**Cis isomer**: $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (s, 3 H), 1.19 (s, 3 H), 1.00 (s, 6 H); mass spectrum, $m/e$ 202 ($M^+$).

**Trans isomer**: $^1$H NMR ($CDCl_3$) $\delta$ 1.28 (s, 6 H), 1.00 (s, 6 H); mass spectrum, $m/e$ 202 ($M^+$).

**Preparation of Dication Solutions.** In a 10-mm NMR tube was dissolved 100 mg of alcohol **9**-$d_3$ in 0.5 mL of $CD_2Cl_2$ and the mixture cooled to -196 °C. $FSO_3H$ (2 mL) was added, and the sample was warmed to about -95 °C. A precooled glass rod was employed to mix and homogenize the contents of the tube carefully, resulting in a solution of cation **1**-$d_3$. A mixture of ions **1** and **1**-$d_3$ was prepared analogously by using 40 mg of alcohol **9**[2a] and 60 mg of alcohol **9**-$d_3$.

Ion **1**-$d_6$ was generated upon dissolution of 50 mg of glycol **10**-$d_6$ in 1.5 mL of $SO_2ClF$ and cooling of the mixture to -196 °C in a 10-mm NMR tube. $FSO_3D/SbF_5$ (1:1 molar ratio) was introduced, and the sample was slowly warmed to -125 °C. The resulting mixture was carefully homogenized with the the aid of a glass rod. A mixture of ions **1** and **1**-$d_6$ was prepared analogously by using 40 mg of diol **6**[8] and 60 mg of **10**-$d_6$. The best spectra of the dication solutions were obtained by employing the superacids mentioned. Other combinations of superacid, cosolvent, and precursor sometimes gave undesired byproducts.

**Acknowledgment.** The authors express their thanks to Professor M. Saunders for correspondence on this subject. E.M.G.A.v.K. is grateful to Professor M. Saunders for a stimulating stay in his laboratory at Yale University, Mr. K. Dijkstra (Department of Physical Chemistry, Groningen) has kindly recorded the 90.52-MHz $^{13}$C NMR spectra.

**Registry No.** **1**, 51257-59-1; **1**-$d_3$, 76010-09-8; **1**-$d_6$, 76010-08-7; **6**, 38525-05-2; **7**, 56745-77-8; **8**, 56745-78-9; **9**, 63963-73-5; **9**-$d_3$, 75934-45-1; *cis*-**10**-$d_6$, 75934-46-2; *trans*-**10**-$d_6$, 75934-47-3; $CD_3L_i$, 15772-82-4.

(25) The authors thank the referee for raising these points.

# Hindered Rotation in Substituted Benzyl Halides

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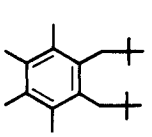
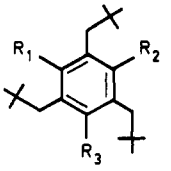
The barriers to internal rotation about sp$^2$(phenyl)-sp$^3$ carbon-carbon single bonds in a series of 2-(trichloroethyl)-3,4,5,6-tetramethylbenzyl halides (I) have been determined by using dynamic NMR spectroscopy. The magnitude of the barrier increases proportionally with the size of the halomethyl group. This leads to the tentative conclusion that steric crowding rather than dipolar repulsion determines the magnitude of the rotational barrier.

## Introduction

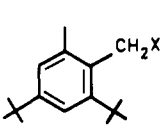
Hindered rotation about sp$^2$(phenyl)-sp$^3$ carbon-carbon single bonds has been studied by NMR techniques in a number of benzyl derivatives,[1] such as substituted neopentylbenzenes **1**[2,3] and **2**[3] and halides **3**[4] The barrier to



