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TERPENOIDS—XLVII

STRUCTURE AND ABSOLUTE CONFIGURATION OF NOR-KETOAGAROFURAN, 4-HYDROXYDIHYDROAGAROFURAN, 3,4-DIHYDROXYDIHYDROAGAROFURAN AND CONVERSION OF β-AGAROFURAN TO α-AGAROFURAN*

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Abstract—In addition to the furanoid compounds reported previously, three more crystalline furanoids of the selinane group have been isolated from agarwood oil, obtained from the fungus infected plant *Aquillaria agallocha* Roxb. The structures and absolute configurations have been determined by their interconversions into the compounds previously reported.

IN ADDITION to the α-, β- and dihydroagarofurans,[1] three new crystalline sesquiterpenic furans of the selinane group have been obtained in small quantities by elaborate chromatography of the lower boiling fractions of agarwood oil, isolated by low temperature solvent extraction procedure from the fungus infected wood[2] (*Aquillaria agallocha* Roxb.).

These are:

(i) Nor-ketoagarofuran, $C_{14}H_{22}O_2$ (IV),
(ii) 4-Hydroxydihydroagarofuran, $C_{15}H_{26}O_2$ (V),
(iii) 3,4-Dihydroxydihydroagarofuran, $C_{15}H_{26}O_3$ (VII).

Nor-ketoagarofuran (IV) was obtained as crystalline material (m.p. 56–57°) after freezing the appropriate chromatographic fraction for a long time. The m.p. 216° remained constant after regeneration from the semi carbazone; the analysis and molecular weight agree with the molecular formula $C_{14}H_{22}O_2$. The occurrence of a C_{14}-terpenoid in nature is somewhat unusual. Its I.R. spectrum (Fig. 1) shows the presence of a six-membered ring ketone with a methylene group next to the keto function (1712 and 1418 cm^{-1}), tetrahydrofuran ring (888, 1013, 1067, 1110, 1149, 1229 and 1295 cm^{-1}) and gem-dimethyl group (doublet at 1379 and 1361 cm^{-1}). It gives a negative colour test with tetranitromethane. Superimposablity of its I.R. spectrum with that of the previously reported liquid C_{14}-keto-oxide obtained by ozonization of β-agaforuan[1] (II), suggested their possible identity. The optical rotation of the liquid C_{14}-keto-oxide $[(\alpha)_D^{30}\ -69{\cdot}2°]$ from β-agarofuran was considerably lower than that of the crystalline nor-ketoagarofuran $[(\alpha)_D^{30} - 118{\cdot}86°]$, but on seeding with a trace of

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[1] M. L. Maheshwari, T. C. Jain, R. B. Bates and S. C. Bhattacharyya, *Tetrahedron*, **19**, 1079 (1963).

[2] T. C. Jain, M. L. Maheshwari and S. C. Bhattacharyya, *Perf. and Ess. Oil Rec.* **53**, 294 (1962).

