Tetrahedron Letters, Vol. 33, No. 20, pp. 2883-2886, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

HALOGENATED ANALOGS OF TRI-*O*-THYMOTIDE (TOT) AND TRI-3-(2-BUTYL)-6-METHYLSALICYLIDE (TSBS): SYNTHESIS AND CLATHRATION STUDIES.

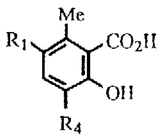
Jallal M. Gnaim,[a] Philip M. Keehn,[b] and Bernard S. Green*,[a]

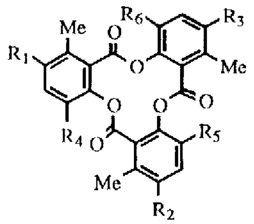
[a] Department of Pharmaceutical Chemistry, The School of Pharmacy, The Hebrew University, P.O. Box 12065, Jerusalem, 91120, Israel, [b] Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254.

Abstract. Halogenated trisalicylide derivatives **1-6**, representing three-fold symmetric C_3 "homo trimers" as well as dissymmetric C_1 "mixed trimers" have been synthesized. Clathration studies indicate that these halogenated TOT analogs do not form clathrates. Reductive removal of the halogen was demonstrated for analog **2**, providing a new entry to TOT-based host molecules.

Tri-*o*-thymotide (TOT, **7**) forms a large number of clathrates with a wide range of guest molecules,[1] including many chiral guests which form diastereomeric complexes, useful for chiral discrimination[2a] and resolution.[2b] Although extensively studied, the reasons for TOT's unique host capabilities are poorly understood. Recently, we found[4] a new, versatile TOT-based host, tri-3-(2-butyl)-6-methylsalicylide (TSBS, **8**) which is the first example where significant substituent changes (*sec*-butyl for *iso*-propyl) retain the wide-ranging clathrating properties of the TOT host structure. In continuation of our studies[3-6] to define the effects of substituent modification in TOT on the clathration properties, and seek improved or modified guest cavities, we have synthesized TOT and TOC (tri-*ortho*-carvacrotide or tri-3-methyl-6-(2-propyl)-salicylide) analogs where one or more of the ring methyl groups is replaced by bromomethyl.[6] We report here the synthesis of ring halogenated TOT and TSBS derivatives **1-6**, where one or more halogen atoms, have been incorporated into the TOT (**7**) and TSBS (**8**) host molecules.

Halogenated salicylic acid derivatives **9-12** were prepared by direct halogenation[7,8] of salicylic acids **13** and **14**, in dimethylformamide (DMF) at ambient temperature using N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS). Recrystallization of the crude product from n-hexane or petroleum ether afforded the new salicylic acids **9-12** in 63-83% yields.





Salicylic acid	R_1	R_2	R_3	R_4	R_5	R_6	Trimer
9	Br	Br	Br	*i*-Pr	*i*-Pr	*i*-Pr	**1**
10	I	I	I	*i*-Pr	*i*-Pr	*i*-Pr	**2**
11	Br	Br	Br	*s*-But	*s*-But	*s*-But	**3**
12	I	I	I	*s*-But	*s*-But	*s*-But	**4**
-	H	H	Br	*s*-But	*s*-But	*i*-Pr	**5**
-	H	Br	Br	*s*-But	*i*-Pr	*i*-Pr	**6**
13	H	H	H	*i*-Pr	*i*-Pr	*i*-Pr	**7**
14	H	H	H	*s*-But	*s*-But	*s*-But	**8**
-	H	H	H	*s*-But	*s*-But	*i*-Pr	**15**
-	H	H	H	*s*-But	*i*-Pr	*i*-Pr	**16**

Cyclodehydration of **9-12** by the method described by Baker *et. al*[9], using $POCl_3$ in refluxing xylene, yielded cyclic trimers **1-4** in 28%, 12%, 23% and 10% yields, respectively. Higher yields of these trimers (49%, 38%, 45% and 35%, respectively) were obtained using an improved, recently reported[5] method. Trisalicylide derivatives **5** and **6** were also prepared by co-condensation of monomers **9** and **14** (molar ratio 1:1); these "mixed trimers" were isolated and purified by chromatography and recrystallized from methanol, giving **5** and **6** as colorless crystals (14% and 10%, respectively). Spectral and microanalytical data corroborate the structures of the new acids **9-12** and trimers **1-6** (Table I).

