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AGAROL, A NEW SESQUITERPENE FROM *AQUILARIA AGALLOCHA**

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Key Word Index—*Aquilaria agallocha*; Thymelaeceae; sesquiterpenes; gmelofuran; agarol; 5-*iso*-propyl-7-methyl-4,5,5a,6,7,8-hexahydro-3H-naphtho-[1,8-bc]-furan-8α-hydroxy-3-one.

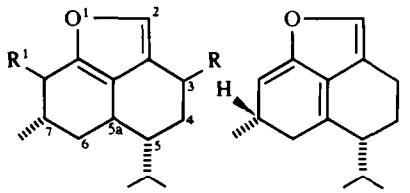
Abstract—The isolation of two sesquiterpenes, gmelofuran and agarol, from *Aquilaria agallocha* is described Gmelofuran has not been previously reported from this genus and the structure of agarol has been elucidated by physical methods and chemical reactions.

Aquilaria agallocha Roxb. (Thymelaeceae), a large evergreen tree, is distributed mainly over the Assam and Khasia hill forests. Two furanosesquiterpenes, α- and β-agarofurans [1], and a novel spirocyclic sesquiterpene, agarospirol [2], have been reported from this taxon. The present investigation of *A. agallocha* was undertaken, since its alcoholic extract was found to exhibit mild cardiotonic activity which was found to be localized in the chloroform-soluble portion of the extractive.

This active fraction was subjected to chromatography over Si gel and neutral alumina, resulting in the isolation of two sesquiterpenes designated as E and H. The latter substance being new, has been named as agarol. Both these substances, however, were found to be inactive. Substance E, mp 120–122°, $C_{15}H_{18}O_3$ [M^+ *m/e* 246.126], was identified as gmelofuran [3] (co-TLC, mp, IR, ^{1}H NMR). The reductive behaviour of gmelofuran under different conditions showed that reaction with $NaBH_4$ led to a diol having the furan ring intact (^{1}H NMR) which was fairly unstable and slowly developed a green colour on storage in the refrigerator. Catalytic hydrogenation yielded a monohydroxy derivative as a result of the opening of the furan ring and it was characterized by the presence of a secondary hydroxyl (3475 cm^{-1}) and four secondary methyl groups (NMR). The MS data and the formation of a monoacetate were in accord with 1-hydroxy-3,8-dimethyl-5-iso-propyldecalin-2,7-dione.

Agarol, $C_{15}H_{20}O_3$ (M^+ *m/e* 248), showed similar spectral data to those of **1**. Its IR spectrum showed bands for OH (3400 cm^{-1}), α,β-unsaturated CO (1670 cm^{-1}) and a furan ring (1530, 870 cm^{-1}). The UV spectrum showed a maximum at 278 nm and the ^{1}H NMR spectrum displayed signals for three secondary methyl groups at δ 0.90, 1.01, 1.30 (each *d*, *J* = 7 Hz), a carbinolic proton centred at 5.03 ($W_{1/2}$ = 6 Hz) and a singlet at 7.68 assignable to the proton of trisubstituted furan ring. Agarol yielded a monoacetate whose ^{1}H NMR showed an acetoxymethyl signal at 2.03 and the carbinolic proton was shifted to 5.85 suggesting the presence of a secondary OH in the molecule.

The pyridinium chlorochromate [4] oxidation of agarol yielded a product which was identical with **1**. This established that one of the carbonyl groups of **1** was reduced to a hydroxyl which was also discernible by the upfield position of the furan ring proton in agarol. Agarol (**1a**) was smoothly dehydrated to a substance (**2**) whose IR spectrum showed the presence of an α,β-unsaturated carbonyl but no hydroxyl and the ^{1}H NMR spectrum showed the appearance of an olefinic proton signal at δ 5.34 without affecting the signal positions of the three secondary methyl groups and the proton of the trisubstituted furan ring. Its structure was inferred to be **2** and the structure of agarol was thus elucidated as 5-*iso*-propyl-7-methyl-4,5,5a,6,7,8-hexahydro-3H-naphtho-[1,8-bc]-furan-8α-hydroxy-3-one (**1a**).



1 R = O, R^1 = O **2**

1a R = O, R^1 = OH, H

The stereochemistry of the hydroxyl group in **1a** was deduced from the ^{1}H NMR signal of the carbinolic proton as a triplet with $W_{\frac{1}{2}}$ = 6 Hz due to axial–equatorial coupling [5] with the equatorial (β) methine proton at C-7 bearing the methyl group in **1**. The hydroxyl group was, therefore, placed as equatorial (α). It is worth mentioning that these substances are an unusual cadinane type of sesquiterpenoid having a furan ring in the *peri*-position, and this communication is the second report of the isolation of **1** from nature [3].

EXPERIMENTAL

Mps are uncorr. The ^{1}H NMR spectra were recorded in $CDCl_3$ unless otherwise stated, with TMS as int. standard. The R_f values

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refer to Si gel plates using ceric sulphate–2 N H_2SO_4 as spray reagent.

