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A single chalcone and additional rotenoids from *Lonchocarpus nicou*

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7′-*Nor*-6′-oxo-2′,3′-dehydro-12aβ-hydroxyrotenone
(6′*S*)-6′,7′-Epoxyrotenone
(6′*R*)-6′,7′-Epoxy-12aβ-hydroxyrotenone

ABSTRACT

The lipophile extract of *Lonchocarpus nicou* roots afforded the new pyranochalcone 3-*O*-methylabyssinone A as well as the new rotenoids 7′-hydroxytephrosin, and 7′-*nor*-6′-oxo-2′,3′-dehydrorotenone, both compounds occurring with the known 7′-hydroxydeguelin and 7′-*nor*-6′-oxo-2′,3′-dehydro-12aβ-hydroxyrotenone. Furthermore, two rotenoid epoxides previously reported as resulting from the direct oxidative conversion of rotenone and 12aβ-hydroxyrotenone, respectively, were isolated for the first time from a plant source. All the structures were established on the basis of UV, MS, and NMR data.

The previous chemical investigation of nonpolar metabolites from *Lonchocarpus nicou* roots, a tropical member of the Fabaceae family,[1] afforded coumaronochromones[2] among the prenylated isoflavonoids major class characterizing this species. A further multistep chromatographic process of the lipophile extract yielded seven natural products. On the basis of spectroscopic evidence (UV, MS, and NMR), the structure of the newly reported products within this species was established as chalcone for **2**, hydroxyrotenoid for **5**–**6**, 7′-*nor*-6′-oxo-2′,3′-dehydrorotenoid for **7**–**8** and 6′,7′-epoxyrotenoid for **9**–**10**.

With a chromatographic behavior similar to that of both 6-hydroxyrotenoids and 6-hydroxy-6a,12a-dehydrorotenoids groups, compound **2** was isolated as a yellow amorphous powder. It showed the UV spectrum with bands at λ_{max}^{MeOH} nm: 242, 258sh, 298, 362sh, and 387 as well as the molecular formula $C_{21}H_{20}O_5$ given by HRESMS (found: 375.1225; calcd: 375.1208 for $[M+Na]^+$). The 12 double-bond equivalent from the molecular formula was in agreement with the recorded ^{13}C NMR data (Table 1) for 17 sp^2 C atoms ($192 > \delta$ ppm > 103) along with four aliphatic carbons ($78 > \delta$ ppm > 28). Besides two hydroxyls indicated by singlets (δ 13.48 and 7.86 ppm), the ^1H NMR spectrum (Table 1) exhibited two distinct shift ranges grouping nine protons each for aromatic and olefinic H ($7.9 > \delta$ ppm > 5.6) as well as aliphatic nuclei ($4.0 > \delta$ ppm > 1.4). The downfield ^{13}C quaternary signal at δ 191.8 ppm

Table 1
^1H (400 MHz) and ^{13}C (100 MHz) NMR data for chalcone **2** in $CDCl_3$ (δ ppm; *J* Hz)

C/H	**2**		
	^{13}C	^1H	HMBC
1	127.2		
2	112.1	6.97 br d (1.7)	C-6, C-7
3	148.5		
4	145.0		
5	121.9		
6	120.2	7.04 br d (1.7)	C-2, C-7, C-4″
7	144.8	7.80 br d (15.4)	C-2, C-6, C-9
8	117.7	7.40 d (15.4)	C-1
9	191.8		
1′	114.5		
2′	162.6		
3′	103.8	6.42 br s	C-1′, C-5′
4′	166.4		
5′	107.7	6.43 br d (9.3)	C-1′, C-3′
6′	131.9	7.83 d (9.3)	C-2′, C-4′
2″	77.7		
3″	131.5	5.69 d (9.9)	
4″	121.7	6.34 d (9.9)	C-2, C-4, C-2″
2″-CH_3	28.2	1.51 s	C-3″
3-OCH_3	56.4	3.93 s	C-3
2′-OH		13.48 s	C-3′, C-4′
4′-OH		7.86 br s	

