Monatshefte für Chemie 114, 1259—1265 (1983)

Monatshefte für Chemie
Chemical Monthly

Bromination of Resin Acid Derivatives

Ernst Haslinger*, Hermann Kalchhauser, and **Harald Steindl**

Institut für Organische Chemie, Universität Wien, A-1090 Wien, Austria

(Received 25 May 1983. Accepted 14 June 1983)

Radicalic bromination of **1**, **2**, and **3** leads to products with halogen in the isopropyl group. The corresponding olefins are obtained by elimination of HBr.

(Keywords: 17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-methylethyl), cyclic-13,14-anhydride (4α,8α,12α) and derivatives; 17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-methylethyl), 4,13,14-trimethylester (4α,8α,12α,13β,14α) and derivatives; 1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-, [1R-(1α,4aα,4bβ,10aα)] and derivatives)

Bromierung von Harzsäurederivaten

Die radikalische Bromierung von **1**, **2** und **3** führt zu in der Seitenkette halogenierten Produkten. Eliminierung von HBr liefert die entsprechenden Olefine.

Introduction

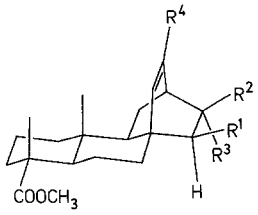
Resin acids appear to present an attractive source of a steroid skeleton. Many attempts have been made to convert abietic acid and related compounds into steroids[1–13]. One of the main problems in the course of these syntheses is the modification or degradation of the isopropyl group[14–18]. Our interest in the degradation or transformation of this group prompted us to examine the radicalic bromination of **1**, **2**, and **3**.

Results and Discussion

Diels-Alder-adducts of levopimaric acid methyl ester with maleic anhydride (**1**) and fumaric acid methyl ester (**2**) are well known and their stereochemistry has been extensively investigated[19–22]. Bromination of **1** and **2** has been described to yield different bromolactones which have been characterized by spectroscopic methods[23–26]. Common to all brominations of **1**, **2** or related

0026-9247/83/0114/1259/$ 01.40

compounds carried out until now is the modification of the carbon—carbon-double bond. Spectroscopic evidence has been obtained that during radicalic bromination an intermediate with a halogen atom in the isopropyl group. i.e. in allylic position to the double bond, might exist[26]. This is in agreement with molecular model considerations which show that the double bond in these compounds is sterically shielded by the C-10-methyl group thus leading to allylic substitution.

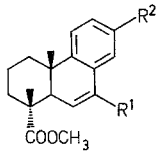


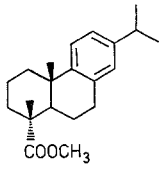
	R^1	R^2	R^3	R^4
1	-C(=O)-O-C(=O)-		-H	$-CH(CH_3)_2$
2	$-COOCH_3$	-H	$-COOCH_3$	$-CH(CH_3)_2$
4	-C(=O)-O-C(=O)-		-H	$-CBr(CH_3)_2$
5	$-COOCH_3$	-H	$-COOCH_3$	$-CBr(CH_3)_2$
6	$-COOCH_3$	-H	$-COOCH_3$	$-CBr(CH_2Br)CH_3$
7	$-COOCH_3$	-H	$-COOCH_3$	$-CBr(CH_2Br)CH_2Br$
8	$-COOCH_3$	-H	$-COOCH_3$	$-C(=CHBr)-CH_3$
9	$-COOCH_3$	-H	$-COOCH_3$	$-C(=CH_2)-CH_2Br$
10	-C(=O)-O-C(=O)-		-H	$-C(=CH_2)-CH_3$
11	$-COOCH_3$	-H	$-COOCH_3$	$-C(=CH_2)-CH_3$

We have obtained compounds **1** and **2** from colophony by a method previously described[27]. Dehydroabietic acid methyl ester (**3**) was prepared in excellent purity by dehydration of abietic acid with Li[28] and subsequent esterification with diazomethane in the usual manner[29].

