Monatshefte für Chemie 120, 1107–1112 (1989)

Monatshefte für Chemie
Chemical Monthly

Preparation and Stereochemical Characterization of Some N-Acyl-[1]benzopyrano[3,4-c]pyrazole Derivatives from Rotenoids

Ivanka Kostova* and **Svetla Simova**

Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia 1040, Bulgaria

Summary. Several new N-acyl derivatives of 1-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9 b,2,3,3 a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazole-1-ene have been prepared by appropriate chemical transformation of isohydrazones of rotenone and amorphigenin. A study of their ^{1}H- and ^{13}C-NMR spectra confirmed the presence of the two *cis* 3aβ, 9bβ, 2′β and 3aα, 9bα, 2′β diastereomers in the parent isohydrazones and revealed the strong predominance of the conformers with *endo* orientation of the 3-N*Ac* group. The conformations due to rotation about the 1,5′-bond between rings C and D in the 4′-OH and 4′-O-substituted compounds were also determined by taking into account the anisotropic effect of aromatic rings A and D, and the hydrogen bond between 4′-OH and the 2-N atom, as well as by inspecting the Dreiding models.

Keywords. N-Acyl-1-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9 b,2 b,2,3,3 a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazole-1-enes; ^{1}H and ^{13}C NMR Spectra; Stereochemistry; Rotenoids; Isohydrazones of rotenone and amorphigenin.

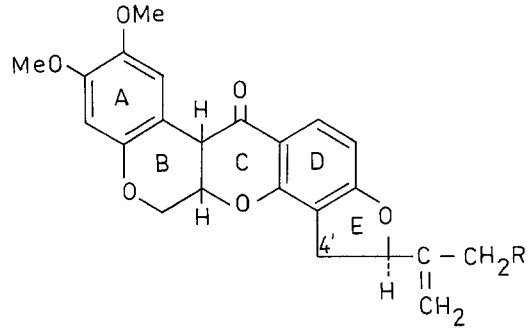
Darstellung und stereochemische Charakterisierung einiger N-Acyl-[1]benzopyrano[3,4-c]pyrazol-Derivate von Rotenoiden

Zusammenfassung. Mittels geeigneter chemischer Transformationen von Isohydrazonen von Rotenon und Amorphigenin wurden einige neue N-Acyl-Derivate von 1-(4-Hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9 b,2,3,3 a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazol-1-en hergestellt. Eine Untersuchung ihrer ^{1}H und ^{13}C-NMR-Spektren zeigt die Gegenwart von zwei *cis* 3aβ, 9bβ, 2′β- und 3aα, 9bα, 2′β-Diastereomeren in den Ausgangs-Isohydrazonen und eine starke Bevorzugung der Konformeren mit *endo*-Orientierung der 3-N*Ac*-Gruppe. Die Konformationen bezüglich der Rotation um die 1,5′-Bindung zwischen Ring C und D werden für die 4′-OH und 4′-O-substituierten Verbindungen unter Berücksichtigung von Anisotropie-Effekten der aromatischen A- und D-Ringe, der Wasserstoffbrücken zwischen 4′-OH und dem 2-N Atom und auch der Betrachtung der entspechenden Dreiding-Modelle diskutiert.

Introduction

Recently, we described [1] the reaction of natural rotenoids rotenone (**1**), amorphigenin (**2**), amorphigenin-β-D-glucoside (**3**) and amorphin (**4**) with hydrazine in alkaline medium to the corresponding [1] benzopyrano[3,4-c]pyrazole

derivatives (so-called isohydrazones) **5a, b–8a, b**, as diastereomeric mixtures of the two *cis* diastereomers 3aβ, 9bβ,2′β and 3aα, 9bα,2′β. However, these 3-NH compounds were not very convenient for biological tests because of their instability. Independently, Nagai and co-workers reported [2] the preparation of **5** by following a different procedure in a more alkaline medium. The same benzopyranopyrazole skeleton with *cis* juncture of the rings B and C had been assigned to this compound, although the reported ^{1}H-NMR data were totally different from ours. The authors observed no presence of two diastereomers.



1: R=H
2: R=OH
3: R= O-Glu
4: R=O-Glu-O-Ar

The discrepancy between the two reports [1, 2], the lack of any literature data on the chemistry and stereochemistry of this type of compounds, as well as the need of stable derivatives for biological tests motivated the preparation and stereochemical characterization of some analogues of **5a, b** and **6a, b**.

