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ACETYL DERIVATIVES OF 3-QUINUCLIDONE

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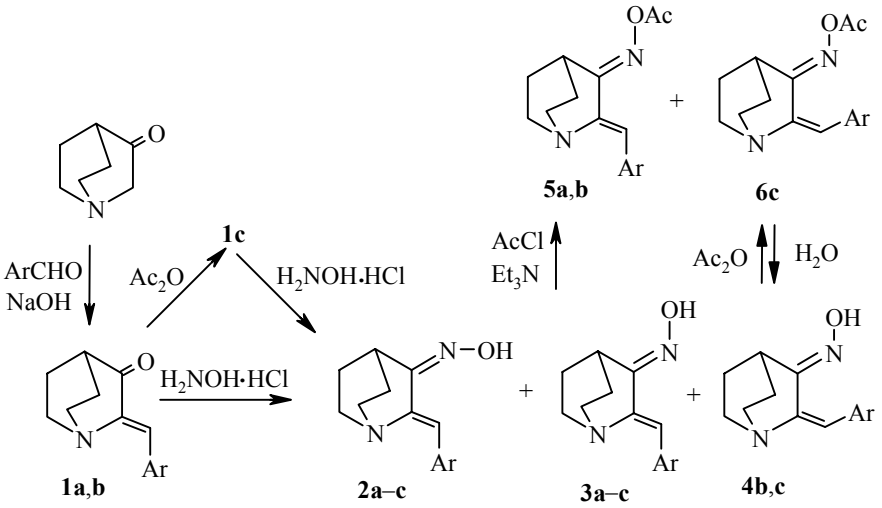
Methods have been developed for the synthesis of mono- and bisacetyl derivatives of 2-hydroxyarylmethylene-3-quinuclidone oximes.

Keywords: quinuclidone oximes, NO donors, acetylation.

Certain 2-arylmethylene- and 2-arylmethyl-3-quinuclidone oximes are able to generate NO upon mild oxidation and to stimulate soluble guanylate cyclase, i.e. the enzyme catalyzing the synthesis of cyclic 5'-guanosine monophosphate which is finally responsible for a whole series of biological effects, in particular for vasodilation [1-3]. The aim of the given work was the preparation of the O-acetyl derivatives of quinuclidone oximes, the large lipophilicities of which might effect their improved bioavailability and likely to form oximes close to potential biotargets as NO donors. Since the greatest NO donor *in vitro* activity is found in oximes with *ortho*-hydroxyphenyl substituents, our basic attention was focused on the synthesis of those derivatives formed by acetylation at the oxime or phenol groups or, indeed, at both.



1–6 a Ar = Ph, **b** Ar = 2-HOC_6H_4 , **c** Ar = 2-$AcOC_6H_4$

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TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
1c	$C_{16}H_{17}NO_3$	71.1 / 70.8	6.4 / 6.3	4.9 / 5.2	234-238 (dec.), *i*-PrOH	0.95	87
2/3c·HCl	$C_{16}H_{18}N_2O_3 \cdot HCl \cdot 0.25H_2O$	58.5 / 58.7	5.9 / 6.0	8.6 / 8.6	165-168 (dec.), *i*-PrOH	0.8/0.6	58
4c·HCl	$C_{16}H_{18}N_2O_3 \cdot HCl$	—	—	—	206 (dec.), *i*-PrOH	0.47	5
5a·HCl	$C_{16}H_{18}N_2O_2 \cdot HCl$	61.6 / 61.8	6.3 / 6.3	8.8 / 8.8	145-147 (dec.), *i*-PrOH	0.95	60
5b·HCl	$C_{16}H_{18}N_2O_3 \cdot HCl$	—	—	—	75-76, *i*-PrOH	0.88	73
6c·HCl	$C_{18}H_{20}N_2O_4 \cdot HCl$	59.3 / 59.3	6.2 / 5.9	7.6 / 7.7	164 (dec.), *i*-PrOH	0.63	72

* $CHCl_3$–MeOH, 50 : 3

Reaction of the oxime **2a** with acetic anhydride occurs readily at room temperature and, while the *Z*-configuration of the phenylmethylene fragment in **5a** is retained, the *anti*-hydroxy group is converted to a *syn*-acetoxy group. Under analogous conditions, the oxime **4b** forms the diacetyl derivative **6c** with retention of configuration both for the *E*-2-hydroxyphenylmethylene and the *syn*-acetoxyimino fragments. Of the two acetoxy groups in **6c** it is the N-acetoxyimino which is more readily hydrolyzed since the ^{1}H NMR spectrum shows the presence of **4c** in the reaction mass (Table 2).

