and poured into water (100 ml). The organic layer was separated, washed with water and, then, aq. $NaHCO_3$, and dried over $MgSO_4$. The solvent was distilled off and the residue was crystallized from 2-propanol to give 2.74 g (52%) of compound **1a**. Products **1b-d** were obtained analogously from the corresponding nitrile and alcohol. 4-Methoxybenzoylacetonitrile **2b** necessary for the synthesis of **1b** and **1c** was obtained according to a standard procedure [22]; mp 114-117°C (hexane). IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1675, 1595, 1510, 1340, 1325, 1265, 1230, 1170, 1125, 1030, 1015, 1005, 935, 830. Products **1b** and **1c** were isolated as oils, which were found to be pure compounds by thin-layer chromatography, were subsequently used without further purification. Product **1d** was crystallized from hexane after distilling off benzene.

Monooxime of 3,3-Dimethyl-3,4-dihydro-1-isoquinolyl Phenyl Diketone (4a). Conc. hydrochloric acid (3 ml) was added to a solution of **1a** (2.8 g, 10 mmol) in glacial acetic acid (20 ml). The mixture was cooled to 10°C and a solution of $NaNO_2$ (0.69 g, 10 mmol) in water (3 ml) was added. The reaction mixture was stirred for 1 h and poured into 100 ml water. The tarry impurities were removed by extraction with toluene or passing through a paper filter. Then, $NaHCO_3$ was added to bring the aqueous layer to pH ~7. The precipitate formed was dried and crystallized from ethanol to give 1.9 g (62%) of compound **4a**. Mass spectrum, *m/z* (I_{rel}, %): M^+ 306 (6), 261 (33), 202 (14), 201 (100) [M^+ - C(O)Ph], 183 (19), 169 (14), 116 (18), 105 (41), 77 (47), 59 (11) (the major fragmentation pathway involves loss of the benzoyl group).

Analogously, oximes **4b-d** were obtained from the corresponding ketones **1b-d**. The nitrosylation of **1d** (10 mmol) was carried out in ethanol (60 ml) with concentrated hydrochloric acid (5 ml).

1-(α-Acetylbenzyl)-3,3-dimethyl-3,4-dihydroisoquinoline (5). A. A drop of conc. sulfuric acid was added to a solution of **7** (2.5 g, 10 mmol) (obtained according to Shklyaev [23]) in acetic anhydride (8 ml) and the mixture was heated at reflux for 1 h. After cooling, the mixture was poured into water (80 ml) and brought to pH ~7 by adding $NaHCO_3$. The precipitate formed was filtered off, dried, and crystallized.

B. Carbinol **3a** (1.5 g) in toluene (15 ml) was added to **6** (2.9 g, 10 mmol) obtained according to a standard procedure [17] dissolved in conc. sulfuric acid (20 ml). The reaction mixture was stirred for 1 h and poured into water (200 ml). The organic layer was separated. The aqueous layer was brought to pH ~7 by adding $NaHCO_3$. The precipitate formed was separated, dried, and crystallized.

Oxime of 3,3-Dimethyl-3,4-dihydro-1-isoquinolyl Phenyl Ketone (8). A. A solution of $NaNO_2$ (0.64 g, 9.3 mmol) in water (2 ml) was added to a solution of **5** (2.7 g, 9.3 mmol) in glacial acetic acid (15 ml) at 15°C and stirred for 2 h at 25°C. The reaction mixture was poured into water (50 ml). The mixture was brought to pH 7 by adding $NaHCO_3$. The oily product was triturated with ether. The precipitate was filtered off, washed with ether, and crystallized from aqueous methanol to give 1.57 g (61%) of compound **8**.

B. A solution of $NaNO_2$ (1.1 g, 16 mmol) in water (2 ml) was added to **7** (4.0 g, 16 mmol) dissolved in glacial acetic acid (10 ml). The reaction mixture was stirred for 0.5 h, poured into water (50 ml), and brought to pH 7 by adding $NaHCO_3$. The precipitate formed was filtered off, washed with ether, and crystallized from aqueous methanol to give 2.75 g (55%) of oxime **8**.

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