Results and Discussion

The selective N-acetylation of **5a, b** and **6a, b** to **9a, b–11a, b** was achieved by treatment with Ac_2O at 90°C for 5 min. Similar treatment for 90 min afforded the respective 4′-O-acetates **12a, b** and **13a, b**. The 4′-OCO*Ph* derivative **14a, b** was prepared by heating of **9a, b** with C_6H_5COCl in *Py* at 90°C for 3 h. The 4′-O-methylation of **9a, b** and N-benzoylation of **5a, b** to the corresponding compounds **15a, b** and **16a, b** was conducted in a catalytic two phase (CTP) system using $C_6H_5CH_2 \cdot N(C_2H_5)_3 + Cl^-$ as catalyst in K_2CO_3/acetone. The structure elucidation of all products obtained as diastereomeric mixtures (3aβ, 9bβ, 2′β and 3aα, 9bα, 2′β) was based mainly on mass and NMR spectral data.

The mass spectra showed the expected $M^+ \cdot$ and ions at m/z192 and m/z191, common for all compounds. The observed fragmentation pathways under electron impact have been discussed elsewhere [3].

The ^{1}H- and ^{13}C-NMR data of all compounds **9a, b–16a, b**, presented in Tables 1–2, confirmed their structures as benzopyranopyrazole derivatives with *cis* juncture of the rings B and C. 3-N-acylation makes the 2-pyrazoline ring more planar and this is reflected in $J_{3a,9b} \sim 11.0$ Hz (for **5a, b–8a, b** $J_{3a,9b} \sim 8.5$ Hz [1]).

The presence of the two *cis* diastereomers in each derivative was clearly indicated by the doubling of most of the proton and some of the ^{13}C-NMR signals (Tables

Table 1. ^{1}H-NMR chemical shifts[a] of compounds **9a, b**–**16a, b** (δ, $CDCl_3$[b], *TMS*)

	3a-H	4-H_{ax}	4-H_{eq}	6-H	8-OMe	9-H	9b-H	2′-H	3′-H_{ax}	3′-H_{eq}	6′-H	7′-H
9a, b	4.81 ddd	3.94 dd	5.09 dd	6.46 s	3.65 s	6.81 s	4.93 d	5.28 dd	2.98 dd	3.32 dd	7.49 d	6.50 d
					3.66 s			5.29 dd	3.01 dd	3.35 dd		
10a, b	4.84 ddd	3.92 dd	5.10 dd	6.46 s	3.66 s	6.80 s	4.91 d	5.42 dd	3.06 dd	3.38 dd	7.50 d	6.49 d
		3.93 dd			3.67 s	6.81 s		5.44 dd	3.14 dd	3.44 dd		
11a, b	4.81 ddd	3.93 dd	5.07 dd	6.46 s	3.66 s	6.80 s	4.93 d	5.38 dd	3.06 dd	3.36 dd	7.49 d	6.49 d
		3.94 dd	5.08 dd		3.67 s	6.81 s			3.13 dd	3.44 dd		
12a, b	4.94 ddd	3.92 dd	4.77 dd	6.45 s	3.50 s	6.39 s	4.68 d	5.26 dd	2.90 dd	3.23 dd	7.13 d	6.69 d
		3.93 dd	4.78 dd		3.52 s	6.40 s	4.70 d			3.24 dd	7.16 d	6.70 d
13a, b	4.96 ddd	3.93 dd	4.77 dd	6.46 s	3.52 s	6.39 s	4.70 d	5.35 dd	3.04 dd	3.31 dd	7.15 d	6.71 d
		3.94 dd	4.78 dd		3.55 s	6.41 s			3.05 dd			
14a, b	4.85 ddd	3.86 dd	4.71 dd	6.46 s	3.57 s	6.49 s	4.65 d	5.27 dd	2.96 dd	3.27 dd	7.19 d	6.75 d
		3.88 dd	4.72 dd		3.59 s	6.50 s	4.67 d	5.29 dd	2.99 dd	3.33 dd		6.76 d
15a, b	4.94 ddd	3.89 dd	4.73 dd	6.44 s	3.48 s	6.51 s	4.71 d	5.22 dd	3.12 dd	3.46 dd	7.04 d	6.47 d
		3.92 dd			3.56 s	6.52 s	4.72 d	5.24 dd	3.17 dd	3.52 dd	7.05 d	
16a, b	5.00 ddd	4.10 dd	5.16 dd	6.50 s	3.64 s	6.84 s	4.94 d	5.24 dd	2.92 dd	3.26 dd	7.47 d	6.49 d
			5.17 dd		3.66 s							
10a	4.20 ddd	3.63 dd	5.32 dd	6.36 s	3.10 s	6.70 s	4.04 d	5.03 dd	3.04 d	3.04 d	7.15 d	6.48 d
10b	4.21 ddd	3.61 dd	5.31 dd	6.34 s	3.08 s	6.67 s	4.05 d	5.08 dd	2.92 dd	3.19 dd	7.15 d	6.48 d

