SYNTHESIS OF 2α,3β- and 2β,3β-CARANEDIOLS

B. A. Arbuzov, V. V. Ratner,
Z. G. Isaeva, V. N. Gudova,
N. R. Rubinova, and M. G. Belyaeva

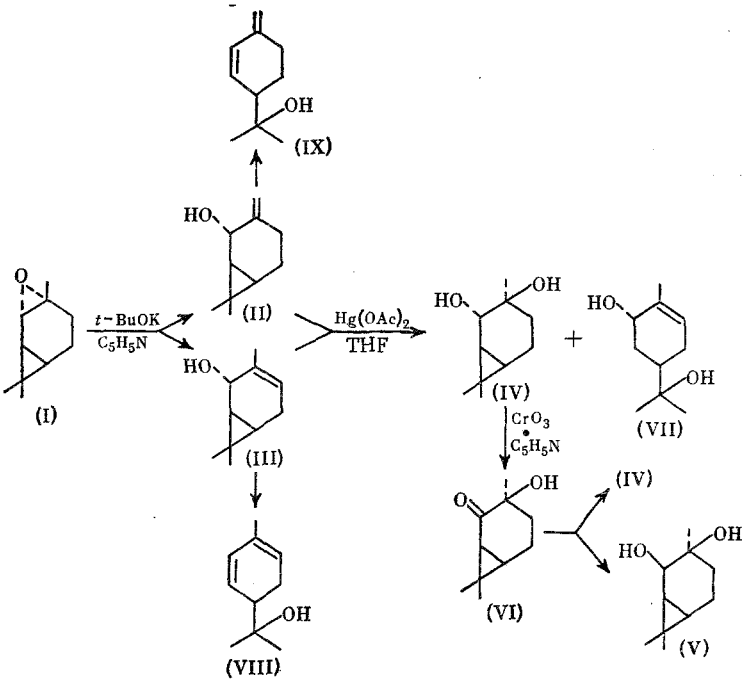
UDC 542.91:547.597

In a continuation of our study on the properties of the stereoisomeric 2,3-caranediols [1], we synthesized the unknown 2α,3β-caranediol (IV) and 2β,3β-caranediol (V) (Scheme 1). As already mentioned, the hydration reaction of 2α,3α-epoxycarane (I) in an acid medium was found to be unsuitable for the preparation of (IV), since it did not lead to the expected (IV), but a monocyclic unsaturated diol, p-menth-5-ene-1,8-diol, was formed [2, 3], i.e., under these conditions (I) rearranges with the opening of the cyclopropane ring (CPR). However, under the conditions of the reaction proceeding according to the S_N2 mechanism, (I) does not undergo rearrangement, and can serve as the starting material for the preparation of the monomethyl ether of 2β,3α-caranediol.*

For the preparation of (IV), we used the oxymercuration—demercuration reaction. As the starting materials, we chose the isomeric 3-carene-trans-2-ol (III) and 3(7)carene-trans-2-ol (II), i.e., compounds containing a 2α-OH group, which is trans-oriented with respect to CPR.

Carenols (II) and (III) are formed during the isomerization of (I) with diethylamine-lithium [4], but in a low yield, and in a complex mixture with other products. During the synthesis of these alcohols, we used isomerization with t-BuOK in pyridine, which in the case of 2α,3α-epoxypinane gave trans-pinocarveol in a yield of 91% [5].

Scheme 1



*The product of the action of sodium methoxide on 2α,3α-epoxycarane in methanol was found to be 3α-hydroxy-2β-methoxycarane; its structure was confirmed by PMR and IR spectra.

A. M. Butlerov Chemical Institute, V. I. Ul'yanov-Lenin Kazan' State University. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1294-1298, June, 1979. Original article submitted January 3, 1978.

