cipitated solid was filtered, washed with water and ethanol and dried.

***N*-[4-[[(2,4-Diaminopyrido[3,2-*d*]pyrimidin-6-yl)methyl]amino]benzoyl]-L-glutamic Acid or 8-Deazaaminopterin (18).** 18 was prepared in 72% yield from 14: mp 100–102 °C; mass spectrum, *m/e* 551 (M^+, octamethyl derivative); UV λ_{max} (pH 1) 318 (ϵ_{max} 10 000); (pH 7) 278 (22 300), 355 (8000); (pH 13) 278 (25 000), 355 (8000); ^1H NMR (Me_2SO-d_6 + D_2O) δ 4.6 (s, 2, CH_2), 7.8 (s, 2, C^7H and C^8H), 6.9 and 7.91 (q, 4, C_6H_4).

Anal. Calcd for $C_{20}H_{21}N_7O_5 \cdot 1.5H_2O$: C, 51.49; H, 5.18; N, 21.02. Found: C, 51.76; H, 4.96; N, 20.67.

***N*-[4-[[(2,4-Diaminopyrido[3,2-*d*]pyrimidin-6-yl)methyl]methylamino]benzoyl]-L-glutamic Acid or 8-Deazamethotrexate (19).** 19 was prepared in 68% yield from 15: mp 260 °C dec; mass spectrum, *m/e* 551 (M^+, heptamethyl derivative); UV λ_{max} (pH 1) 318 (ϵ_{max} 11 000), 333 (7700); (pH 7) 275 (16 000), 305 (20 400); (pH 13) 278 (19 500), 307 (25 500); ^1H NMR (Me_2SO-d_6 + D_2O) δ 3.27 (s, 3, $N^{10}CH_3$), 6.91 and 7.9 (q, 4, C_6H_4), 7.58 and 7.85 (q, 2, C^7H and C^8H).

Anal. Calcd for $C_{21}H_{23}N_7O_5 \cdot 2.0H_2O$: C, 51.52; H, 5.55; N, 20.03. Found: C, 51.92; H, 5.20; N, 20.49.

***N*-[4-[[(2,4-Diaminopyrido[3,2-*d*]pyrimidin-6-yl)methyl]oxy]benzoyl]-L-glutamic Acid or 8-Deaza-10-oxaaminopterin (20).** 20 was prepared in 62% yield from 16: mp 260–262 °C; mass spectrum, *m/e* 538 (M^+, heptamethyl derivative); UV λ_{max} (pH 1) 246 (ϵ_{max} 32 000), 318 (8300); (pH 7) 248 (35 500), 333 (6600); (pH 13) 250 (36 000), 343 (6300); ^1H NMR (Me_2SO-d_6 + D_2O) δ 5.43 (s, 2, CH_2–O), 7.31 and 8.05 (q, 4, C_6H_4), 7.93 (s, 2, C^7H and C^8H).

Anal. Calcd for $C_{20}H_{20}N_6O_6 \cdot 1.0H_2O$: C, 52.39; H, 4.83; N, 18.33. Found: C, 52.46; H, 4.67; N, 18.60.

***N*-[4-[[(2,4-Diaminopyrido[3,2-*d*]pyrimidin-6-yl)methyl]thio]benzoyl]-L-glutamic Acid or 8-Deaza-10-thiaaminopterin (21).** 21 was prepared in 68% yield from 17: mp 208–210 °C; mass spectrum, *m/e* 554 (M^+, heptamethyl derivative); UV λ_{max} (pH 1) 243 (ϵ_{max} 21 900), 275 (16 000), 320 (6600); (pH 7) 277 (16 000), 335 (5500); (pH 13) 277 (20 000), 343 (5500); ^1H NMR (Me_2SO-d_6 + D_2O) δ 4.63 (s, 2, CH_2-S), 7.66 and 8.03 (q, 4, C_6H_4), 7.98 and 8.01 (q, 2, C^7H and C^8H).

Anal. Calcd for $C_{20}H_{20}N_6O_5S \cdot 0.5H_2O$: C, 51.60; H, 4.54: N, 18.05. Found: C, 51.45; H, 4.75; N, 17.95.