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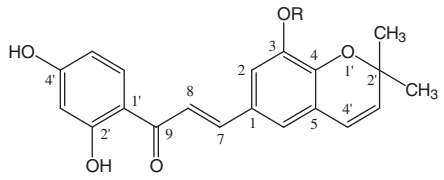
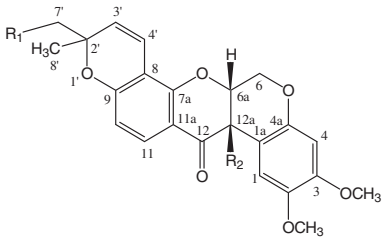
identified a keto group (C-9) α,β- and α′,β′-conjugated to two deshielded tertiary carbons: C-7 (δ 144.8 ppm) and C-6′ (δ 131.9 ppm). In the ^{1}H NMR spectrum, the coupling constant values of the corresponding two very nearly lowfield protons H-7 (δ 7.80 ppm, br d, J = 15.4 Hz) and H-6′ (δ 7.83 ppm, d, J = 9.3 Hz) established *trans*-coupling for H-7 on an ethylenic chain and *ortho*-coupling for H-6′ belonging to a 1,2,4-trisubstituted aromatic ring, with respect to the carbonyl. Furthermore, the broadening exhibited by the H-7 doublet was suitable for long range coupling (J < 1 Hz) with two aromatic nuclei: H-2 (δ 6.97 ppm, br d, J = 1.7 Hz) and H-6 (δ 7.04 ppm, br d, J = 1.7 Hz) *meta*-coupled on a supplementary aromatic ring which was therefore 1,3,4,5-tetra-substituted.



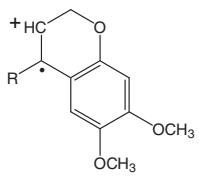
1 R = H
2 R = CH_3

Consequently, the keto group was located between an aromatic ring and a *trans*-styryl moiety of a 2′,3,4,4′,5-pentasubstituted chalcone. The remaining four oxygen atoms from the molecular formula were located as follows. In the ^{13}C NMR spectrum, occurrence of two distinct shift pairs of quaternary O-bonded C sp^2 signals at δ 166.4 and 162.6 ppm, δ 148.5 and 145.0 ppm, clearly supported a conjugated electron-withdrawing group for the downfield C-4′ and C-2′, thus *para*- and *ortho*-oriented, respectively, to the carbonyl and a *ortho* dioxy system for the C-3 and C-4 upfield nuclei. From this, the chalcone core requiring a 10 double-bond equivalent was deduced to be 2′,3,4,4′-tetra-O-substituted and 5-C-substituted. The remaining two unsaturations for the complete molecule were one π-bond and a cyclized C_5H_8 chain belonging to a six-membered heterocyle fused to the chalcone through the O-4 and C-5 positions. The resulting *gem*-dimethylpyran was characterized in the ^{1}H NMR spectrum by three sets of signals divided into one singlet for 2 equiv methyls at δ 1.51 ppm and two doublets at δ 5.69 and 6.34 ppm (J = 9.9 Hz) relative to *cis*-ethylenic H-3″ and H-4″, respectively. The ^{13}C NMR spectrum, in agreement with this partial structure, identified the corresponding C atoms at δ 28.2 ppm for the methyls and δ 121.7 and 131.5 ppm for the tertiary C-4″ and C-3″, respectively,. Finally, the fifth nucleus was quaternary and O-bonded and as expected recorded at δ 77.7 ppm. Moreover, in front of the three ^{1}H NMR singlets (δ 13.48 and 7.86 ppm integrating for one proton each and a methyl at δ 3.93 ppm) and the O-2′, O-3, and O-4′ as still unattached bonds, it was just concluded that the lowfield H must be linked to O-2′ to agree with the pronounced deshielding produced by the carbonyl anisotropic effect, owing to a strong intramolecular bridging proton. Discrimination of the O-3 and O-4′ functions as either OH or OCH_3 was deduced from the ^{1}H–^{13}C HMBC spectrum (Table 1) showing C-3 (δ 148.5 ppm) linked to the methoxyl (δ 3.93 ppm), according to the recorded ^3J appropriate cross-peak and as expected C-4′ (δ 166.4 ppm), at lower field than the hindered C-2′ (δ 162.6 ppm) following the suitable ^4J connectivity with HO-2′ (δ 13.48 ppm). Thus, the new structure issued from the above results was 2′,4′-dihydroxy-3-methoxy-2″,2″-dimethylpyrano(5″,6″:5,4)chalcone. A complete analysis of the ^{1}H–^{13}C HMBC map supported the substitution pattern of the benzene rings and allowed unambiguous assignments of all other ^{1}H and ^{13}C NMR signals. Derived from the recently reported abyssinone A (**1**) in the *Erythrina abyssinica* stem bark,[3] another member of the Fabaceae family but belonging to the tribe Phaseolae,[1] 3-*O*-methylabyssinone A (**2**) is the firstly isolated chalcone from *L. nicou*. Despite 29 prenylated chalconoids in 15 *Lonchocarpus* members,[4–18] mainly reported from roots and seeds, when compared to other structural tissues like stem bark and leaves, the new representative **2** is unlike all others, the only one displaying the A-ring prenylation within this genus.