The action of one mole bromine in dry CCl_4 during irradiation with a 100 W light bulb on **1** and **2** produced **4** and **5** in high yields; no other products could be detected. Although **4** and **5** eliminate HBr readily to give **10** and **11** resp., they could be isolated. These compounds

correspond to the above mentioned intermediate[26] and are the products of allylic bromination. Thus the first step during direct bromination of **1**, **2** and similarly 17,19-Dinoratis-15-ene compounds is the attack of bromine at the allylic position of the isopropyl group. We could not isolate any sideproducts which indicate that the C—C-double bond is attacked by the halogen. Elimination of HBr with dry pyridine from **4** and **5** yields **10** and **11**, respectively, in quantitative yields.





3

	R^1	R^2
12	-Br	$-C(=CH_2)-CH_3$
13	-H	$-C(=CH_2)-CH_3$
14	-H	$-CH(CH_3)_2$

While bromination of **1** with an excess of bromine leads to a mixture of products, the reaction of **2** with two moles of bromine yielded a compound **6** which eliminates HBr very easily to give either **8** (by treatment with pyridine) or a mixture of **8** and **9** (by chromatography on silicagel). **6**, **8**, and **9** have been characterized by spectroscopic methods and **6** has been shown to exist as a mixture of epimers (ratio 1:2; by ^{1}H-NMR).

Application of an excess of bromine on **2** gave compound **7** in good yield. The presence of **6** as an intermediate was indicated by NMR-analysis of the reaction mixture, suggesting that further halogenation proceeds via the assistance of the neighbouring bromine[30,31]. **7** is remarkably stable and did not eliminate HBr by treatment with pyridine. This is probably due to the fact that the remaining isopropyl protons are shielded from the attack of the base by the bulk of bromine atoms.

Bromination of **3** with three moles of bromine yielded a mixture of bromo compounds. After elimination of HBr and chromatography on silicagel **12** was obtained. Reaction of **3** with *NBS* in CCl_4 gave

bromoproducts in poor yields which after treatment with pyridine and separation by TLC were characterized by spectroscopic methods. For these compounds we assume the structures **12**, **13**, and **14**.

Acknowledgements

This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung (Projekt Nr. 4009) and by the Hochschuljubiläumsstiftung der Gemeinde Wien. The authors wish to thank Dr. *H. Ronge* and Dr. *E. Prantz* (Fa. Krems-Chemie) for helpful discussions and for providing starting material. *H. S.* is grateful to Fa. Krems-Chemie for financial support. We are grateful to Dr. *A. Nikiforov* for recording the mass spectra.

Experimental Part

Spectra were recorded on the following instruments: NMR: Bruker WM-250; IR: Perkin-Elmer IR 337; UV: Perkin-Elmer 330; MS: Varian MAT 311 A. Melting points were detected on a *Kofler* apparatus and are uncorrected. Molar rotations were measured using a Perkin-Elmer-141-polarimeter. Elementary analyses were performed by Dr. *J. Zak*, University of Vienna.

Purification of solvents and reagents: CCl_4 was destilled from P_2O_5, pyridine from CaH_2. Bromine was stirred with concentrated sulphuric acid, isolated after phase separation and destilled.

Bromination

Dilute solution of **1**, **2** or **3**, respectively, in CCl_4 were prepared dissolving about 5 mmol of substance in approximately 100 ml of solvent. The appropriate amount of bromine in four times of its volume CCl_4 was slowly added from a dropping funnel under stirring and irradiating with a 100 W light bulb at room temperature unless otherwise stated. HBr-fumes were conducted to a vent. After the addition was complete, the reaction mixture was stirred and irradiated for approximately 0.5 h and the solvent removed *in vacuo* at room temperature.

Elimination

The bromo compounds were dissolved in an excess of dry pyridine and kept at room temperature for some hours. Pyridine was removed under vacuum and the residue acidified with dilute sulphuric acid. The aqueous solution was extracted three times with ether, the organic phase washed with water and dried over anhydrous sodium sulphate and the ether was removed. The purification of the compounds is described below.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-bromo-1-methylethyl), cyclic 13,14-anhydride, methyl ester [4α,8α,12α] (**4**)

Yield: 100%; m.p. 218-224 °C; $[\alpha]_D = -30.2°$ (C_2H_5OH); $C_{25}H_{33}BrO_5$; mol. wt. 493.