***N*-[4-[[(2-Amino-3,4-dihydro-4-oxopyrido[3,2-*d*]pyrimidin-6-yl)methyl]amino]benzoyl]-L-glutamic Acid or 8-Deazafolic Acid (26).** 26 was prepared in 65% yield from 23: mp 238–240 °C; mass spectrum, *m/e* 552 (M^+, octamethyl derivative); UV λ_{max} (pH 1) 251 (ϵ_{max} 16 000), 305 (11 000); (pH 13) 283 (23 000) (the UV spectrum is similar to that reported by DeGraw et al.[5]); ^1H NMR (Me_2SO-d_6 + D_2O) δ 4.63 (s, 2, CH_2), 6.95 and 7.91 (q, 4, C_6H_4), 7.86 (s, 2, C^7H and C^8H).

***N*-[4-[[(2-Amino-3,4-dihydro-4-oxopyrido[3,2-*d*]pyrimidin-6-yl)methyl]methylamino]benzoyl]-L-glutamic Acid or 8-Deaza-N^{10}-methylfolic Acid (27).** 27 was prepared in 58% yield from 24: mp 267–270 °C; mass spectrum, *m/e* 538 (M^+, hexamethyl derivative); UV λ_{max} (pH 1) 250 (ϵ_{max} 17 000), 307 (12 000); (pH 7) 273 (15 200), 305 (27 000); (pH 13) 305 (26 000); ^1H NMR (Me_2SO-d_6 + D_2O) δ 3.26 (s, 3, $N^{10}CH_3$), 4.86 (s, 2, CH_2), 6.91 and 7.91 (q, 4, C_6H_4), 7.48 and 7.76 (q, 2, C^7H and C^8H).

Anal. Calcd for $C_{21}H_{22}N_6O_6 \cdot 1.5H_2O$: C, 52.34; H, 5.20; N, 17.45. Found: C, 52.60; H, 4.70; N, 17.39.

***N*-[4-[[(2-Amino-3,4-dihydro-4-oxopyrido[3,2-*d*]pyrimidin-6-yl)methyl]thio]benzoyl]-L-glutamic Acid or 8-Deaza-10-thiafolic Acid (28).** 28 was prepared in 72% yield from 25: mp 228–231 °C; mass spectrum, *m/e* 514 (M^+, tetramethyl (incomplete permethylation) derivative); UV λ_{max} (pH 1) 252 (ϵ_{max} 20 000), 284 (15 000); (pH 7) 274 (21 500), 325 (6400); (pH 13) 282 (21 500), 335 (7200); ^1H NMR (Me_2SO-d_6 + D_2O) δ 4.63 (s, 2, CH_2S), 7.71 and 8.05 (q, 4, C_6H_4), 7.81 and 7.95 (q, 2, C^7H and C^8H).

Anal. Calcd for $C_{20}H_{19}N_5O_6S$: C, 52.50; H, 4.18; N, 15.30. Found: C, 52.40; H, 4.31; N, 15.13.

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Registry No. 2, 76822-61-2; 3, 76807-52-8; 4, 2499-96-9; 5, 76807-53-9; 6, 76807-54-0; 7, 76807-55-1; 8, 76832-40-1; 9, 76807-56-2; 10, 13726-52-8; 11, 2378-95-2; 12 free alcohol, 57963-63-0; 12, 76807-57-3; 13, 76807-58-4; 14, 76807-59-5; 15, 76807-60-8; 16, 76807-61-9; 17, 76807-62-0; 18, 76807-63-1; 19, 76822-62-3; 20, 76807-64-2; 21, 76822-63-4; 22, 76832-41-2; 23, 76807-65-3; 24, 76807-66-4; 25, 76807-67-5; 26, 51989-25-4; 27, 76807-68-6; 28, 76807-69-7.

Reassignment of the Structures of Iodonitroimidazole, Its *N*-Methyl Derivatives, and Related Compounds[1]

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Condensation of ethyl 4-(2-thioethoxy)benzoate (4) with the compound hitherto described[3,4] as 2-iodo-1-methyl-5-nitroimidazole (2) does not lead to the expected product, ethyl 4-[2-[(1-methyl-5-nitro-2-imidazolyl)thio]ethoxy]benzoate (1), whereas condensation of 4 and the bromoimidazole 3 does give 1. An X-ray crystallographic analysis of the sodium salt of the corresponding acid confirms the structure of 1. Reinvestigation of the synthesis of 2 shows that its precursor, diiodoimidazole, is formed with retention of deuterium when 2-deuterioimidazole is used as the starting material and therefore has structure 16 rather than 14. The origin of this error in the literature was the assignment to a derivative of 16 of the structure 18 rather than 23. The nitration product of 16 has structure 9 rather than 11, and the derivatives assigned structures 2 and 12 are in fact 8 and 10, respectively. Authentic 12 can be prepared by nitration of 2-iodo-1-methylimidazole. Reaction of 9 with hydrobromic acid gives 29 and not, as reported previously, 27.

