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STUDIES IN SESQUITERPENES—XXIV

SYNTHESIS OF (±)-CADINENE DIHYDROCHLORIDE*

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Abstract—A total synthesis of (±)-4-isopropyl-*trans*-decalin-1,6-dione, a key intermediate in the cadinane series, and its conversion into (±)-cadinene dihydrochloride, is reported.

THE cadinene class of sesquiterpenoids which are fairly widely distributed in nature,[1] are characterized by their ability to furnish crystalline cadinene dihydrochloride on interaction with hydrogen chloride, a reaction first reported by Soubeiran and Capitaine[2] and used for detecting cadinene sesquiterpenes in essential oils. Although the majority of cadinene sesquiterpenes yield (—)-cadinene dihydrochloride in this reaction, the formation of (+)-cadinene dihydrochloride[3-6] and (±)-cadinene dihydrochloride[7,8] has also been reported.

Of the nine theoretically possible cadinenes[9,13] (dienes, $C_{15}H_{24}$) six (I–VI) have

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* An advance communication appeared in *Tetrahedron Letters* No. 27, 27 (1960). Since publication of this work, a synthesis of (+)-4-isopropyl-*trans*-decalin-1,6-dione has been reported: M. D. Soffer, G. E. Gunay, O. Korman and M. B. Adams, *Tetrahedron Letters* 389 (1963).

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[1] E. Gildmeister and F. Hoffmann, *Die Atherischen Öle* (4th Edition revised by W. Triebs and D. Merkel) Vol. IIIa, p. 248. Akademie-Verlag, Berlin (1960); 4th Edition (Revised by D. Merkel) Vol. IIIb, p. 256. Akademie-Verlag, Berlin (1962). The name cadinene was first used by O. Wallach [*Liebigs Ann.* **271**, 297 (1892)] for the chief sesquiterpene constituent of the 'oil of cade'.

[2] E. Soubeiran and H. Capitaine, *Liebigs Ann.* **34**, 323 (1840).

[3] Y. Sebe, *J. Chem. Soc. Japan* **61**, 1269 (1940).

[4] A. J. Birch, *J. Chem. Soc.* 715 (1953).

[5] A. S. Rao, K. L. Surve, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* **19**, 233 (1963).

[6] C. C. Kartha, P. S. Kalsi, A. M. Shaligram, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* **19**, 241 (1963).

[7] R. O. Hellyer and H. H. G. McKern, *Austral. J. Chem.* **9**, 547 (1956).

[8] R. P. Hildebrand and M. D. Sutherland, *Austral. J. Chem.* **12**, 678 (1959).

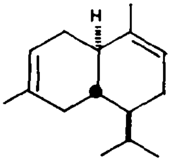
[9] Sukh Dev and P.C. Guha, *J. Indian Chem. Soc.* **26**, 263 (1949). This does not take into account the the optical antipodes or the (±)-modifications.

[10] V. Herout and V. Sykora, *Tetrahedron* **4**, 246 (1958). The so called ε-cadinene has been found[11] to possess *cis*-ring fusion and has been identified as ε-muurolene; however the preparation of ε-cadinene from (−)-cadinene dihydrochloride has been described.[11]

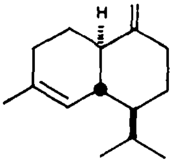
[11] L. Westfelt, *Acta Chem. Scand.* **18**, 572 (1964).

[12] In view of the isolation of muurolenes,[11] it must be emphasized that the fact that a bicyclic sesquiterpene gives cadinene dihydrochloride, is no guaranty that it must have cadinenic framework, as inversion could occur during treatment with hydrochloric acid, as has been found to be the case with ε-muurolene.

been reported.[6,10,12] Likewise, two (VII, VIII) cadinols (mono olefinic t-alcohols, $C_{15}H_{26}O$) of the twelve possible,[13] have been isolated and their structures established.[10,14,15] The absolute stereochemistry (as depicted in I–VIII) of these compounds is based on (−)-cadinene dihydrochloride (IX), which has been established unambiguously.[16,17]



I



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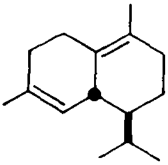

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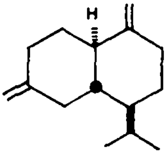

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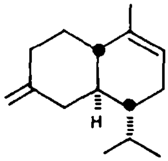
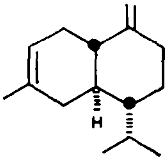