0568-5230/79/2806-1209$07.50

Under the action of t-BuOK, (I) forms a mixture of two isomeric carenols (III) and (II) in the ratio of 2.5 : 1, and in a yield of 80%.* According to the data of IR spectra, the alcohols have a carene structure. As known, the oxymercuration reaction of olefins of the carane series proceeds stereospecifically, with an attack at the double bond from the less screened α-side of the olefin molecule, and with entry of the nucleophile into the cis-position with respect to CPR [6-8]. An attack by the reagent on the second unsaturated part of the molecule, the CPR, is also possible. While the first course of the reaction of carenols (II) and (III) would lead to the formation of (IV), the second course would lead to a product with a p-menthane structure, trans-sobrerol (VII) (see Scheme 1).

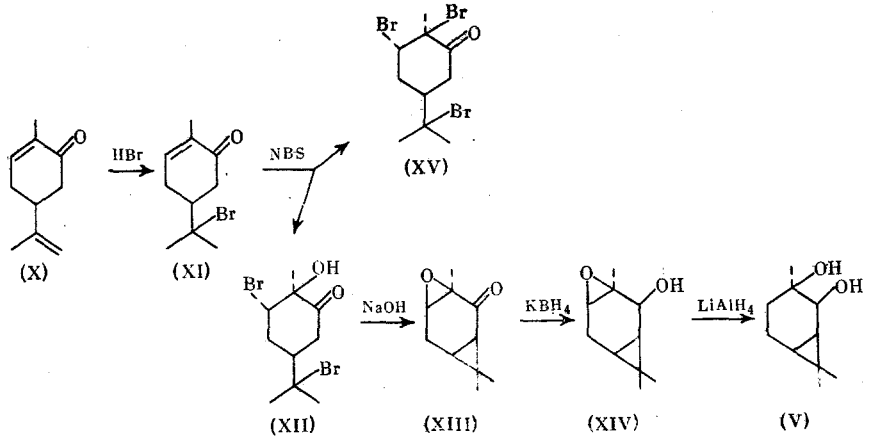
In fact, during the study of the oxymercuration—demercuration products (II) and (III) by chromatography, compound (VII) (mp 148-149°C) and the isomeric diol (IV), which according to the data of IR and PMR spectra belongs to the carane series, were isolated. Its IR spectrum has absorption bands of secondary and tertiary OH groups (1070, 1120, 3400 cm^{-1}) and of CPR (2730, 3010 cm^{-1}). The PMR spectrum (δ, ppm) contains the signals of the H atom at C^2 (3.25 d (1H)), of the CH_3 group geminal with OH (11.6 s (3H)), the gem-dimethyl group attached to the CPR (1.06 and 1.03 s (6H)), and the CPR protons (0.61, 0.95).

According to IR and PMR spectra and the melting point of p-nitrobenzoate, the isolated diol differs from 2α,3α-caranediol [1]. But since the OH groups at C^2 in these diols are known to be oriented in the same way, the difference between them should consist only in the orientation of the OH groups at the C^3 atom, and in the diol (IV) it clearly has a β-orientation. This is also confirmed by the fact that during the oxidation of diol (IV) by CrO_3·pyridine complex [9], a ketol is formed, which according to the absorption frequency of the C=O group and the GLC data differs from the 3α-hydroxycaran-2-one obtained before [1], and hence should be its stereoisomer, 3β-hydroxycaran-2-one (VI).

The IR and PMR spectra confirmed the carane structure of (VI). The IR spectrum contained the absorption bands at (cm^{-1}): 1695 (C=O), 3400 (OH), 2730, 3005 (CPR). The PMR spectrum (δ, ppm) has proton signals of the gem-dimethyl group at the CPR (1.16, 11.3 s (6H)), and of the CH_3 group attached to the carbinyl carbon atom (1.13 s (3H)). Thus, from the formation of 3β-hydroxycaran-2-one (VI) and the IR and PMR spectral data, it is also possible to conclude that the oxymercuration—demercuration product of the allyl carenols (II) and (III) is in fact 2α,3β-caranediol. Its formation corresponds to the concepts on the stereochemistry of the oxymercuration of olefins as a trans-addition of the mercury salt to the double bond.

Carvone hydrobromide (XI) was chosen as the starting material for the synthesis of the fourth stereoisomer, 2β,3β-caranediol (V). By splitting HBr from this compound, it is possible to pass to compounds of the carane series (Scheme 2).

