Di(2-adamantyl) Disulfide (7)

A solution of 1.27 g (5 mmoles) of iodine in 25 ml of ethanol was added dropwise to a stirred solution of 1.68 g (10 mmoles) of 2-adamantanethiol and 0.54 g (10 mmoles) of sodium methoxide in 50 ml of a 1:1 mixture of ethanol and 1,2-dimethoxyethane. The disulfide precipitated and was isolated by filtration (weight 1.61 g). It was very well soluble in carbon tetrachloride, benzene, ethylacetate, and petroleum ether, only slightly in hot acetonitrile or hot ethanol. It was twice recrystallized from benzene – acetonitrile (1:2) giving 1.32 g of di(2-adamantyl) disulfide (yield 79%), m.p. 275°.

Anal. Calcd. for $C_{20}H_{30}S_2$: C, 71.80; H, 9.04; S, 19.16. Found: C, 71.44; H, 8.95; S, 19.14.

Mass spectrum: *m/e* 334 (M^+). For the n.m.r. spectrum see Table 1 and text.

N-(2-Adamantylthio)-phthalimide (10)

A solution of 2-adamantanesulfenyl chloride (**9**) was prepared as follows (10): to a stirred suspension of 2.72 g (20.4 mmoles) of *N*-chlorosuccinimide in 30 ml of benzene was added a solution of 3.36 g (20 mmoles) of 2-adamantanethiol in 10 ml of benzene. The vigorously stirred reaction mixture turned yellow–orange and was filtered after 15 min.

The clear filtrate, containing the sulfenylchloride was added to 2.94 g (20 mmoles) of phthalimide in 20 ml of *N,N*-dimethylformamide containing 2.7 g (27 mmoles) of triethylamine. After 20 min of stirring at 25°, the reaction mixture was left standing for 40 h. After filtration to remove the formed triethylammonium chloride the filtrate was poured into 200 ml of water. After extraction with carbon tetrachloride (three times) the extract was washed with water, dried ($MgSO_4$), and concentrated till almost dry. Addition of 100 ml of petroleum ether, filtration, and drying of the product gave 4.5 g of almost colorless *N*-(2-adamantylthio)-phthalimide (72%), which could be recrystallized from ethanol; m.p. 166–167°.

Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; S, 10.23. Found: C, 69.20; H, 6.16; N, 4.28; S, 10.46.

Mass spectrum: *m/e* 313 (M^+). The i.r. spectrum ν_{max}(KBr): 1755 cm^{-1} (very strong, C=O); n.m.r. τ (CCl_4): 2.19 (multiplet, 4H, aromatic protons), 6.52 (singlet, 1H, proton at C-2), τ 6.4–8.7 (unresolved multiplet, 14H).

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1. J. W. Greidanus and W. J. Schwalm. Can. J. Chem. **47**, 3715 (1969).
2. J. W. Greidanus. Can. J. Chem. This issue.
3. J. R. Geigy A.-G. Belg. Pat. 629 370 (1963); Chem. Abstr. **60**, 9167*c* (1964).
4. P. von R. Schleyer and R. D. Nicholas. J. Amer. Chem. Soc. **83**, 182 (1961). R. C. Fort, Jr. and P. von R. Schleyer. Chem. Rev. **64**, 277 (1964). C. R. Carpenter. Ph.D. Thesis. The Pennsylvania State University, University Park, Pennsylvania, 1967.
5. W. Hoek, J. Strating, and H. Wynberg. Rec. Trav. Chim. **85**, 1045 (1966).
6. S. Landa, J. Burkhard, and J. Vais. Z. Chem. **7**, 388 (1967).
7. J. C. Powers and F. H. Westheimer. J. Amer. Chem. Soc. **82**, 5431 (1960).
8. R. M. Dodson and P. B. Sollman. U.S. Pat. 2753361 (1956); Chem. Abstr. **51**, 2079 (1957). R. M. Dodson and P. B. Sollman. U.S. Pat. 2840577 (1958); Chem. Abstr. **53**, 453 (1959).
9. W. D. Kingsbury and C. R. Johnson. Chem. Commun. 365 (1969).
10. H. Emde. German Pat. 804572 (1951); Chem. Abstr. **46**, 529 (1952).
11. F. W. van Deursen and P. K. Korver. Tetrahedron Lett. 3923 (1967).
12. T. Ledaal. Tetrahedron Lett. 1683 (1968).
13. M. Fetizon, J. Goré, P. Laszlo, and B. Waegell. J. Org. Chem. **31**, 4047 (1966).
14. H. Lumbroso and G. Dumas. Bull. Soc. Chim. France, 651 (1955).
15. F. A. Cotton and R. Francis. J. Amer. Chem. Soc. **82**, 2986 (1960).
16. H. Lumbroso and R. Passerini. Bull. Soc. Chim. France, 1179 (1955).

