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TWO ANTIBACTERIAL BIPHENYLS FROM *RHYNCHOSIA SUAVEOLENS**

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Key Word Index—*Rhynchosia suaveolens*; Leguminoseae; biphenyls; 4-(3-methyl-but-2-enyl)-5-methoxy-[1,1′-biphenyl]-3-ol; 2-carboxy-4-(3-methyl-but-2-enyl)-5-methoxy-[1,1′-biphenyl]-3-ol; structural analysis; antibacterial activity.

Abstract—Two new biphenyls characterized as 4-(3-methyl-but-2-enyl)-5-methoxy-[1,1′-biphenyl]-3-ol **1** and 2-carboxy-4-(3-methyl-but-2-enyl)-5-methoxy-[1,1′-biphenyl]-3-ol **5** have been isolated from *Rhynchosia suaveolens*. Both compounds displayed antibacterial activity.

INTRODUCTION

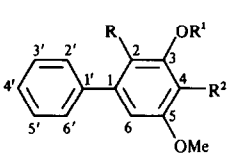
In pursuance of a programme of research aimed at the development of drugs from natural sources in this Institute, [1–3], a 50% aqueous ethanol extract of the whole plant of *Rhynchosia suaveolens*, was found to exhibit antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. Subsequent studies led to the location of this activity in benzene-soluble fraction from which two new biphenyl derivatives have been isolated. Their structural elucidation is described in the present communication.

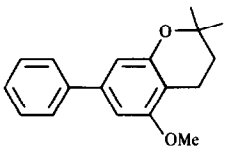
RESULTS AND DISCUSSION

The biphenyl **1**, mp 51–52°, $C_{18}H_{20}O_2$, $[M]^+$ *m/z* 268, optically inactive, indicated in its ^1H NMR spectrum the presence of a mono-substituted phenyl ring (δ7.4, *m*), a two-aromatic proton singlet (δ6.64) an isopentenyl side chain (δ5.23, *t*, 1H; 3.38, *d* 2H; 1.78 and 1.70, 2*s*, 3H each), one methoxyl (δ3.80) and one hydroxyl group masked by a vinylic H. It gave a monoacetate **2**, mp 61°, $C_{20}H_{22}O_3$, $[M]^+$ *m/z* 310 (ν_{max}^{KBr} cm^{-1}: 1757, phenolic ester) in which the aromatic two-proton-singlet split as a result of experiencing deshielding of expected magnitudes. The one at δ6.83 and the other at δ6.9 were thus located *ortho* and *para* to the hydroxyl, respectively [4]. The proximity of the isopentenyl side chain and the hydroxyl in **1** was inferred by observing the deshielding of the benzylic CH_2 (δ3.23) in **2** and confirmed by the acid-catalysed conversion of **1** into **3**, [viscous liquid, $C_{18}H_{20}O_2$, $[M]^+$ *m/z* 268]. At this stage an alternative structure **4** for this biphenyl cannot be ruled out. The structure **1** was, however, favoured on the basis of the following observations.

In the NOE difference spectrum of **3** irradiation at the frequency of methoxyl enhanced the intensity of only one (δ6.53) of the two aromatic doublets (δ6.64, 6.53) suggesting the former to be adjacent to the methoxyl. Besides, the ^1H NMR spectrum of **1** recorded in C_6D_6 created solvent-induced magnetic non-equivalence of the two-aromatic proton singlet which split to two *meta*-coupled doublets (δ6.54 and 6.48, J = 2.0 Hz) and thus suffered shielding of unequal magnitudes. Hence a different environment around the methoxyl could be inferred. This evidence combined with the expected chemical shift values [5], δ107.85 and 102.59 for C-2 and C-6, respectively, in the ^{13}C NMR spectrum of **1** confirmed the assigned structure for this biphenyl.