In the course of studies of methods for the large-scale preparation of 2-alkylthio-substituted nitroimidazoles, for example, 1,[2] we investigated the reactions of thiols with the compound reported as 2-iodo-1-methyl-5-nitro-

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Chart I

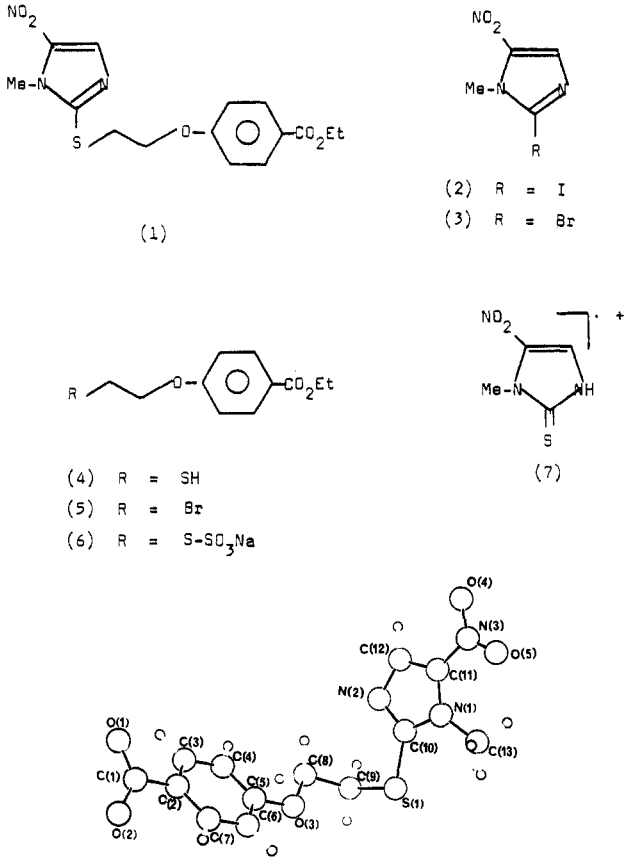


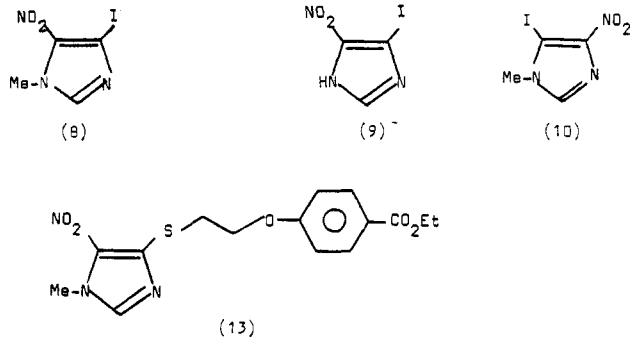
Figure 1. Perspective view of the carboxylate ion of which 1 is the ester. The sodium ions, which are not shown, are irregularly coordinated to four oxygen atoms from three different carboxylate ions.

imidazole (2, Chart I). The preparation of the compound assigned structure 2 from diiodoimidazole has been reported independently by Hoffer[3] and Lebedev,[4] and it was used by Winkelmann[5] in the synthesis of compounds described as 2-(arylthio)nitroimidazoles.

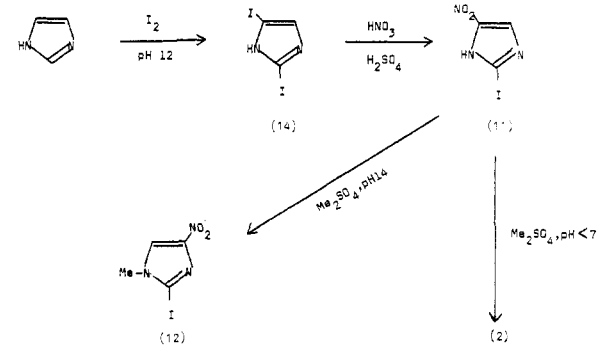
The thiol 4 required for synthesis of 1 was prepared from ethyl 4-(2-bromoethoxy)benzoate[6] (5) via the Bunte salt (6). Acidic hydrolysis of 6 gave a complex mixture of products, but borohydride reduction smoothly effected conversion to 4. This compound was rather unstable, possibly because of self-polymerization, and could not be obtained in a state of analytical purity. However, freshly prepared material was suitable for use in condensation reactions without further purification.

