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MACROCYCLIC MUSK COMPOUNDS—IX*

NEW SYNTHESES OF CYCLOHEXADECENONE AND CYCLOHEXADECANONE FROM ALEURITIC ACID

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Abstract—Hexadec-7-enedioic acid and the corresponding saturated acid have been prepared from aleuritic acid in good yield and subsequently cyclized to the respective acyloins, which in the form of acetates were reduced with calcium in liquid ammonia to furnish cyclohexadecenones and cyclohexadecanone respectively, along with the related mono-alcohols and 1,2-diols.

MACROCYCLIC ketones having sixteen carbon atoms in the ring have not been found to occur in nature. It may be therefore, that less attention has been paid to the syntheses of cyclohexadecenone and the corresponding saturated ketone, both possessing musk odour. After the pioneering synthesis of macrocyclic ketones by Ruzicka,[1] Blomquist prepared cyclohexadec-8-ene-1-one[2] and cyclohexadecanone[3] starting from cyclohexadecane-1,9-dione. Stoll[4] has employed the acyloin condensation for the preparation of cyclohexadecanone which was also obtained by Tong.[5] Various syntheses have been reported for hexadecanedioic acid.[6]

In this paper we report practical syntheses of diethyl *trans*-hexadec-7-enedioate and diethyl hexadecanedioate,[7] and their subsequent cyclization to the corresponding macrocyclic ketones. The reactions are summarized in the chart.

7,8-Dihydroxyhexadecanedioic acid[8] (III) has been prepared from aleuritic acid and then hydrobrominated, esterified and debrominated[9] to yield diethyl *trans*-hexadec-7-enedioate (V), which on hydrogenation furnished diethyl hexadecanedioate (XI). The diesters were cyclized to the acyloins, the acetates of which were reduced with calcium in liquid ammonia and the reaction products were resolved by column chromatography.[9] As the musk odour is not influenced by the position of the olefinic bond in the macrocyclic ring, the two cyclohexadecenones (VIII) will have

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[1] L. Ruzicka, M. Stoll, W. Scherrer, H. Schinz and C. F. Seidel, *Helv. Chim. Acta* **15**, 1459 (1932); L. Ruzicka, M. Stoll and H. Schinz, *Ibid.* **9**, 249 (1926).

[2] A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.* **77**, 5423 (1955).

[3] A. T. Blomquist, J. Prager and J. Wolinsky, *J. Amer. Chem. Soc.* **77**, 1804 (1955).

[4a] M. Stoll, *Helv. Chim. Acta* **30**, 1837 (1947); [b] M. Stoll and A. Commarmont, *Ibid.* **31**, 1077 (1948).

[5] S. T. Tong, *Soap, Perfumery and Cosmetics* **27**, 58 (1954).

[6a] P. Chuit, *Helv. Chim. Acta* **9**, 264 (1926); [b] L. Schmid and C. Kemeny, *Monatsh.* **66**, 3 (1935); [c] T. Motoda and M. Ota, *Koryo, Aromatics* No. **8**, 18 (1949); T. Yumoto, *Reports Govt. Ind. Res. Inst. Nagoya* **2**, 401 (1953).

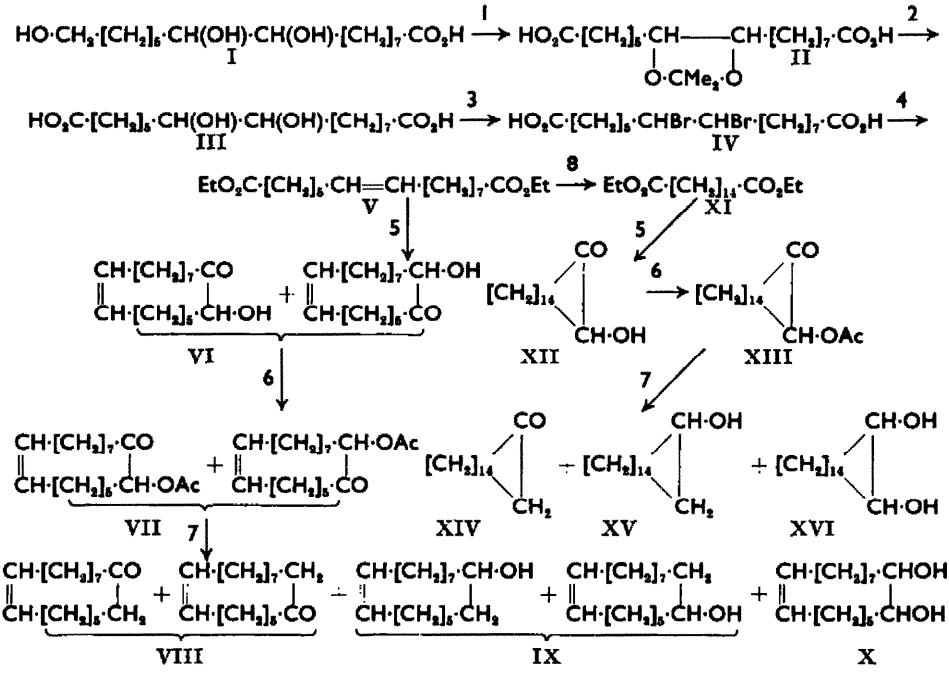
[7] H. H. Mathur and S. C. Bhattacharyya, *Indian Pat.* 65, 543/1958.