V



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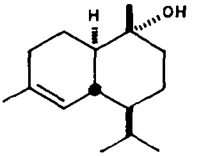
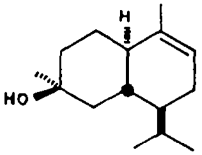
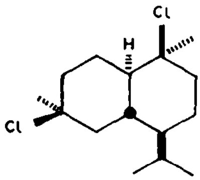


VII



VIII



IX

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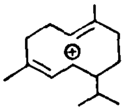
[13] This does not imply that all these are equally probable biogenetically. The biogenesis of cadinenic sesquiterpenes may as well be proceeding through the cation (A) [P. de Mayo, J. R. Robinson, E. Y. Spencer and R. W. White, *Experientia* **18**, 359 (1962)] rather than through an initial 1,6-cyclization of the farnesol chain, as suggested earlier [L. Ruzika **9**, 357 (1953); *Proc. Chem. Soc.* 341 (1959)].



(A)

[14] M. D. Soffer, M. Brey and J. Fournier, *J. Amer. Chem. Soc.* **81**, 1678 (1959).

[15] W. G. Dauben, B. Weinstein, P. Lim and A. B. Anderson, *Tetrahedron* **15**, 217 (1961).

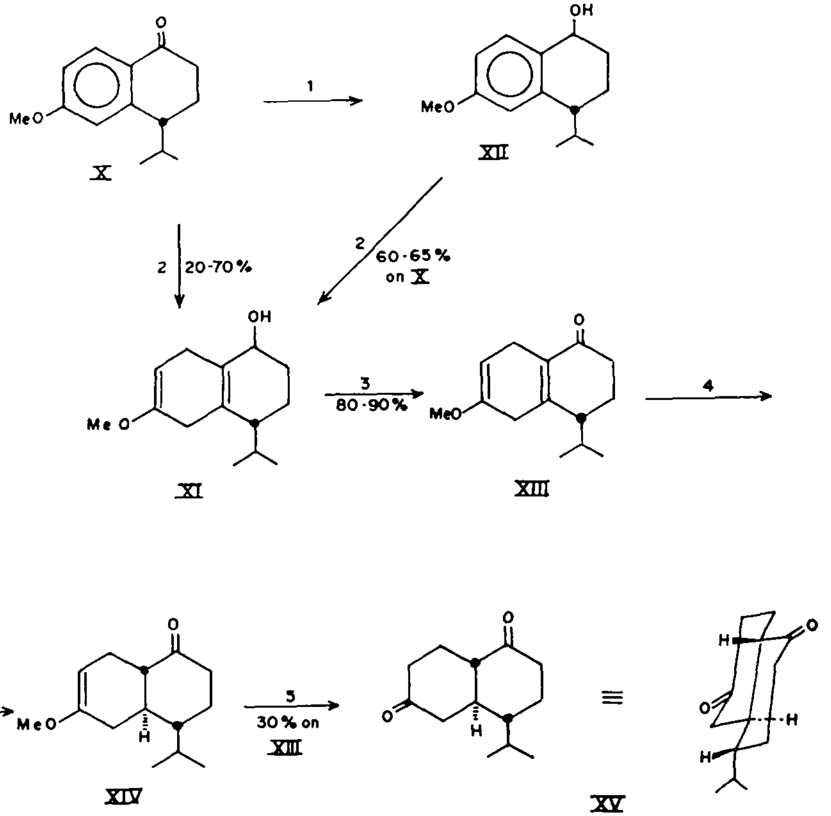
[16] F. Hanic, *Chem. Listy.* **52**, 165 (1958).

[17] V. Sykora, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2181 (1958).

A survey of these structures reveal that the dione XV should occupy a key-position in the synthesis[18] of these compounds. The levorotatory antipode of XV has been obtained by Herout and Santavy[19] as a degradation product of "ε-cadinene".[10]

(±)-4-*Isopropyl*-trans-*decalin*-1,6-*dione* (XV)

The route successfully developed for the sythesis of XV is outlined in Fig. 1. Birch reduction of 4-isopropyl-6-methoxytetralone (X)[20,21] with sodium in liquid



Reagents: 1, LAH
2, Na, liq.NH$_3$, EtOH
3, Al(OPr^i)$_3$, acetone
4, Li, liq.NH$_3$
5, aq. dioxan–HCl

Fig. 1.