Compounds **1-6** were crystallized from hexane, ethyl acetate, nitromethane, and 2-chlorobutane, all of which readily form TOT clathrates. However ^{1}H NMR spectra indicate that none of these halogenated trisalicylides form inclusion compounds. Polarimetric studies indicate that they crystallized without undergoing spontaneous optical resolution of the host. Our results thus indicate that substitution by bromine or iodine at positions C-2, C-8, and C-14 on the aromatic rings effectively eliminates clathration based on the TOT motif. Structural studies may clarify whether guest...halogen(s) and/or host...halogen(s) interactions prevent clathrate formation, even in the monobromo analog **5**.

Table I. Physical properties of trisalicylide derivatives (1-6) and salicylic acid derivatives (9-12).

Compound	Yield (%)	MP °C	IR[i], cm^{-1} ν C=O	^{1}H NMR[j] δ	MS (m/e)	Atom	Anal. Calcd.	Found
1	49[a]	284-5[e]	1763 1748	1.23 (18 H, dd, J = 8 Hz), 2.49 (9 H, s), 3.04 (3 H, sep, J ≈ 8 Hz), 7.71 (3 H, s).	765 (M$^+$, $C_{33}H_{33}Br_3O_6$) 510, 170.	Br	31.37	30.79
2	38[a]	253-5[f]	1769	0.79 (9 H, tt, J = 7 Hz), 1.22 (9 H, dd, J = 7 Hz), 1.55 (6 H, m), 2.49 (9 H, s), 2.75 (3 H, m), 7.65 (3 H, s).	807 (M$^+$, $C_{36}H_{39}Br_3O_6$) 528, 269.	C H Br	53.55 4.87 29.69	53.38 4.78 29.59
3	45[a]	> 300[g]	1764 1751	1.23 (18 H, dd, J = 8 Hz), 2.53 (9 H, s), 2.99 (3 H, sep, J = 8 Hz), 7.97 (3 H, s).	906 (M$^+$, $C_{33}H_{33}I_3O_6$) 604, 302.	C H I	43.73 3.67 42.01	44.00 3.73 41.50
4	35[a]	271-2[f]	1771	0.79 (9 H, tt, J = 7 Hz), 1.22 (9 H, dd, J = 7 Hz), 1.57 (6 H, m), 2.53 (9 H, s), 2.76 (3 H, m), 7.92 (3 H, s).	948 (M$^+$, $C_{36}H_{39}I_3O_6$) 632, 505, 316.	C H I	45.59 4.14 40.14	45.80 4.08 39.90
5	14[b]	202-4[g]	1771 1751	0.84 (6 H, tt, J = 8 Hz), 1.24 (12 H, m) 1.69 (4 H, m), 2.46 (9 H, s), 2.58 (1 H, , m), 2.80 (1 H, m), 3.02 (1 H, m), 7.23 (2 H, d, J = 8 Hz), 7.38 (2 H, d, J = 8 Hz), 7.69 (1 H, s).	636 (M$^+$, $C_{35}H_{39}Br_3O_6$) 446, 366, 191, 190, 162, 161.	C H Br	66.14 6.18 12.57	66.68 6.24 12.42
6	10[b]	140-7[g]	1769 1750	0.85 (3 H, tt, J = 7 Hz), 1.23 (9 H, m) 1.57 (2 H, m), 2.47 (3 H, s), 2.49 (6 H, s), 2.80 (1 H, m), 3.01 (2 H, m), 7.25 (1 H, d, J = 7 Hz), 7.39 (1 H, d, J = 7 Hz), 7.70 (2 H, s).	700 (M$^+$, $C_{34}H_{36}Br_2O_6$) 446, 256.	C H	58.30 5.15	58.54 5.37
9	83[c]	165-8[h]	1630	1.22 (6 H, d, J = 8 Hz), 2.69 (3 H, s) 3.32 (1 H, m), 7.56 (1 H, s).	273 (M$^+$, $C_{11}H_{13}BrO_3$) 255, 227, 213, 175.	C H Br	48.35 4.76 29.30	48.77 4.94 29.50
10	77[c]	110-2[f]	1636	0.86 (3 H, t, J = 8 Hz), 1.19 (3 H, d, J = 7 Hz), 1.59 (2 H, m), 2.69 (3 H, s), 3.11 (1 H, m), 7.52 (1 H, s).	287 (M$^+$, $C_{12}H_{15}BrO_3$) 269, 255, 243.	C H Br	50.19 5.26 27.83	49.89 5.14 28.13
11	73[d]	183-5[h]	1628	1.21 (6 H, d, J = 8 Hz), 2.73 (3 H, s) 3.28 (1 H, m), 7.81 (1 H, s).	320 (M$^+$, $C_{11}H_{13}IO_3$) 302, 287, 274, 175.	C H I	41.28 4.06 39.66	41.38 4.12 40.45
12	63[d]	135-6[f]	1631	0.84 (3 H, t, J ≈ 7 Hz), 1.15 (3 H, d, J = 7 Hz), 1.53 (2 H, m), 2.67 (3 H, s), 3.01 (1 H, m), 7.70 (1 H, s)	334 (M$^+$, $C_{12}H_{15}IO_3$) 316, 301, 287, 277, 151.	C H I	43.13 4.52 37.98	43.37 4.60 37.50