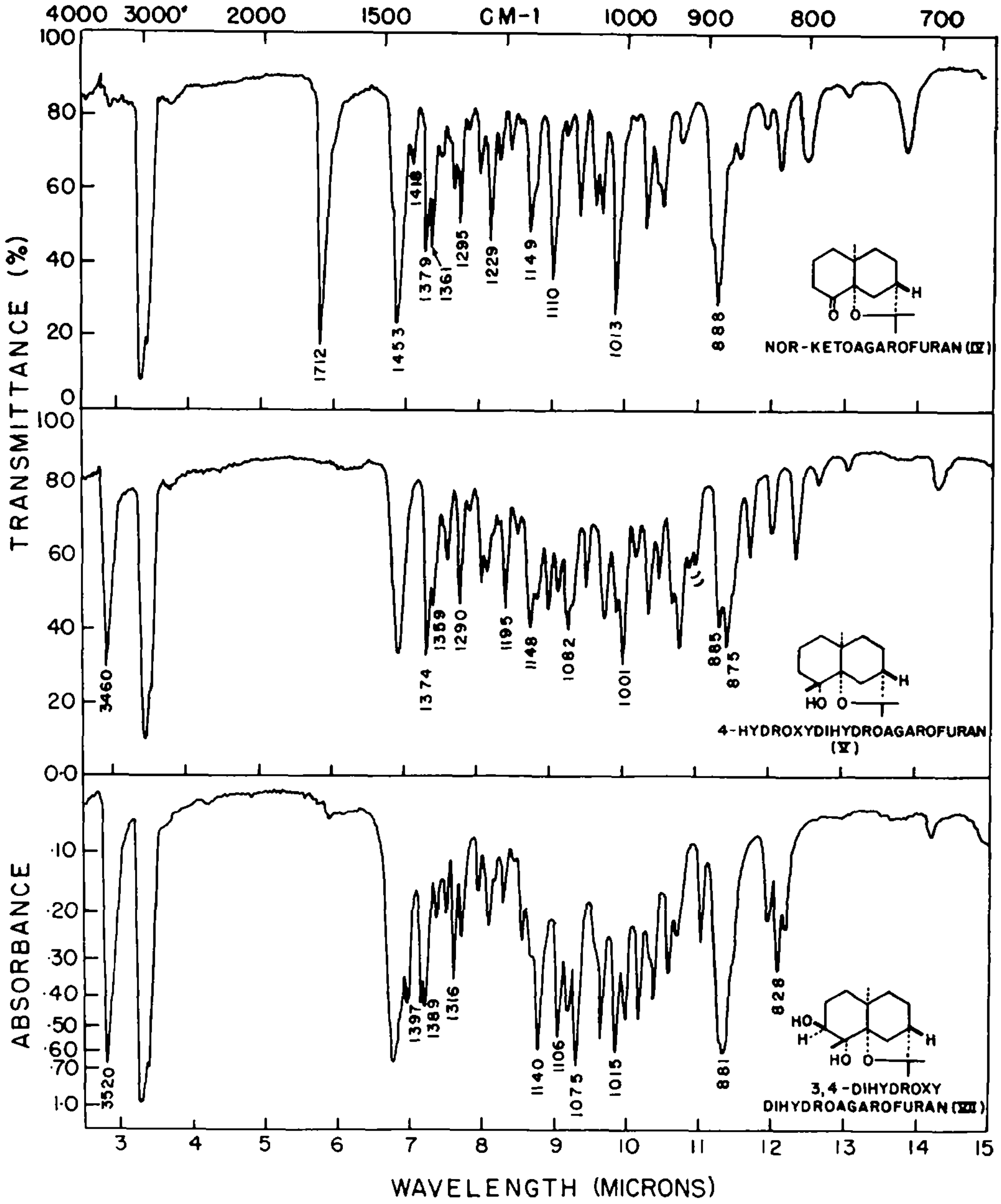


FIG. 1

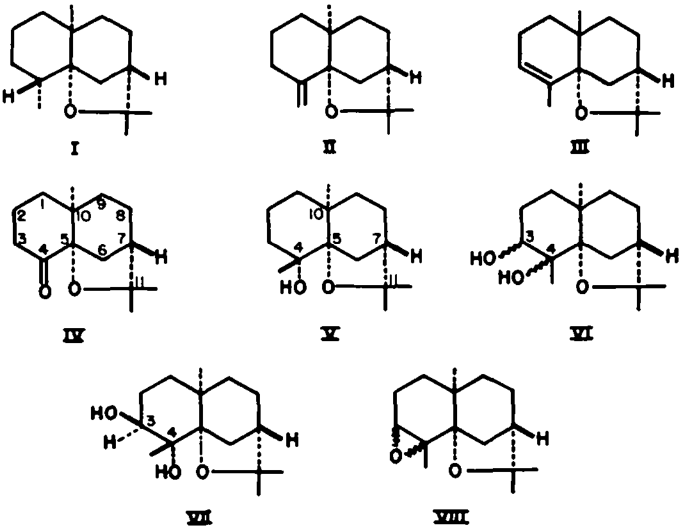
the crystalline nor-ketoagarofuran, the liquid keto-oxide crystallized immediately. On further crystallization from pet. ether (40–60°) the crystals melted at 56–57°; $(\alpha)_D^{30}$ − 116·54° (c, 0·35) and a mixed m.p. with crystalline nor-ketoagarofuran was undepressed. The low rotation of the liquid C_{14}-keto-oxide was presumably due to the presence of impurities having high opposite rotation.