Calcd.: C 60.85 H 6.74 Br 16.19.
Found: C 59.00 H 6.72 Br 20.63.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.43$ (s, 3 H), 0.59 (dt, 1 H), 0.83 (dd, 1 H), 1.16 (s, 3 H), 1.50 (s, 3 H), 1.69 (s, 3 H), 1.88 (d, 1 H), 2.22 (dd, 1 H), 2.57 (td, 1 H), 3.17 (m, 1 H), 3.40 (s, 1 H), 5.48 (s, 1 H).

MS (70 eV, 90 °C): $m/e = 412$ (M^+-HBr, 11%), 181 (61), 121 (93), 82 (100), 81 (36), 80 (94).

IR (CH_2Cl_2): 2940, 2880, 1860, 1840, 1790, 1730 cm^{-1}.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-bromo-1-methylethyl), trimethyl ester [4α,8α,12α] (**5**)

Yield: 100%; $C_{27}H_{39}BrO_6$; mol. wt. 539.

Calcd.: C 60.10 H 7.29 Br 14.83.
Found: C 59.32 H 7.14 Br 17.34.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.56$ (s, 3 H), 1.25 (s, 3 H), 1.80 (s, 3 H), 1.89 (s, 3 H), 2.98 (m, 1 H), 3.23 (d, 1 H), 3.27 (s, 3 H), 3.34 (s, 3 H), 3.40 (s, 3 H), 3.57 (m, 1 H), 5.63 (s, 1 H).

MS (70 eV, 105 °C): $m/e = 458$ (M^+-HBr, 6%), 313 (33), 146 (100), 131 (32), 121 (34), 114 (32).

IR (CH_2Cl_2): 2950, 2880, 1730 cm^{-1}.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1,2-dibromo-1-bromomethyl-ethyl), trimethyl ester [4α,8α, 12α] (**7**)

Bromination was carried out under reflux (3 h) and the crude product was chromatographed on silicagel (benzene:ethylacetate = 10:1). Yield: 90%; $C_{27}H_{37}Br_3O_6$; mol. wt. 697.

Calcd.: C 46.48 H 5.31 Br 34.43.
Found: C 46.21 H 6.44 Br 33.81.

Vapor pressure osmosis: 689 ± 33.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.48$ (s, 3 H), 1.19 (s, 3 H), 3.29 (s, 3 H), 3.38 (s, 3 H), 3.05 (m, 1 H), 3.14 (d, 2 H), 3.40 (s, 3 H), 3.82 (d, 1 H), 3.94 (d, 2 H), 4.05 (d, 1 H), 5.77 (s, 1 H).

MS (field desorption): $m/e = 697$ (M^+, 14%), 618 (71), 617 (74), 616 (100), 538 (74), 536 (81).

IR (CH_2Cl_2): 2950, 2880, 1735, 1630 cm^{-1}.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(2-bromo-1-methylethenyl), trimethyl ester [4α,8α,12α] (**8**)

Elimination was carried out on the boiling water bath. The product was chromatographed in the same way as compound **7**. Yield: 76%; $C_{27}H_{37}BrO_6$; mol. wt. 537.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.30$ (s, 3 H), 0.61 (dt, 1 H), 1.30 (s, 3 H), 1.94 (s, 3 H), 2.84 (d, 1 H), 3.10 (d, 1 H), 3.16 (m, 1 H), 3.26 (s, 3 H), 3.34 (s, 3 H), 3.40 (s, 3 H), 5.76 (s, 1 H), 6.35 (s, 1 H).

MS (70 eV, 120 °C): $m/e = 538/536$ (M^+, 1.5/1.5%), 146 (100), 145 (18), 131 (15), 121 (28), 59 (31).

IR (CH_2Cl_2): 2950, 2870, 1730 cm^{-1}.

