Some Benzylseleno- and β-Phenylethylseleno-substituted Alkanoic Acids

ARNE FREDGA

Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala 1, Sweden

The title compounds have been prepared for two reasons. The original purpose was to test their activity in preventing dietary liver necrosis in rats (factor-3-effect) [1-4] and to study the influence of structural factors, *e.g.* the distance between the selenium atom and the carboxyl group, and the presence of substituents in the benzene nucleus. This part of the work has been carried out in collaboration with Professor Klaus Schwarz * and the results have in part been published.[5,6]

The compounds have also found use for studying the NMR-effects of the isotope ^{77}Se.

* Laboratory of Experimental Metabolic Diseases, Veterans Administration Hospital, Long Beach, California, and Department of Biological Chemistry, School of Medicine, University of California in Los Angeles.

These investigations were carried out in collaboration with Professor Salo Gronowitz and his group * and the results will be published elsewhere.

The present paper describes 38 acids (compounds I – IV and higher homologues). Three of these acids have been mentioned in earlier publications.[7,8] Since compounds of the types II and IV were found to be of minor interest regarding the factor-3-effect, only a limited number of these acids were prepared. The data are summarized in Tables 1 – 4.

$C_6H_5-CH_2-Se-CH_2-COOH$ (I)
$4\text{-}CH_3-C_6H_4-CH_2-Se-CH_2-COOH$ (II)
$4\text{-}Br-C_6H_4-CH_2-Se-CH_2-COOH$ (III)
$C_6H_5-CH_2-CH_2-Se-CH_2-COOH$ (IV)

In earlier papers, a number of naphthylmethylseleno acids [9] and nitro-substituted acids [10] have been reported.

Experimental. Diseleno-dicarboxylic acids were reduced in alkaline solution to selenol-substituted acids. These were not isolated but directly reacted with the appropriate chlorides or bromides. For the reduction, four methods have been used:

* Chemical Center, Division of Organic Chemistry 1, University of Lund, Sweden.

Table 1. (Benzylseleno)-alkanoic acids.

Acid	m.p. °C	Calculated C	H	Se	Found C	H	Se
Acetic	71 – 72	47.17	4.40	34.46	47.29	4.45	34.45
					47.28	4.44	–
2-Propionic	68 – 69	49.39	4.97	32.47	49.46	5.01	32.34
3-Propionic	75 – 76	49.39	4.97	32.47	49.41	5.02	32.51
					49.40	4.97	32.37
3-Butyric	70 – 71	51.37	5.49	30.70	51.28	5.52	30.58
					51.39	5.43	30.55
4-Butyric	47 – 48	51.37	5.49	30.70	51.42	5.53	30.83
					51.43	5.50	–
2-Isobutyric	94 – 95	51.37	5.49	30.70	51.40	5.53	30.62
3-Isobutyric	46.5 – 47.5	51.37	5.49	30.70	51.50	5.52	30.66
					51.55	5.48	30.54
5-Valeric	45 – 46.5	53.14	5.95	29.11	53.04	5.99	29.20
					53.09	6.01	29.19
6-Caproic	40 – 41	54.74	6.36	27.68	54.48	6.36	27.68
					54.55	6.35	27.67
7-Oenanthic	49.5 – 50.5	56.19	6.74	26.40	56.18	6.77	26.26
					–	–	26.25
8-Caprylic	51 – 52	57.50	7.08	25.20	57.23	7.25	25.07
					57.22	7.33	25.03
9-Pelargonic	59.5 – 60.5	58.71	7.39	24.12	58.67	7.38	24.25
					58.68	7.40	24.21
10-Capric	61 – 62	59.81	7.68	23.13	59.95	7.78	22.94
					59.80	7.85	22.96
11-Undecanoic	67 – 68	60.83	7.94	22.22	60.79	7.98	22.14
					61.00	8.01	22.15

Table 2. (4-Methylbenzylseleno)-alkanoic acids.

