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SYNTHESIS OF THREE NATURAL 1,3-DIARYLPROPANES: TWO REVISED STRUCTURES*

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Key Word Index—*Virola multinervia*; *Iryanthera coriaceae*; *I. laevis*; Myristicaceae; 1,3-diarylpropanes; synthesis; reduction of chalcones and dihydrochalcones.

Abstract—1-(2′,4′-dihydroxy-3′,5′-dimethylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-Propane, isolated from *Iryanthera coriacea* and *I. laevis*, 1-(2′-hydroxy-4′-methoxy-5′-methylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-propane, isolated from *I. laevis*, and 1-(2′-hydroxy-4′-methoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)-propane, isolated from *Virola multinervia*, were synthesized by processes which involved catalytic hydrogenation of the appropriate chalcones and Clemmensen reduction of dihydrochalcones. Only the structures of 1,3-diarylpropanes isolated from *V. multinervia* and *I. laevis* were revised.

INTRODUCTION

1,3-Diarylpropanes isolated from species of *Iryanthera* and *Virola* have been reported by Gottlieb *et al.* [1]. The structures of these 1,3-diarylpropanes were determined mainly on the basis of their spectral data.

In previous work [2], 1-(4′-hydroxy-2′-methoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)-propane (**1a**), isolated from *Virola multinervia* Ducke [3], was synthesized in order to confirm their structural proposal. The comparison between the spectral data of the synthetic product and those of the natural one showed that they were not identical, and a new structure was suggested for this compound, namely, 1-(2′-hydroxy-4′-methoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)-propane (**1b**).

In this paper, we report the synthesis of **1b**, 1-(2′,4′-dihydroxy-3′,5′-dimethylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-propane (**1c**), isolated from *I. coriacea* [4] and *I. laevis* [5], and 1-(2′-hydroxy-4′-methoxy-5′-methylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-propane (**1d**), isolated from *I. laevis* [5], in order to confirm the earlier structural proposals.

RESULTS AND DISCUSSION

The synthetic pathway employed in order to obtain the desired 1,3-diarylpropanes (**1b–1d**) involved first the base-catalysed condensation of the appropriate acetophenone (**6–8**: Chart 1) and benzaldehyde (**9** and **10**: Chart 2), next the catalytic hydrogenation of the resulting chalcones (**2a–2c**) and Clemmensen reduction of the corresponding dihydrochalcones (**3a–3c**) which were intermediates to the 1,3-diarylpropanes (**1b–1d**). The acetophenones, prepared (Chart 1) from resorcinol (**4**→**6** and **8**) and 2-methylresorcinol (**5**→**7**) as starting materials, and 3-hydroxy-4-methoxybenzaldehyde (**9**) and 2-hydroxypiperonal (Chart 2), were protected by benzylation [6] of the hydroxyl group, in order to stabilize the substrate towards the basic condition in the condensation reaction: **6** + **9a** → **2a**; **7a** + **10a** → **2b** and **8** + **10a** → **2c**.

The catalytic hydrogenation of the chalcone **2a** furnished a mixture of 1,3-diarylpropane **1b** and dihydrochalcone **3a** (major component), while **2b** and **2c** afforded only **3b** and **3c**, respectively, after 4.5 hr of reaction (H_2, Pd-10% C, 50 psi, $CHCl_3$–EtOH–AcOH) in a Parr apparatus. The MS of dihydrochalcones **3a** [$M^{\cdot+}$ 302 (62%): $C_{17}H_{18}O_5$] and **3b** [$M^{\cdot+}$ 330 (31%): $C_{18}H_{18}O_6$] revealed main peaks at *m/z* 151 (100%: **11**) and 137 (73%: **12**) and 165 (100%: **13**) and 151 (70%: **14**), respectively.