**1**



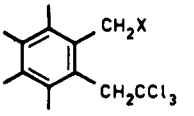

**2** (R=H, alkyl, halogen)




**3** (X = I, Br, Cl)

internal rotation of the neopentyl groups in compound **1** was calculated to be $\Delta G_{298}^{\ddagger}$ = 16.3 kcal/mol.[3b] The rotamer of lowest energy in the case of **1** was considered to have the neopentyl groups on opposite sides of the benzene ring. The magnitude of the barrier is most likely determined by the steric interactions between the neopentyl groups and the *o*-methyl substituents during the passage of the neopentyl past the methyl groups.[3a,b] This is supported by the finding that in the parent 1,2-dineopentylbenzene in which the ortho substituents are hydrogen atoms, the internal rotation could not be frozen out down to -90 °C.[3b] Also for benzyl halides **3** the conclusion was reached that the magnitude of the barrier to rotation of the $CH_2X$ group is largely determined by the steric interaction between X and the smaller ortho substituent, viz., the methyl group.[4] The barrier in **3** increases with increasing size of the substituent X; it varies from $E_a$ = 11.3 kcal/mol for X = Cl to $E_a$ = 15.9 kcal/mol for X = I. Conversely, the heights of such rotational barriers give an indication of the "effective size" of the substituent.[3b,5]

Recently we reported[6] the preparation of compounds **5** and **6** which show a substantial barrier to rotation about the phenyl-$CH_2$ bonds. In principle, the origin of the barrier might be attributed to steric crowding as well as to dipolar repulsion between X and $CCl_3$ groups. In order to evaluate the influence of the substituent X on the barrier height, the dynamic behavior for a series of benzyl halides of type I with X = I (**4**), Br (**5**), Cl (**6**), and F (**7**) was examined and the results are presented in this article.




**I**

(1) S. Sternhell in "Dynamic Nuclear Magnetic Resonance Spectroscopy", L. M. Jackman and F. A. Cotton, Eds., Academic Press, New York, 1975, pp 170-178.
(2) D. T. Dix, G. Fraenkel, H. A. Karnes, and M. S. Newman, *Tetrahedron Lett.*, 517 (1966).
(3) (a) P. Martinson, *Acta Chem. Scand.*, **26**, 3568 (1972); (b) B. Nilsson, P. Martinson, K. Olsson, and R. E. Carter, *J. Am. Chem. Soc.*, **96**, 3190 (1974); (c) E. Dahlberg, B. Nilsson, K. Olsson, and P. Martinson, *Acta Chem. Scand., Ser. B*, **29**, 300 (1975).
(4) C. A. Cupas, J. M. Bollinger, and M. Haslanger, *J. Am. Chem. Soc.*, **90**, 5502 (1968).
(5) H. Förster and F. Vögtle, *Angew. Chem.*, **89**, 443 (1977).
(6) J. Elzinga and H. Hogeveen, *J. Org. Chem.*, **44**, 2381 (1979).

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Table I. NMR Data for the $CH_2X$ and $CH_2CCl_3$ Groups of Compounds I

| | $^1$H NMR[a] | | | | $^{13}$C NMR[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | $CH_2X$ | | $CH_2CCl_3$ | | $CH_2X$ | | $CH_2CCl_3$ | |
| compd | δ | $J_{AB}$,[g] Hz | δ | $J_{AB}$,[g] Hz | δ | $J_{CH}$,[h] Hz | δ | $J_{CH}$,[h] Hz |
| 4 (X = I) | 4.89 | 10.0 | 4.37 | 14.5 | 7.7 | 150 | 52.7 | 132 |
| 5 (X = Br) | 5.02 | 11.0 | 4.42 | 14.5 | 32.5 | 150 | 52.3 | 130 |
| 6 (X = Cl) | 5.10 | 11.0 | 4.43 | 14.5 | 43.2 | 148 | 52.3 | 132 |
| 7 (X = F) | 5.65[c] | 11.5 | 4.36[d] | *f* | 80.7[e] | 150 | 52.2 | 132 |

[a] The chemical shifts were determined in acetone-$d_6$ solution at normal probe temperatures (ca. 30 °C) and coupling constants $G_{AB}$ at low temperature (ca. −40 °C). [b] Spectra taken in $CDCl_3$ solution at normal probe temperature (ca. 30 °C). [c] $J_{HF}$ = 49 Hz. [d] $J_{HF}$ = 0.8 Hz. [e] $J_{CF}$ = 160 Hz. [f] Could not be determined (see text). [g] Absolute values; estimated error 0.3 Hz. [h] Estimated error 1 Hz.