UV (C_2H_5OH): $\lambda_{max} = 252$ nm, $\varepsilon = 1700$; shoulders at 245, 235 and 262 nm.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-bromomethyl-ethenyl), trimethylester [4α,8α,12α] (**9**)

Chromatography of 500 mg **6** (silicagel, benzene:ethylacetate = 10:1) yielded 140 mg of **9** and 220 mg of **8**. Yield: 32%; $C_{27}H_{37}BrO_6$; mol. wt. 537.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.30$ (s, 3 H), 1.22 (s, 3 H), 2.91 (d, 1 H), 3.17 (d, 1 H), 3.25 (s, 3 H), 3.32 (s, 3 H), 3.37 (s, 3 H), 3.77 (d, 1 H), 3.91 (d, 1 H), 4.91 (s, 1 H), 5.15 (s, 1 H), 6.04 (s, 1 H).

MS (70 eV, 100 °C): *m/e* = 538/536 (M^+, 0.9/0.7%), 397 (17), 146 (100), 145 (20), 121 (38), 114 (39).

IR (CH_2Cl_2): 2940, 2860, 1730, 1610 cm^{-1}.

UV (C_2H_5OH): $\lambda_{max} = 234$ nm; $\varepsilon = 7000$.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-methylethenyl), cyclic 13,14-anhydride, methyl ester [4α,8α,12α] (**10**)

The crude product was recrystallized from ethylacetate. Yield: 90%; m.p. 223-235 °C; $[\alpha]_D = +26.7$ (C_2H_5OH); $C_{25}H_{32}O_5$; mol. wt. 412.

Calcd.: C 72.78 H 7.81.
Found: C 72.20 H 7.74.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.22$ (s, 3 H), 0.61 (dt, 1 H), 1.13 (s, 3 H), 1.58 (s, 3 H), 1.97 (d, 1 H), 2.35 (dd, 1 H), 2.54 (td, 1 H), 3.28 (m, 1 H), 3.40 (s, 3 H), 4.88 (s, 1 H), 5.19 (s, 1 H), 5.56 (s, 1 H).

MS (70 eV, 120 °C): *m/e* = 412 (M^+, 14%), 181 (73), 132 (30), 131 (30), 121 (100), 91 (37).

IR (CH_2Cl_2): 2950, 2880, 1870, 1860, 1790, 1730 cm^{-1}.

UV (C_2H_5OH): $\lambda_{max} = 240$ nm, $\varepsilon = 29000$; shoulder at 234 nm.

17,19-Dinoratis-15-ene-4,13,14-tricarboxylic acid, 16-(1-methylethenyl), trimethyl ester [4α,8α,12α] (**11**)

The reaction mixture was chromatographed in the same way as compound **7**. Yield: 92%; $C_{27}H_{38}O_6$; mol. wt. 458.

Calcd.: C 70.72 H 8.35.
Found: C 68.87 H 8.14.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.42$ (s, 3 H), 0.61 (dt, 1 H), 1.17 (s, 3 H), 1.87 (s, 3 H), 2.87 (d, 1 H), 3.12 (d, 1 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 3.39 (s, 3 H), 3.49 (s, 1 H), 4.86 (s, 1 H), 5.18 (s, 1 H), 5.82 (s, 1 H).

MS (70 eV, 80 °C): *m/e* = 458 (M^+, 8%), 314 (32), 313 (37), 146 (100), 131 (29), 114 (39).

IR (CH_2Cl_2): 2950, 2920, 1730, 1645, 1635 cm^{-1}.

UV (C_2H_5OH): $\lambda_{max} = 242$ nm; $\varepsilon = 16000$; shoulders at 235 and 250 nm.

1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,10a-hexahydro-9-bromo-1,4a-dimethyl-7-(1-methylethenyl) (**12**)

Bromination was carried in boiling CCl_4 and the reaction mixture chromatographed in the same way as compound **7**. Yield: 5%; b.p. 100 °C (10^{-3} torr); $C_{21}H_{25}BrO_2$; mol. wt. 389.

Calcd.: C 64.78 H 6.43 Br 20.57.
Found: C 63.59 H 6.36 Br 21.33.

^{1}H-NMR (250 MHz, C_6D_6): $\delta = 0.96$ (s, 3 H), 1.29 (s, 3 H), 2.00 (m, 3 H), 3.06 (d, 1 H), 3.23 (s, 3 H), 5.01 (m, 1 H), 5.42 (m, 1 H), 6.45 (d, 1 H), 6.85 (d, 1 H), 7.28 (dd, 1 H), 7.96 (d, 1 H).