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[18] Several unsuccessful attempts at the synthesis of β-cadinene (I) have been recorded: J. C. Bardhan and S. K. Banerjee, *J. Chem. Soc.* 476 (1935); S. M. Mukherji and P. B. Talukdar, *Sci. and Culture* 225 (1951); J. K. Roy, *Ibid.* 266 (1953). Condensation of cryptone and isoprene was investigated by G. S. Krishna Rao (Ph.D. Thesis, pp. 106–123, Bombay University (1955), but since the yield of the adduct was very small, this route, which could have led to a synthesis of β-cadinene, was not pursued further.

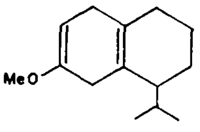
[19] V. Herout and F. Santavy, *Coll. Czech. Chem. Comm.* **19**, 118 (1954).

[20] G. S. Krishna Rao and Sukh Dev, *J. Indian Chem. Soc.* **34**, 255 (1957).

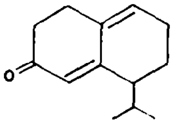
[21] J. C. Bardhan and D. N. Mukherji, *J. Chem. Soc.* 4629 (1956).

ammonia–ethanol gave the desired compound XI, but in variable[22] yields (20–70%); the chief by-product being the hydrogenolysis product XVI. However, consistent 60–65% yields of XI could be obtained by first reducing the tetralone (X) to 4-isopropyl-6-methoxytetralol (XII) with LAH and then subjecting the crude tetralol to Birch reduction, as above.[23] The assignment of structure XI to the product of Birch reduction is supported by its spectral characteristics (UV spectrum: no maximum in the 220–300 mμ region; IR spectrum: OH 3333 cm^{-1}) and its reaction with 2,4-dinitrophenylhydrazine, when a deep red 2,4-dinitrophenylhydrazone ($\lambda_{max}^{CHCl_3}$ 402 mμ, ε 30,000), evidently, derived from XVII was obtained.

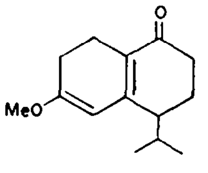
Oxidation of XI to the ketone (XIII) proved quite elusive; with pyridine–chromic acid[24] or active manganese dioxide[25] the tetralone (X) was quantitatively regenerated. Oppenauer oxidation of XI with aluminium isopropoxide in acetone–toluene,[23] under essentially identical conditions, gave either the required XIII (λ_{max}^{EtOH} 238 mμ, ε 6900, 241 mμ, ε 7000) or the fully conjugated XVIII (λ_{max}^{EtOH} 339 mμ, ε 9300), or a mixture of both. Attempted separation of XIII and XVIII in a mixture, on a column of alumina led to complete isomerization and yielded fully conjugated dienone XVIII.



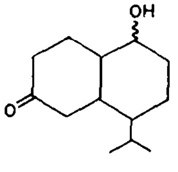
XVI



XVII



XVIII



XIX

The dienone (XIII) was reduced with lithium in liquid ammonia and the resulting crude enol-ether monoketone (XIV), which was expected because of mechanistic considerations[26] to possess the *trans*-ring fusion, was treated with aqueous hydrochloric acid to furnish the required (±)-4-isopropyl-*trans*-decalin-1,6-dione (XV). The IR spectrum of the product was identical,[27] in all respects, with that of the

[22] It is conceivable that some trace impurities present in the liquid ammonia, which was used directly from the cylinder, affected the results in an unpredictable manner: cf. H. L. Dryden, G. M. Webber, R. R. Burtner and J. A. Cella, *J. Org. Chem.* **26**, 3237 (1961).

[23] A. J. Birch, J. A. K. Quartey and H. Smith, *J. Chem. Soc.* 1768 (1952).

[24] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

[25] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).

[26] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.* 3045 (1954); A. J. Birch, H. Smith and R. E. Thornton, *Ibid.* 1339 (1957); H. E. Zimmerman, *J. Amer. Chem. Soc.* **78**, 1168 (1956); G. Stork and S. D. Darling, *Ibid.* **82**, 1512 (1960); **86**, 1761 (1964).

[27] M. V. R. Koteswara Rao, G. S. Krishna Rao and Sukh Dev, *Tetrahedron Letters* No. 27, 27 (1960).

(−)-diketone of Herout and Santavy,[19] thus proving that the synthetic diketone has the required stereochemistry.

In an effort to simplify the synthesis of XV from X, a few experiments employing lithium–amine as the reducing system were carried out. Following the work of Benkeser *et al.*[28] reduction of X with lithium in ethylamine was hoped to furnish, after acid work-up, the keto-alcohol (XIX). However, only a complex mixture of products resulted. Likewise, reduction of 6-hydroxy-4-isopropyltetralone with lithium in ethylenediamine,[29] or lithium in ethylenediamine-morpholine,[30] yielded only small amounts of a non-phenolic product and was not studied further.