Table II. Coalescence Temperatures ($T_c$) and Free Enthalpies of Activation at $T_c$ ($\Delta G_c^{\ddagger}$) for the Averaging Processes in Compounds I (Acetone-$d_6$)

| | $CH_2X$ | | $CH_2CCl_3$ | |
|---|---|---|---|---|
| compd | $T_c$,[a] °C | $\Delta G_c^{\ddagger}$,[b] kcal/mol | $T_c$,[a] °C | $\Delta G_c^{\ddagger}$,[b] kcal/mol |
| 4 (X = I) | 12 | 14.2 | 13 | 14.1 |
| 5 (X = Br) | 0 | 13.6 | 1 | 13.6 |
| 6 (X = Cl) | −9 | 13.1 | −10 | 13.1 |
| 7 (X = F) | −22 | 12.5 | c | c |

[a] Estimated error 1 °C. [b] Estimated error 0.1 kcal/mol. [c] Could not be determined (see text).

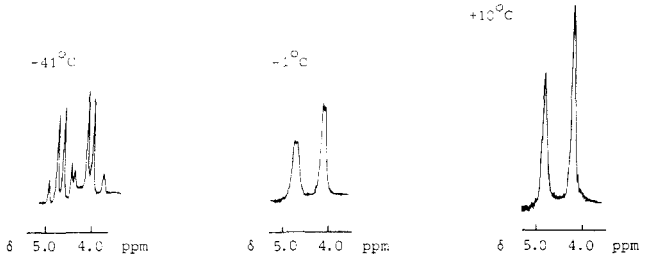


**Figure 1.** Temperature-dependent $^1$H NMR spectra (methylene region) of compound **12** (acetone-$d_6$).

## Results and Discussion

The 60-MHz $^1$H NMR spectrum of compound **5** in acetone-$d_6$ solution at the normal probe temperature (ca. 30 °C) showed for the $CH_2CCl_3$ and $CH_2Br$ protons sharp singlets at δ 5.02 and 4.42, respectively. When the sample was cooled (reversible) line broadening of both singlets occurred; at −41 °C two well-resolved AB quartets were observed for both the $CH_2Br$ and $CH_2CCl_3$ protons (see Figure 1). The coalescence temperatures $T_c$ were found to be 0 and 1 °C for the $CH_2Br$ and $CH_2CCl_3$ absorptions, respectively. Hence, the low-temperature (−41 °C) $^1$H NMR spectrum of **5** reveals that the protons $H_A'$ and $H_B'$ of the $CH_2CCl_3$ group and the protons $H_A''$ and $H_B''$ of the $CH_2Br$ group are magnetically inequivalent. At room temperature these protons are observed as being equivalent due to a temperature-dependent exchange process.

Similar phenomena were observed with compounds **4**, **6**, and **7**. The chemical shifts and coupling constants of compounds I are summarized in Table I; the pertinent data for the coalescence temperatures $T_c$ and free enthalpies of activation at the coalescence temperatures ($\Delta G_c^{\ddagger}$) for the averaging processes are compiled in Table II. The $\Delta G_c^{\ddagger}$ values were calculated from[7] eq 1, in which $T_c$ is the

$$\Delta G_c^{\ddagger} = 4.57 T_c \left( 9.97 + \log \frac{T_c}{\Delta \nu} \right) \qquad (1)$$

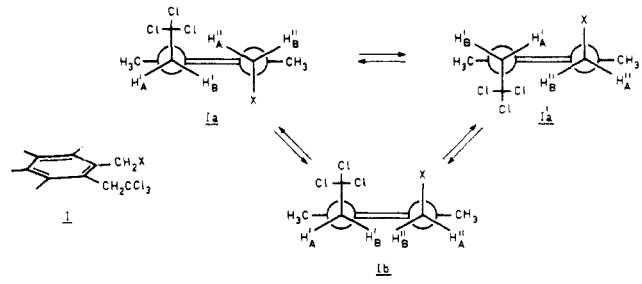


**Figure 2.** End-on view of the low-energy rotamers Ia and Ia' and the high-energy rotamer Ib.

Table III. van der Waals Volumes ($V_W$) of Substituents[a] ($cm^3$/mol)

| | | | |
|---|---|---|---|
| $CH_3$ | 13.67 | $CH_2I$ | 29.41 |
| $CH_2F$ | 15.95 | $CH_2CH_3$ | 23.90 |
| $CH_2Cl$ | 21.85 | $CH_2CCl_3$ | 50.28 |
| $CH_2Br$ | 24.63 | $CH_2CMe_3$ | 54.57 |