Identification of 1-(4-methoxyphenyl)-1-methoxy-2-aminopropane diastereoisomers

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A method for the assignment of *erythro* and *threo* configurations to the diastereoisomeric 1-(4-methoxyphenyl)-1-methoxy-2-aminopropanes and related compounds based on p.m.r. data is presented and discussed.

Canadian Journal of Chemistry, **48**, 3597 (1970)

The physiological activities of the (+) and (−) forms of the *erythro* and *threo* isomers of derivatives of phenylpropanolamine, $C_6H_5CH(OH)CH(CH_3)NH_2$ may be expected to differ, and a positive identification of the forms is essential in analysis and for investigations of structure–activity relationships (1). Synthetic compounds of the type $ArCH(OR^1)CHR^2NH_2$ (2, 3) are a case in point, and the difficulties in assigning configurations to the potentially hypo-

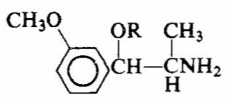
TABLE 1

The p.m.r. spectral data* from β-nitrostyrene derivatives

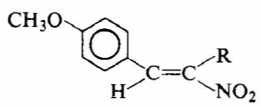
Compound	β-R	4-OCH_3	α-OCH_3	α-H	β-H	β-CH_3
5	NO_2	6.20	6.77	*ca.* 5.10 q (4, 8)	*ca.* 5.35 q (12, 8) and *ca.* 5.65 q (12, 4)	—
6*a*	NO_2	6.22	6.75	5.15——5.7	α-H and β-H give overlapping multiplet	8.47 d (6.5)
6*b*	NO_2	6.20	6.85	5.15——5.7		8.76 d (6.5)
7	NH_2 7.77	6.21	6.77	5.90 t (6)	7.13 d (6)	—
8*a*	NH_2 8.30	6.20	6.78	~6.15 d?	6.85 m	8.93 d (6.5)
8*b*	NH_2 8.30	6.20	6.80	~6.28 d?	6.85 m	9.13 d (6.5)
9	N^+H_3 1.55	6.21	6.73	5.38 q (6.5, 7.5)	6.85 m	—
10*a*	N^+H_3 1.45	6.20	6.61	5.33 d (4.5)	6.50 m	8.72 d (6.5)
10*b*	N^+H_3 1.25	6.20	6.73	5.77 d (9)	6.55 m	8.72 d (6.5)
11	NH_2 8.22	6.25	—	*ca.* 7.60 q (13, 8) and *ca.* 7.32 q (13, 5.5)	*ca.* 6.88 m	8.92 d (6.5)

*τ-Values, measured with a Varian A-60A spectrometer using solutions *ca.* 15% in $CDCl_3$ containing TMS as internal standard, CH_3 signals were experimentally reproducible within ± 0.01 p.p.m. Chemical shift differences cited in the text were confirmed by measuring spectra of appropriate mixtures. Signals were singlets except when d = doublet, t = triplet, q = quartet, and m = multiplet, with first-order coupling constants (Hz) indicated. The α- and β-protons of **5**, **6** and **11** give complex signals and τ-values are approximate. The α-H of **8***a* and of **8***b* gives a doublet, one branch obscured by the 4-OCH_3. The spectrum of **8***b* was obtained only in the presence of **8***a*.

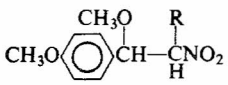
tensive derivatives **1** and **2** have been alluded to recently (3). In the present study the p.m.r. spectra of some derivatives of 4-methoxy-β-nitrostyrene (**3**) which exist as *erythro* and *threo* racemates, were examined in an attempt to assign their relative configurations by methods of conformational analysis.