Scheme 2



Scheme 2 shows that (V) can be obtained by synthesizing the β-oxide (XIII) from (XI) and successively reducing it with KBH_4 and $LiAlH_4$. For the synthesis of (XIII), we used the method for the preparation of β-oxides via bromohydrins [10]. However, under the action of

*The ratio between carenols (II) and (III) was judged from the ratio between their rearrangement products (IX) and (VIII). Under the conditions of GLC analysis and chromatography on Al_2O_3, these alcohols are unstable and, as the result of a homoallylic rearrangement, convert into p-menthadienols (IX) and (VIII), respectively [4].

N-bromosuccinimide (NBS) in aqueous ether on (XI), the reaction products include not only 1-hydroxy-6,8-dibromo-trans-tetrahydrocarvone (XII) but also a considerable amount of 1,6,8-tribromo-trans-tetrahydrocarvone (XV). Compound (XII) isolated from the products of this reaction by chromatography gave (XIII) after treatment with alkali. Successive hydrogenation of (XIII) with KBH_4 and $LiAlH_4$ led to a diol having a carane structure according to its IR and PMR spectral data. In the IR spectrum there are absorption bands of the secondary and tertiary OH groups (1050, 1090, 1130, 3400 cm^{-1}) and of CPR (2730 cm^{-1}). The PMR spectrum (δ, ppm) contains proton signals of CPR [0.76, 0.85 (2H)], the gem-dimethyl grouping [1.06, 1.26 s (6H)], and the CH_3 group at the carbinyl carbon atom (1.33 s (3H)). According to the properties of p-nitrobenzoate and the IR and PMR spectra, the diol obtained differs from the other three stereoisomeric 2,3-carbanediols, and according to the IR spectrum it is identical with (V) obtained by the reduction of 3β-hydroxycaran-2-one (VI). Thus, the product of the successive hydrogenation of 3β,4β-epoxycaran-2-one (XIII) with KBH_4 and $LiAlH_4$ has the structure of 2β,3β-caranediol (V).

EXPERIMENTAL

The IR spectra were run on the UR-10 apparatus, and the PMR spectra on the "Varian-T-60" apparatus. The melting points were determined on the Kofler block. The GLC analysis was carried out on the "Chrom-2" chromatograph (carrier gas N_2, Chromosorb G with 5% ethylene glycol sebacate).

α-2,3-Epoxycarane (I) according to [11]. A 64.8 ml portion of 30% H_2O_2 was added, with stirring, to a mixture of 52 g of 2-carene, 18.7 g of $KHCO_3$, 520 ml of MeOH and 42 ml of PhCN at such a rate that the temperature of the reaction did not rise above 17-18°C. The mixture was stirred for 24 h, and then diluted twice with water, and extracted with hexane. After removal of the solvents and distillation of the residue (60 g) on a column with 30 theoretical plates, 46 g of a product was obtained, bp 72-73°C (10 mm), $[\alpha]_D^{20}$ +54°. The parameters of the product and its IR spectrum were completely identical with those of α-2,3-epoxycarane, already synthesized [12].

Isomerization of 2α,3α-Epoxycarane (I) with t-BuOK in Pyridine. A 3 g portion of (I) was added to 4.8 g of t-BuOK in 32 ml of pyridine [5], and the mixture was heated for 5 h at 145°C, diluted with water, and extracted with ether. The extracts were washed free of pyridine with water, and dried over $MgSO_4$. After evaporation of ether and distillation of the 2.44 g residue at bp 84-87°C (5 mm) (2 g), $[\alpha]_D^{20}$ +1.6°, a mixture of 3-carene-trans-2-ol (III) and 3(7)-carene-trans-2-ol (II) was obtained. The IR spectrum of the mixture (ν, cm^{-1}): 870, 910, 1000, 1025, 1380, 1645, 2730, 3000, 3010, 3080, 3350. p-Nitrobenzoate of carenol (III), mp 98-101°C: Found: C 67.80; H 6.42%. $C_{17}H_{19}O_4N$. Calculated: C 67.75, H 6.35%. p-Nitrobenzoate of carenol (II), mp 87-88.5°C (comp. [4]): Found: C 67.68; H 6.37%. $C_{17}H_{19}O_4N$. Calculated: C 67.75; H 6.35%.

