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3,045,028

TRIMETHYL-DODECAHYDRONAPHTHOFURANS

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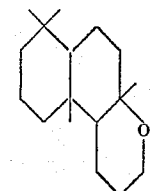
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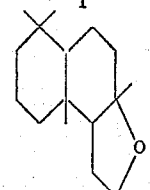
1 Claim. (Cl. 260—346.2)

Odorants of the amber type are important materials in perfumery.

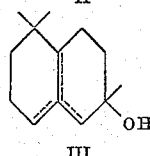
Extensive studies of the degradation of natural amber and of related products by M. Stoll and his coworkers (Industries de la parfumerie 9 (1954), 4 and 48) and by E. Lederer and his coworkers (Industries de la parfumerie 8 (1953), 189, and 12 (1957), 231), have led, in recent years, to the discovery of a number of compounds possessing an amber odor. I—III are mentioned as examples.



I



II

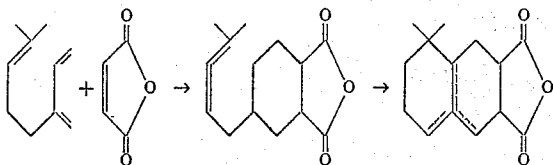


III

All amber compounds known at this moment however are accessible only by means of relatively complicated procedures using natural products as starting materials.

It is the purpose of the present application to disclose a series of compounds with an odor of the amber type which can be produced in a simple way, starting from readily available, inexpensive materials.

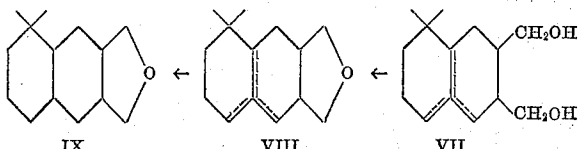
Condensation of myrcene (IV) with maleic anhydride (V), followed by cyclisation (VI), reduction (VII), cyclisation and hydrogenation leads to the formation of a tricyclic ether (IX) with an odor of the woody type which, however, has no amber character.



IV

V

VI



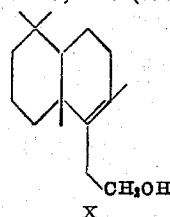
IX

VIII

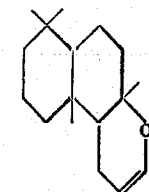
VII

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We have now discovered that the introduction of one or two methyl groups into compounds of type IX causes a shift of the odor character and produces a definite and often strong, tenacious amber odor. Also methyl homologs of the unsaturated ether VIII often possess an amber note but this is much weaker than that of the saturated compounds. This is surprising since many cases are known in which the disappearance of one or more double bonds either reduces or does not influence the olfactive properties of the compound. In the series of compounds with amber odor this is the case with X, the amber odor of which practically disappears upon hydrogenation of the double bond (M. Stoll and M. Hinder, *Helv. Chim. Acta* 33, 1251 (1950)), while the odor of XI remains unaltered when the double bond is reduced (L. Ruzicka and C. F. Seidel, *Helv.* 33, 1285 (1950)).

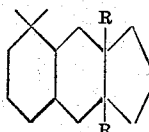


X

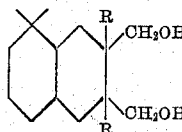


XI

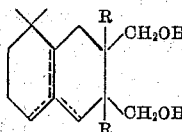
It is the purpose of the present application to provide new compounds with an odor of the amber type and with the general Formula XII



XII



XIII



XIV

in which the substituents R are either both methyl groups or one methyl group and one hydrogen atom.