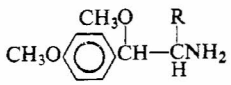
1 R = CH_3
2 R = C_2H_5



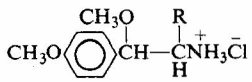
3 R = H
4 R = CH_3



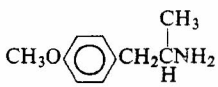
5 R = H
6 R = CH_3



7 R = H
8 R = CH_3



9 R = H
10 R = CH_3



11

Nitrostyrenes react with methoxide ion in methanol to give methoxynitropropanes (2, 3), and the nitrostyrene **4** produces a mixture of the (±) *threo* and (±) *erythro* compounds **6** in the ratio major product *a*:minor *b* = 2:1 (by integrated p.m.r.). These isomers could not be separated by analytical t.l.c. using several systems. Reduction of the mixture **6** with lithium aluminum hydride afforded the amino compounds (±) **8** in the ratio major *a*:minor *b* = 3:2 (by p.m.r.). The high yield (90%) shows that the ratio change is not due to preferential reduction or recovery of one form, but that some racemization of the acidic β-carbon occurs under the influence of the reagent. A net inversion under these conditions is unreasonable and contraindicated by the observation that in both **6** and **8** the (generally similarly environed, see below) downfield β-CH_3 compound predominates. Compound (±) **7** was obtained similarly. The two diastereoisomers of **8** were separated in small amounts by column chromatography, and then converted into the (±) hydrochlorides **10**.

Salient features of the p.m.r. spectra of compounds **5**–**10** are presented in Table 1. Newman projections of the staggered-form rotamers corresponding with *erythro* and *threo* forms are depicted in Fig. 1. Assuming that steric interactions principally govern the relative conformational energies, rotamer **A** should dominate in every case. (In an investigation of ephedrine and ψ-ephedrine, Hyne (4) pointed out that such views must be held with caution). Hence, in compounds **6**, **8**, and **10**, effects on the α-OCH_3 and β-CH_3 due to electric fields and the magnetic anisotropies of the nitro and aryl groups respectively would be more marked in the *threo* form. Comparing **7** and **8** the (upfield) α-OCH_3 shifts on methylation of the β-carbon are very small in both series. However, when compounds **5** and **6** are compared there results an α-OCH_3 upfield shift of 0.08 p.p.m. for the minor product **6***b* and a downfield shift of only 0.02 p.p.m. for **6***a*.

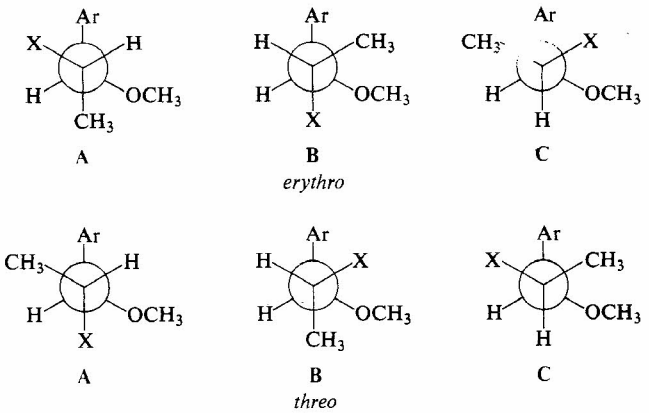


FIG. 1. *erythro* and *threo* **6**, **8**, and **10** where X = NO_2, NH_2, and N^+H_3 respectively.

Since the highly anisotropic NO_2 group would be expected to exert greater through-space effects than a CH_3 group, this indicates (assuming that rotamers about the C_α–C_β bond in **5** are roughly equally populated) that the upfield shift is due to resultant net shielding of the α-OCH_3 by the β-NO_2 group and therefore that the *threo* form is probably the minor product **6***b*. In compounds **8** the α-OCH_3 groups fall into similar electronic environments, but the β-CH_3 groups are seen to be disposed fairly similarly to their average in **6**.