a) By cyclodehydration of the corresponding salicylic acid at 100 C for 2 h in $POCl_3$ b) By condensation of 9 and 14 at 100 C for 2 h in $POCl_3$ c) By bromination at 25 C for 4 h in DMF d) By iodination at 25 C for 15 h in DMF e) Crystallized from ethyl acetate f) Crystallized from n-hexane g) Crystallized from methanol h) Crystallized from petroleum ether i) KBr j) NMR spectra taken in $CDCl_3$ with TMS as an internal standard.

The halogenated trimers, **5** and **6**, are also interesting as precursors to the mixed TOT-analogs **15** and **16** which contain "monomeric" units of TOT and of TSBS, both of which, exhibit, superior host properties. Since **5** and **6** can readily be separated from one another, and from **1** and **8**, by chromatography while **15**, **16**, **7**, and **8** cannot, the process of dehalogenation may be synthetically useful for the preparation of mixed analogs, **15** and **16**. The feasibility of halogen removal was demonstrated with **2**. A cooled, ethereal solution (-40 °C) of **2** was treated with an excess of n-BuLi (1.6M in hexane). After quenching with water, TOT (**7**) was the major product; minor products, 2-methyl-5-(2-propyl)-6-hydroxy-butyrophenone and its *ortho*-thymotoyl ester, were characterized by ^{1}H NMR. Preliminary results indicate that **15** and **16** form clathrates very similar to TOT and TSBS hosts.[10]

Acknowledgements. This research was supported by Grant No. 84-00162 from the U.S.-Israel Binational Science Foundation (BSF), Jerusalem, Israel.

REFERENCES

(1) Gerdil, R. *Top. Curr. Chem.* **1987**, *140*, 71 and references therein.

(2) a) Ripmeester, J. A.; Burlinson, N. W. *J. Am. Chem. Soc.* **1985**, *107*, 3713; b) Arad-Yellin, R.; Green, B. S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1983**, *105*, 4561-4571.

(3) Harris, T. D.; Oruganti, S. R.; Davis, L. M.; Keehn, P. M.; Green, B. S. *Tetrahedron* **1987**, Vol. 43, *7*, 1519-1540.

(4) Gnaim, J. M.; Green, B. S.; Arad-Yellin, R.; Vyas, K.; Levy, J.; Frolow, F.; Keehn, P. M. **1992** (in press).

(5) Gnaim, J. M.; Green, B. S.; Arad-Yellin, R.; Keehn, P. M. *J. Org. Chem.* **1991**, *56*, 4525.

(6) Xu, L.; Green, B. S.; Gnaim, J. M.; Keehn, P. M. *J. Org. Chem.* **1992** (in press).

(7) Mitchell, R. H.; Lai, Y.; Williams, R. V. *J. Org. Chem.* **1979**, *44* (25), 4733.

(8) Mitchell, R. H.; Flyes, T.; Ralph, L. M. *Can. J. Chem.* **1977**, *55*, 1480.

(9) Baker, W.; Harborne, J. B.; Price, A. J.; Rutt, A. *J. Chem. Soc.* **1954**, 2042.

(10) Unpublished results.

(Received in UK 8 November 1991)