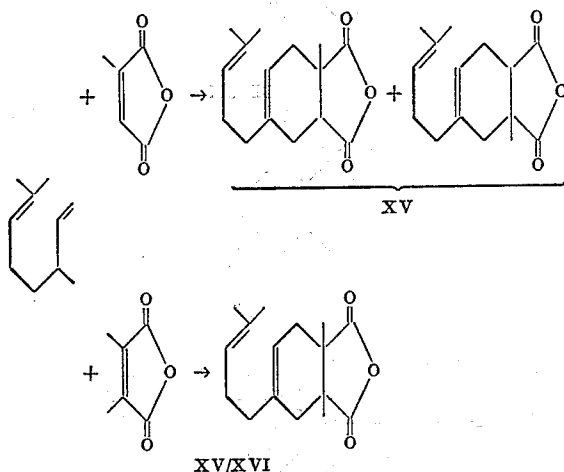
By far the strongest amber odor is obtained when one of the substituents R is a methyl group and the other a hydrogen atom.

Compounds of type XII are easily accessible by cyclisation of a diol type XIII in which the symbols R have the meaning mentioned above. Such cyclisations may be realized conveniently by any suitable dehydrating agent such as aryl- or alkane sulphonic acids, sulphuric acid, phosphoric acid, oxalic acid, maleic anhydride or similar anhydrides, potassium hydrogen-sulphate or similar acid salts, alumina, chromous oxide, silica or alum, in the liquid as well as in the vapor phase. A large number

of such agents have been described by W. Reppe *c.s.* (Ann. 596 (1955) 81). Useful results may also be obtained by means of indirect methods of cyclisation, e.g. by treatment of the corresponding di-halide with magnesium hydroxide according to L. Schmerling and J. P. West (J.A.C.S. 74 (1952), 2885), by elimination of sulphonic acid from the corresponding monosulphonate by means of pyridine or lutidine according to Reynolds and Kenyon (J.A.C.S. 72 (1950), 1953) or by elimination of methyl bromide from an ether of the corresponding bromohydrin by means of ferric chloride as described by A. Kirrmann and N. Hamaide (Bull. Soc. Ch. Fr. 1957, 798).

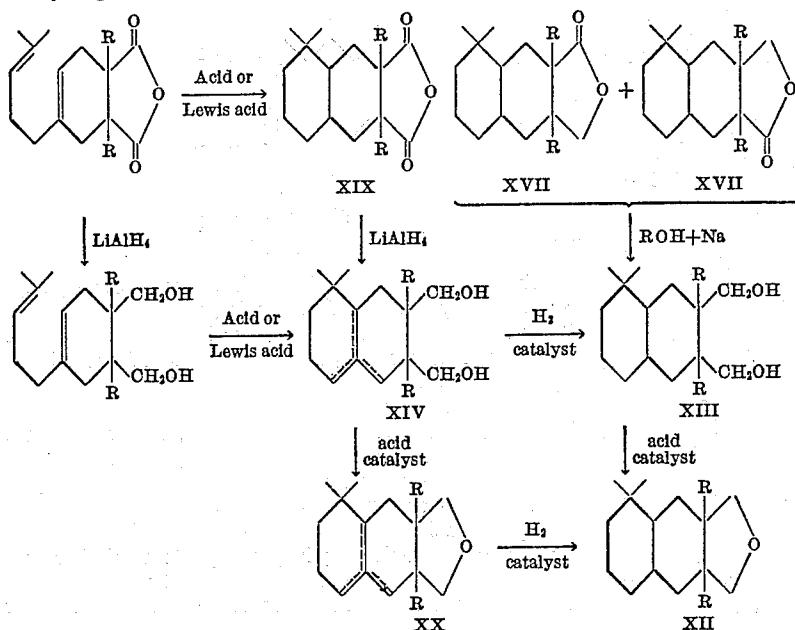
A second convenient method for the preparation of ethers of type XII is the cyclisation of unsaturated diols of type XIV according to one of the methods mentioned above, followed by hydrogenation of the double bond.

Diols of types XIII and XIV in which the symbol R has the meaning mentioned above may be prepared conveniently by condensation of myrcene with either citraconic anhydride and with pyrocinchonic anhydride followed by cyclisation and reduction steps, the sequence of which is of minor importance.