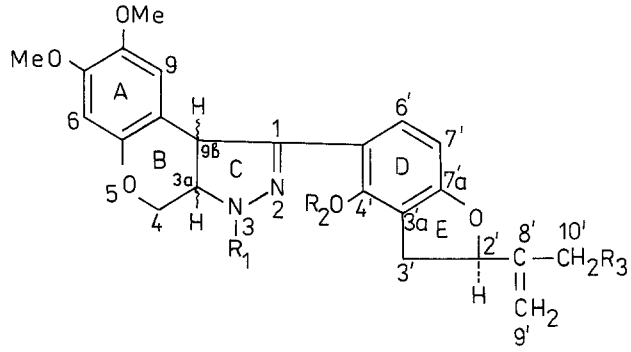
[a] *J* in Hz common for all compounds: 4_{eq}, 3a ~ 2.0; 4_{ax}, 3a ~ 2.0; 4_{ax}, 4_{eq} ~ 11.7; 3a, 9b ~ 11.0; 2′, $3'_{ax}$ ~ 7.9 and 2′,$3'_{eq}$ ~ 9.7

[b] The spectra of **10a** and 10b were recorded in C_6D_6

Table 2. ^{13}C-NMR chemical shifts for compounds **5a, b**, **9a, b** and **12a, b** (δ, $CDCl_3$, *TMS*)[a]

	1-C	3a-C	4-C	5a-C	6-C	7-C	8-C	9-C	9a-C	9b-C	3a′-C	4′-C	5′-C	6′-C	7′-C	7a′-C
5a, b	158.6	59.6	63.0	149.0	102.0	149.3	144.0	112.4	110.3	43.0	109.3	155.8	113.5	129.2	100.6	162.5
		59.7								43.1		155.9				
9a, b	157.9	58.7	65.6	151.3	102.4	149.6	144.2	112.4	110.4	45.4	108.7	155.3	113.8	130.0	101.2	163.5
12a, b	145.6	58.2	65.7	150.8	101.8	149.0	144.1	110.3	110.3	46.9	116.8	154.5	121.1	130.8	107.1	162.5
						149.1						154.6				

[a] Chemical shifts of the remaining carbon atoms: 7-O*Me* (55.9), 8-O*Me* (56.2–56.5), 2′ (87.0–87.4), 3′ (31.7–32.7), 8′ (143.2–143.9), 9′ (112.4–112.8), 10′ (16.9–17.2), 3-N*Ac* (22.5, 169.9–170.3) and 4′-O*Ac* (20.8, 167.6)



5a, b: $R_1 = R_2 = R_3 = H$
6a, b: $R_1 = R_2 = H$, $R_3 = OH$
7a, b: $R_1 = R_2 = H$, $R_3 =$ O-Glu
8a, b: $R_1 = R_2 = H$, $R_3 =$ O-Glu-O-Ar
9a, b: $R_1 = Ac$, $R_2 = R_3 = H$
10a, b: $R_1 = Ac$, $R_2 = H$, $R_3 = OH$
11a, b: $R_1 = Ac$, $R_2 = H$, $R_3 = OAc$
12a, b: $R_1 = R_2 = Ac$, $R_3 = H$
13a, b: $R_1 = R_2 = Ac$, $R_3 = OAc$
14a, b: $R_1 = Ac$, $R_2 = COPh$, $R_3 = H$
15a, b: $R_1 = Ac$, $R_2 = Me$, $R_3 = H$
16a, b: $R_1 = COPh$, $R_2 = R_3 = H$

a. 3aβ, 9bβ, 2′β
b. 3aα, 9bα, 2′β

1 and 2). In the case of the 3-N*Ac* compounds **10a, b** the two diastereomers were successfully resolved by multiple development on TLC plates. We were unable to determine their configuration by the NMR data. However, while recording the proton NMR spectra of **10a** and **10b** in C_6D_6 (see Table 1), we observed a pattern for the 3′-H_2 protons, similar to that observed for the 4′-H_2 protons in the 12a-substituted rotenoids [4]: there was no difference between the chemical shifts of the two 3′-protons in **10a**, whereas in **10b** it amounted to 0.27 ppm. Although the rotenoid and benzopyranopyrazole ring systems are rather different, a similar solvent-solute complexation in C_6D_6 is possible, because of the similarity of their bent molecules (see below). Thus, by analogy with rotenoids, the **10a** isomer could be assigned to the 3aβ, 9bβ, 2′β diastereomer and **10b** to the corresponding 3aα, 9bα, 2′β diastereomer (upper TLC spot). A detailed CD investigation of **10a** and **10b** is already in progress.