[8] W. Nagel and W. Mertens, *Ber. Dtsch. Chem. Ges.* **69**, 2050 (1936).

[9] H. H. Mathur and S. C. Bhattacharyya, *J. Chem. Soc.* 114 (1963).

similar odour characteristics. It, therefore, did not interest us to isolate and characterize these isomeric ketones.

A *trans* hydrocarbon, $C_{16}H_{30}$, was isolated as a liquid and found to contain some impurity on GLC analysis. It could not be further purified. Similarly, the saturated hydrocarbon $C_{16}H_{32}$ was also obtained as a liquid. On GLC analysis it was found to be composed of two components, the major one being 87%. In the NMR spectrum only at higher amplitude, it gave a signal at τ 9·12 indicating the presence, as impurity, of a hydrocarbon having a secondary methyl group. This hydrocarbon could not be purified further through column chromatography over alumina and silica gel and is being closely examined.



Reagents: 1, $Me_2O(H_2SO_4)$; $KMnO_4$. 2, H_2SO_4. 3, HBr—AcOH. 4, Esterifn.; Zn—EtOH. 5, Na—xylene. 6, Ac_2O—pyridine. 7, $Ca \cdot NH_3$. 8, H_2—Ni.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on a Grubb–Parsons double beam spectrometer with NaCl optics unless otherwise stated. The spectra of solids were obtained for Nujol mulls. The NMR spectra were measured on a Varian Associates A60 instrument at 60 Mc in CCl_4 solution, using TMS as the internal standard. Acid washed activated alumina (pH 8·5) was employed for chromatography.

7,8-*Dihydroxyhexadecanedioic acid* (III). Aleuritic acid (100 g) was converted to the isopropylidene derivative by stirring in pure dry acetone (2·5 l.) containing conc. H_2SO_4 (2 ml) and oxidized with $KMnO_4$ (75 g) following the procedure described earlier.[10] The MnO_2 sludge was filtered off, dispersed in water (500 ml) and SO_2 bubbled in to liberate (II) which separated as an oily material. It was not isolated but directly deacetonylated by boiling, with stirring, in water (500 ml) containing 5 N H_2SO_4 (25 ml) for 30 min. On cooling, III crystallized. It was filtered off, washed free from mineral acid and dried (64 g), m.p. 126–128°. From the acetone solution obtained as the filtrate,

[10] S. D. Sabnis, H. H. Mathur and S. C. Bhattacharyya, *J. Chem. Soc.* 2477 (1963).

solvent was recovered and the residue on deacetonylation gave a further quantity of III (4 g). 7,8-Dihydroxyhexadecanedioic acid, on two crystallizations from alcohol melted at 129·5–130° (lit.[8] 125–127°) ν_{max} 3100, 1680, 1130 cm^{-1} (Found: C, 60·1; H, 9·8. Calc. for $C_{16}H_{30}O_6$: C, 60·35; H, 9·5%).

Diethyl trans-*Hexadec-7-enedioate* (V). Compound III (100 g) was treated with HBr in acetic acid (1·36 l, 15% w/v). The crude IV (140 g) was esterified and the diethyl ester, n_D^{27} 1·4865, was debrominated by treatment with Zn dust and EtOH to obtain *diethyl* trans-*hexadec-7-enedioate*, b.p. 145–146°/0·05 mm. (86 g), n_D^{29} 1·4510. ν_{max} 969 cm^{-1} (*trans* CH = CH) (Found: C, 70·8; H, 10·35. $C_{20}H_{36}O_4$ requires: C, 70·5; H, 10·7%). *trans*-Hexadec-7-enedioic acid obtained from V, on crystallization from acetic acid melted at 96–97° (lit.[11] 75–76°), ν_{max} 2860 (associated hydroxyl[12]), 1684, and 962 cm^{-1} (Found: C, 67·7; H, 10·1. Calc. for $C_{16}H_{28}O_4$: C, 67·6; H, 9·9%).