Other attractive starting materials are lactones of types XVII and XVIII which can also be prepared conveniently from myrcene.

Both types of intermediates may be converted into diols of types XIII and XIV by 1-3 steps, illustrated by the following flowsheet (the groups R are either both methyl or hydrogen and methyl)



Some of the steps involved, irrespective of the chosen sequence, give rise to the formation of more than one isomer. This isomerism may have two causes.

- 1st, the position of the methyl group in case one of the substituents R is hydrogen.
- 2nd, conformational factors. Since the final product contains three saturated rings a number of conformational isomers is possible.

It is therefore inevitable that the product obtained by one of the reaction sequences described above consists of a certain number of isomers but since even by distillation in powerful columns no complete separation is possible and since such a distillation yields fractions, all of which possess the typical amber odor, such a distillation has no practical value. It is, however, possible by using pure isomers or stereoisomers of intermediate products as starting materials to obtain pure isomers or stereoisomers of the amber compounds disclosed here.

In this way several of such isomers or stereoisomers have been obtained, some of which are described in the examples. During this work it was noticed that the various isomers or stereoisomers do not all have amber odors of the same intensity.

The invention is illustrated by the following examples. Unless stated otherwise, melting points are corrected, boiling points are uncorrected.

All structural assignments are sustained by elementary analyses. The suffix *a* refers to the products with R=hydrogen and methyl, the suffix *b* to those with both R=methyl.

Example 1

224 g. (2 moles) of citraconic anhydride in dry xylene are heated to reflux temperature (150° C.) and 327 g. of redistilled commercial myrcene (containing about 1.9 moles of pure myrcene) are added dropwise in the course of 25 mins., maintaining reflux without external heating. The mixture is stirred for an additional hour at reflux temperature which at the end of that period is 170° C.

After fractionation through a column of 16 theor. plates the adduct XV is obtained in 90% yield (calcd. on myrcene), B.P. 114°-117° C. at 0.01 mm., *n*_D²⁰ (const.) 1.4950.

The product undoubtedly consists of more than one isomer and/or stereoisomer, as is shown by the inconstant relative densities and relative viscosities throughout the fractionation. One of the constituents is characterized by means of a tetrabromide C₁₅H₂₀O₃Br₄, with melting point 149.7°-150.5° C.

5

248 g. (1 mole) of adduct XV in 248 g. of dry benzene are heated with 25 g. (0.18 mole) of boron trifluoride etherate for 1 hr. 20 mins. at 80–81° C. (reflux). After removal of catalyst and solvent the tricyclic dicarboxylic anhydride formed, XIXa, is fractionated in vacuo to yield 87% of the theory of a product with boiling point 154–157° C. at 0.8 mm., n_D^{20} 1.506–1.509. This material partly crystallizes on standing and a pure isomer of melting point 150.4°–150.7° C. can be isolated (see Example 4).

25 g. (0.65 mole) of lithium aluminum hydride are suspended in 300 ml. of refluxing dry ether in a nitrogen atmosphere and in the course of 2 hrs. 15 mins. a solution of 107 g. (0.43 mole) of anhydride XIXa in 450 ml. of dry ether is added dropwise at such a rate that reflux is maintained without external heating. The reaction mixture is refluxed with stirring for an additional period of 2 hrs. 30 mins. and then worked up.

The diol XIVa is obtained as a viscous oil (mixture of isomers and/or stereoisomers) which is used without purification. Yield 90%, n_D^{20} (approx.) 1.516–1.519.

558 g. (2.4 moles) of this mixture of diol-isomers are dissolved in 1350 ml. of dry benzene, 11 g. of paratoluenesulphonic acid are added and the mixture is refluxed under a Dean-Stark watertrap until no more water separates. After 15 hrs. 39.5 g. of water (about 90% of theory) have collected in the trap.