To confirm the stereochemistry of this naturally occurring nor-ketoagarofuran, its

O.R.D. curve* (Fig. 2) was measured. As in the case of the previously reported liquid C_{14}-keto-oxide it also showed negative cotton effect at 305 mμ but with considerable increase in magnitude.

Both compounds have identical N.M.R. spectra† (Fig. 3) showing the presence of three tertiary methyl groups (0·86 p.p.m. due to C_{10}-angular methyl group, 1·11 and 1·37 ppm due to two methyl groups on C_{11}). The positions of the peaks are comparable with those of β- and α-agarofurans. The above evidence confirms the structure (IV) for the naturally occurring nor-ketoagarofuran.

CHART I



4-Hydroxydihydroagarofuran (V), m.p. 130–131° was obtained from subsequent chromatographic fractions. It analyses for $C_{15}H_{26}O_2$ and is saturated towards tetranitromethane. Its I.R. spectrum (Fig. 1) shows the presence of hydroxyl group (3460 cm^{-1}), gem-dimethyl group (doublet at 1374 and 1359 cm^{-1}) and tetrahydrofuran moiety (875, 885, 1001, 1082, 1099, 1195, 1242 and 1290 cm^{-1}). Its I.R. spectrum is closely similar to those of agarofurans in the fingerprint region. Its N.M.R. spectrum (Fig. 3) shows the presence of four tertiary methyl groups (1·15 p.p.m. due to C_{10}-angular methyl group and overlapping of one of the methyl groups at C_{11}; 1·24 p.p.m. due to the other methyl group on C_{11} and 1·32 p.p.m. due to tertiary methyl group on C_4). The absorption at 1·65 p.p.m. is probably due to the presence of tertiary hydroxyl group.

The nature and position of hydroxyl group and the structure of the molecule was proved by its conversion into α-agarofuran (III) on dehydration with thionyl chloride

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* We thank Prof. W. Klyne, Westfield College, University of London, for the measurement of the O.R.D. curve.

† N.M.R. spectra were measured by Dr. P. M. Nair and his colleagues on A-60 (Varian instrument set at 60 Mc). Tetramethyl silane was used as an internal standard; carbon tetrachloride solutions were used.

in pyridine at room temperature. The mode of dehydration[3] suggested the axial nature of the tertiary hydroxyl function and established the structure and stereochemistry of the alcohol as V.

The stereochemistry at C_4 was further confirmed by preparing the alcohol (V) from nor-ketoagarofuran (IV) by reaction with methyl lithium,[4] which is known to give an axially oriented tertiary hydroxyl group. Construction of the model of the alcohol (V) shows that orientation of hydroxyl is α-axial and that of the C_4-methyl is β-equatorial, keeping the orientation of all other centres as in α-agarofuran.

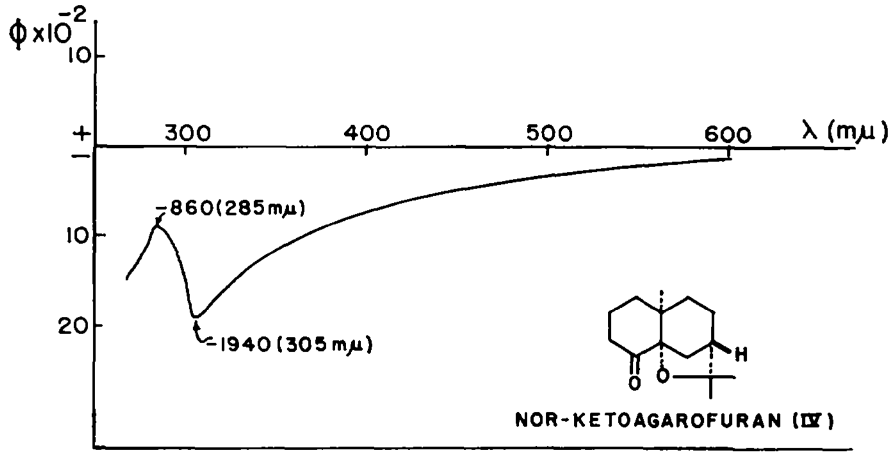

Fig. 2

All the physical constants of the natural alcohol and that prepared from nor-keto agarofuran are similar and their mixed m.p.s are undepressed. Their I.R. and N.M.R spectra are superimposable. The alcohol ($C_{15}H_{26}O_2$) prepared from nor-keto agarofuran also yields α-agarofuran (III) on dehydration with thionyl chloride in pyridine at room temperature.