Acid	m.p. °C	Calculated C	H	Se	Found C	H	Se
Acetic	94.5 – 95.5	49.39	4.97	32.47	49.54	4.91	32.29
					49.58	4.98	32.32
3-Propionic	76 – 77	51.37	5.49	30.70	51.62	5.55	30.61
					51.62	5.39	30.59
4-Butyric	57 – 58	53.14	5.95	29.11	52.83	5.87	29.39
					52.69	5.84	29.01
5-Valeric	(55) 60[a]	54.74	6.36	27.68	57.74	6.09	27.65
					57.48	6.27	27.60
8-Caprylic	65.5 – 67	58.71	7.39	24.12	58.67	7.42	23.98
					58.71	7.48	23.95

[a] Polymorphism.

Table 3. (4-Bromophenylseleno)-alkanoic acids.

Acid	m.p. °C	Calculated C	H	Se	Found C	H	Se
Acetic	99 – 100.5	35.09	2.95	25.63	35.03	2.93	25.48
					35.15	2.99	25.46
2-Propionic	71 – 72	37.29	3.44	24.52	37.22	3.43	24.48
					37.28	3.43	24.44
3-Propionic	81 – 82	37.29	3.44	24.52	37.31	3.41	24.46
					37.27	3.42	24.49
2-Butyric	77.5 – 78.5	39.31	3.90	23.49	39.22	3.85	23.41
					39.46	3.89	23.50
3-Butyric	53.5 – 54.5	39.31	3.90	23.49	39.50	3.92	23.49
					39.34	3.87	23.46
4-Butyric	70 – 71	39.31	3.90	23.49	39.41	3.92	23.46
					39.45	3.95	23.51
3-Isobutyric	64.5 – 65.5	39.31	3.90	23.49	39.42	3.92	23.48
					39.46	3.90	23.42
5-Valeric	63.5 – 64.5	41.16	4.32	22.55	41.29	4.38	22.50
					41.16	4.29	22.53
6-Caproic	58 – 59	42.88	4.71	21.68	42.70	4.64	21.60
					42.87	4.68	21.56
5-(3-Methyl)-valeric	43 – 44.5	42.88	4.71	21.68	42.92	4.71	21.57
					42.95	4.78	21.49
7-Oenanthic	63 – 64.5	44.46	5.06	20.88	44.48	5.09	20.74
					44.60	5.06	20.73
8-Caprylic	64 – 65.5	45.93	5.40	20.13	45.92	5.42	20.15
					45.80	5.42	20.07
9-Pelargonic	69 – 71	47.30	5.71	19.44	47.29	5.77	19.34
					47.30	5.78	19.27
10-Capric	72.5 – 74	48.58	6.00	18.79	48.51	6.04	18.79
					48.64	6.01	18.78
11-Undecanoic	75 – 77	49.78	6.27	18.18	49.87	6.37	18.28
					49.92	6.38	18.06

(1) Reduction with formaldehyde-sulphoxylate (rongalite) in aqueous ammonia.[9]

(2) Reduction with zinc powder in aqueous ammonia.[9]

(3) Reduction with sodium amalgam: the solution of the diselenide acid is stirred with the amalgam and the halogen compound is gradually added.[8]

(4) The diselenide acid is converted to mercury selenolate by shaking with metallic mercury in a suitable solvent.[11,12] The mercury selenolate acid is dissolved in slightly alkaline

Table 4. (β-Phenylethylseleno)-alkanoic acids.