The reaction mixture is processed and fractionated in vacuum through a column of 16 theor. plates. Trimethyl-decahydronaphthofuran (2,3-c) XXa, is obtained as a mixture of isomers and stereoisomers, boiling range 74–80° C. at 0.05 mm., n_D^{20} 1.502–1.510. All fractions possess a characteristic but relatively weak odor of the amber type.

Similar results are obtained when 18 g. (0.075 mole) of the same diol XIVa are treated with 250 g. of aqueous sulphuric acid (20% vol./vol.) at 108° C. for 4 hours.

133 g. (0.6 mole) of the unsaturated ether XXa are hydrogenated in a stainless steel rocking autoclave in isopropanol as the solvent, with Raney nickel as the catalyst at an initial pressure of 1100 p.s.i. at 125° C. The calculated amount of hydrogen is absorbed in about 15 hrs. At 1500 p.s.i. and at 200° C. the hydrogenation is completed in 10 hrs.

The product is worked up and fractionated through a column of 28 theor. plates. Trimethyl-dodecahydronaphthofuran (2,3-c) XIIa, boiling range 100–110° C. at 0.25 mm. n_D^{20} 1.499–1.495–1.500 is obtained in 96% yield.

All fractions have a strong and tenacious amber odor.

The complete mixture shows the following constants n_D^{20} 1.4980, d_4^{20} 0.9816. G.L.P.C. analysis indicates the presence of at least seven components, four of which occur in minor amounts ($\leq 5\%$ of the total mixture), and three of which are major components, A, B, and C, constituting about 27%, 42% and 18% of the total mixture respectively.

In a series of fractions from the abovementioned fraction (column of 28 plates) with B.P. 101–102° C. at 0.3 mm. n_D^{20} 1.4990 the major constituent A occurs for about 70%, at least four minor peaks showing up in the chromatogram. The major constituent B is found enriched in a series of fractions with B.P. 106–107° C. at 0.3 mm. n_D^{20} 1.4950. These fractions contain about 85% of the isomer B which can be isolated in crystalline form, M.P. 492–50.0° C. by recrystallization from acetone at low temperatures.

Example 2

850 g. (3.6 moles) of a mixture of lactones XVIIa and XVIIIa are treated with 340 g. (14.8 gram-atoms) of finely dispersed sodium in 1800 g. of toluene and 1150 g. (8.7 moles) of diisobutyl carbinol for 4 hrs. 30 mins. at reflux temperature (110°–115° C.). After working up, a 90% yield of a mixture of isomers of the diol XIIIa is

6

obtained as a viscous oil, hydroxyl assay 80%, which is used without purification.

1080 g. (4.5 moles) of diol mixture and 100 g. of potassium hydrogensulphate are slowly heated to 150° C. in a vacuum of 25 mm. Hg, water being collected in a cold trap. After 1 hr. the distillation of water comes to an end (65 ml., 80%, of water is collected).

The pressure is decreased to 3 mm. Hg and the product is flash distilled; residue 220 g. The material obtained has a residual hydroxyl assay of 0.2%, and is fractionated through a Vigreux column of 28 theor. plates. A mixture of isomers and stereoisomers of trimethyl-dodecahydronaphthofuran (2,3-c), XIIa, boiling range 94–103° C. at 0.2 mm., n_D^{20} 1.4990–1.4967–1.5000, is obtained in 91% yield. The total mixture has n_D^{20} 1.4986, d_4^{20} 0.9824, and shows a strong and lasting amber odor.

Exactly the same results are obtained when the dehydration is carried out with the aid of paratoluenesulphonic acid catalyst in refluxing benzene, according to the method described in Example 1, or by leading the vapors, diluted with dry nitrogen, at a pressure of 10–20 mm. through a horizontal tube partly filled with 25 g. of activated alumina and heated to a temperature of 260° to 280° C. by means of an electric oven. G.L.P.C. of the complete mixture shows the presence of at least seven components, all of which are presumably identical to those described in Example 1, be it in a somewhat different ratio. The four minor constituents comprise together about 22% of the mixture, the three major components A, B and C occur in amounts of approx. 32%, 28% and 18% resp.