The structures of the compounds synthesized were identified by spectroscopic data (see Experimental). The structure proposals for the 1,3-diarylpropanes isolated from *V. multinervia* (**1a**) [3] and from *I. laevis* (**1d**) [5] were revised to 1-(2′-hydroxy-4′-methoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)- and 1-(4′-hydroxy-2′-methoxy-5′-methylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-propanes, **1b** and **1e** respectively. Compound **1b** was shown to be identical to the natural product from *V. multinervia* by comparison of their spectral data. Analogous comparison of **1d** with the corresponding compound isolated from *I. laevis* showed they were not identical, requiring a change in structure to **1e**. The structure **1e** is the only remaining alternative which is in accordance with the spectral data provided for the natural product from *I. laeveis* [5].

The structure 1-(2′,4′-dihydroxy-3′,5′-dimethylphenyl)-3-(2″-hydroxy-4″,5″-methylenedioxyphenyl)-propane (**1c**), proposed for the compound isolated from *I. coriacea* and *I. laevis*, was confirmed by comparison with the synthetic product (**1c**).

Comparison of the ^1H NMR spectra of 1,3-diarylpropanes containing aryl groups 2′-hydroxy-4′-methoxyphenyl and 2′-methoxy-4′-hydroxyphenyl revealed diagnostic data to provide a classification of such compounds

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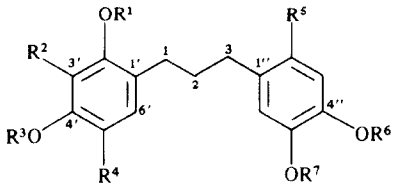
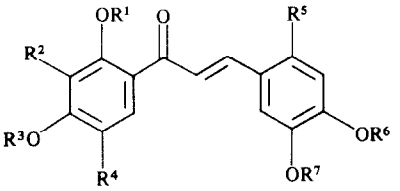
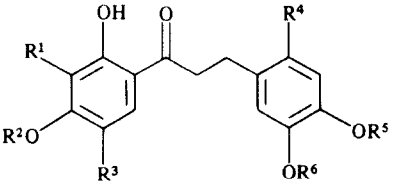


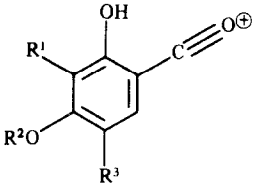
1a $R^1 = R^6 = Me$; $R^2 = R^3 = R^4 = R^5 = R^7 = H$
1b $R^1 = R^2 = R^4 = R^5 = R^7 = H$; $R^3 = R^6 = Me$
1c $R^1 = R^3 = H$; $R^2 = R^4 = Me$; $R^5 = OH$; $R^6, R^7 = CH_2$
1d $R^1 = R^2 = H$; $R^3 = R^4 = Me$; $R^5 = OH$; $R^6, R^7 = CH_2$
1e $R^1 = R^4 = Me$; $R^2 = R^3 = H$; $R^5 = OH$; $R^6, R^7 = CH_2$

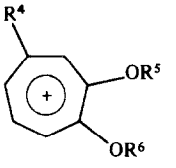


2a $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = R^6 = Me$; $R^7 = CH_2C_6H_5$
2b $R^1 = R^3 = CH_2C_6H_5$; $R^2 = R^4 = Me$; $R^5 = OCH_2C_6H_5$; $R^6, R^7 = CH_2$
2c $R^1 = R^2 = H$; $R^3 = R^4 = Me$; $R^5 = OCH_2C_6H_5$; $R^6, R^7 = CH_2$



3a $R^1 = R^3 = R^4 = R^6 = H$; $R^2 = R^5 = Me$
3b $R^1 = R^3 = Me$; $R^2 = H$; $R^4 = OH$; $R^5, R^6 = CH_2$
3c $R^1 = H$; $R^2 = R^3 = Me$; $R^4 = OH$; $R^5, R^6 = CH_2$





11 $R^1 = R^3 = H$; $R^2 = Me$ [*m/z* 151 (100%)]
12 $R^4 = R^6 = H$; $R^5 = Me$ [*m/z* 137 (73%)]
13 $R^1 = R^3 = Me$; $R^2 = H$ [*m/z* 165 (100%)]
14 $R^4 = OH$; $R^5, R^6 = CH_2$ [*m/z* 151 (70%)]