Condensation of 4 and the compound assigned structure 2 by use of cuprous oxide as a base[7] gave a compound whose properties were similar to but not identical with those of 1.[2] The 60-MHz ^{1}H NMR spectra recorded in Me_2SO-d_6 were almost identical, while spectra recorded in deuteriochloroform showed that the resonance of the single imidazole proton in the condensation product was

Chart II



Scheme I



shifted 0.45 ppm upfield relative to that in 1.

Since the proton in the 2-position is normally the most deshielded proton in the imidazole nucleus, this could imply that the 2-position of 1 is unsubstituted and that structure 1 is incorrect. However, Rapoport[8] has seriously questioned the common practice of assigning the most downfield resonance of imidazoles to the 2-proton, particularly in the case of nitroimidazoles. In addition, the effect of the thio substituent on the chemical shift of the residual imidazole proton was unknown.

In view of this uncertainty, an X-ray crystallographic analysis of the sodium salt of the organic acid of which 1 is the ethyl ester was undertaken and confirmed that the structural assignment of 1 is correct. A perspective view of the molecule is shown in Figure 1. Atomic parameters defining the crystal structure, bond lengths, and angles are given in the supplementary material. In addition, condensation of 4 with the unambiguously synthesized 2-bromo-1-methyl-5-nitroimidazole[9] (3) gave 1.

Electron-impact mass spectra of 1 and of the condensation product of 4 and the compound assigned structure 2 showed that the two compounds were isomeric, but the fragmentation patterns were different. The base peak in the spectrum of 1 occurred at m/e 159; this was assigned to 7, the product of McLafferty rearrangement into the 3-position of the imidazole. The corresponding peak in the mass spectrum of the isomeric compound was very weak, suggesting that the thio substituent is not in the 2-position of the imidazole ring.

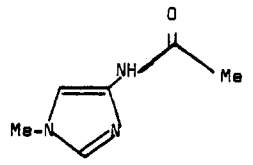
We now assign the structures 8–10 (Chart II) to the compounds hitherto described[3,4] as having structures 2, 11, and 12, respectively, and assign the structure 13 to the condensation product of 8 and 4 on the basis of the following evidence.

^{1}H NMR double-resonance studies of 1 and its isomer 13 demonstrated the existence of a small four-bond cou-

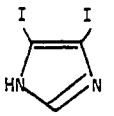
(1) Preliminary report: J. P. Dickens, R. L. Dyer, B. J. Hamill, and T. A. Harrow, *J. Chem. Soc., Chem. Commun.*, 523 (1979).
(2) R. C. Tweit, R. D. Muir, and S. Ziecina, *J. Med. Chem.*, **20**, 1697 (1977).
(3) M. Hoffer, V. Toome, and A. Brossi, *J. Heterocycl. Chem.*, **3**, 454 (1966).
(4) S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, L. V. Epishina, and V. V. Sevost'yanova, *Chem. Heterocycl. Comp. (Engl. Transl.)*, **6**, 614 (1970).
(5) E. Winkelmann, W. Raether, U. Gebert, and A. Sinharay, *Arzneim.-Forsch.*, **27**, 2251 (1977).
(6) Eastman Kodak Co., U.S. Patent 2 790 825.
(7) R. G. R. Bacon, and H. A. O. Hill, *J. Chem. Soc.*, 1108 (1964).
(8) H. R. Matthews and H. Rapoport, *J. Am. Chem. Soc.*, **95**, 2297 (1973).
(9) G. B. Barlin, *J. Chem. Soc. B*, 641 (1967).

pling between the protons of the *N*-methyl group and the imidazole proton in **13** which was absent in **1**. By analogy with the work of Takeuchi,[10] who has observed such couplings between protons of the *N*-alkyl group and those in the 2- or 5-positions of *N*-alkyl imidazoles, this is evidence for the structure **13**.