Obtained as a white amorphous powder, compound **5** was assigned the molecular formula $C_{23}H_{22}O_7$ by HRESMS (found: 433.1274; calcd: 433.1263 for $[M+Na]^+$). Analysis of the ^{1}H and ^{13}C NMR data revealed a close relationship with deguelin (**3**) the parent rotenoid, as predicted by the coincident UV spectra of both products (λ_{max}^{MeOH} nm: 252, 273, 301 and 321). The difference between the two components was that the ^{1}H and ^{13}C NMR features of **5** (Table 2) exhibited only one *C*-methyl signal (H-8′: δ 1.33 ppm; C-8′: δ 23.0 ppm) c.f. two in deguelin (H-7′: δ 1.39 ppm and H-8′: δ 1.45 ppm; C-7′: δ 28.2 ppm, and C-8′: δ 28.5 ppm). The missing methyl group in **5** was replaced by a hydroxymethyl substituent (H-7′: δ 3.66 ppm; C-7′: δ 69.1 ppm). Although not clearly detected in the ^{1}H NMR, the hydroxyl group was supported by both, the IR broad band (ν_{max}^{KBr}3480 cm^{-1}) and the significant EIMS fragment-ion at m/z 379 (19%) = M−31, resulting from the direct loss of an hydroxymethylene radical. On the basis of spectral evidence, compound **5**, unknown in the plant kingdom, was established as 7′-hydroxydeguelin. Discrimination between *cis*- and *trans*-B/C ring rotenoid junctions is usually based on the ^{1}H NMR of H-1 and H-6a.[19–26] The H-1 chemical shift value depending on the orientation of H-1 with respect to the carbonyl gives accurate information about the orientation of H-12a: H-1 nearly coplanar with the carbonyl implies H-12a (α) and a downfield move (H-1 δ 7.7–8.4 ppm in $CDCl_3$), consequent to the anisotropic effect of the carbonyl group; conversely, H-1 outside the carbonyl plane implies H-12a (β) and an upfield shift (H-1 δ 6.4–6.8 ppm in $CDCl_3$) since unaffected by the carbonyl. Parallely, according to the relative orientation of H-6a and the C-6 protons, the coupling values $J_{H\text{-}6a,H\text{-}6ax}$ and $J_{H\text{-}6a,H\text{-}6eq}$ can also distinguish the B/C ring junctures: combination of one large coupling value (10.0–11.5 Hz) and one smaller (3.5–4.5 Hz) characterizes the *trans*-junction while a set of two small coupling values (2.0–3.5 and 0-1.0 Hz) is representative of the *cis*-junction. Likely deguelin (**3**), previously isolated from the same source, **5** was considered to have a *cis*-B/C ring junction as indicated by both the upfield chemical shift value for H-1 (δ 6.78 ppm) outside the carbonyl plane and the small coupling values ($J_{H\text{-}6a,H\text{-}6ax}$ = 3.1 Hz, $J_{H\text{-}6a,H\text{-}6eq}$ = 0.8 Hz) supporting both H-6a and H-12a to have β orientation. This compound is listed in the literature as being prepared from 4′-hydroxy-rot-2′-enonic acid[27] but without any information about the structural identification.