[a] Calculated according to ref 10.

coalescence temperature (in K) and $\Delta\nu = [(\nu_A - \nu_B)^2 + 6J_{AB}^2]^{1/2}$.

The $^1$H NMR spectrum of **7** exhibited in the rapid exchange region for the $CH_2F$ protons a doublet with $J_{HF}$ = 49 Hz and for the $CH_2CCl_3$ protons a doublet with $J_{HF}$ = 0.8 Hz. At low temperature (−58 °C) the absorption due to the $CH_2F$ protons consisted of two AB quartets; the line broadening of the $CH_2CCl_3$ group of **7** was insufficient—owing to the nearly equal chemical shifts of the protons $H_A'$ and $H_B'$—to permit any accurate measurement of the coalescence temperature.

Some projections of idealized conformations involved in the rotational process for benzyl derivatives of type I are visualized in Figure 2. The low-temperature $^1$H NMR spectra of compounds **4**–**7** reveal the existence of only one low-energy rotamer in each case, which agrees with the $^{13}$C NMR spectrum of **5** taken at −35 °C. The rotational process can be regarded as the interconversion of the enantiomeric rotamers Ia and Ia'. When this interconversion is slow on the $^1$H NMR time scale, the benzylic protons become diastereotopic and give rise to AB quartets as observed in the low-temperature $^1$H NMR spectra. The results compiled in Table II show that the $\Delta G_c^{\ddagger}$ values for the $CH_2CCl_3$ and $CH_2X$ exchange processes are equal (within experimental error) for each separate compound. This might be indicative of a concerted, disrotatory movement of the $CH_2CCl_3$ and $CH_2X$ groups. However, the equality of the $\Delta G_c^{\ddagger}$ values can in principle also be rationalized in terms of induced magnetic nonequiva-

(7) H. Günther, "NMR-Spektroskopie", Georg Thieme, Stuttgart, 1973, p 248.