The reported synthesis[3,4] of the compound hitherto regarded as **2** (Scheme I) involved the conversion of imidazole to diiodoimidazole **14**, substitutive nitration of **14** to give **11**, and N-methylation of **11** to give either **2** or **12**, depending on the reaction conditions. The disposition of the methyl and nitro groups in **2** and **12** is consistent with the well-understood mechanism of N-alkylation of nitroimidazoles.[11] In addition, the isolation by Hoffer[3] of the known compound **15** by hydrogenation of **12** in the pres-



(15)



(16)

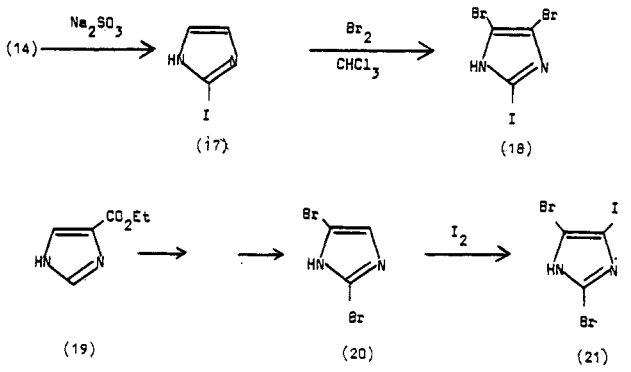
ence of acetic anhydride confirms that the relative positions of methyl and nitro groups in these compounds are correct. The position of the iodo substituent in **2**, **11**, and **12** was then examined. Naidu and Bensusan[12] have argued that the structure of diiodoimidazole is in fact **16** rather than **14**, on the basis that the chemical shift of the residual proton in this compound is more typical of a proton occupying the 2-position in the imidazole ring rather than the 4-position. In view of the findings of Rapoport[8] referred to above, we considered it prudent to establish the structure of this compound unequivocally.

Reaction of 2-deuterioimidazole[13] with iodine under the conditions originally described by Pauly[14] gave diiodoimidazole in which all the original deuterium was retained. This was demonstrated by a quantitative ^{1}H NMR comparison with unlabeled diiodoimidazole and by comparing mass spectra. In electron-impact mass spectra, the base peak is the molecular ion, and the deuterium content of the deuterated diiodoimidazole is the same as that of the 2-deuterioimidazole used as starting material. Chemical ionization mass spectra (reactant gas ammonia) show stepwise replacement of iodine atoms by protons (or deuterons with deuterioammonia reactant gas).

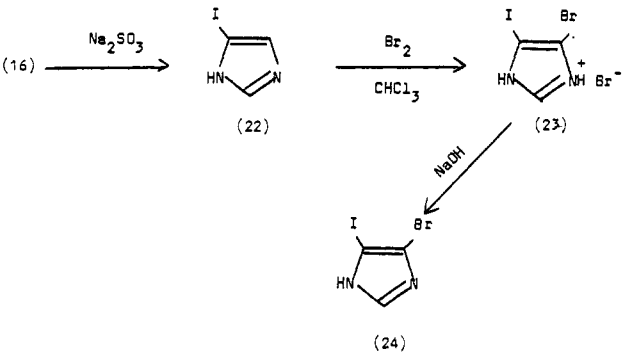
To ascertain that the course of the iodination had not been altered by the inclusion of deuterium in the imidazole nucleus, we back-exchanged the deuteriodiiodoimidazole that was obtained; the material thus obtained was identical in all respects with diiodoimidazole prepared from undeuterated imidazole.

The above data are consistent with the structure **16** for diiodoimidazole which has previously been assigned structure **14**. This is supported by the ^{13}C NMR spectrum of diiodoimidazole, which shows that the one-bond, C–H coupling constant for the unsubstituted carbon is 212 Hz. Published data[15] for imidazole give values of 188 and 206 Hz for one-bond couplings of C-4(5) and C-2, respectively.

Scheme II



Scheme III



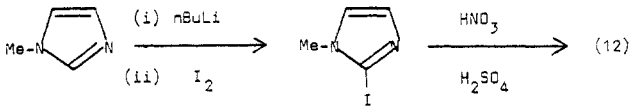
In order to resolve outstanding ambiguities in the literature, we reinvestigated Pauly's[16] original arguments for the structure **14**; these are summarized in Scheme II. Pauly found that sodium sulfite reduction of diiodoimidazole gave an iodoimidazole **17**, bromination of which gave a dibromoiodoimidazole (**18**) which was not identical with the compound (**21**) obtained by iodination of 2,4-dibromoimidazole (**20**), whose structure was defined by virtue of its mode of synthesis[17] from 4(5)-(carboethoxy)imidazole (**19**). Pauly therefore argued that the iodo substituent in iodoimidazole is in the 2-position and that diiodoimidazole has structure **14**.