trans-2-*Hydroxycyclohexadecen*-1-*one* (*Mixture*) (VI). Compound V (20 g) was cyclized to VI (14 g), b.p. 133–138°/0·05 mm ν_{max} 3300, 1711, and 966 cm^{-1}. (Found: C, 76·4; H, 11·4. Calc. for $C_{16}H_{28}O_2$: C, 76·1; H, 11·2%). The acyloins (10 g) were acetylated and VII (11·6 g), b.p. 131–133°/0·04 mm ν_{max} 1732, 1242, and 970 cm^{-1}. (Found: C, 73·2; H, 10·3. Calc. for $C_{18}H_{30}O_3$: C, 73·4; H, 10·3%), were reduced with Ca (6 g) in liquid NH_3 (750 ml). The reaction product (9·5 g), n_D^{29} 1·4980 was chromatographed over alumina grade II (190 g) in a column (79 × 1·7cm).

Fraction A (0·5 g) eluted with hexane (100 ml) was free from ketone. It was rechromatographed over alumina grade I (50 g) and the hexane eluate was distilled over Na (0·37 g), b.p. 180° (bath)/1 mm, n_D^{28} 1·4695, ν_{max} (Infracord 0·1 mm cell) 2920, 2646, 1439, 1361, 1333, 1290, 1147, 1012, 962, 883 and 716 cm^{-1}. (Found: C, 86·4; H, 13.9. Calc. for $C_{16}H_{30}$: C, 86·4; H, 13·6%). GLC analysis showed the presence of some impurity. NMR spectrum gave a signal at τ 9·13 indicating the presence of a secondary methyl group possibly formed due to ring contraction.

Fraction B (0·46 g), ν_{max} 1708 cm^{-1}, eluted with hexane (400 ml) was distilled to afford VIII (0·37 g), b.p. 170° (bath)/0·01 mm, n_D^{28} 1·4967, ν_{max} (Infracord,) 2950, 2874, 1709 (C=O), 1458, 1404, 1372, 1290, 1029 and 971 (*trans*-CH=CH−) cm^{-1}. (Found: C, 81·2; H, 11·7. Calc. for $C_{16}H_{28}O$: C, 81·3; H, 11·9%), semicarbazone, m.p. 180–181° (lit.[1] 180–181°), ν_{max} 3445, 3160, 1692, 1581, 1311, 1294, 1208, 1137, 1104, 1079, 965, 764 and 722 cm^{-1}. (Found: N, 13·95. Calc. for $C_{17}H_{31}N_3O$: N, 14·3%).

Fraction C (0·79 g), n_D^{29} 1·5041 eluted with hexane–benzene mixture (1:2; 100 ml) displayed bands at 3505 w and 1708 cm^{-1}. This mixture was not processed further.

Fraction D (1·93 g), n_D^{29} 1·5005, eluted with benzene (600 ml) absorbed at 3355m and 1703m cm^{-1}. It was rechromatographed over 100 fold amount of alumina grade II. The hexane–benzene (1:1) eluate gave a sticky solid m.p. 61–70° which on repeated sublimations melted at 70–72° and analysed for IX, ν_{max} 3320, 1455, 1347, 1229, 1189, 1077, 1051, 1009, 964, 869 and 722 cm^{-1}. (Found: C, 80·6; H, 12·9. Calc. for $C_{16}H_{30}O$: C, 80·6; H, 12·7%).

Fraction E (1·86 g) eluted with ether (500 ml) on crystallization from hexane yielded trans-*cyclohexadec-8-ene*-1,2-*diol* (X), m.p. 87–88·5°, ν_{max} 3355, 2355, 1292, 1174, 1133, 1072, 1012 and 964 cm^{-1}. (Found: C, 75·55; H, 12·0. $C_{16}H_{30}O_2$ requires: C, 75·5; H, 11·9%).

Fraction F (2·68 g) eluted with $CHCl_3$, (500 ml) and Fraction G (0·65 g) eluted with EtOH (350 ml) were similarly crystallized from hexane to yield X possibly in its epimeric forms, m.ps 76–77° and 111–112° respectively. Both the products analysed for $C_{16}H_{30}O_2$ and had comparable IR spectra, ν_{max} (lower melting), 3250 and 963 cm^{-1} and (higher melting), 3200 and 964 cm^{-1}.

2-*Hydroxycyclohexadecanone*[13] (XII). Compound V was hydrogenated (hexadecanedioic acid, m.p. 124–125°, lit.[6a] 124–124.2°) and the saturated XI (18·6 g), m.p. 37–37·5° (lit.[6d] 35–37°) was cyclized to the acyloin (9·75 g), b.p. 139–141°/0·05 mm, ν_{max} 3400, 1716, 1453, 1410, 1353, 1297 and 1060 cm^{-1}. (Found: C, 75·8; H, 11·95. Calc. for $C_{16}H_{30}O_2$: C, 75·5; H, 11·9%).