(±)-*Cadinene dihydrochloride* (DL-IX)

The synthetic diketone on interaction with excess methyl-lithium yielded a glycol as a gum which on further treatment with hydrogen chloride in ether solution readily gave crystalline (±)-cadinene dihydrochloride, m.p. 105–106°. This compound has been prepared from natural (±)-δ-cadinene,[31] and an authentic sample (m.p. 105–106°) did not depress the m.p. of the synthetic material and both exhibited identical IR spectra and, single crystal rotation and Weissenberg photographs (CuK_α radiation).[32]

It is hoped to report, later, the conversion of the diketone (XV) into several cadinenic sesquiterpenoids.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet. ether refers to the fraction b.p. 40–60°. IR spectra were taken on a Perkin–Elmer infracord, model 137B. UV spectra, unless otherwise stated, were determined in 95% EtOH on a Beckman DU spectrophotometer.

1,2,3,4-*Tetrahydro-7-methoxy-*1*-isopropylnaphthalene*

This tetralin[30] was more conveniently prepared according to Bardhan and Mukherji,[31] with the following modification. The hydrogenation of isobutyl 4-methoxystyryl ketone (50 g) with Pd–$CaCO_3$ catalyst[33] (2%; 4·0 g) in EtOH (25 ml) at room temp and press, selectively reduced the olefinic linkage to isobutyl 4-methoxyphenylethyl ketone (b.p. 155°/3 mm, n_D^{24} 1·5020) in over 85% yield.

4-*Isopropyl-6-methoxytetralone*-1 (X)

Oxidation of the above tetralin to X was carried out with $Na_2Cr_2O_7$ in AcOH and benzene, as described previously.[30] IR spectrum (liquid): C=O 1681; aromatic ring 1600, 1567 cm^{-1}. *The* 2,4-*dinitrophenylhydrazone* was obtained from AcOH as dark red plates, m.p. 190–191° (Lit. 202–202·5°,[30] 187°[31]). The *semicarbazone* was crystallized from dil alcohol to furnish a crystalline powder, m.p. 180–181° (Lit. 163°[30], 185–186°[31]).

1,2,3,4,5,8-*Hexahydro*-1-*hydroxy-4-isopropyl-6-methoxynaphthalene* (XI)

(i) *Birch reduction of tetralone* (X). Sodium (10·4 g, 0·45 g atom) in small pieces was added during 30 min to a stirred solution of 4-isopropyl-6-methoxytetralone (10·9 g, 0·05 mole) in dry EtOH (100 ml) and liq. ammonia (350 ml). The stirring was continued till practically all the ammonia had

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[28] R. A. Benkeser, C. Arnold, R. F. Lambert and O. H. Thomas, *J. Amer. Chem. Soc.* **77**, 6042 (1955).

[29] L. Reggel, R. A. Friedel and I. Wender, *J. Org. Chem.* **22**, 891 (1957).

[30] R. A. Benkeser, R. K. Agnihotri and M. L. Burrows, *Tetrahedron Letters* No. 16, 1 (1960).

[31] R. O. Hellyer and H. H. G. McKern, *Austral. J. Chem.* **9**, 547 (1956); R. P. Hildebrand and M. D. Sutherland, *Ibid.* **12**, 678 (1959).

[32] This comparison was made in the Physics department, Indian Institute of Science, Bangalore, by the kind courtesy of Prof. S. Ramaseshan and Dr. N. V. Mani [N. V. Mani, *Z. für Kristallogr.* **118**, 103 (1963)].

[33] M. Busch and K. Schulz, *Ber. Dtsch. Chem. Ges.* **62**, 1458 (1929).

evaporated (~ 3 hr). The product was diluted with water (300 ml), extracted with ether (30 ml × 5) and the combined extracts washed with brine (10 ml × 3) and dried (K_2CO_3). The solvent was flashed off under suction through a column from a water-bath and the residue fractionated to give two cuts: (a) b.p. 67–135°/0·6 mm, yield 3·3 g, and (b) b.p. 134–136°/0·6 mm, n_D^{26} 1·5260, yield 7·2 g.