In a series of fractions from the abovementioned fractionation with boiling point 94°–96° C. at 0.2 mm., n_D^{20} (const.) 1.4990 the constituent A occurs for about 70%, at least four minor peaks showing up in the chromatogram.

The component B is enriched in a group of fractions with boiling point 100°–101° C. at 0.2 mm., n_D^{20} 1.4968, of which it constitutes about 70%. It may be isolated by recrystallization from acetone to yield a crystalline isomer of M.P. 49.1°–49.9° C. which proves identical with the corresponding material described in Example 1 (no depression of mixed melting point).

Example 3

From the adduct of myrcene and citraconic anhydride XV, obtained as described in Example 1 a di-carboxylic acid of M.P. 127.8–128.3° can be isolated by repeated crystallizations from aqueous acetic acid.

By treatment of this acid with boron trifluoride etherate, in the way described in Example 1 the corresponding bicyclic dicarboxylic acid M.P. 218–222° C. (uncorr.) is obtained in a relatively small yield.

The same compound is obtained in 53% yield when 42 g. (0.16 mole) of adduct XV are refluxed with 200 ml. of 20% hydrochloric acid for 15 hrs. After recrystallization from ethyl acetate a pure compound, M.P. 224.8–225.5° C. is obtained. No depression is caused by admixture with the compound described in the preceding section.

The same compound is also obtained when 62 g. (0.25 mole) of tricyclic anhydride XIXa are refluxed with 300 ml. of 20% hydrochloric acid for 15 hrs. In 64% yield a product with M.P. 224.6–225.5° C, identical to that described above, is obtained.

By reduction with lithium aluminum hydride according to the method described in Example 1, but in tetrahydrofuran as the solvent, the bicyclic dicarboxylic acid is converted into the corresponding diol XIVa, obtained as a viscous oil in practically quantitative yield. From this material a pure isomer of M.P. 112.4–112.8° C. can be isolated.

2.7 g. of this crystalline diol are heated with 0.27 g. of potassium hydrogensulphate as described in Example 2. After working up, trimethyl-decahydronaphthofuran

(2,3-c) XXa, M.P. 57.9–58.9° C. is obtained. This isomer is practically odorless.

The crystalline unsaturated ether cannot be hydrogenated with Adams' catalyst slightly above atmospheric pressure, but after treatment with hydrogen at an initial pressure of 1400 p.s.i. at 160° C. in a stainless steel rocking autoclave, with Ruthenium on carbon catalyst, for 6 hrs., trimethyl-dodecahydronaphthofuran (2,3-c) of M.P. 49.7–50.2° C., identical to the corresponding compound described in Examples 1 and 2, is obtained. This compound has a pronounced amber odor.

Example 4

From the tricyclic anhydride XIXa, obtained as described in Example 1, a crystalline isomer M.P. 150.4–150.7° C. can be isolated. Upon recrystallization from aqueous acetic acid the corresponding bicyclic dicarboxylic acid, M.P. 190.8–192.5° C. (dec.) is obtained.

7.5 g. (0.03 mole) of crystalline anhydride XIXa in 25 ml. of tetrahydrofuran are slowly added to a refluxing solution of 1.7 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran. After refluxing for 6 hrs. 30 mins. the mixture is worked up. In practically quantitative yield a crystalline diol XIVa, M.P. 123.6–124.3° is obtained.

3 g. (0.012 mole) of this diol are dehydrated by treatment with 0.3 g. of potassium hydrogensulphate as described in Example 2. The trimethyl-decahydronaphthofuran (2,3-c) XXa thus obtained in practically quantitative yield has M.P. 67.4–67.9° C.