MS (70 eV, 90 °C): $m/e = 390/388$ (M^+, 12/11%), 309 (12), 249 (15), 69 (100), 68 (100), 41 (100).

References

1 *Zeiss H. H., Martin W. B. jr.*, J. Amer. Chem. Soc. **75**, 5935 (1953).
2 *Huffman J. W., Stockel R. F.*, J. Org. Chem. **28**, 506 (1963).
3 *Huffman J. W., Arapakos P. G.*, J. Org. Chem. **30**, 1604 (1965).
4 *Bennett C. R., Cambie R. C., Fullerton T. J.*, Aust. J. Chem. **21**, 2473 (1968).
5 *Cambie R. C., Denny W. A.*, Aust. J. Chem. **22**, 1699 (1969).
6 *Pettit G. R., Dias J. R.*, Can. J. Chem. **47**, 1091 (1969).
7 *Huffman J. W.*, J. Org. Chem. **35**, 478 (1970).
8 *Cambie R. C., Franich R. A.*, Aust. J. Chem. **23**, 93 (1970); **24**, 117 (1971); **24**, 217 (1971).
9 *Wirthlin T., Wehrli H., Jeger O.*, Helv. Chim. Acta **57**, 351 (1974).
10 *Tahara A., Shimagaki M.*, Chem. Lett. **1974**, 651.
11 *Tahara A., Akita H., Ohtsuka Y.*, Chem. Pharm. Bull. **22**, 1547 (1974).
12 *Tahara A., Shimagaki M., Itoh M., Harigaya Y., Onda M.*, Chem. Pharm. Bull. **23**, 3189 (1975).
13 *Tahara A., Harigaya Y., Onda M.*, Chem. Pharm. Bull. **23**, 1989 (1975); **23**, 1996 (1975); **24**, 421 (1976).
14 *Ritchie P. F.*, J. Amer. Chem. Soc. **76**, 723 (1954).
15 *Sanderson T. F.*, U.S. Patent 2750367 (1956); cf. C.A. **51**, 1278 c (1957).
16 *Ohta M., Ohmori L.*, Chem. Pharm. Bull. **5**, 91 (1957).
17 *Tahara A., Akita H.*, Chem. Pharm. Bull. **23**, 1984 (1975).
18 *Tahara A.*, Chem. Pharm. Bull. **24**, 1497 (1976).
19 *Ayer W. A., McDonald C. E., Stothers J. B.*, Can. J. Chem. **41**, 1113 (1963).
20 *Halbrook N. J., Lawrence R. V., Dressler R. L., Blackstone R. C., Herz W.*, J. Org. Chem. **29**, 1017 (1964).
21 *Maciejewski C., Gastambide B.*, Helv. Chim. Acta **60**, 524 (1977) and refs. cited therein.
22 *Haslinger E., Kalchhauser H., Robien W.*, Monatsh. Chem. **113**, 805 (1982).
23 *Zalkow L. H., Ford R. A., Kutney J. P.*, J. Org. Chem. **27**, 3535 (1962).
24 *Huffman R. W.*, Diss. Abstr. **B 25**, 6232 (1965).
25 *Maciejewski C., Gastambide B.*, Chimia **31**, 8 (1977).
26 *Herz W., Mirrington R. N., Young H., Yen Lin Young*, J. Org. Chem. **33**, 4210 (1968).
27 *Langlois N., Gastambide B.*, Bull. Soc. Chim. France **1965**, 2966.
28 *Blade-Font A., Rocabayera T. d. m., Salomo S. A.*, Afinidad **28** (292), 1301 (1971).
29 *Fleck E. E., Palkin S.*, J. Amer. Chem. Soc. **60**, 921 (1938).
30 *Skell P. S., Tuleen D. L., Readio P. D.*, J. Amer. Chem. Soc. **85**, 2849 (1963).
31 *Cava M. P., Krieger M., Pohlke R., Mangold D.*, J. Amer. Chem. Soc. **88**, 2615 (1966).