Fraction (a) on further rectification gave 1-*isopropyl-7-methoxy*-1,2,3,4,5,8-*hexahydronaphthalene* (XVI) as a colourless liquid, b.p. 105°/8 mm, n_D^{26} 1·5015, yield 32%. (Found: C, 81·28; H, 10·98. $C_{14}H_{22}O$ requires: C, 81·50; H, 10·75%.)

Fraction (b) was the required compound XI. (Found: C, 75·53; H, 9·82. $C_{14}H_{22}O_2$ requires: C, 75·68; H, 9·91%.) The product readily furnished a 2,4-*dinitrophenylhydrazone* on interaction with ethanolic 2,4-dinitrophenylhydrazine sulphate as deep red needles (AcOH), m.p. 185–186°. (Found: N, 15·03. $C_{19}H_{22}O_4N_4$ requires: N, 15·13%.)

The yield of XI was variable in several experiments. The product, which is a colourless very viscous liquid is sensitive to air and may be stored for a while under N_2 at 0°.

(ii) *Birch reduction of tetralol* (XII). 4-Isopropyl-6-methoxytetralone (2·2 g) in dry ether (15 ml) was added (15 min) to a slurry of LAH (0·26 g) in ether (20 ml) at 0°. After stirring for 4 hr at room temp (~25°), the excess reagent was destroyed by the cautious addition of ice-water and the complex decomposed with 20% sodium potassium tartrate aq (100 ml). The tetralol was obtained as a viscous liquid (2·2 g) which was used as such in the next step. Attempted distillation of the crude product led to extensive dehydration to furnish, after further rectification, 1-*isopropyl-7-methoxy*-1,2-*dihydronaphthalene* as a colourless liquid, b.p. 103°/0·8 mm, n_D^{27} 1·5660, λ_{max}^{EtOH} 271 mμ (ε 11,600). (Found: C, 83·33; H, 8·55. $C_{14}H_{18}O$ requires: C, 83·12; H, 8·97%.)

The crude tetralol (11 g) was reduced with Na (10·0 g) in dry EtOH (100 ml) and liquid ammonia (350 ml) as described under (i) and worked up in a similar manner to give XI.

Oppenauer oxidation of 1,2,3,4,5,8-*hexahydro*-1-*hydroxy*-4-*isopropyl*-6-*methoxynaphthalene*

A solution of XI (6·0 g, 0·027 mole) in dry toluene (30 ml) and dry acetone (18 ml) containing freshly distilled aluminium isopropoxide (1·0 g, 0·005 mole) was gently refluxed under N_2 for 4½ hr. To the cooled reaction mixture, water (60 ml) was added and the product containing suspended $Al(OH)_3$ was extracted as such with ether (60 ml × 5). The extracts were washed with brine (50 ml × 2) and dried (K_2CO_3). The solvent was flashed off and the residue fractionated. After a small fore-run (b.p. 60–130°/0·7 mm, 0·15 g) the desired product, 1,2,3,4,5,8-*hexahydro*-1-*oxo*-4-*isopropyl*-6-*methoxynaphthalene* (XIII) was collected as a colourless, viscous liquid, b.p. 138–140°/0·7 mm, n_D^{29} 1·5280, yield 5·8 g. IR spectrum (liquid): C═O 1679; C═C 1658, 844; C—O 1212 cm^{-1}. (Found: C, 75·74; H, 9·21. $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%.)

The *bis*-2,4-*dinitrophenylhydrazone* was readily prepared from XIII by the H_2SO_4 method, and after recrystallization from AcOEt–alcohol was obtained as deep red prisms, m.p. 198–199°. (Found: N, 19·67. $C_{26}H_{26}O_8N_8$ requires: N, 19·79%.) The *dioxime* (AcONa method) separated from dioxan as a powder, m.p. 215–217°. (Found: N, 12·25. $C_{13}H_{20}O_2N_2$ requires: N, 11·87%.)

Compound XIII (0·5 g) in pet. ether (5 ml) was passed through a column of alumina (Basic/I, 10 g) and after rejecting the first 10 ml of eluate (pet. ether), the next 60 ml (pet. ether–benzene; 1:1) was separately collected. This on removal of solvent and distillation gave the isomeric 1,2,3,4,7,8-*hexahydro*-1-*oxo*-4-*isopropyl*-6-*methoxynaphthalene* (XVIII): b.p. 130–134°/0·5 mm, n_D^{26} 1·5605, yield 0·3 g; λ_{max}^{EtOH} 339 mμ (ε 9,130). (Found: C, 75·90; H, 9·00. $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%.) Sometimes, this isomerization took place during the Oppenauer oxidation itself.