The last fractions from the chromatography of agar oil gave small quantities of a crystalline dihydroxy dihydroagarofuran, m.p. 176° with a molecular formula $C_{15}H_{26}O_3$. Its I.R. spectrum (Fig. 1) shows strong absorption for hydroxyl groups (3520 cm^{-1}), a doublet at 1397 and 1389 cm^{-1}) for gem dimethyl group and the presence of tetrahydrofuran ring (881, 1015, 1075, 1089, 1106, 1235, 1295, and 1316 cm^{-1}).

All the properties of this natural diol-oxide are identical with those of the diol-oxide (VI), which was previously obtained as one of the reaction products during the treatment of epoxy α-agarofuran (VIII) with borontrifluoride ethereate[1]. The I.R. spectra of both the diol-oxides are superimposable and their mixed m.p.s are undepressed.

As the diol-oxide is formed from epoxy-α-agarofuran (VIII) in acidic media, according to Barton and Cookson[5] the opening of the epoxide ring will be *trans* diaxial. On the basis of this, the stereochemistry of the diol will be represented by the

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[3] D. H. R. Barton, A. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).

[4] G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.* **83**, 3114 (1961).

[5] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

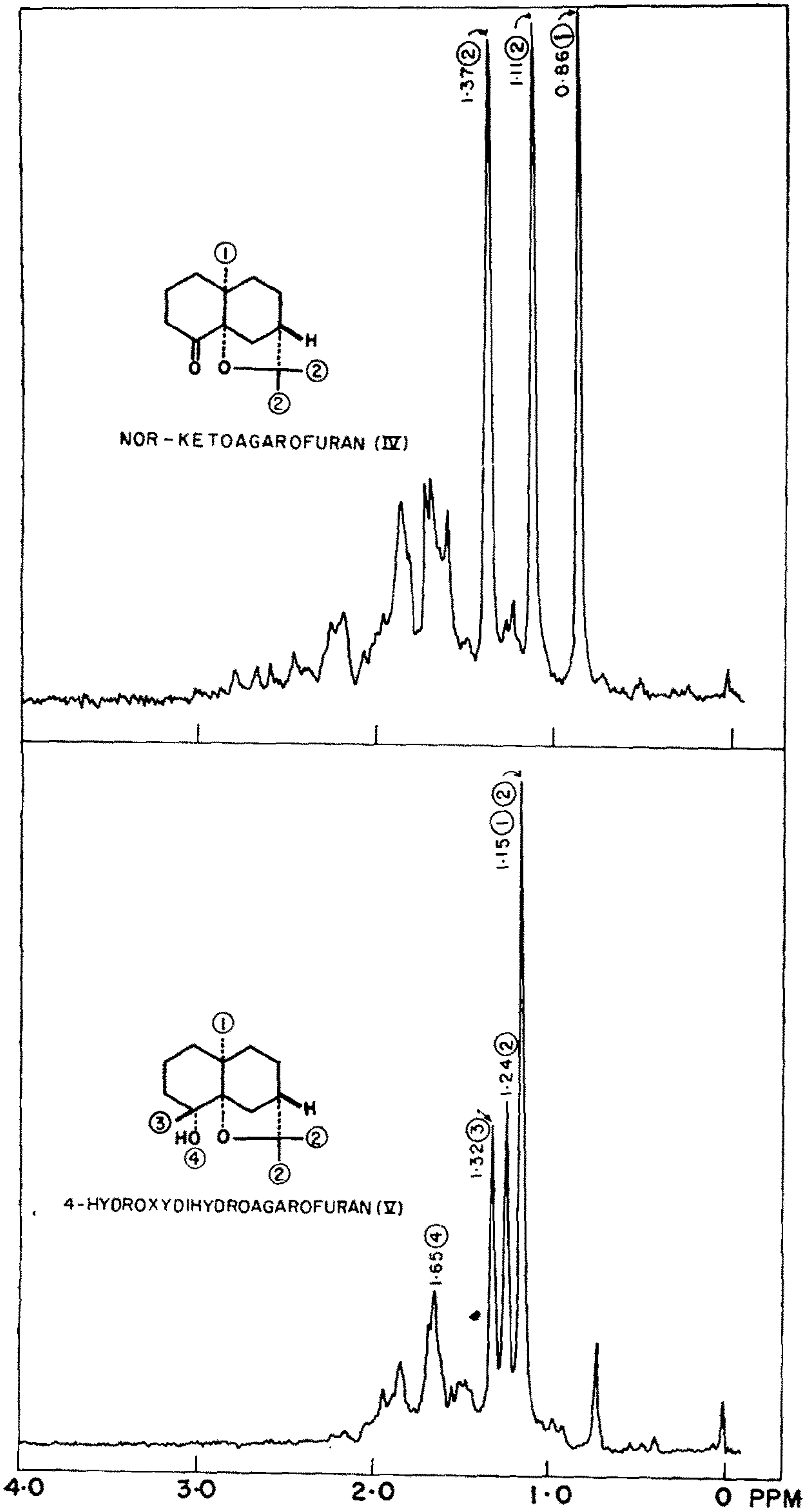
1·37②
1·11②
0·86①
①
H
O
O
②
②
NOR-KETOAGAROFURAN (IV)
1·15①②
1·24②
1·32③
1·65④
①
③
H
HO
④
O
②
②
4-HYDROXYDIHYDROAGAROFURAN (V)
4·0
3·0
2·0
1·0
0 PPM