The amino function of the ephedrines relatively deshields *gauche* protons (4). If the NO_2 shielded the *gauche* OCH_3 of *threo* **6**, on reduction the *threo* α-OCH_3 of **8** would be the more deshielded (0.05 p.p.m.) and changing inductive effects could account for the small upfield shift (0.03 p.p.m.) of the *erythro* α-OCH_3. However, if the NO_2 group deshielded the *gauche* α-OCH_3, the *threo* isomers would be the major components *a*, but it seems unlikely that the *erythro* α-OCH_3 would shift downfield by 0.05 p.p.m. (from 6.85 to 6.80τ) on reduction of the generally remote NO_2. These interpretations, favoring shielding of the α-OCH_3 by a *gauche* β-NO_2 require simultaneous relative shielding of the β-CH_3 by the *gauche* aromatic ring. A comparison of the β-CH_3 shifts in mixed and single samples of **8** and *p*-methoxyamphetamine (**11**) shows a large (0.21 p.p.m., **8***b*) and small (*ca.* 0.01 p.p.m., **8***a*) upfield shift results on α-methoxylation. Following the argument presented for **5** and **6** above the aryl group shields the *gauche* CH_3, and **8***b* is the *threo* isomer. The p.m.r. spectra (CS_2) (5) of *meso* and *dl*-2,3-diphenylbutane, in which the CH_3 and C_6H_5 groups are predominantly *gauche* and *trans* disposed respectively, demonstrated relative shielding of the CH_3 groups (at 9.04 and 8.78 respectively) by the *gauche* benzene ring, and a study of a 1,2-diphenyl-propyl series (6) showed a shielding of about 0.3 p.p.m. ($CDCl_3$) for a predominantly *gauche vs. trans* CH_3/C_6H_5 conformation.

The shielding effects of a NO_2 group qualitatively resemble those of a carbonyl function (7) and Barbieux and Martin (8) investigated *erythro* and *threo* ethyl α,β-dialkyl-*p*-methoxydihydrocinnamates. Coupling constants between the α and β protons were not reported, assignments were made on the basis that *gauche* aryl and carboethoxy groups in the *threo* isomers would result in a relatively upfield position of those ethyl protons (9). Their spectra show that an α-CH_3 is overall shielded (higher field) by anisotropic effects of a *gauche* compared with a *trans* carboxyl function.

Because the aryl and nitro groups of **6** and **8** rotate and different relative rotamer populations of **5**–**8** and **11** are expected, the criteria for comparative shielding effects are difficult to assess. However, these results leave little doubt that **6***b* and **8***b* are the *threo* isomers.

Conversion of isomers **8** into the amine salts **10** preserves the stereochemical integrity of each form. Table 1 shows that the more widely split α-H of **10** is from the minor component **10***b* and appears at higher field than in isomer **10***a*. Vicinal coupling constants of this magnitude (9 Hz) are generally associated with dihedral angles of about 180° (10), indicating that **10***b* exists largely in the **A** form (*erythro* or *threo*) and that the major product has relatively greater contributions from **B** and **C** type rotamers. Since

in **B** and **C** rotamers the α-protons are on average further away from the ammonium ion, overall relative shielding of the *gauche* protons by it (or its ion pair/ion complex moiety) is indicated. In **10***b* the α-H and α-OCH_3 are *both* upfield of their positions in diastereoisomer **10***a*. This simultaneous shielding seems reasonable for the **A** rotamer of the *threo* series where both the α-H and α-OCH_3 are *gauche* to the ionic moiety, and it follows that **10***b* and therefore **8***b* and **6***b* are the *threo* isomers, consistent with the evidence for **8** and **6** assignments presented above. The designation *threo* to the isomer **10***b* with larger coupling here is in line with results for ephedrines (4) and agrees with the magnitudes of the H_α–H_β coupling constants for the appropriate diastereoisomers of 1-substituted-1,2-diphenylpropanes (6).

In monosubstituted cyclohexanes, conformational (steric) preferences in aprotic solvents increase as $NO_2 < NH_2 < N^+H_3$ (12). The β-CH_3 groups of the salts **10** appear at the same chemical shift, again suggesting that *erythro* rotamers **B** and **C** (*gauche* aryl/CH_3) abnormally contribute. In these three forms the α-OCH_3 and β-N^+H_3 are *gauche*; possibly polar interactions have a stabilizing influence.