On reexamining this reaction sequence, we found that the bromination of iodoimidazole in chloroform solution gives a strongly acidic compound which requires 1 equiv of sodium hydroxide for neutralization. The neutral compound thus obtained was shown to be a bromoiodoimidazole by elemental analysis and mass spectrometry. The ^{1}H NMR spectrum showed a single absorption at δ 7.88, while the ^{13}C NMR spectrum gave a value of 215 Hz for the one-bond, C–H coupling constant of the unsubstituted carbon, indicating that C-2 is unsubstituted.

On this basis, we assign the structure **23** to the bromination product of iodoimidazole, and interpret Pauly's reaction sequence as shown in Scheme III. The preparation of authentic 2-iodoimidazole (**17**) has recently been reported,[18] and this material is not identical with Pauly's iodoimidazole. The assignment of structure **16** to diiodoimidazole implies that the derived iodonitroimidazoles have structures **8**–**10** rather than **2**, **11**, and **12**. To exclude the possibility that isomerization may occur during the nitration of **16**, we examined more closely the spectroscopic properties of these compounds.

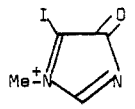
(10) Y. Takeuchi, H. J. C. Yeh, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3565 (1978).
(11) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1357 (1960).
(12) M. S. R. Naidu and H. B. Bensusan, *J. Org. Chem.*, **33**, 1307 (1968).
(13) J. H. Bowie, R. G. Cooks, S.-O. Lawesson, and G. Schroll, *Aust. J. Chem.*, **20**, 1613 (1967).
(14) H. Pauly and K. Gundermann, *Ber. Dtsch. Chem. Ges.*, **41**, 3999, 4011 (1908).
(15) M. C. Thorpe and W. C. Coburn, Jr., *J. Magn. Reson.*, **12**, 225 (1973).
(16) H. Pauly and E. Arauner, *J. Prakt. Chem.*, [2] **118**, 33 (1928).
(17) (a) F. L. Pyman and G. M. Timmis, *J. Chem. Soc.*, **123**, 494 (1923); (b) I. E. Balaban and F. L. Pyman, *ibid.*, **121**, 947 (1922).
(18) R. J. Sundberg, *J. Heterocycl. Chem.*, **14**, 517 (1977).

Scheme IV

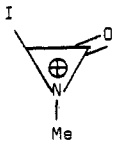


The relative positions of the methyl and nitro substituents in the compounds to which we assign structures **8** and **10** were not in question, particularly in view of the fact that the chemical shift of the *N*-methyl protons in **8** was increased relative to that in **10**, because of the proximity of the nitro group in **8**. ^{1}H NMR double-resonance experiments on **8** and **10** revealed a small four-bond coupling between the *N*-methyl protons and the residual aromatic proton, supporting the premise that the 2-position was unsubstituted in both compounds. The one bond C-H coupling constants of **8**–**10** also supported the 4,5-disubstituted structures for these compounds. The ^{13}C NMR spectrum of 4-nitroimidazole demonstrates values of 201 and 216 Hz for the one-bond coupling constants of C-5 and C-2, respectively; the ^{13}C NMR spectra of **8**–**10** give values of 218, 217, and 219 Hz, respectively, for these constants, implying that the 2-position in these compounds is unsubstituted.

The electron-impact mass spectrum of **10** shows prominent fragments at *m/e* 223 and 196, corresponding to loss of NO and further loss of HCN to give the fragments **25** and **26**, respectively.



(25)



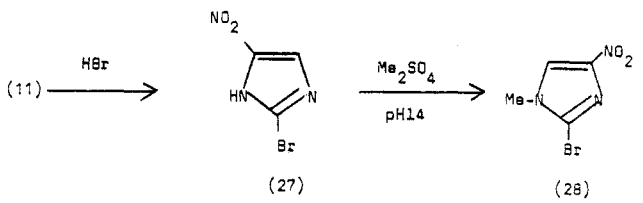
(26)

Since the assigned structures **2**, **11**, and **12** were obviously incorrect, we attempted to synthesise one or more of these compounds by alternative routes. Nitration of 2-iodo-1-methylimidazole,[19] although attended by considerable decomposition of substrate, yielded authentic 2-iodo-1-methyl-4-nitroimidazole (Scheme IV). In agreement with the conclusions of Rapoport,[8] the 5-proton in this compound resonates at lower field than the 2-proton of **10**, and the one-bond, C–H coupling constant was found by ^{13}C NMR spectroscopy to be 203 Hz, indicating that the 5-position is unsubstituted.