The biphenyl **5**, mp 138°, $C_{19}H_{20}O_4$, $[M]^+$ *m/z* 312, optically inactive, exhibited the presence of chelated hydroxyl and carboxylic acid functionalities at ν_{max}^{KBr} cm^{-1}: 3375 and 1653, respectively, together with the bands characteristic of a mono-substituted phenyl ring (755, 700) and tri-substituted double bond (835). Further insight into its structure was gained by the study of its ^1H NMR spectrum which revealed the presence of a chelated hydroxyl (δ11.6) [6], an isopentenyl side chain, one methoxyl group, a 5H multiplet and a lone aromatic H (δ6.22). Deshielding of the expected magnitude experienced by the latter (δ6.62) in its acetate **6**, mp 140°, $[M]^+$ *m/z* 354, $C_{21}H_{22}O_5$, together with a positive Gibb's test by **5** decided its placement *para* to the hydroxyl group. The vicinal disposition of the hydroxyl and COOH as





3

	R	R^1	R^2
1	H	H	$CH_2CH{=}CMe_2$
2	H	OAc	$CH_2CH{=}CMe_2$
4	$CH_2CH{=}CMe_2$	H	H
5	COOH	H	$CH_2CH{=}CMe_2$
6	COOH	OAc	$CH_2CH{=}CMe_2$
7	COOMe	H	$CH_2CH{=}CMe_2$
8	COOMe	OAc	$CH_2CH{=}CMe_2$
9	$CH_2CH{=}CMe_2$	H	COOH

*CDRI communication No. 3378. Part 11 in the series "Studies in Medicinal Plants". For part 10 see Vishwakarma, R. A., Kapil, R. S. and Popli, S. P. (1983) *Indian J. Chem. Sec. B*, **21**, 1873.

indicated in IR and ^{1}H NMR spectra of **5** got further support from EI mass spectral studies of **5** and **6** in which the elements of water were expelled due to *ortho* effects from their respective molecular ions. Compound **5** on treatment with diazomethane gave **7** ([M]$^+$ *m/z* 326, $C_{20}H_{22}O_4$) which formed an acetate **8** (mp 111.5°, [M]$^+$ *m/z* 368, $C_{22}H_{24}O_5$). **8** was also obtained by reacting **6** with diazomethane. The preferential methylation of the COOH in **7** is in contradiction to an earlier report where the hydroxyl was methylated in preference to the COOH in a similar environment in the case of a phytoalexin isolated from *Cajanus cajan* [7]. The shielding of the benzylic CH_2 in the ^{1}H NMR spectrum of **6** and **8** suggested the close vicinity of the hydroxyl and the isopentenyl chain in **5**. Moreover, a strong upfield shift ($\delta CDCl_3 - C_6D_6 = \Delta 0.6$ ppm) suffered by the methoxyl in **5** indicated the location of the COOH either *ortho* or *para* to this group [8–10]. At this stage an alternate structure **9** for this biphenyl could also be proposed. The final proof in favour of **5** was achieved by its decarboxylation. A brief exposure to 170–175° resulted in the quantitative conversion of **5** into **1**. The absence of any change in the chemical shift of the methoxyl in **1** and **5** confirmed that the COOH group cannot be placed *ortho* to methoxyl in **5**, thus discarding the structure **9**.

Compounds **1** and **5** exhibited activity against *Bacillus subtilis* and *Staphylococcus aureus*. The minimum inhibitory concentration (MIC) of **1** and **5** for *B. subtilis* and *S. aureus* was found to be 15.625 and 31.25 μg/ml, respectively.

EXPERIMENTAL

All mps are uncorr. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 and 20, MHz respectively, using TMS as int standard. MS were recorded using a direct inlet system.

Isolation of constituents. Air-dried whole powdered plant *R. suaveolens* DC. (5 kg) were percolated with 95% EtOH (4 × 20 l) which after removal of solvent *in vacuo* gave a residue (375 g). 200 g of this residue was fractionated successively with hexane (70.5 g), C_6H_6 (56.0 g), Me_2CO (9.8 g) and MeOH (63.0 g). CC of a part of the C_6H_6-soluble residue (16 g) over silica gel (600 g, 60–120 mesh) yielded **1** and **5**.