Acetylation of the mixture **2/3b** using acetyl chloride in the presence of triethylamine at -20°C gives only the N-acetoxyimino compound **5b** in high yield. Moreover, similarly to **2a**, a mixture of the *syn-anti*-oximes gives only the *syn*-acetoxime **5b** and this is likely due to the larger steric demand of the acetoxy when compared with the hydroxy group. In the absence of triethylamine, the HCl formed hydrolyses the acetyl derivative **5b** and pure **3b** is obtained in 78% yield from the reaction mixture. Hence acetylation of a mixture of *syn-anti*-oximes and subsequent hydrolysis of the acetoxy derivatives may attract interest as a method for the preparation of pure *syn*-oximes.

The isomeric acetoxyphenyl derivative **2/3c** was prepared by the reaction of the acetylated ketone **1c** with $NH_2OH \cdot HCl$. According to ^{1}H NMR spectroscopic data, the reaction mixture contains **2/3c** in the ration 9:1 and heating increases the content of **3c**. In the prepared crystalline sample the ration of isomers **2/3c·HCl** is 2:1.

The structure of the acetylated ketones and oximes was proved on the basis of their ^{1}H and ^{13}C NMR spectra (Tables 2 and 3). Comparison of the chemical shifts of analogous protons in the ketones **1b** and **1c** has shown that acetylation of the phenolic hydroxyl leads to a marked low field shift of the signals for the *meta* protons and that this is true for both the *Z*- and *E*-isomers. In the ^{13}C NMR spectra, acetylation of the phenolic hydroxyl leads to a low field shift of 6-7 ppm for the $C_{m,p}$ signals and a high field shift for the C_o signal. Acetylation of the oxime group causes a shift of 7-9 ppm to low field for the $C_{(3)}$ signals and of 4-5 ppm for the $C_{(9)}$ signals. Its effect on the chemical shifts of protons is ambiguous.

TABLE 2. ^{1}H NMR Chemical Shifts for the Compounds Synthesized, δ, ppm

Compound	Solvent	4H*	5,8-CH_2	6, 7-CH_2	9-H	3'-H	4'-H	5'-H	6'-H	OAc
1c	$CDCl_3$–CD_3OD, 1:3	2.56	1.95-2.10	2.95, 3.19	7.07 (s)	7.10	7.39	7.26	8.56	2.35 (s)
2c·HCl	DMSO-d_6–D_2O, 1:1	2.93	1.85-2.05	3.30-3.45	8.12 (s)	7.20	7.48	7.30	7.40	2.18 (s)
3c·HCl	DMSO-d_6–D_2O, 1:1	3.71	1.85-2.05	3.30-3.45	7.10 (s)	7.17	7.46	7.32	7.35	2.20 (s)
4c·HCl	CD_3OD	3.90	1.90-2.10	3.47, 3.64	7.09 (s)	7.07	7.33	7.17	8.01	2.29 (s)
5a·HCl	DMSO-d_6–D_2O, 10:1	3.70	1.84, 2.03	3.31, 3.45	7.47 (s)		7.40-7.60			2.17 (s)
5b·HCl	DMSO-d_6	3.66	1.82, 1.99	3.19, 3.42	7.21 (s)	6.90	7.26	6.80	7.35	2.20 (s)
6c·HCl	CD_3OD	3.89	2.05-2.25	3.61, 3.78	7.33 (s)	7.19	7.47	7.31	8.17	2.04 (s)
										2.36 (s)

* The 4H signal is a quintet; the remaining signals are multiplets unless indicated otherwise in the brackets.

TABLE 3. ^{13}C NMR Shifts for the Compounds Synthesized, δ, ppm

Compound	Solvent	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$, $C_{(8)}$	$C_{(6)}$, $C_{(7)}$	$C_{(9)}$	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(6')}$
4c·HCl*[3]	CD_3OD	135.5	151.8	24.5	22.3	51.3	120.9	126.3	150.5	123.3*[2]	131.8*	126.4*[2]	132.0*
5b·HCl*[4]	DMSO-d_6	131.6	162.7	25.6	22.0	48.4	122.0	118.7	157.0	117.4*[2]	132.0*	118.7*[2]	134.0*
6c·HCl*[5]	CD_3OD	133.3	159.4	27.2	21.8	51.1	126.7	125.7	150.3	123.4*[2]	132.3*	126.9*[2]	132.7*

,[2] Possible reversed signal assignments are marked equally.
*[3] MeCOO: 21.1, MeCOO: 170.7.
*[4] MeCOO: 19.6, MeCOO: 168.1.
*[5] MeCOO 19.5 and 21.1, MeCOO: 171.0 and 171.1.