In view of these findings, the structures of the alkoxy and aryloxy imidazoles[3,20] derived by reaction of compounds **8**–**10** with alkoxides and aryl oxides require appropriate revision, as do those of the (arylthio)imidazoles and (alkylamino)imidazoles described by Winkelmann[5] and the structures of other derivatives described in the patent literature.[20,21]

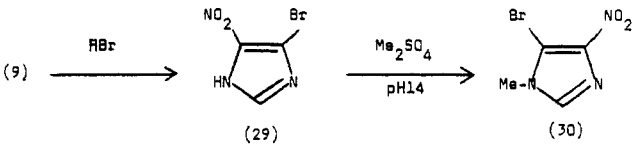
The correction of structure **11** to **9** clarifies the report by Lebedev[4] that further nitration of this compound gives 4,5-dinitroimidazole. It is less easy, however, to reconcile our results with those of Sharnin and co-workers. These authors recently reported synthetic routes to chloronitroimidazoles[22] and bromonitroimidazoles[23] by reaction of dinitroimidazoles with phosphoryl halides or hydrohalic acids. In both cases, the structures of some of the compounds reported were determined by correlation with iodonitroimidazole, which they believed to have structure **11**. For example, the structures **27** and **28** were supported by independent synthesis from iodonitroimidazole as outlined in Scheme V. In our hands, reaction of iodonitroimidazole **9** with hydrobromic acid gave **29**, methylation of which gave **30**, Scheme VI. The physical and spectroscopic properties of both compounds were in good agreement with those quoted in the literature.[9,24,25] In addition, the ^{13}C NMR spectrum of **29** gave a value of 218 Hz for the one-bond, C–H coupling constant, indicating that C-2 is unsubstituted. Unfortunately, Sharnin does not give experimental details of these transformations.

Scheme V



(27) (28)

Scheme VI



(29) (30)

Experimental Section

Melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded (of KBr, disks, unless otherwise stated) on a Perkin-Elmer 257 spectrometer. ^{1}H NMR spectra were obtained on a Varian EM360 spectrometer, while double-resonance experiments and recording of ^{13}C NMR spectra were performed on a Varian XL-100 or a JEOL FX-60 instrument, in all cases with Me_4Si as internal standard. Mass spectra were recorded on a Finnigan 4000 spectrometer with a dual EI/CI source and an on-line 6100 data system. Microanalyses were performed by C.H.N. Analysis Ltd.

Diiodoimidazole 16. This compound was prepared as described previously[14] (for the preparation of **14**). Recrystallization from aqueous acetone gave material which had the following: mp 191–192 °C dec (lit. mp (a)[14] 180 °C, (b)[12] 197–198 °C); IR 3440 (br), 3075, 2960, 2900–2100 (br), 1805 (br), 1640 (w), 1540 (w), 1455, 1440 (sh), 1287, 1272 (sh), 1182, 1154, 958, 950 (sh), 821, 657, 622 (w) cm^{-1}; NMR (Me_2SO-d_6) δ 7.80 (s); mass spectrum (EI), *m/e* 320 (M^+), 166. Anal. Calcd for $C_3H_2I_2N_2$: C, 11.26; H, 0.63; N, 8.76; I, 79.35. Found: C, 11.26; H, 0.58; N, 8.76;, I, 79.08.

4-Iodo-5-nitroimidazole (9). This compound was prepared by the published procedure[3] (for **11**) and recrystallized from DMF/water (1:2) to give yellow crystals: mp 285–286 °C dec (lit.[3] mp 281 °C); IR 3200–2300 (br), 3140 (w), 1710, 1540 (sh), 1530 (br), 1488, 1468, 1415, 1390 (sh), 1348 (br), 1248, 1210, 1021, 946, 924, 847, 813, 756 (w) cm^{-1}; NMR (Me_2SO-d_6) δ 8.05 (s). Anal. Calcd for $C_3H_2IN_3O_2$: C, 15.08; H, 0.84; N, 17.58; I, 53.11. Found: C, 15.25; H, 0.92; N, 17.44, I, 52.92.