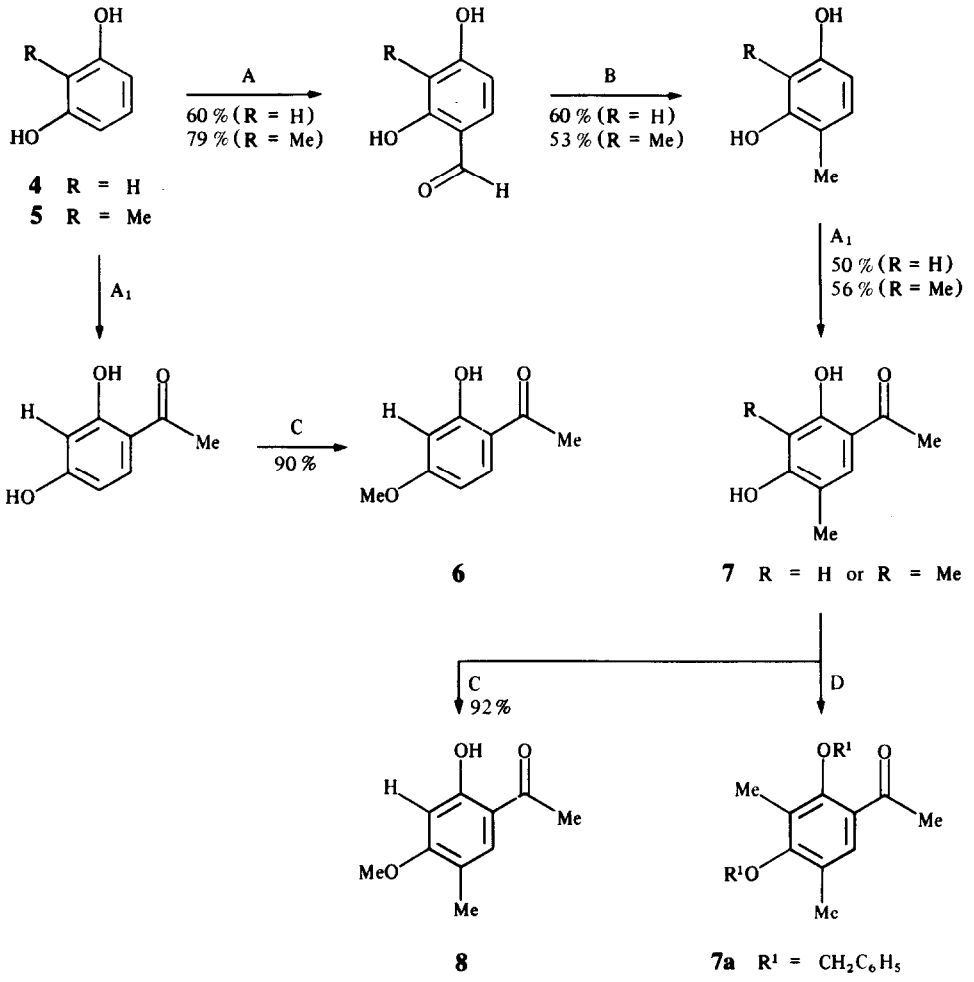
through of chemical shifts of H-3′ and H-5′ {e.g. **1a**: δ 6.40 (*d*, $J = 2$ Hz, H-3′), 6.35 (*dd*, $J = 2$ and 8 Hz, H-5′) [7]; **1b**: δ 6.35 (*d*, $J = 2$ Hz, H-3′), 6.40 (*dd*, $J = 2$ and 8 Hz, H-5′)}.

EXPERIMENTAL

Mps: uncorr. Identities of compounds were established by co-TLC, IR and ^{1}H NMR comparison. PLC was carried out on Merck kieselgel 60 PF_{254}. TMS was used as int. standard in ^{1}H NMR spectra. MS were recorded at 70 eV on a low resolution spectrometer.