In connection with the ease of deacetylation in basic medium we did not study the oxidation of the acetylated oximes **4c, 5a,b, 6c** by $K_3[Fe(CN)_6]$; this method having been developed for the rapid testing of the ability of a compound to generate NO [2], In experiments *in vivo* their effect on arterial pressure did not exceed those of oxime analogs [1, 2] and this may be linked to the kinetics of their conversion to NO.

EXPERIMENTAL

NMR spectra were taken on a Varian Unity Plus 400 instrument working at 400 MHz for protons and 100 MHz for carbon and mass spectra were recorded on a Finnigan MAT SSQ 710 instrument. TLC was carried out on Silufol UV-254 plates with visualization in UV light and using the Dragendorff reagent. The characteristics of the compounds obtained are given in Table 1.

***Z*-2-(2'-Acetoxyphenyl)methylene-3-quinuclidone (1c).** *Z*-2-(2'-Hydroxyphenyl)methylene-3-quinuclidone **1b** (8.7 mmol) [2] and freshly distilled acetic anhydride (20 ml) were heated for 8 h at 100°C until TLC showed the disappearance of the starting ketone and the acetic anhydride was distilled off in vacuo. The residue was basified using K_2CO_3 solution, extracted with chloroform (3 × 40 ml), the extracts dried with K_2CO_3, chloroform distilled off, and the residue was crystallized from 2-propanol.

Hydrochlorides of *Z*-2-(2'-Acetoxyphenyl)methylene-3-quinuclidone *anti*- and *syn*-Oxime (2/3c·HCl). A mixture of ketone **1c** (1.8 mmol) and $NH_2OH \cdot HCl$ (2 mmol) in MeOH was allowed to stand for 2 days at room temperature. Evaporation of the clear solution and crystallization of the residue from 2-propanol gave **2/3c·HCl** in the ratio 2 : 1.

***syn*-3-N-Acetoxyimino-*Z*-phenylmethylene-3-quinuclidone (5a).** The oxime **3a** (6.5 mmol) [2] in freshly distilled acetic anhydride (20 ml) was allowed to stand overnight at room temperature. The excess anhydride was distilled off on a rotary evaporator, and the mixture was basified using K_2CO_3 solution, extracted with chloroform (3 × 30 ml), the extracts dried with K_2CO_3, and the chloroform distilled off. The residue was dissolved in 2-propanol (15 ml), HCl solution in anhydrous ether was added (6.5 mmol), and the precipitated solid was filtered off.

***syn*-3-N-Acetoxyimino-*Z*-2-(2'-hydroxyphenyl)methylene-3-quinuclidone (5b).** A solution of AcCl (5.7 mmol) in CH_2Cl_2 (2 ml) was added dropwise with stirring to a solution of the mixture of bases **2/3b** (5.7 mmol) and Et_3N (5.7 mmol) in anhydrous CH_2Cl_2 (40 ml) at -20°C. The product was held at -20°C for 1 h and then left overnight at room temperature. Water (20 ml) was added and then a solution of $NaHCO_3$ to pH 10 and the product was extracted with CH_2Cl_2 (3 × 30 ml) and the extracts dried with K_2CO_3. The solvent was distilled off and the residue was dissolved in 2-propanol and then converted to the hydrochloride by addition of a solution of HCl in anhydrous ether (5.1 mmol, 90% of that calculated).

***E*-2-(2'-Hydroxyphenyl)methylene-3-quinuclidone oxime (4b).** A suspension of **4b·HCl** (10 mmol) [2] was stirred for 15 min with water (10 ml), MeOH (15 ml), and K_2CO_3 (11 mmol) and then subjected to continuous extraction with refluxing chloroform until the solid phase had disappeared. Evaporation of the chloroform gave **4b** (2.5 g); mp 208-210°C.

***syn*-3-N-Acetoxyimino-*E*-2-(2-acetoxyphenyl)methylene-3-quinuclidone Hydrochloride (6c·HCl)** and ***E*-2-(2'-acetoxyphenyl)methylene-3-quinuclidone *syn*-Oxime Hydrochloride (4c·HCl).** A suspension of **4b** (7.2 mmol) and acetic anhydride (30 ml) was stirred at room temperature until dissolved (4 days). The reaction mass was decomposed using a saturated K_2CO_3 solution, extracted with chloroform (3 × 60 ml), the extracts dried with K_2CO_3, and the chloroform distilled off. The residue was refluxed in 2-propanol (15 ml) with activated carbon (0.1 g) for 30 min, filtered, and a solution of HCl in dry ether (6.5 mmol, 90% of that calculated) was added to the cooled filtrate. The precipitated **6c·HCl** was separated. When the filtrate was evaporated to 5 ml, **4c·HCl** (20 mg) was obtained after a week. M^+ 286.

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