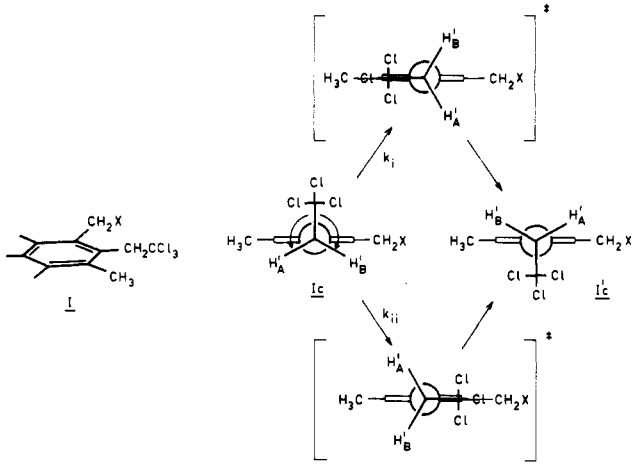

**Figure 3.** Possible pathways (i and ii) for rotation of the $CH_2CCl_3$ group.

lence:[3a] the assumption that at low temperature only the rotation of the larger substituent ($CH_2CCl_3$, Table III) is frozen out will render not only the $CH_2CCl_3$ protons diastereotopic but simultaneously also the $CH_2X$ protons, independently of whether the rotation of the smaller $CH_2X$ group is fast or slow on the $^1H$ NMR time scale. Consequently, the intimate details of the rotational process cannot be deduced in a simple fashion from the fact that the $\Delta G_c^{\ddagger}$ values for the $CH_2CCl_3$ and $CH_2X$ groups are equal for the compound studied. However, for instance in the case of compound **2** ($R_1$ = neopentyl; $R_2 = R_3$ = H) an explanation in terms of induced magnetic nonequivalence has been strongly preferred to that involving concerted rotations in order to explain the nonequivalence of the 1- and 3-neopentyl methylene protons at low temperature.[3a] If it is assumed that the same explanation is the preferred one for compounds I, then the nonconcerted rotations of the $CH_2CCl_3$ and $CH_2X$ moieties require the existence of a high-energy rotamer Ib[8] (not observed) which proceeds to either Ia or Ia'. In that case, the increase of the barrier to rotation of the $CH_2CCl_3$ group with increasing size of the $CH_2X$ group (Table III) can be rationalized by considering the two possible pathways i and ii for the interconversion of Ic and Ic' (Figure 3). It seems reasonable that $k_i$ will not be (strongly) affected by X, whereas $k_{ii}$ will decrease with increasing size of $CH_2X$. Hence, the value of $\Delta G_c^{\ddagger}$ for rotation of the $CH_2CCl_3$ group, which is dependent on the sum of $k_i$ and $k_{ii}$, will increase with increasing size of the substituent $CH_2X$.

In view of the current interest in correlating rotational barriers with the size[3b,5] of (functional) groups, a plot was made of the $\Delta G_c^{\ddagger}$ values[9] against Van der Waals volumes $V_W$[10] of the substituent $CH_2X$ (Table III) to give a straight line with $r$ = 0.995 (Figure 4). From this linear relationship between rotational barriers and size of $CH_2X$ the tentative conclusion can be drawn that steric crowding rather than dipolar repulsion between $CCl_3$ and X determines the magnitude of the rotational barrier of the $CH_2CCl_3$ group in compounds I. It has been suggested[11]

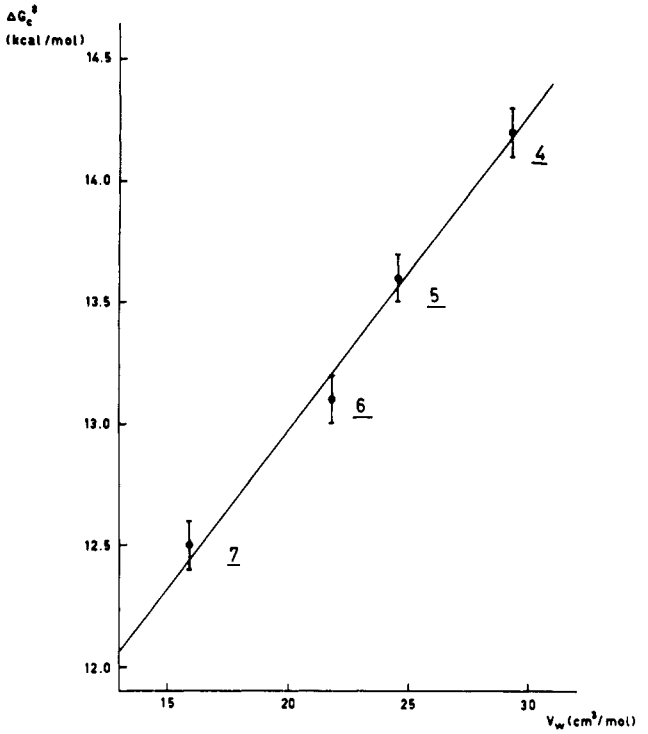


**Figure 4.** Plot of $\Delta G_c^{\ddagger}$ values (Table II) vs. van der Waals volumes of substituents $CH_2X$ ($V_W$, Table III) for compounds I.

that the rotational process in I is probably also affected by buttressing effects from the other methyl groups. This is supported by the finding that the barrier for internal rotation of a neopentyl group past a methyl group is 15.4 kcal/mol in trineopentylbenzene derivatives of type **2**, whereas it amounts to 16.3 kcal/mol in 1,2-dineopentyltetramethylbenzene (**1**).

## Experimental Section

**General Procedures.** Compounds **5** and **6** were prepared according to ref 6. $^1H$ NMR spectra were recorded in acetone-$d_6$ solution on a JEOL-C60HL spectrometer. The coalescence temperatures were determined with the aid of a calibrated temperature-dependent methanol chemical shift curve.