4-(3-*Methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*]-3-*ol* (**1**). 790 mg of this compound eluted with a mixture of C_6H_6–hexane (1:1) had mp 51–52° (hexane): IR ν_{max}^{KBr} cm^{-1}: 3500–3000 (OH), 2900 (C–H stretching), 1588, 1566, 1445, 1401, 1340, 1220, 1158, 1082; UV λ_{max}^{MeOH} nm (log ε): 262 (6.06), 205 (6.9); ^{13}C NMR ($CDCl_3$): δ158.37 (*s*, C-5), 155.39 (*s*, C-3), 141.17 (*s*, C-1), 140.57 (*s*, C-1′), 128.64 (*d*, C-3′ and C-5′), 127.25 (*d*, C-4′), 126.94 (*d*, C-2′ and C-6′), 114.79 (*s*, C-4), 107.85 (*d*, C-2), 102.59 (*d*, C-6), 55.85 (*q*, Ar–OMe), isopentenyl side chain, 133.76 (*s*, =C<), 122.17 (*d*, CH=), 25.73 (*q*, Me), 22.33 (*t*, CH_2), 17.77 (*q*, Me); MS *m/z*: 268 [M]$^+$, 253, 212, 199, 165, 77.

3-*Acetoxy*-4-(3-*methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*]-3-*ol* (**2**). A mixture of **1** (40 mg), Ac_2O (1 ml) and pyridine (2.5 ml) was left overnight at room temp. Usual work up followed by crystallization yielded white silky flakes **2** (30 mg), mp 61° (MeOH–H_2O): IR ν_{max}^{KBr} cm^{-1}: 2900, 1757, 1573, 1456, 1412, 1375; ^{1}H NMR ($CDCl_3$): δ7.35 (*m*, 5H), 6.9 (*s*, 1H), 6.83 (*s*, 1H), 5.1 (*t*, 1H), 3.83 (*s*, Ar–OMe), 3.23 (*d*, 2H), 2.26 (*s*, 3H), 1.71 and 1.64 (2 *s*, 3H each); MS *m/z*: 310 [M]$^+$, 267, 253, 213, 200, 165, 115, 77.

Cyclization of **1** *into* **3**. A mixture of **1** (100 mg), HOAc (4.3 ml) and conc HCl (0.1 ml) was refluxed at 120–125° for 2 hr. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$ (3 × 5 ml). On evapn of solvent **3** was obtained as a viscous liquid (95 mg). IR ν_{max}^{neat} cm^{-1}: 2950, 1600, 1582, 1466, 1420, 1168; ^{1}H NMR ($CDCl_3$): δ7.6–7.16 (*m*, 5H), 6.64 (*d*, *J* = 2 Hz, 1H), 6.53 (*d*, *J* = 2 Hz, 1H), 3.79 (*s*, Ar–OMe), 2.63 (*t*, *J* = 7 Hz, Ar–CH_2) 1.72 (*t*, *J* = 7 Hz, 2H), 1.27 (*s*, 6H); MS *m/z*: 268 [M]$^+$, 253, 213, 165, 115, 77.

2-*Carboxy*-4-(3-*methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*]-3-*ol* (**5**). 65 mg eluted with C_6H_6, mp 138° (hexane–CH_2Cl_2); UV λ_{max}^{MeOH} nm (log ε): 305 (5.8), 268 (6.1), 231 (6.6); IR ν_{max}^{KBr} cm^{-1}: 3375, 3000–2800, 1653, 1625, 1600, 1560, 1440, 1370, 1336, 1276, 1227; ^{1}H NMR ($CDCl_3$): δ7.23 (*m*, 5H), 5.22 (*t*, *J* = 6 Hz, 1H), 3.79 (*s*, Ar–OMe), 3.37 (*d*, *J* = 6 Hz, 2H), 1.73 and 1.66 (2 *s*, 3H each); MS *m/z*: 312 [M]$^+$, 294, 279, 251, 239, 213, 165, 139, 115.