The *cis* juncture of the rings B and C determines the bent molecular structure of the compounds under study. In the 4′-OH derivatives **9a, b–11a, b** the aromatic ring D and the 2-pyrazoline ring C are approximately co-planar. The position of ring D is governed by two opposite interactions—the hydrogen bonding (see Experimental) between the 4′-OH and 2-N atom, which holds up ring D in the plane of ring C, and the steric repulsion between the 9-H and 6′-H, which acts in the opposite direction, i.e. tends to pull ring D out of this plane. Ring A and atoms 5 and 9b are also co-planar; a strain is released by deviation of atom 4 from coplanarity with either system. Dreiding models indicated that the angle between the plane of ring A and the plane of rings C-D is approximately 120°. The ^{1}H-NMR data (Table 1) revealed a conformation of ring B in which 3a-H nearly bisects the dihedral angle between 4_{ax} and 4_{eq} ($J_{3a,4eq} = J_{3a,4ax} \sim 2.0$ Hz).

A comparison of the ^{1}H-NMR spectra of the 4′-OH compounds **9a, b–11a, b** and **16a, b**, and of the 4′-O-substituted derivatives **12a, b–15a, b** revelaled great

changes in the chemical shifts ($\Delta\delta$ = 0.3–0.4 ppm upfield) of 9-H and 6′-H. By inspecting the Dreiding models and taking into account the anisotropic effects [5] of aromatic rings A and D, a different preferred conformation of ring D in the 4′-O-substituted compounds could be deduced: ring D is approximately perpendicular to the plane of ring C with the 4′-substituents on the site of 3 a-H and 9 b-H. This is the only arrangement in which 9-H falls in the shielding zone of ring D, while 6′-H is shielded by ring A, and at the same time avoids the steric repulsion between 9-H and 6′-H. The smaller changes in the chemical shifts of the remaining protons (3 a-H, 9 b-H, 8-OMe and 7′-H) supported the predominance of this conformation.

Another important question was the conformation of the N-acetyl group in compounds **9 a, b–15 a, b**. For neither of them any rotamers were observed at room temperature, which indicated the strong predominance of one conformer. This should be the *endo*-conformer with the oxygen of the carbonyl group oriented towards ring B, supported by the following observations: a. the great difference (~1.1 ppm for the 4′-OH and ~0.8 ppm for the 4′-O-substituted compounds) between the chemical shifts of 4-H eq and 4-H ax, due to the anisotropy of the carbonyl group; b. irradiation of the protons of the N-acetyl group in **9 a, b** showed 2.8% nuclear Overhouser enhancement of the intensity of only the signal for 4′-OH.

In addition, our results showed that the product obtained by following the procedure of Nagai et al. in a more alkaline medium is identical with the isohydrazone **5 a, b** prepared by us (UV, IR, ^{1}H-NMR, MS and co-TLC). As expected, the 250 MHz ^{1}H-NMR spectrum of Nagai's product also indicated the presence of two diastereomers. This supports the intramolecular *cis* cycloaddition mechanism proposed for the formation of these derivatives [1].

Experimental

Melting points (uncorrected): Kofler hot-stage microscope. IR: Bruker IFS 113V, in KBr or solutions in CCl_4 · UV: Zeiss Specord UV/VIS, ethanol. TLC: Silica gel GF_{254}, Merck, UV detection. The elemental analyses correspond to the requirements. All NMR spectra were recorded in 5 mm o.d. tubes at ambient temperature with internal D lock on a Bruker WM-250 spectrometer supplied with an Aspect 2000 Data System. The recording conditions for the proton NMR spectra (250.13 MHz) were: spectral width 3kHz, pulse width 4 μs (ca. 30°), pulse repetition time 4.1 s, 16 scans 16 K of data memory. The samples were prepared by blowing argon through the $CDCl_3$ solution for 15 min for the NOE difference experiments.

The ^{13}C-NMR spectra were measured at 62.89 MHz. The recording conditions for the proton decoupled spectra were as follows: spectral width 200 ppm, pulse width 8 μs (ca. 45°), pulse repetition time 1.5 s, approximately 2000 scans, decoupling power 1.5 W, 16 K of data memory. The assignment of the ^{13}C signals was carried out on the basis of DEPT and selective decoupling experiments. The assignment of the quarternary carbons was achieved by selective elimination of the long-range couplings. This was done by low-power irradiation (roughly $\gamma B_2/2\pi$ 20 Hz) during the acquisition in the gated decoupling experiments.