1 g. (4.5 millimoles) of crystalline unsaturated ether is hydrogenated in acetic acid at room temperature over 0.15 g. of Adams' catalyst at a pressure slightly above atmospheric. The trimethyl-dodecahydronaphthofuran (2,3-c) XIIa obtained in practically quantitative yield, is the crystalline isomer already described in Examples 1, 2 and 3, M.P. 49.2–50.0° C.

Example 5

From the mixture of isomers of the lactone of structure XVIIa and XVIIIa a crystalline isomer with M.P. 162.0–162.4° C. can be isolated.

5 g. (0.02 mole) of this crystalline lactone were converted into the corresponding diol by treatment with 0.62 g. (0.016 mole) of lithium aluminum hydride in 30 ml. of tetrahydrofuran at reflux temperature for 5 hrs. After working up in the usual way a crystalline material was obtained in quantitative yield. The pure compound had a melting point of 77.8–78.7° C. and elementary analysis proved it to be a complex of a diol of structure XIIIa with tetrahydrofuran (mole ratio 1:1).

4 g. of crude diol-tetrahydrofuran complex were heated with 0.4 g. of potassium hydrogensulphate as described in Example 2. The oily material obtained in this way solidified upon cooling in an acetone-Dry Ice mixture. After recrystallization from acetone it showed a melting point of 40.7–41.4° C. (considerable depression on admixture with the compound of melting point 49.2–50.0° C.). The new compound has a strong and lasting amber odor.

Example 6

By saponification of 60 g. (0.24 mole) of adduct XV with 200 ml. of 10% sodium hydroxide, for 1 hr. at reflux temperature, working up in the usual way and recrystallization of the product from 1-nitropropane, ethyl formate and acrylonitrile a pure isomer of the corresponding dicarboxylic acid melting point 140.7–141.7° C. is obtained.

By treatment of this dicarboxylic acid with boron trifluoride etherate according to the method described in Example 1, a tricyclic anhydride XIXa of melting point 102.1–103.1° is obtained.

The same tricyclic anhydride is obtained in the following way.

125 g. (0.5 mole) of adduct XV are dissolved in 125 g. of dry benzene and this solution is cooled to –5° C. A slow stream of boron trifluoride is introduced from a cylinder. After several minutes the reaction starts suddenly and the temperature rises to 45° C. The introduction of BF₃ is interrupted to allow the mixture to cool to 25° C., and is then resumed until the mixture is saturated, total weight increase 24.5 g. The mixture is stirred for another 2 hrs. at room temperature, water is added and the mixture is processed in the usual way. The crystalline isomer of the tricyclic anhydride XIXa, with melting point 102–103° C. is obtained in about 70% yield.

The tricyclic anhydride XIXa is reduced by means of lithium aluminum hydride in tetrahydrofuran as described in Example 4, to give a crystalline diol XIVa of M.P. 92.6–93.1° C. in practically quantitative yield.

1.5 g. of this diol are dehydrated by heating with potassium hydrogensulphate according to the method described in Example 2. The trimethyl-decahydronaphthofuran (2,3-c) XXa, obtained in quantitative yield shows n_D^{20} 1.5001.

The unsaturated ether thus obtained is hydrogenated with Adams' catalyst, in acetic acid at room temperature. The hydrogenation is complete in 11 hrs. 30 mins. After elimination of the solvent, the trimethyl-dodecahydronaphthofuran (2,3-c) XIIa is obtained as an oil, n_D^{20} 1.4960.

G.L.P.C. analysis of this oil indicates the presence of at least four of the seven isomers referred to in Examples 1 and 2. The major component, different from the constituents A, B and C of the mixtures referred to in the forementioned examples, constitutes about 60% of the total mixture.