2α,3β-Caranediol (IV). A 0.4 g portion of a mixture of carenols (II) and (III) was added dropwise to a suspension of 1 g of $Hg(OAc)_2$ in a mixure of 3.1 ml of THF and 3.1 ml of water. After the disappearance of the yellow color (∿ 4 min), a solution of 0.24 g of $NaBH_4$ and 0.2 g of NaOH in 6.2 ml of water was added dropwise to the ice-cooled reaction mixture. The solution was decanted from the mercury separating out, and extracted with ether. The ether extract was washed with water, and dried over $MgSO_4$. After removal of solvents from the reaction products, the initial alcohols (II) and (III) (0.17 g) were distilled from the reaction products (0.3 g) and were again subjected to oxymercuration. The residue (0.12 g) was chromatographed over SiO_2. To accumulate this product, 7.54 g of a mixture of (II) and (III) was thrice subjected to oxymercuration. After removal of initial alcohols, 3 g of products was obtained. Chromatography of this mixture on SiO_2 (60 g) with a petroleum ether—ether mixture (7 : 3) gave a fraction containing the initial alcohols (II) and (III) (0.52 g). The fractions eluted by a mixture of petroleum ether—ether (4 : 6) contained 1.7 g of (IV), mp 49-51°C, $[\alpha]_D^{20}$ −12.4° (C 20.1, C_6H_6). IR spectrum (ν, cm^{-1}): 1060, 1120, 1380, 2730, 3005, 3400. PMR spectrum (δ, ppm): 0.61, 0.95 (H of the Δ-ring), 1.03, 1.06 s (9-CH_3, 10-CH_3, 6H), 1.16 s (CH_3CO, 3H), 3.25 (CHO, 1H). Its p-nitrobenzoate had mp 129-130°C. Found: C 64.07; H 6.61%. $C_{17}H_{20}O_5N$. Calculated: C 63.97; H 6.58%. In fractions eluted by ether, trans-sobrerol (VII) was identified, yield 0.6 g, mp 148-149°C. IR spectrum (mineral oil, cm^{-1}): 765, 810, 830, 865, 930, 945, 965, 990, 1030, 1040, 1060, 1080, 1115, 1140, 1160, 1180, 1220, 1250, 1295, 1310, 3010, 3270, 3340. Found: C 70.57; H 10.58%. $C_{10}H_{18}O$. Calculated C 70.6; H 10.59%.

3β-Hydroxycaran-2-one (VI). A 0.8 g portion of CrO_3 was added cautiously to 1.2 ml of pyridine in 15 ml of CH_2Cl_2, and the mixture was stirred for 15 min. The mixture was kept cool in ice, and a solution of 0.3 g of (IV) in 2 ml of CH_2Cl_2 was added. The mixture was stirred for 1 h, and diluted with ether. The ether layer was washed with water, and dried over $MgSO_4$. After evaporation of ether, the reaction products (0.25 g) were chromatographed on SiO_2 (5 g). Elution of the mixture with a petroleum ether–ether mixture (7 : 3) gave 0.068 g (27%) of (VI), $[\alpha]_D^{20}$ – 58.4° (C 11.3, EtOH). Found: C 71.58; H 9.45%. $C_{10}H_{16}O_2$. Calculated: C 71.44; H 9.52%. IR spectrum (ν, cm^{-1}): 980, 990, 1020, 1110, 1120, 1140, 1150, 1220, 1330, 1370, 1700, 2730, 3005, 3450. PMR spectrum (δ, ppm): 1.13, 1.16 s (9-CH_3, 10-CH_3, 6H), 1.3 s (CH_3CO, 3H), 3.53 s (OH, 1H).