3 R_1 = R_2 = H
4 R_1 = H, R_2 = OH
5 R_1 = OH, R_2 = H
6 R_1 = R_2 = OH



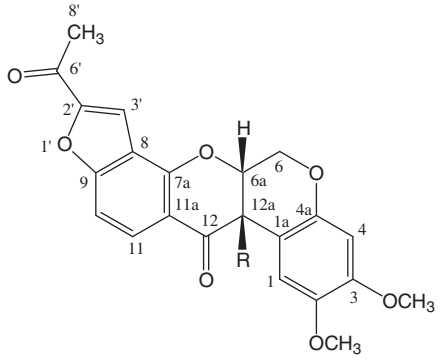
5a R = H
6a R = OH

More polar than **5**, compound **6** was also isolated as a white amorphous powder. The HRESMS measurement indicated one more oxygen atom than for **5** in the molecular formula $C_{23}H_{22}O_8$ (found: 449.1225; calcd: 449.1212 for $[M+Na]^+$). A close similarity between

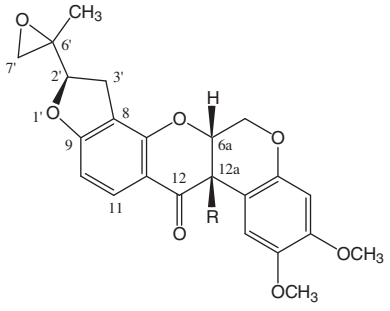
Table 2
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data for rotenoids **5**–**7** in $CDCl_3$ (δ ppm; J Hz)

C/H	5		6		7	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1a	104.6		108.4		104.0	
1	110.4	6.78 br s	109.3	6.54 s	110.2	6.73 br s
2	143.9		144.0		144.1	
3	149.5		151.2		149.8	
4	101.1	6.46 s	101.1	6.48 s	101.1	6.47 s
4a	147.5		148.4		147.5	
6	66.3	4.65 dd (12.1, 3.1)	63.8	4.63 dd (12.1, 2.5)	66.0	4.74 dd (12.2; 3.1)
		4.19 br d (12.1)		4.49 br d (12.1)		4.27 br d (12.2)
6a	72.5	4.92 ddd (4.0, 3.1, 0.8)	76.3	4.58 br d (2.3)	73.3	5.13 br t (3.1)
7a	157.0		156.7		157.3	
8	109.0		108.9		117.5	
9	159.6		160.3		160.5	
10	111.2	6.49 br d (8.7)	111.6	6.50 br d (8.8)	107.2	7.21 dd (8.9; 0.6)
11	128.9	7.77 d (8.7)	128.9	7.74 d (8.8)	127.8	8.05 d (8.9)
11a	113.1		111.5		114.0	
12	189.2		191.4		189.3	
12a	44.4		67.5		44.6	3.99 br d (4.1)
2′	80.9		81.0		152.8	
3′	124.9	5.55 d (10.2)	124.9	5.53 d (10.2)	111.3	7.65 d (0.6)
4′	118.4	6.82 br d (10.2)	118.1	6.77 br d (10.2)		
6′					187.6	
7′	69.1	3.66 br s	68.8	3.64 br s		
8′	23.0	1.33 s	23.3	1.41 s	26.4	2.58 s
2-OCH_3	56.3	3.77 s	56.4	3.73 s	56.5	3.76 s
3-OCH_3	55.9	3.81 s	55.9	3.82 s	55.9	3.80 s
12a-OH			4.38s			
7′-OH		Not detected		Not detected		