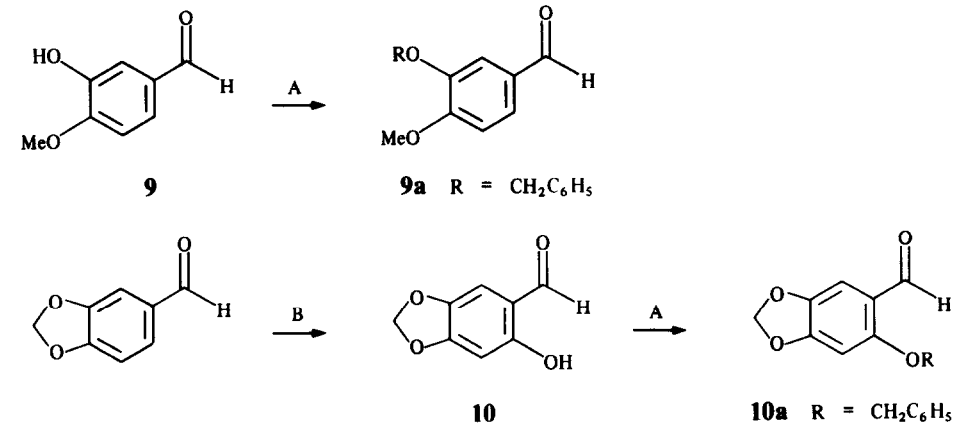
Preparation of the chalcones. Aldol condensation of the appropriately substituted acetophenones (**6**, **7a** and **8**) and benzaldehydes (**9a** and **10a**) [12] gave **2a** (**6** + **9a**, yield 64%), **2b** (**7a** + **10a**, 86%) and **2c** (**8** + **10a**, 78%).

Hydrogenation of the chalcones. In a Parr apparatus a soln of the chalcone (**2a**: 1.8 g; **2b**: 0.8 g; **2c**: 0.9 g) in $CHCl_3$ (10 ml) and EtOH (**2a**: 100 ml; **2b**: 80 ml; **2c**: 45 ml) was flushed with N_2. Catalyst [10% Pd-C: 0.5 g (**2a**); 0.75 g (**2b**); 0.3 g (**2c**)] and AcOH (**2a**: 15 ml; **2b**: 15 ml; **2c**: 10 ml) were added, vacuum was applied and H_2 was admitted under pressure (50 psi, 4.5 hr). Usual work-up, followed by crystallization and/or silica gel chromatography of the crude reaction mixture gave from **2a** → **3a** (86%) + **1b** (3%), **2b** → **3b** (75%) and **2c** → **3c** (revealed by ^{1}H NMR spectrum of the crude reaction mixture and used for the Clemmensen reduction without further purification).



A = 1. $Zn(CN)_2$, HCl, ether; 2. H_2O, Δ (Gattermann–Adams reaction) [8].
B = Zn/Hg, HCl (d 1.19) EtOH (Clemmensen reduction) [9].
A_1 = 1. $ZnCl_2$, MeCN, HCl, ether; 2. H_2O, Δ (Houben–Hoesch reaction) [10].
C = CH_2N_2, MeOH / ether.
D = $C_6H_5CH_2Cl$, K_2CO_3, KI, Me_2CO, Δ [6].

Chart 1. Preparation of acetophenones **6**, **7**, **7a** and **8**.



A = $C_6H_5CH_2Cl$, K_2CO_3, KI, Me_2CO, Δ [6].
B = 1. HNO_3 (d 1.38); 2. $FeSO_4$, NH_4OH, EtOH; 3. $NaNO_2$, $CuSO_4$, H_2SO_4 [11].

Chart 2. Preparation of benzaldehydes **9**, **10** and **10a**.

Clemmensen reduction of the dihydrochalcones. To a stirred suspension of freshly prepared amalgamated zinc (5.5 g) in conc. HCl ($d = 1.19$) was added dropwise a soln of the dihydrochalcone [**3b**: 0.4 g; **3c**: 0.5 g (crude reaction mixture described above)] in 95% EtOH (8 ml) and concd HCl (6 ml) for 20 min. After being stirred and under reflux for further 30 min, the reaction mixture was filtered and extracted twice with $CHCl_3$ (30 ml). The organic layer was washed successively with 5% $NaHCO_3$ (2×50 ml) and H_2O (50 ml), dried (Na_2SO_4) and evapd under red. pres. to give from **3b**→**1c** (66%) and from **3c**→**1d** (69%), after crystallization from C_6H_6 and prep. TLC (silica gel and $CHCl_3$), respectively.