Synthesis of 2β,3β-Caranediol (V)

Carvone Hydrobromide (XI) [13]. A 90-ml portion of a 36% solution of HBr in acetic acid was added cautiously to an ice-cooled solution of 30 g of carvone (X), bp 78°C (2 mm), $[\alpha]_D^{20}$ +58°, in 20 ml of glacial acetic acid. The mixture was diluted with water, and extracted with ether. The ether extracts were washed with water, a $NaHCO_3$ solution, and again with water. After evaporation of ether, carvone hydrobromide (XI) (45 g) crystallized on cooling, mp 31-32°C. IR spectrum (ν, cm^{-1}): 700, 720, 810, 910, 1070, 1100, 1260, 1310, 1375, 1395, 1440, 1460, 1680, 3030.

1-Hydroxy-6,8-dibromo-trans-tetrahydrocarvone (XII) [10]. A 8.9 g portion of N-bromosuccinimide was added with stirring to a mixture of 5.4 g of carvone hydrobromide, 250 ml of H_2O and 250 ml of ether. The course of the reaction was controlled by TLC and IR spectroscopy. The aqueous layer was extracted with ether, the ether extracts were washed with water, and dried over $MgSO_4$. After evaporation of ether the products (7.3 g) were chromatographed on SiO_2 (80 g). The fractions eluted with a petroleum ether–ether mixture (9 : 1) contained 3 g of 1,6,8-tribromo-trans-tetrahydrocarvone (XV). Found: C 30.78; H 3.78%. $C_{10}H_{15}Br_3O$. Calculated: C 30.71; H 3.83%. IR spectrum (ν, cm^{-1}): 540, 550, 615, 890, 1060, 1110, 1120, 1250, 1300, 1380, 1450, 1720. PMR spectrum (CCl_4, δ, ppm): 1.77, 1.79 2 s ($(CH_3)_2$-CBr, 6H), 1.96 s (CH_3Br, 3H), 4.76 m (HCBr, 1H).

The IR and PMR spectra correspond well to those given in [14]. The fractions eluted by the petroleum ether–ether mixture (5 : 5) contained 1.1 g of (XII). Found: C 36.62; H 5.01% $C_{10}H_{16}Br_2O_2$. Calculated: C 36.61; H 4.88%. IR spectrum (ν, cm^{-1}): 750, 885, 930, 970, 1050, 1110, 1120, 1190, 1250, 1300, 1380, 1720, 3450.

3β,4β-Epoxycaran-2-one (XIII). A 5-ml portion of 4 N NaOH was added to a solution of 1.87 g (from two batches) of (XII) in 15 ml of MeOH. The mixture was left to stand overnight, and then diluted with water, and extracted with ether. After evaporation of ether the residue (1 g) had the IR spectrum (ν, cm^{-1}): 780, 860, 900, 990, 1050, 1070, 1120, 1150, 1380, 1680, 2730.

3β,4β-Epoxycaran-2β-ol (XIV). A 1 g portion of KBH_4 in 2 ml of H_2O was added with cooling to 1 g of (XIII) in 25 ml of MeOH. The mixture was diluted with water, and extracted with ether. The ether extracts were washed with water, and dried over $MgSO_4$. After evaporation of ether, 0.5 g of (XIV) was obtained. IR spectrum (ν, cm^{-1}): 770, 865, 880, 1025, 1050, 1380, 1455, 2730, 3450.

2β,3β-Caranediol (V). A solution of 0.5 g of compound (XIV) in 5 ml of absolute ether was added to a suspension of 0.25 g of $LiAlH_4$ in 25 ml of ether, and the mixture was left to stand overnight. The precipitate after successive additions of 0.3 ml of H_2O, 0.3 ml of a 15% solution of NaOH, and 0.9 ml of HCO was filtered and washed with ether. The ether layer was washed with water, and dried over $MgSO_4$. After evaporation of ether, 0.26 g of a product was obtained, from which compound (V) was isolated by chromatography on SiO_2, $[\alpha]_D^{20}$ +6.2° (C 2.5, C_6H_6). IR spectrum (ν, cm^{-1}): 1050, 1090, 1135, 1145, 1380, 1440, 2730, 3400. PMR spectrum (δ, ppm): 0.85, 0.76 (H of the Δ-ring), 1.06, 1.21 s (9-CH_3, 10-CH_3, 6H), 1.33 s (7-CH_3CO), 3.9 d (CHO, 1 H). Found: C 70.5; H 10.66%. $C_{10}H_{18}O_2$. Calculated: C 70.6; H 10.59%. p-Nitrobenzoate, mp 99-101°C (from petroleum ether). Found: C 63.98; H 6.52%. $C_{17}H_{20}O_5N$. Calculated: C 63.97; H 6.58%.