It is probable that for diastereomeric pairs similar to **6**, **8**, and **10** (*i.e.* with different aromatic substitutions), the (±) *threo* configuration may be assigned to the isomer with the relatively upfield α-H, β-CH_3, and/or α-OCH_3 signals, the latter two being easily visible and so diagnostically useful. The analysis may be extendable to the corresponding signals from compounds with other α-alkoxyl and β-alkyl groups, but this has not been investigated.

Experimental

Melting points are uncorrected. The known nitrostyrenes used here were prepared by the condensation of anisaldehyde with nitromethane or nitroethane using NH_4OAc/HOAc (11).

1-(4-Methoxyphenyl)-1-methoxy-2-nitroethane (5)

This was prepared by the general method of Howe *et al.* (3) from 4-methoxy-β-nitrostyrene (**3**). Crude yield (oil) 97%. Distillation (partial dec.) gave **5** (55%), b.p. 136°/2 mm, m.p. 50–51°; oil ν_{max} (film): 1555 and 1380 cm^{-1} (NO_2); (Nujol): 1550 and 1375 cm^{-1}; lit. m.p. 57–58° (2).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.01; H, 6.29; N, 6.49.

1-(4-Methoxyphenyl)-1-methoxy-2-nitropropane (6)

This was obtained similarly from 4-methoxy-β-methyl-β-nitrostyrene, (**4**) in 95% yield as a pale yellow oil, examined and used without purification. The t.l.c. (silica gel and alumina, Et_2O, $CHCl_3$, C_6H_6, and C_6H_{14}: Me_2CO = 2:1) gave a single spot or streak, ν_{max} (film): 1555 and 1370 cm^{-1} (NO_2).

2-(4-Methoxyphenyl)-2-methoxyethylamine (7)

A crude sample of **5** (3.3 g) in dry ether (30 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (2 g) in dry ether (50 ml). The mixture was kept at reflux for 5 h, cooled, and treated with ordinary ether (50 ml) followed by the cautious addition of water (6 ml). The ethereal suspension was filtered under weak vacuum and the ether solution dried ($MgSO_4$) and concentrated to give the amine **7** as a colorless oil, 1.9 g. This was quantitatively converted into the hydrochloride **9** using a saturated solution of hydrogen chloride in ether. Recrystallization from chloroform–hexane gave prisms, m.p. 162–163°, lit. 165–166.5°, dec. 186–187 (2) and 186–187° (13); ν_{max} (Nujol) 2800–2600 cm^{-1} (N^+H_3).

Anal. Calcd. for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; N, 6.43. Found: C, 55.07; H, 7.50; N, 6.31.

The amine was regenerated from its hydrochloride by treatment with sodium carbonate solution and was extracted with chloroform.

1-(4-Methoxyphenyl)-1-methoxy-2-aminopropane (8)

The crude *erythro–threo* mixture **6** (4 g) was reduced in ether with lithium aluminum hydride (2 g), furnishing the amine **8** as a colorless oil (3.1 g, 90%). This was examined by p.m.r. and then adsorbed on to silica gel (50 g). Elution with chloroform (50 ml fractions, 350 ml) afforded the major component (0.23 g). Continued elution (700 ml) gave mixtures of **8***a* and **8***b* (1.39 g). Elution with 1% methanol (200 ml) and 2% methanol in chloroform (50 ml) gave **8***a* and **8***b* (0.51 g). Continued elution with 2% methanol in chloroform (500 ml) gave **8***b* containing traces of **8***a* (by t.l.c.) (0.22 g). Samples of **8***a*·HCl, m.p. 177–178 raised to 178–180° by recrystallization from $CHCl_3$ and **8***b*·HCl, m.p. 171–173 raised to 178–179° had mixed m.p. 160–162°. Their i.r. spectra (KBr) were similar, but the samples showed no detectable amounts of the other by i.r. and p.m.r.

Anal. Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.00; H, 7.83; N, 6.05; Cl, 15.31. Found for **8***a*·HCl: C, 57.17; H, 7.61; N, 6.01; Cl, 15.25. Found for **8***b*·HCl: C, 56.87; H, 7.85; N, 5.97.