**Synthesis of 1-(2,2,2-Trichloroethyl)-2-(iodomethyl)-3,4,5,6-tetramethylbenzene (4).** To a solution of 320 mg (0.90 mmol) of **5** in 25 mL of acetone was added 1.00 g (6.6 mmol) of NaI. The mixture was refluxed for 1 h, followed by filtration and evaporation of the solvent. The residue was extracted with pentane, giving after removal of the pentane 360 mg of a yellow oil which contained 0.70 mmol (yield 78%, determined by $^1H$ NMR spectroscopy using benzene as reference) of **4**. Further purification could not be achieved due to the instability of **4** toward chromatography (silica gel, alumina); also attempts to crystallize **4** (pentane and methanol, −40 °C) were unsuccessful. A correct elemental analysis could not be obtained (compare ref 4). The sample of **4** obtained was, however, free of extraneous absorptions in the methylene region of the $^1H$ NMR spectrum. Spectroscopic data for **4**: $^1H$ NMR ($CCl_4$) $\delta$ 4.70 (s, 2 H), 4.27 (s, 2 H), 2.35 (s, 3 H), 2.25–2.20 (overlapping signals, 9 H) (also see Table I); $^{13}C$ NMR ($CDCl_3$) $\delta$ 136.6, 136.4, 135.3, 134.1, 133.5, 127.4, 99.4 ($CCl_3$), 52.7 (t, $J_{CH}$ = 132 Hz), 19.7 (q), 17.4 (q), 17.1 (q), 16.5 (q), 7.7 (t, $J_{CH}$ = 150 Hz) (also see Table I); mass spectrum, $m/e$ 277 ($M^+ - I$, $C_{13}H_{16}{}^{35}Cl_3I$), 241 ($M^+ - I - H^{35}Cl$).

(8) A referee has pointed out that the structure of the high-energy rotamer may be different from Ib. An alternative explanation for the conversion Ia → Ia' involves the intermediacy of high-energy rotamers that are formed from Ia by rotating the $CH_A{}''H_B{}''X$ group in Ia 120° (counterclockwise) followed by rotating the $CH_A{}'H_B{}'CCl_3$ group 120° (counterclockwise). There is no evidence in favor of or against this alternative.

(9) It is tacitly assumed that the $T\Delta S^{\ddagger}$ contributions to the $\Delta G^{\ddagger}$ values are negligibly small.

(10) A. Bondi, "Physical Properties of Molecular Crystals, Liquids and Glasses", Wiley, New York, 1968, Chapter 14.

(11) Dr. P. Martinson, private communication. Dr. Martinson has also pointed out that, assuming that the Van der Waals volume of F is equal to that of H, the observed $\Delta G_c^{\ddagger}$ of 7 corresponds to $2k_i$ (see Figure 3). Consequently, the barrier ($\Delta G_c^{\ddagger}$) for rotation of the $CH_2CCl_3$ group past the $CH_3$ (or $CH_2F$) group amounts to 12.9 kcal/mol (12.5 + $RT$ ln 2). In any case the barrier lies between 12.5 and 12.9 kcal/mol. It is interesting to note that the corresponding barrier for the larger (see Table III) neopentyl group past a methyl group is 15.4 kcal/mol.