Synthesis of 3α-Hydroxy-2β-methoxycarane (XVI). An ampul with a solution of MeONa (from 0.3 g of Na) in 10.6 ml of MeOH and 5 g of (I) was heated for 26 h at 155°C (control by TLC method). The mixture was diluted with water and extracted with ether. After evaporation of

solvents and after distillation of the residue (11.3 g from two batches), 8 g of a fraction, bp 85-98°C (4 mm) was isolated. A 2 g portion of this fraction was chromatographed on SiO_2 (60 g), and 1 g of a product was eluted with a petroleum ether—ether mixture (9 : 1). After purification via 3,5-dinitrobenzoate, this product melted at 37-40°C; $[\alpha]_D^{20}$ −22.4° (C 6.3, C_6H_6). IR spectrum (ν, cm^{-1}): 1095 and 1105 (very intense), 1170, 2740, 3005, 3450. PMR spectrum (δ, ppm): 0.66 t (H of the Δ-ring), 1.06, 1.09 s (9-CH_3, 10-CH_3, 6H), 1.14 s (7-CH_3CO, 3H). Calculated: C 57.15; H 5.82%. From the data of IR and PMR spectra, the structure of 3α-hydroxy-2β-methoxycarane (XVI) was assigned to this compound.

CONCLUSIONS

2α,3β- and 2β,3β-caranediols were synthesized by the oxymercuration—demercuration of 3-carene- and 3(7)-caren-2-trans-ols with successive reduction of 3β,4β-epoxycaran-2-one with KBH_4 and $LiAlH_4$, respectively.

LITERATURE CITED

1. B. A. Arbuzov, V. V. Ratner, Z. G. Isaeva, and N. Kh. Abaeva, Izv. Akad. Nauk SSSR, Ser. Khim., 2762 (1974).
2. B. A. Arbuzov, V. V. Ratner, Z. G. Isaeva, and M. G. Belyaeva, Dokl. Akad. Nauk SSSR, 204, 1115 (1972).
3. G. Ohloff and W. Giersch, Helv. Chim. Acta, 51, 1328 (1968).
4. B. A. Arbuzov, Z. G. Isaeva, A. R. Vil'chinskaya, and M. G. Belyaeva, Dokl. Akad. Nauk SSSR, 199, 1304 (1971).
5. Z. Rykowski, K. Burak, and Z. Chabudzinski, Rocz. Chem., 48, 1619 (1974).
6. W. Cocker, D. P. Hanna, and P. V. R. Shannon, J. Chem. Soc., C, 1302 (1969).
7. B. A. Arbuzov, V. V. Ratner, Z. G. Isaeva, and É. Kh. Kazakova, Izv. Akad. Nauk SSSR, Ser. Khim., 385 (1972).
8. B. A. Arbuzov, V. V. Ratner, Z. G. Isaeva, M. G. Belyaeva, and I. P. Povodyreva, Izv. Akad. Nauk SSSR, Ser. Khim., 1049 (1979).
9. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
10. W. Cocker and D. Grayson, Tetrahedron Lett., 4451 (1969).
11. G. P. Payne, Tetrahedron, 18, 763 (1962).
12. B. A. Arbuzov and A. R. Vil'chinskaya, Izv. Akad. Nauk SSSR, Ser. Khim., 954 (1967).
13. O. Wallach and H. Löhr, Lieb. Ann. Chem., 305, 237 (1899).
14. J. Wolinsky, J. Hamsher, and R. Hutchins, J. Org. Chem., 35, 207 (1970).