3-*Benzyloxy*-4,4′-*dimethoxy*-2′-*hydroxychalcone* (**2a**). Yellow, mp 142–144° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1634, 1613, 1563, 1511, 1351, 1253, 1230, 1119, 1017, 840, 792, 695. ^1H NMR (60 MHz, $CDCl_3$): δ 3.83 (*s*, OMe), 3.93 (*s*, OMe), 5.20 (*s*, OCH_2Ph), 6.48 (*d*, $J = 2$ Hz, H-3′; *dd*, $J = 2$, $J = 8$ Hz, H-5′), 6.97 (*d*, $J = 8$ Hz, H-5), 7.20–7.60 (*m*, H-6, H-α), 7.20 (*d*, $J = 2$ Hz, H-2), 7.50 (*s*, Ph), 7.76 (*d*, $J = 8$ Hz, H-6′), 7.80 (*d*, $J = 16$ Hz, H-β), 13.40 (*s*, OH). EIMS *m/z* (rel. int.): 390 [$M^{\cdot+}$, (11)], 299 (8), 151 (15), 91 (100).

3′,5′-*Dimethyl*-4,5-*methylenedioxy*-2,2′,4′-*tribenzyloxychalcone* (**2b**). Yellow oil. IR ν_{max}^{KBr} cm^{-1}: 3046, 2910, 1654, 1621, 1590, 1501, 1480, 1440, 1369, 1129, 1040, 735, 696. ^1H NMR (60 MHz, $CDCl_3$): δ 2.20 (*s*, ArMe), 2.26 (*s*, ArMe), 4.78 (*s*, OCH_2Ph), 4.80 (*s*, OCH_2 Ph), 5.00 (*s*, OCH_2Ph), 5.90 (*s*, OCH_2O), 6.52 (*s*, H-3), 6.97 (*s*, H-6), 7.16 (*d*, $J = 16$ Hz, H-α) 7.22–7.42 (*m*, 3 Ph, H-6′), 8.16 (*d*, $J = 16$ Hz, H-β).

2-*Benzyloxy*-2′-*hydroxy*-5′-*methyl*-4,5-*methylenedioxy*-4′-*methoxychalcone* (**2c**). Yellow oil. ^1H NMR (100 MHz, $CDCl_3$): δ 2.18 (*s*, ArMe), 3.87 (*s*, OMe), 5.13 (*s*, OCH_2Ph), 5.95 (*s*, OCH_2O), 6.40 (*s*, H-3′), 6.56 (*s*, H-3), 7.10 (*s*, H-6), 7.20–7.55 (*m*, H-α, H-6′, Ar), 7.98 (*d*, $J = 16$ Hz, H-β).

2′,3-*Dihydroxy*-4,4′-*dimethoxydihydrochalcone* (**3a**). Mp 87–88° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3550, 3200–2400, 1645, 1625, 1592, 1515, 1439, 1376, 1274, 1212, 1200, 1130, 1020, 952, 829, 806, 764. ^1H NMR (60 MHz, CCl_4): δ 2.90–3.20 (*m*, $ArCH_2 + CH_2CO$), 3.83 (*s*, OMe), 3.86 (*s*, OMe), 5.37 (*s*, OH), 6.35 (*d*, $J = 2$ Hz, H-3′ and *dd*, $J = 2$, $J = 9$ Hz, H-5′), 6.65–6.80 (*m*, H-2, H-5, H-6), 7.60 (*d*, $J = 9$ Hz, H-6′), 11.67 (*s*, OH). EIMS *m/z* (rel. int.): 302 [$M^{\cdot+}$ (62)], 151 (100), 137 (73).