The EtOH extractive of the stem wood of the plant (500 g) was macerated with $CHCl_3$ and a part (4.8 g) of the soluble fraction was chromatographed over Si gel (100 g). Sixteen fractions (250 ml each) were collected using hexane containing increasing amounts of Et_2O. The hexane–Et_2O (1:1) eluate gave a fraction containing substance E (0.66 g) which was purified by rechromatography over neutral Al_2O_3 (act. 2.5, 20 g). Elution with hexane–Et_2O (2:1) gave pure substance E (**1**, 0.48 g). The Et_2O eluate of the original column yielded a fraction (1.5 g) containing substance H, 0.3 g which was purified by PLC to give pure substance H (**1a**, 0.2 g).

Substance E (**1**, gmelofuran). Mp 120–122° (Et_2O–hexane), R_f 0.32 (hexane–Et_2O, 2:1). ν_{max}^{KBr} cm^{-1}: 3115, 2960, 2870, 1700, 1675 (C=O), 1528, 870 (furan). λ_{max}^{MeOH} nm: 231, 265; MeOH/NaOH: 232.5, 265, 411. ^1H NMR: δ 0.95, 1.00, 1.35 (3 H each *d*, J = 7 Hz, 3 Me), 1.8–3.2 (8 H), 8.01 (1 H, *s*, furan α-H). MS *m/e*: 246.126 (M^+). The $NaBH_4$-reduced product was obtained as a viscous liquid. ^1H NMR: δ 0.83, 0.95, 1.11 (3 H, each *d*, J = 7 Hz, 3 Me), 2.43 (2 H, *s* (*br*), exchangeable with D_2O, 2-CHOH), 4.76 (2 H, *m*, 2-CHOH), 7.30 (1 H, *s*). Hydrogenation of **1** over PtO_2 yielded a crystalline product (EtOH), mp 113–115°. ν_{max}^{KBr} cm^{-1}: 3475 (OH), 1705, 1685 (C=O). ^1H NMR (C_5D_5N): δ 0.51, 0.55, 0.66, 1.12 (3 H each *d*, J = 7 Hz, 4 Me), 3.6 (1 H, −CHOH). MS *m/e*: 252 (M^+), 234, 219, 209, 191, 163, 148. It gave a monoacetate. ^1H NMR. δ 2.1 (3 H, *s*, −OCOMe, 4.65 1 H, −CHOAc).

Substance H (**1a**, agarol). Viscous liquid, R_f 0.5 (hexane–Et_2O, 1:2). ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1670 (α,β-Δ C=O), 1530, 870 (furan). λ_{max}^{MeOH}: 278 nm. ^1H NMR: δ 0.90, 1.01, 1.30 (3 H each, *d*, J = 7 Hz, 3 Me), 2.7 (1 H, *m*, quenched with D_2O, −CHOH), 5.03 (1 H, $W_{\frac{1}{2}}$ = 6 Hz, −CHOH), 7.68 (1 H, *s*, furan α-H). MS *m/e*: 248 (M^+). Acetylation of **1a** with Ac_2O–Py gave a viscous oil, R_f 0.5 (hexane–Et_2O, 2:1). ^1H NMR: δ 0.90, 1.05, 1.33 (3 H each *d*, J = 7 Hz, 3 Me), 2.03 (3 H, *s*, −OCOMe), 5.85 (1 H, $W_{\frac{1}{2}}$ = 6 Hz, −CHOAc), 7.68 (1 H, *s*).

Dehydration of **1a**. Agarol (30 mg) in dry C_6H_6 was stirred with $SOCl_2$ (0.5 ml) for 1 hr and then worked up. The product (**2**) was obtained as a viscous oil. R_f 0.6 (hexane–Et_2O, 3:1). ν_{max}^{KBr} cm^{-1} 2950, 1675, 1420, 930, 890, 760. ^1H NMR: δ 0.9, 1.05, 1.30 (3 H each, *d*, J = 7 Hz, 3 Me), 5.34 (1 H, −C=CH−), 7.6 (1 H).

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REFERENCES

1. Maheshwari, M. L., Jain, T. C., Bates, R. B. and Bhattacharya, S. C. (1963) *Tetrahedron* **19**, 1079.
2. Verma, K. R., Maheshwari, M. L. and Bhattacharya, S. C. (1965) *Tetrahedron* **21**, 115.
3. Joshi, K. C., Singh, P., Pardasani, R. T., Pelter, A., Ward, R. S. and Reinhardt, R. (1978) *Tetrahedron Letters* 4719.
4. Corey, E. J. and Suggs, J. W. (1975) *Tetrahedron Letters* 2647.
5. Ganguli, A. K., Govindachari, T. R. and Mohammed, P. A. (1966) *Tetrahedron* **22**, 1513.