Acid	m.p. °C	Calculated C	H	Se	Found C	H	Se
Acetic	71.5 – 72.5	49.39	4.97	32.47	49.44	5.02	32.46
					49.35	4.97	32.54
3-Propionic	46.5 – 47.5	51.37	5.49	30.70	51.45	5.50	30.72
					51.51	5.45	30.68
5-Valeric	37.5 – 38.5	54.74	6.36	27.68	54.75	6.40	27.62
					54.64	6.38	27.60
9-Pelargonic	44 – 45	59.81	7.68	23.13	59.89	7.69	23.10
					59.76	7.64	23.09

solution and the mercury is precipitated by adding an equivalent quantity of sodium sulphide ($Na_2S.12H_2O$) and shaking for some hours.[7]

Method 1 is generally most convenient and has been used for the majority of the compounds. Methods 3 and 4 can be used when foreign ions (zinc, sulphite) are not desirable. The procedure has been described in more detail in earlier papers.[7–9] A further example is given below.

11-(Benzylseleno)-undecanoic acid. Diseleno-11,11′-diundecanoic acid (6.7 g, 0.0125 mol) is placed in a strong flask or bottle of about 300 ml. Concentrated aqueous ammonia (75 ml) and water (25 ml) is added; since the ammonium salt of the acid is sparingly soluble in water, ethanol must be added with shaking to obtain a clear solution. Rongalite in slight excess is then added; if the solution is still yellow after 15 – 20 min, additional small amounts are added until the solution is quite colourless. The calculated amount of benzyl chloride (3.2 g, 0.025 mol), dissolved in 50 ml ethanol is finally added and the mixture is shaken until the milky suspension is practically clear. If the solution is yellow (due to partial oxidation to diselenide by the halogen compound), it is decolourised by adding some rongalite, after which a little benzyl chloride is added. Sometimes this operation must be repeated. A moderate excess of benzyl chloride is not harmful since it is converted to benzylamine by the ammonia. The solution is left to stand overnight.

The ethanol is then evaporated by a fan or a current of air, ammonia is added to strongly alkaline reaction and the solution is diluted to about 300 ml and finally shaken with ether to remove non-acidic impurities. The dissolved ether is removed by a current of air and the acid is precipitated by excess hydrochloric acid. The acid is obtained as a rapidly crystallising oil and recrystallised, first from formic acid (diluted with a little water) and then from ligroin or carbon tetrachloride. M.p. 67 – 68 °C. The yield of crude product is practically 100 %. Analyses see Table 1.

Acknowledgements. The analyses were carried out by the Analytical Department of the Institute. The author is greatly indebted to Mr. Ragnar Öhberg for preparing starting materials. Thanks are also due to Boliden AB for generous gifts of selenium. Grants from the Royal Swedish Academy of Sciences, the Swedish Natural Science Research Council, the Natural Institutes of Health, U.S.A. (U.S. Public Health Service Grant No. AM 03417) and AB Astra are gratefully acknowledged.

1. Schwarz, K. and Foltz, C. M. *J. Amer. Chem. Soc. 79* (1957) 3292.
2. Schwarz, K. *et al. Federation Proc. 20* (1961) 655.
3. Schwarz, K. *Federation Proc. 20* (1961) 666.
4. Schwarz, K. and Fredga, A. *J. Biol. Chem. 244* (1969) 2103.
5. Schwarz, K., Porter, L. A. and Fredga, A. *Ann. N. Y. Acad. Sci. 192* (1972) 200.
6. Schwarz, K. and Fredga, A. *Bioinorg. Chem. 2* (1972) 171.
7. Fredga, A. *Sv. Kem. Tidskr. 48* (1936) 91; *Houben-Weyl*, 4th Ed., *9* 979.
8. Fredga, A. and Bendz, G. *Sv. Kem. Tidskr. 53* (1942) 119; *Houben-Weyl*, 4th Ed., *9* 979.
9. Fredga, A. *Acta Chem. Scand. 24* (1970) 1117.
10. Fredga, A. *Acta Chem. Scand. 25* (1971) 2765.
11. Fredga, A. *Arkiv Kemi, Mineral. Geol. 11 B* (1934) No. 44.
12. Fredga, A. *Uppsala Univ:s Årsskrift 1935:5* 146.

Received May 22, 1974.