Fig. 3

structure VII in which the C_3-hydroxyl group is β-axial and the C_4-hydroxyl group α-axial.

The results described in this paper establish that the various furanoids occurring in agarwood oil are closely related. It is also seen that β-agarofuran (II), via nor-ketoagarofuran (IV) and 4-hydroxydihydroagarofuran (V) can be easily converted to α-agarofuran (III).

EXPERIMENTAL

All m.ps. are uncorrected. The b.ps. unless otherwise stated, correspond to bath temps. Rotations were taken in chloroform solution. Neutral alumina, graded according to the Brockmann scale[6,7] of activity was used in chromatography. The pet. ether refers to the fraction boiling between 60–80°. The I.R. spectra were recorded as liquid film or in nujol suspension on a Perkin-Elmer Model No. 137B infracord spectrophotometer by Mr. Deshpande and Mr. Gopinath. Microanalyses were carried out by Mr. Pansare and colleagues.

Isolation. After separating the 3 agarfurans, the lower boiling fractions[1] of agar distillate were subjected to rigorous stage-wise chromatography on grade II alumina (50–100 times) to furnish nor-ketoagarofuran (IV, 3·0 g), 4-hydroxydihydroagarofuran (V, 500 mg) and 3,4-dihydroxydihydroagarofuran (VI, 100 mg) in the sequence indicated. These compounds were eluted with pet. ether-benzene mixture (1 : 1) and benzene.

Nor-ketoagarofuran (IV). This crystallized from pet. ether (40–60°); m.p. 56–57°; $(\alpha)_D^{30}$ −118·86° (*c*, 3·88); I.R. bands at: 1712, 1418, 1379, 1361, 1295, 1229, 1149, 1110, 1067, 1013, and 888 cm^{-1}. (Found: C, 75·71; H, 10·15. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%). Semicarbazone after repeated crystallization melted at 216°. (Found: C, 64·16; H, 8·75; N, 15·1. $C_{15}H_{25}O_2N_3$ requires: C, 64·48; H, 9·02; N, 15·04%).

4-*Hydroxydihydroagarofuran* (V). This was obtained as needle shaped crystalline material (m.p. 130–131°) from the chromatographic fraction (earlier benzene-eluates) and further purified by crystallization from pet. ether, $(\alpha)_D^{30}$ −75·7° (*c*, 1·29); no colouration with tetranitromethane; I.R. bands at: 3460, 1374, 1359, 1323, 1290, 1242, 1229, 1195, 1148, 1136, 1114, 1099, 1082, 1054, 1028, 1011, 1001, 985, 966, 954, 939, 929, 910, 885, 875, 852, 831, 810, 789, 768 and 700 cm^{-1}. (Found: C, 75·82; H, 10·98. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·0%).