2-*Carboxy*-3-*acetoxy*-4-(3-*methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*] (**6**). A mixture of **5** (40 mg), Ac_2O (1 ml) and pyridine (2.5 ml) was kept overnight at room temp. Usual work up gave the acetate **6** (30 mg), mp 140° (MeOH–H_2O), IR ν_{max}^{KBr} cm^{-1}: 2900, 1768, 1680, 1602, 1417; ^{1}H NMR ($CDCl_3$): δ7.28 (*s*, 5H), 6.62 (*s*, 1H), 5.07 (*t*, *J* = 6 Hz, 1H), 3.77 (*s*, Ar–OMe), 3.19 (*d*, *J* = 6 Hz, 2H), 2.2 (*s*, 3H), 1.67 and 1.6 (2 *s*, 3H each): FDMS *m/z*: 354 [M]$^+$, 346, 311, 293, 279, 251, 239, 165, 115.

2-*Carbmethoxy*-4-(3-*methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*]-3-*ol* (**7**). Compound **5** (25 mg) was methylated with CH_2N_2 to give **7** (20 mg) as an amorphous residue. ^{1}H NMR ($CDCl_3$): δ7.26 (*m*, 5H), 6.25 (*s*, 1H), 5.23 (*t*, *J* = 6 Hz, 1H), 3.8 (*s*, Ar–OMe), (*s*, OCOMe), 3.37 (*d*, 2H), 1.76 and 1.65 (2 *s*, 3H each): MS *m/z*: 324 [M]$^+$, 294, 279, 251, 239, 165, 115.

2-*Carbmethoxy*-3-*acetoxy*-4-(3-*methyl-but-2-enyl*)-5-*methoxy*-[1,1′-*biphenyl*] (**8**). A mixture of **7** (20 mg), Ac_2O (0.5 ml) and pyridine (1.5 ml) was kept overnight at room temp. Usual work up followed by purification by crystallization yielded **8** (15 mg), mp 111.5° (MeOH–H_2O); FDMS *m/z*: 368 [M]$^+$, 336 [M − MeOH]$^+$, 325, 293, 279, 251.

Decarboxylation of **5**. Compound **5** (20 mg) when heated at 170–175° for 5 min afforded a residue (17 mg) identical in all respects with **1**.

REFERENCES

1. Shoeb, A., Manandhar, M. D., Kapil, R. S. and Popli, S. P., (1978) *J. Chem. Soc. Chem. Commun.* 281.
2. Rizvi, S. H., Shoeb, A., Kapil, R. S. and Popli, S. P. (1980) *Phytochemistry* **19**, 2409.
3. Sharma, P. N., Shoeb, A., Kapil, R. S. and Popli, S. P. (1981) *Phytochemistry* **20**, 335.
4. Highet, R. J. and Highet, P. F. (1965) *J. Org. Chem.* **30**, 902.
5. Wehrli, F. W. and Wirthlin, T. (1976) *Interpretation of Carbon-13 NMR Spectra*, p. 47. Heyden & Son, London.
6. Askari, A., Warthen, L. R. and Shimizu, Y. (1972) *Lloydia* **35**, 49.
7. Cooksey, C. J., Dahiya, J. S., Carratt, P. J. and Strange, R. N. (1982) *Phytochemistry* **21**, 2935.
8. Bowie, J. H., Ronaye, J. and Williams, D. H. (1966) *J. Chem. Soc.* (*B*) 785.
9. Bowie, J. H., Cameron, D. W., Schutz, P. E. and Williams, D. H. (1966) *Tetrahedron* **22**, 1771.
10. Bowie, J. H., Ronaye, J. and Williams, D. H. (1967) *J. Chem. Soc* (B) 535.