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1. G. A. Alles. J. Pharmacol. Exp. Ther. **47**, 339 (1933).
2. K. W. Rosenmund. Ber. Deut. Chem. Ges. **46**, 1034 (1913).
3. R. Howe, E. H. P. Young, and A. D. Ainley. J. Med. Chem. **12**, 998 (1969).
4. J. B. Hyne. Can. J. Chem. **39**, 2536 (1961).
5. A. A. Bothner-By and C. Naar-Colin. J. Amer. Chem. Soc. **84**, 743 (1962).
6. C. A. Kingsbury and D. C. Best. J. Org. Chem. **32**, 6 (1967).
7. K. Tori and K. Kuriyama. Tetrahedron Lett. 3939 (1964).

8. M. BARBIEUX and R. H. MARTIN. Tetrahedron Lett. 2919 (1965).
9. D. Y. CURTIN and S. DAYAGI. Can. J. Chem. **42**, 867 (1964).
10. M. KARPLUS. J. Chem. Phys. **30**, 11 (1959).
11. M. G. S. RAO, C. SRIKANTIA, and M. S. IYENGAR. Helv. Chim. Acta, **12**, 581 (1929); L. C. RAIFORD and D. E. FOX. J. Org. Chem. **9**, 170 (1944).
12. J. MCKENNA. Conformational analysis of organic compounds. Royal Institute of Chemistry Lecture Series No. 1 (1966).
13. B. REICHERT. Arch. Pharm. **274**, 369 (1936).

Reactions of trifluoromethyl and methyl radicals with ethylene oxide

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The reaction between CF_3 radicals and ethylene oxide was studied in the range 60–228 °C using CF_3I as a radical source. For the reactions,

$$CF_3 + CH_2\text{—}CH_2O \xrightarrow{k_H} CF_3H + CH_2\text{—}CHO$$

$$CF_3 + CF_3 \xrightarrow{k_c} C_2F_6$$

we obtain

$$\log k_H/k_c^{1/2}(cm^{3/2}\ mole^{-1/2}\ s^{-1/2}) = (5.77 \pm 0.12) - (11.02 \pm 0.22)/\theta$$

where $\theta = 2.3RT$ kcal mole^{-1}.

Published data of Phibbs and Darwent on the reaction

[5] $$CH_3 + CH_2\text{—}CH_2O \rightarrow CH_4 + CH_2\text{—}CHO$$

have been re-calculated and it is suggested that both the original and re-calculated values of the activation energy E_5 are too low. The Arrhenius parameters for the reactions of CF_3 and CH_3 radicals with ethylene oxide are compared with those for related reactions.

Canadian Journal of Chemistry, **48**, 3601 (1970)

As part of a study of the vapor phase reactions of free radicals with cyclic compounds, we have determined Arrhenius parameters for the abstraction of hydrogen by CF_3 radicals from ethylene oxide. The radicals were generated by photolysis of CF_3I.

We have also re-calculated the data of Phibbs and Darwent (1) on the corresponding reaction involving CH_3 radicals with ethylene oxide. Their results on CH_3 + cyclopropane have also been re-interpreted. It is found that published data on the reaction between CH_3 radicals and ethylene oxide are anomalous and the system appears to require re-investigation.

Experimental

Ethylene oxide was purified by bulb-to-bulb distillation retaining a middle cut which was stored in liquid nitrogen. It was better than 99.9% pure as indicated by g.l.c. No impurities could be detected by i.r. spectroscopy.

Mixtures of CF_3I and ethylene oxide were photolyzed and the products analyzed using procedures described elsewhere (2).

Results

Blank experiments without photolysis showed that there is no dark reaction between CF_3I and ethylene oxide, EtO. When the mixture is photolyzed, important reactions are [1]–[3]. The

[1] $$CF_3I + h\nu \rightarrow CF_3 + I$$

[2] $$CF_3 + CH_2\text{—}CH_2O \rightarrow CF_3H + CH_2\text{—}CHO$$

[3] $$CF_3 + CF_3 \rightarrow C_2F_6$$

radical produced by reaction 2 is probably scavenged by various reactions producing iodides (2, 3). If CF_3H and C_2F_6 are formed only by reactions 2 and 3, the rate constants of which we donate by k_H and k_c respectively, then

[4] $$k_H/k_c^{1/2} = R_{CF_3H}/R_{C_2F_6}^{1/2}\ [EtO]$$

where R denotes rate of formation of product. The photolyses covered the range 60–228 °C and the results are given in Table 1. It is seen that at