3,4-*Dihydroxy dihydroagarofuran* (VII). This was obtained from the benzene-eluates during the last stages in the chromatography and was purified by recrystallization from ethyl acetate and drying under vacuum at 90°; m.p. 176°, $(\alpha)_D^{30}$ −40·98° (*c*, 0·29), no colouration with tetranitromethane; I.R. bands at: 3520, 1431, 1397, 1389, 1316, 1295, 1235, 1140, 1106, 1089, 1075, 1038, 1015, 1003, 983, 962, 945, 933, 909, 881, 836, 828 and 811 cm^{-1}. (Found: C, 70·53; H, 10·42. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%).

Preparation of crystalline nor-ketoagarofuran (IV) *from β-agarofuran* (II). β-agarofuran (200 mg) in chloroform (40 ml) was ozonized for 1 hr at 0° and processed in the usual way to give a neutral fraction (173 mg) which on chromatography over alumina (grade II, 10 g, elution by 50 ml of benzene) followed by distillation (b.p. 145° at 4 mm) gave a liquid keto-oxide (110 mg). On seeding with a small crystal of natural nor-ketoagarofuran it immediately crystallized. On recrystallization from pet. ether (40–60°) it gave pure nor-keto agarofuran m.p. mixed m.p. with natural nor-ketoagarofuran 56–57°; $(\alpha)_D^{30}$ −116·54° (*c*, 0·35), I.R. bands at: 1712, 1418, 1379, 1361, 1295, 1229, 1149, 1110, 1067, 1013, 980, 950, 888, 826, 803 and 725 cm^{-1}. (Found: C, 75·71; H, 9·75. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%).

Preparation of α-agarofuran (III) *from 4-hydroxydihydroagarofuran* (V). 4-Hydroxydihydroagarofuran (150 mg) was dissolved in dry pyridine (6 ml) and the solution was cooled to about 5°. Thionyl chloride (0·75 g) was added dropwise with shaking during 10 min. After standing for 2 hr sodium carbonate (0·45 g) in water (5 ml) was added slowly. The mixture was extracted 3 times with ether and the ether layer was washed with saturated tartaric acid solution until all pyridine has been removed. After washing with water the ethereal solution was worked up to give a mobile liquid (110 mg), which was purified by chromatography over alumina (grade I, 10 g, elution with 40 ml pet. ether) followed by distillation to afford α-agarofuran (III, 80 mg), b.p. 134° at 4 mm, n_D^{30} 1·5062,

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[6] H. Brockmann and F. J. McQuillin, *J. Chem. Soc.* 2423 (1955).

[7] E. Lederer and M. Lederer, *Chromatography* p. 26. Elsevier, N.Y. (1957).

$(\alpha)_D^{30}$ +39·8° (*c*, 2·1), yellow colouration with tetranitromethane; I.R. bands at: 1667, 1389, 1370, 1326, 1307, 1285, 1250, 1239, 1202, 1164, 1155, 1136, 1099, 1080, 1046, 1012, 965, 950, 935, 887, 856, 838(s), 825, 805, 770 and 703 cm^{-1}. (Found: C, 81·60; H, 11·14. $C_{15}H_{24}O$ requires: C, 81·70; H, 10·98%). N.M.R. spectra identical with that of α-agarofuran reported previously.[1]

Preparation of 4-hydroxydihydroagarofuran (V) *from nor-ketoagarofuran* (IV). Methyl lithium was prepared by adding methyl iodide (6 ml) to lithium (1·8 g in 6 pieces) in dry ether (40 ml), with stirring and cooling in ice. When the initial vigrous reaction had subsided, the mixture was refluxed with stirring for 4 hr. The mixture was then cooled and the unreacted lithium was mechanically removed.

The nor-ketoagarofuran (IV, 440 mg) in dry ether (20 ml) was added slowly to the solution of methyl lithium and the mixture was refluxed with stirring for 19 hr. Excess of methyl lithium was decomposed by adding aqueous sodium sulphate solution containing some sodium thiosulphate to the stirred, ice-cold solution. Water was added and the ether layer was separated and washed well with water, dried over anhydrous sodium sulphate and evaporated to give crude alcohol (430 mg), m.p. 127°. It was purified by repeated crystallizations from pet. ether to furnish needle shaped crystalline (m.p. 130–131°) 4-hydroxydihydroagarofuran (V, 360 mg), $(\alpha)_D^{30}$ −74·34° (*c*, 1·52). (Found: C, 75·77; H, 10·94. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

I.R. and N.M.R. spectra were identical with those of natural 4-hydroxydihydroagarofuran.