Example 7

163 g. (1.2 moles) of commercial myrcene are heated with 126 g. (1 mole) of pyrocinchonic anhydride in 100 g. of propionic acid for 16 hrs. at 143° C. The reaction product is purified by distillation. About 50 g. of pyrocinchonic anhydride are recovered and a product of structure XVI is obtained in nearly quantitative yield. Boiling point 114–117° C. at 0.05 mm.; n_D^{20} (const.) 1.4933.

209 g. (0.8 mole) of XVI are refluxed with 20 g. (0.14 mole) of boron trifluoride ether complex in 200 g. of dry benzene for 2 hrs. The anhydride XIXb is obtained as a viscous oil which solidifies partly on standing. Yield 90% of the theoretical. The crystalline isomer has a melting point of 90.1–90.7° C.

145 g. (0.55 mole) of the tricyclic anhydride XIXb are without previous purification treated as described in Example 1 with 42 g. (1.1 moles) of lithium aluminum hydride in 400 ml. of dry ether. The diol of structure XIVb, a mixture of isomers and stereoisomers is obtained as a viscous oil. Yield 98% of the theoretical. A pure isomer, M.P. 126.8–127.5° C. can be isolated.

139 g. (0.55 mole) of the diol XIVb are refluxed in 150 ml. of dry benzene with 3 g. of p-toluene sulphonic acid under continuous azeotropic removal of the water formed during the reaction until no more water is collected. The reaction product is worked up and fractionated through a column of 16 theoretical plates.

93 g. (73% of the theory) of fractions, boiling range 92–106° C. at 0.2 mm., n_D^{20} 1.5007–1.5096, all of which have an odor of the amber type, are obtained.

The values obtained by elementary analysis of head, heart and tail cuts from this fractionation agree well with those calculated for tetramethyldecahydronaphthofuran (2,3-c). The product undoubtedly is a mixture of 75 isomers.

90 g. (0.38 mole) of this mixture are dissolved in 400 ml. of isopropyl alcohol and hydrogenated in a stainless steel rocking autoclave in the presence of Raney nickel at an initial pressure of 1850 p.s.i. at 205° C.

The reaction mixture is processed and the product is again carefully fractionated.

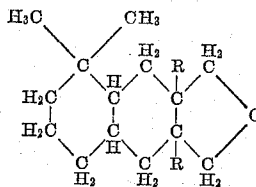
Tetramethyldodecahydronaphthofuran (2,3-c), XIIb, boiling point 120–124° C. at 0.6 mm., n_D^{20} 1.4970–1.4990 has a distinct amber odor, weaker but more tenacious than the trimethyl analogue XIIa.

A group of fractions from the above distillation partly solidify. After recrystallization a pure isomer of structure XIIb, melting point 53.1–53.7° C. is isolated.

What is claimed is:

New saturated tricyclic ethers with amber odor having

the structure



10 in which R is selected from the group consisting of hydrogen and methyl and at least one R is methyl.

References Cited in the file of this patent

Hinder et al.: *Helv. Chim. Acta*, vol. 33 (1950), pp.

1308–1312.

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

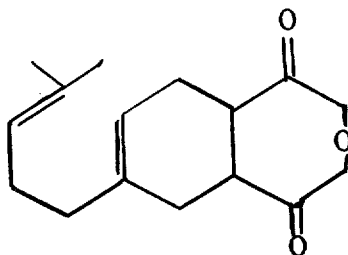
Patent No. 3,045,028

July 17, 1962

Robert Enninga et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, lines 57 to 63, the formula numbered "V" should appear as shown below instead of as in the patent:



column 2, line 5, for "posses" read -- possess --; columns 3 and 4, above the bracket, for "XVII", second occurrence, read -- XVIII --; column 5, lines 58 and 59, for "fraction" read -- fractionation --; line 66, for "492-" read -- 49.2- --; line 73, for "dlisobutyl" read -- diisobutyl --.

Signed and sealed this 20th day of November 1962.

(SEAL)

Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of
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