Designations of type **10 a** and **10 b** denote pure diastereomers, while **10 a, b** means a mixture of them.

Preparation of 3-N-Acetates **9 a, b–11 a, b**

Treatment of **5 a, b** or **6 a, b** with Ac_2O at 90°C for 5 min. Usual work up, followed by pTLC separation (**9 a, b** – C_6H_6 : $CHCl_3$: *Me*OH = 17 : 8 : 1; **10 a, b** and **11 a, b** – C_6H_6 : acetone = 6 : 1). pTLC resolution of **10 a, b**: Multiple developement of silica TLC plates consecutively in C_6H_6 : *Et*OAc = 10 : 1 and C_6H_6 : acetone = 6 : 1.

Preparation of 3-NAc-4'-OAc Compounds **12a, b–13a, b**

Treatment of **5a, b** and **6a, b** with Ac_2O at 90°C for 30 min. Usual work up, followed by pTLC purification (for **12a, b** see **9a, b**; for **13a, b** see **10a, b** and **11a, b**).

Preparation of 4'-O-Benzoyl Compound **14a, b**

Treatment of **9a, b** with C_6H_5COCl in *Py* at 90°C for 3 h. Usual work-up, pTLC purification (C_6H_6 : acetaone = 10 : 1).

Catalytic Two Phase [6] Methylation of **9a, b** *and Benzoylation of* **5a, b**

To a mixture of **5a, b** or **9a, b** ($4 \cdot 10^{-3}$ mol) and K_2CO_3 ($4 \cdot 10^{-3}$ mol) in acetone (10 ml) an equimolar amount of methyl iodide or benzyl chloride ($4 \cdot 10^{-3}$ mol) and a catalytic amount of triethyl-benzylammonium chloride ($1 \cdot 10^{-4}$ mol) was added. The mixture was vigourously stirred for 2–6 h and after completion of the reaction (TLC) filtered, dried, evaporated under reduced pressure. pTLC separation of the reaction mixtures afforded **15a, b** and **16a, b** in more than 80% yield (C_6H_6 : *EtOAc* = 10 : 1).

All benzopyranopyrazole derivatives were ~1 : 1 mixtures of the two *cis* 3aβ, 9bβ, 2'β and 3aα, 9bα, 2'β diastereomers. The recorded m.p. are valid for these diastereomeric mixtures, prepared in more than 80–85% yield.

Melting Points. **9a, b**: 214–223°C (*Et*OH); **10a, b**: 199–207°C (*Et*OH); **11a, b**: 160–165°C (*Me*OH); **12a, b**: 147–148°C (ether); **13a, b**: 204–206°C (*Et*OH); **14a, b**: 226–230°C (*Et*OH-acetone); **15a, b**: 168–170°C (*Et*OH); **16a, b**: 153–155°C (ether).

UV (λ_{max}nm). **9a, b–11a, b** and **16a, b**: 302, 322 sh; **12a, b–15a, b**: 292 nm.

IR [ν_{max} (KBr), cm^{-1}]. **9a, b**: 1676, 1636; **10a, b**; 1658, 1635, 3530; **11a, b**: 1741, 1671, 1635; **12a, b**: 1752, 1664, 1618; **13a, b**: 1754, 1738, 1659, 1618: **14a, b**: 1740, 1659, 1619; **15a, b**: 1657, 1619; **16a, b**: 1662, 1633.

IR (ν_{max}(CCl_4, $10^{-4}M$, NaCl). **11a, b**: 3176 cm^{-1}.

Acknowledgements

The authors thank Prof. I. Ognyanov, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia 1040, for a helpful discussion. The partial financial support of this work by UNDP/UNESCO Project BUL 81/001 is gratefully acknowledged.

References

[1] Kostova I., Spassovska N., Maneva L., Golovinsky E., Ognyanov I. (1986) Heterocycles **24**: 2471
[2] Nagai S., Akiyama T., Ueda T., Oda N., Sakakibara J. (1986) Heterocycles **24**: 913
[3] Kostova I., Mollova N. (1988) Org. Mass Spectrom. **23**: 601
[4] Kostova I., Ognyanov I. (1986) Monatsh. Chem. **117**: 689
[5] Johnson C. E., Bovey F. A. (1985) J. Chem. Phys. **29**: 1012
[6] El-Schaffi A. K., Al-Sayed A. M., Khalaf A. (1983) Bull. Chem. Soc. Jpn. **56**: 918

Received February 13, 1989. Accepted March 16, 1989