3′,5′-*Dimethyl*-4,5-*methylenedioxy*-2,2′,4′-*trihydroxydihydrochalcone* (**3b**). Mp 154–156°. IR ν_{max}^{KBr} cm^{-1}; 3204, 1629, 1588, 1535, 1481, 1451, 1355, 1286, 1224, 1163, 1128, 1035, 939, 853, 839. ^1H NMR (60 MHz, $CDCl_3$): δ 2.15 (*s*, ArMe), 2.23 (*s*, ArMe), 2.93 (*m*, CH_2CO), 3.40 (*m*, $ArCH_2$), 5.35 (*br s*, OH), 5.95 (*s*, OCH_2O), 6.50 (*s*, H-3), 6.63 (*s*, H-6), 7.30–7.50 (*br s*, OH), 7.47 (*s*, H-6′), 12.50 (*s*, OH) EIMS *m/z* (rel. int.): 330 [$M^{\cdot+}$ (30)], 312 (23), 192 (70), 165 (100), 151 (70), 138 (29).

1-(2′-*hydroxy*-4′-*methoxyphenyl*)-3-(3″-*hydroxy*-4″-*methoxyphenyl*)-*Propane* (**1b**). Oil. IR ν_{max}^{film} cm^{-1}: 3426, 2938, 2852, 1621, 1595, 1515, 1439, 1271, 1140, 1031, 956. ^1H NMR (100 MHz, $CDCl_3$): δ 1.65–2.20 (*m*, CH_2), 2.56 (*t*, $J = 8$ Hz, $ArCH_2$), 2.58 (*t*, $J = 8$ Hz, $ArCH_2$), 3.76 (*s*, OMe), 3.86 (*s*, OMe), 4.98 (*br s*, OH), 5.60 (*s*, OH), 6.35 (*d*, $J = 2$ Hz, H-3′), 6.40 (*dd*, $J = 2$, $J = 8$ Hz, H-5′), 6.65 (*dd*, $J = 2$, $J = 8$ Hz, H-6″), 6.75 (*d*, $J = 2$ Hz, H-5″), 6.78 (*d*, $J = 2$ Hz, H-2″), 6.96 (*d*, $J = 8$ Hz, H-6′). EIMS *m/z* (rel. int.): 288 [$M^{\cdot+}$ (27)], 152 (41), 151 (65), 138 (55), 137 (100).

1-(2′,4′-*Dihydroxy*-3′,5′-*dimethylphenyl*)-3-(2″-*hydroxy*-4″,5″-*methylenedioxyphenyl*)-*propane* (**1c**). Mp 126–128° (C_6H_6). IR ν_{max}^{KBr} cm^{-1}: 3175, 2941, 2857, 1620, 1500, 1449, 1243, 1198, 1184, 1095, 1037, 930, 855, 826, 676. ^1H NMR (60 MHz, $CDCl_3$): δ 1.60–2.20 (*m*, CH_2), 2.16 (*s*, 2 Ar-Me), 2.53 (*t*, $J = 7$ Hz, $ArCH_2$), 2.56 (*t*, $J = 7$ Hz, Ar-CH_2), 4.50 (*br s*, OH), 4.60 (*br s*, 2OH), 5.83 (*s*, OCH_2O), 6.38 (*s*, H-3″), 6.60 (*s*, H-6″), 6.72 (*br s*, H-6′). EIMS *m/z* (rel. int.): 316 [$M^{\cdot+}$ (51)], 178 (26), 165 (33), 151 (100).

1-(2′-*Hydroxy*-5′-*methyl*-4′-*methoxyphenyl*)-3-(2″-*hydroxy*-4″,5″-*methylenedioxyphenyl*)-*propane* (**1d**). Oil. ^1H NMR (100 MHz, $CDCl_3$): δ 1.70–2.06 (*m*, CH_2), 2.12 (*s*, $ArCH_3$), 2.56 (*t*, $J = 8$ Hz, $ArCH_2$), 2.58 (*t*, $J = 8$ Hz, $ArCH_2$), 3.77 (*s*, OCH_3), 5.85 (*s*, OCH_2O), 6.32 (*s*, H-3″), 6.37 (*s*, H-3′), 6.58 (*s*, H-6″), 6.82 (*s*, H-6′), 6.20–7.10 (*br s*, 2OH). EIMS *m/z* (rel. int.): 316 [$M^{\cdot+}$ (41)], 178 (20), 164 (29), 151 (100).

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