4-*Isopropyl*-trans-*decalin*-1,6-*dione* (XV)

A solution of XIII (1·5 g, 0·0052 mole) in dry ether (60 ml) was added during 5 min to a stirred solution of Li (0·3 g, 0·043 g atom) in liquid ammonia (500 ml) the blue colour persisting for about 15 min. After stirring for another 20 min, NH_4Cl (6 g) was slowly added and the reaction mixture stirred till all ammonia disappeared (~3 hr). After adding water (200 ml) the product was taken up in ether (25 ml × 5), which was washed with water (20 ml) and dried (K_2CO_3). Removal of the solvent under suction at room temp yielded a viscuous liquid (chiefly XIV, ε_{241} ~ 500) which was used as such in the next step.

The above product (3·0 g) was mixed with dioxan (90 ml) and 6N HClaq (11 ml) and stirred at 10 ± 2° for 2 hr. The reaction mixture was diluted with water (300 ml) and extracted with ether

(20 ml × 6). The extracts were washed with brine and dried ($NaSO_4$). Removal of solvent yielded a gum, which on trituration with pet. ether and chilling gave a solid (1 g), which was recrystallized from benzene–pet. ether to furnish colourless fine needles, m.p. 71–71·5°, λ_{max}^{EtOH} 286 mμ (ε 53), $\nu_{C=O}^{CCl_4}$ 1710 cm^{-1}. (Found: C, 74·78; H, 10·00. $C_{13}H_{20}O_2$ requires: C, 74·96; H, 9·68%.)

The *bis-2,4-dinitrophenylhydrazone* (H_2SO_4 method) crystallized from $CHCl_3$–EtOH to give yellow soft needles, m.p. 206–207°. (Found: N, 19·38. $C_{25}H_{28}O_8N_8$ requires: N, 19·71%.) The *dioxime* was prepared by the AcONa method and, after recrystallization from alcohol–pet. ether was obtained as colourless needles, m.p. 205–206°. (Found: N, 11·80. $C_{13}H_{22}O_2N_2$ requires: N, 11·76%.)

4-Isopropyl-6-hydroxy-tetralone-1

A mixture of 4-isopropyl-6-methoxy-tetralone-1 (3·1 g) and pyridine hydrochloride (64 g) was heated (N_2) at 195–200° for 1 hr. The reaction mixture was cooled, diluted with ice-water (50 ml) and dil HClaq (1:2, 300 ml). The product was taken up in ether (30 ml × 4), which was extracted with 8% NaOHaq (30 ml × 5). From the alkaline extracts when acidified with HClaq a gum separated, which was taken up in ether and worked up to furnish the phenol ketone as a gum (3·0 g). This was purified by evaporative distillation (~170°/0·05 mm) yielding a pale yellow glass; λ_{max}^{EtOH} 228, 286 and 338 mμ (ε 13,300; 14,510; 4,232 respectively). IR spectrum ($CHCl_3$): OH 3226; C=O 1645; aromatic ring 1585, 1560 cm^{-1}. (Found: C, 76·00; H, 7·80. $C_{13}H_{16}O_2$ requires: C, 76·44; H, 7·90%.)

The 3,5-*dinitrobenzoate* (pyridine method) crystallized from alcohol to give needles, m.p. 115–116°. (Found: N, 7·08. $C_{20}H_{18}O_7N_2$ requires: N, 7·03%.)

(±)-*Cadinene dihydrochloride*

Compound XV (0·260 g) in dry ether (50 ml) was added during 30 min to an EtOH solution of MeLi (from 0·05 g Li, 40 ml ether and 0·5 ml MeI in 30 ml ether) at 0°. The reaction mixture was left at room temp overnight (15 hr) and then refluxed for 45 min. The complex was decomposed with 5% NH_4Claq (20 ml) and the product taken up in ether (30 ml × 5), and the extracts washed with brine (20 ml × 2) and dried (Na_2SO_4). Removal of solvent yielded a gum, which was taken up in dry ether (5 ml) and saturated with HCl at −10°. The reaction mixture was kept at this temp for 5 hr, after which the solvent was removed under suction in a current of dry air. The residual solid was crystallized from AcOEt to give colourless needles, m.p. 105–106°, yield 70 mg; mixed m.p. with an authentic sample of (±)-cadinene dihydrochloride (m.p. 105–106°) remained undepressed. (Found: C, 65·50; H, 9·55. $C_{15}H_{26}Cl_2$ requires: C, 65·01; H, 9·39%.)

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