Compound XII (7·0 g) was converted to the *acetate* (XIII) (7·2 g) b.p. 125–127°/0·005 mm, ν_{max} 1729, 1440, 1360, 1237, 1114 and 1022 cm^{-1}. (Found: C, 73·0; H, 10·7, $C_{18}H_{32}O_3$ requires: C, 72·9; H, 10·9%). The acetate (7·1 g) was reduced with Ca (3·85 g) in liquid NH_3 (500 ml) and the reaction product (5·64 g) obtained as a low melting solid, was chromatographed on alumina grade II (100 g) in a column (42 cm × 1·7 cm) and resolved into seven fractions.

[11] P. C. Mitter, M. C. Sen Gupta and A. Bose, *J. Indian Chem. Soc.* **21**, 295 (1944).

[12] P. J. Corish and W. H. T. Davison, *J. Chem. Soc.* 2431 (1955).

[13] M. Stoll and A. Rouve, *Helv. Chim. Acta* **31**, 1822 (1947).

Fraction A (0·52 g) eluted with hexane (50 ml) appeared to be a hydrocarbon having a slight unsaturation ν_{max} 967 vw cm^{-1}. It was therefore treated with oleum and chromatographed over sixty fold amount of activated silica (BDH). The hexane eluate (0·45 g) was rechromatographed over alumina grade I (60 g). The first two fractions of 10 ml each eluted with hexane contained 0·36 g of the hydrocarbon which was distilled over Na (0·18 g), b.p. 150° (bath)/0·05 mm, n_D^{26} 1·4600, ν_{max} 2830, 1458, 1375, 1300, and 721 cm^{-1}. (Found C, 85·4; H, 14·5. Calc. for $C_{16}H_{32}$: C, 85·6; H, 14·4%). The hydrocarbon purified as above was found to be 87% pure on GLC analysis. In the NMR spectrum, only at higher amplitude, it gave a signal at τ9·12 indicating the presence of a related hydrocarbon having a secondary methyl group, present as the minor constituent.

Fraction B (0·43 g) eluted with hexane (450 ml) was distilled, b.p. 158° (bath)/0·001 mm, λ_{max} 234 mμ, ε 3709. It appeared to contain some quantity of the α,β-unsaturated ketone and was hydrogenated to yield XIV, which on crystallization from MeOH melted at 62–63·5° (lit.[4b] 63–64·5°) ν_{max} 1711, 1412, 1284, 1206, 1177, 1149, 1123, 1086, 1046, and 730 cm^{-1}. (Found: C, 80·6; H, 12·6. Calc. for $C_{16}H_{30}O$: C, 80·6; H, 12·7%); semicarbazone, m.p. 184–184·5° (lit.[4b] 184–185°), ν_{max} 3445, 3085, 2340, 1660, 1581, 1345, 1231, 1080, and 770 cm^{-1}. (Found: C, 68·8; H, 11·2; N, 14·0. Calc. for $C_{17}H_{33}N_3O$: C, 69·1; H, 11·3; N, 14·2%).

Fraction D (0·61 g) eluted with hexane–benzene mixture (1:1); (900 ml), was crystallized from MeOH and then sublimed to yield pure XV m.p. 82–83·5° (lit.[14] 79–80°) ν_{max} (Infracord), 3310, 2940, 1335, and 1274 cm^{-1}. (Found: C, 79·75; H, 13·1. Calc. for $C_{16}H_{32}O$: C, 79·9; H, 13·4%).

Fraction F (0·83 g) eluted with ether (500 ml) and Fraction G (2·14 g) from EtOH (200 ml), on repeated crystallizations from hexane afforded epimeric cyclohexadecane-1,2-diols, m.p.s 102–103° and 107–108° (Stoll[4b] 110–111°; Svoboda[15] 100–101°). The higher melting compound displayed IR bands at 3240, 2350, 1299, 1171, 1149, 1129, 1058 and 917 cm^{-1}. (Found: C, 75·8; H, 12·5. Calc. for $C_{16}H_{32}O_2$: C, 75·9; 12·6%).

Fractions C and E absorbed both in the hydroxyl and carbonyl regions and were not processed further.

Acknowledgement—The assistance received from our microanalytical and spectroscopy sections is appreciated.

[14] M. Kobelt, P. Barman, V. Prelog and L. Ruzicka, *Helv. Chem. Acta* **32**, 256 (1949).
[15] M. Svoboda and J. Sicher, *Chem. Listy* **52**, 1586 (1958).