5 and **6** was reflected in their UV, NMR, and MS spectra. Indeed, the identical EIMS fragmentation [m/z 395 (15%) = M−31] and co-occurrence of a *C*-methyl (H-8′: δ 1.41 ppm; C-8′: δ 23.3 ppm) and a hydroxymethylene (H-7′: δ 3.64 ppm; C-7′: δ 68.8 ppm) in the ^{1}H and ^{13}C NMR spectra (Table 2) clearly allowed to consider **6** as an oxy derivative of **5**. The supplementary oxygen in **6** was belonging to another hydroxyl group (δ 4.38 ppm) attached to the downfield shifted quaternary C-12a (δ 67.5 ppm) instead of δ 44.4 ppm for the corresponding tertiary C in **5**. This result was in full agreement with the EIMS base peaks m/z 192 (**5a**) and m/z 208 (**6a**) generated by the C-ring retro Diels–Alder rearrangement[28–30] for **5** and **6**, respectively. Hence, compound **6** was determined to be 7′-hydroxytephrosin, a new natural product. Likely tephrosin (**4**), common in this species, **5** was also characterized by a *cis*-B/C ring junction according to the shielded H-1 (δ 6.54 ppm) and the H-6a,H_2-6 couplings ($J_{H\text{-}6a,H\text{-}6ax}$ = 2.5 Hz, $J_{H\text{-}6a,H\text{-}6eq}$ < 0.8 Hz).[19–26]



7 R = H
8 R = OH



9 R = H; (6′*S*)
10 R = OH; (6′*R*)

The last four compounds **7**–**10** isolated from *L. nicou* roots were all identified as rotenone derivatives. Likely **5** and **6**, they also showed either unsubstituted C-12a (**7** and **9**) or β-hydroxylated C-12a (**8** and **10**). Known products **8**–**10** were fully characterized by comparison of their spectral data (UV, MS, and NMR) with those of published results. They corresponded, respectively, to 7′-*nor*-6′-oxo-2′,3′-dehydro-12aβ-hydroxyrotenone[31] (**8**), (6′*S*)-6′,7′-epoxyrotenone[19,32] (**9**), and (6′*R*)-6′,7′-epoxy-12aβ-hydroxyrotenone[19] (**10**). Occurrence of epoxides **9** and **10** within *L. nicou* roots constitutes the first instance of their plant origin since they have been previously obtained by the direct oxidative conversion of the parents rotenone[19,32] and 12aβ-hydroxyrotenone,[19] respectively. Unknown in the literature, compound **7** displayed a UV spectrum (λ_{max}^{MeOH} nm: 248, 274, 281, and 342) superimposable on that of **8**. It showed one oxygen atom less in the molecular formula $C_{22}H_{18}O_7$ determined by HRESMS (found: 417.0966; calcd: 417.0950 for $[M+Na]^+$) and very close NMR data (Table 2). Indeed, the 2-isopropenyl-2,3-dihydrobenzofuran moiety of rotenone was likely **8**, replaced by a 2-acetylbenzofuran consecutive to two structural modifications involved by the oxidative cleavage of the isopropenyl side chain and 2,3-dehydrogenation process. These

results were deduced from the downfield shifted ^{1}H and ^{13}C NMR signals at δ 2.58 ppm (H-8′), δ 26.4 ppm (C-8′) and, δ 187.6 ppm (C-6′) for the acetyl group and δ 7.65 ppm (H-3′) δ 111.3 ppm (C-3′), and δ 152.8 ppm (C-2′) for the additional 2′-π bond[31] clearly supported by long range coupling (J = 0.6 Hz) exhibited by H-10 (δ 7.21 ppm) and the *anti* periplanar H-3′. Accordingly, the novel 7′-*nor*-6′-oxo-2′,3′-dehydrorotenone chemical structure was attributed to **7**. As the parent rotenone, the main rotenoid in *L. nicou* roots, this metabolite was also characterized by a *cis*-B/C ring junction according to the H-1 upfield shift (δ 6.73 ppm) and the small H-6a,H_2-6 coupling values ($J_{H\text{-}6a,H\text{-}6ax}$ = 3.1 Hz, $J_{H\text{-}6a,H\text{-}6eq}$ < 0.8 Hz).[19–26]

From a phytochemical view-point, occurrence of varied isoflavonoids based either on rotenone or deguelin as resulting from B-ring contraction (coumaronochromones), B-ring extension (13-*homo*-13-oxa-6a,12a-dehydrorotenoids), and C-ring opening (*seco*-rotenoids) was previously established in this species. The increased number of rotenone and deguelin derivatives with *cis*-B/C ring fusion, issued from E-ring changes with or without 12aβ-hydroxylation as reported in the present work, contributes to strengthen the dominance of this group of metabolites on the polyphenols profile shown by *L. nicou* roots.

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