**Synthesis of 1-(2,2,2,-Trichloroethyl)-2-(fluoromethyl)-3,4,5,6-tetramethylbenzene (7).** To a stirred solution of 320 mg (0.90 mmol) of **5** in 10 mL of acetonitrile was added 400 mg of anhydrous AgF. Stirring was continued for 1 h at room temperature, followed by filtration and evaporation of the solvent. The residue was extracted with pentane, leaving after removal of the pentane in vacuo 240 mg of a yellow oil which contained 0.52 mmol (yield 58%, determined by $^1H$ NMR spectroscopy using benzene as reference) of **7**. Further purification could not be achieved due to the instability of **7** at room temperature (when stored at −40 °C, no decomposition was observed after several days). Also attempts to crystallize **7** (pentane and methanol, −40 °C) were unsuccessful. The sample of **7** obtained was free of extraneous absorptions in the methylene region of the $^1H$ NMR spectrum. Spectroscopic data for **7**: $^1H$ NMR ($CCl_4$) δ 5.57 (d, $J_{HF}$ = 49 Hz, 2 H), 4.28[12] (s, 2 H), 2.35–2.23 (overlapping signals, probably with $J_{HF}$ couplings, 12 H) (also see Table I); $^{13}C$ NMR (acetone-$d_6$) δ 137.8 136.9, 135.8, 135.3, 132.6, 129.1, 101.4 ($CCl_3$), 80.7 (dt, $J_{CF}$ = 160 Hz, $J_{CH}$ = 150 Hz), 52.5 (t, $J_{CH}$ = 132 Hz), 19.6 (q), 17.5 (q), 16.9 (q), 16.8 (q) (see also Table I); exact mass calcd for $C_{13}H_{16}{}^{35}Cl_3F$ ($M^+$) 296.030, found 296.031.

**Acknowledgment.** We are grateful to Dr. Per Martinson, Mölndal, for helpful comments on our results.

**Registry No.** **4**, 76036-49-2; **5**, 70130-76-6; **6**, 70130-74-4; **7**, 76036-50-5.

(12) In the 100-MHz $^1H$ NMR spectrum this absorption is split into a doublet ($J_{HF}$ = 0.8 Hz).

# Antileukemic C-15-Functionalized Ambrosanolides from *Rudbeckia mollis*[1]

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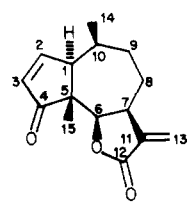
Four new C-15-functionalized ambrosanolides were isolated from *Rudbeckia mollis*. The structure and stereochemistry of the principal lactone constituent rudmollin (**2a**) were deduced by a combination of chemical and spectroscopic methods and by X-ray crystallography. Minor lactones 4-acetoxyrudmollin (**2b**), 15-acetoxyrudmollin (**2c**), and rudmollitrin (**4b**) were also obtained. Rudmollin and 15-acetoxyrudmollin exhibited activity in the P-388 lymphoid leukemia system.

Ambrosin (1, Chart I), damsin (2,3-dihydroambrosin), and some of their relatives[2] possess cytoxic or antitumor activity,[3,4] and much recent effort has been devoted to their synthesis.[5] Members of this group of sesquiterpene lactones, the ambrosanolides, are almost exclusively found in subtribe Ambrosiinae of Heliantheae[6] and appear to be responsible for the allergic contact dermatitis produced by various species of this subtribe.[4,7,8]

Chart I



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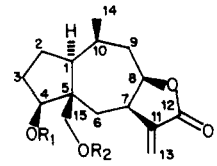
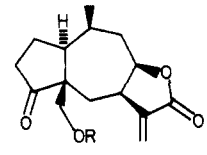
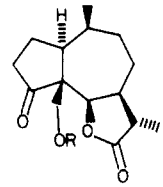


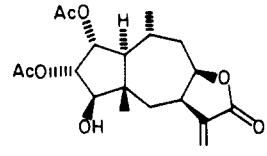
2a, $R_1$, $R_2$ = H
b, $R_1$ = Ac, $R_2$ = H
c, $R_1$ = H, $R_2$ = Ac
d, $R_1$, $R_2$ = Ac
e, $R_1$, $R_2$ = 



3a, R = H
b, R = Ac



4a, R = H
b, R = Ac



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In continuing our search for biologically active lactones[9] we had occasion to study *Rudbeckia mollis* Ell., a coneflower found in the coastal plain of Alabama, south Georgia, and north Florida. We now report isolation and

(1) Work at the Florida State University was supported in part by a grant from the U.S. Public Health Service (CA-13121) through the National Cancer Institute.

(2) For references to the chemistry, see: Fischer, N. H.; Oliver, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.

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(9) Previous paper: Herz, W.; Govindan, S. V.; Blount, J. F. *J. Org. Chem.* **1981**, *46*, 761.

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