4-Iodo-1-methyl-5-nitroimidazole (8). This compound was prepared by the published procedure[3] (for **2**) and recrystallized from DMF/water (1:2) to give bright yellow crystals: mp 151 °C (lit.[3] mp 150–151 °C); IR 3117, 1738, 1526, 1489, 1443, 1390–1310 (br), 1374, 1237, 1188, 1143, 1072, 967, 870, 819, 739 (w), 713 (w), 657 (w) cm^{-1}; NMR (Me_2SO-d_6) δ 8.05 (s, 1 H), 3.92 (s, 3 H); mass spectrum (EI), *m/e* 253 (M^+), 180. Anal. Calcd for $C_4H_4IN_3O_2$:

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C, 18.99; H, 1.59; N, 16.61; I, 50.16. Found: C, 18,83; H, 1.64; N, 16.51; I, 50.17.

5-Iodo-1-methyl-4-nitroimidazole (10). This compound was prepared by the published procedure[3] (for **12**) and recrystallized from DMF/water (1:2) to give pale yellow crystals: mp 240 °C (lit.[3] mp 240 °C); IR 3112, 1721, 1522, 1491, 1447, 1419, 1370, 1347, 1311, 1282, 1270 (sh), 1220, 1084, 1056 (sh), 1005, 860, 821, 754, 703 cm^{-1}); NMR (Me_2SO-d_6) δ 8.12 (s, 1 H), 3.75 (s, 3 H); mass spectrum (EI), m/e 253 (M^+), 223, 196, 168. Anal. Calcd for $C_4H_4IN_3O_2$: C, 18.99; H, 1.59; N, 16.61; I, 50.16. Found: C, 19.06; H, 1.59; N, 16.55; I, 50.22.

Ethyl 4-(2-Thioethoxy)benzoate (4). A solution of sodium thiosulfate pentahydrate (10 g, 40.3 mmol) in water (50 mL) was treated with a solution of ethyl 4-(2-bromoethoxy)benzoate[6] (10 g, 36.6 mmol) in ethanol (160 mL). The reaction mixture was heated under reflux for 16 h, concentrated to 50 mL, diluted with 25 mL water, and filtered to remove unreacted starting material. The filtrate was extracted with toluene (3 × 25 mL) and evaporated. The residue, crude **6**, was dissolved in water (100 mL), and the mixture was stirred vigorously at ambient temperature in a 500-mL beaker and treated with a solution of sodium borohydride (3 g, 79 mmol) in water (30 mL). After 10 min the white precipitate was filtered off, washed with water (4 × 50 mL), and dried in vacuo to give crude **4** (4.9 g, 59%) as a rather unstable white powder, mp 72–74 °C. This material is suitable for synthetic use without further purification. Fresh material obtained by recrystallization from ether/hexane (1:1) at 5 °C had the following: mp 73.5–74 °C; IR (film) 3030–2800 (br), 2975, 2930, 1704, 1603, 1579 (sh), 1505, 1455 (w), 1416 (w), 1382 (sh), 1362, 1308 (sh), 1272, 1243, 1163, 1097, 1057 (w), 1010, 839 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (d, 2 H, J = 9 Hz), 6.95 (d, 2 H, J = 9 Hz), 4.4 (q, 2 H, J = 7 Hz), 4.3 (t, 2 H, J = 7 Hz), 3.2 (t, 2 H, J = 7 Hz), 1.7 (br s 1 H, exchanged with D_2O), 1.5 (t, 3 H, J = 7 Hz); mass spectrum (NH_3 CI), m/e 227 (M + 1).

Ethyl 4-[2-[(1-Methyl-5-nitro-2-imidazolyl)thio]ethoxy]benzoate (1). Method A. This compound was prepared by esterification of the corresponding acid[2] with a 3% solution of hydrogen chloride in ethanol. Recrystallization from ethanol gave fine yellow needles: mp 100–100.5 °C; IR 3112, 3040–2860 (br), 1697, 1613, 1585, 1521, 1514, 1463, 1425, 1394, 1385, 1360, 1313, 1306, 1288, 1260 (sh), 1247, 1171, 1107, 1073, 1027, 869, 853, 820, 766, 738, 694, 687, 645 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (d, 2 H, J = 9 Hz), 7.95 (s, 1 H), 6.95 (d, 2 H, J = 9 Hz), 4.3 (t, 2 H, J = 6 Hz), 4.3 (q, 2 H, J = 7 Hz), 3.9 (s, 3 H), 3.7 (t, 2 H, J = 6 Hz), 1.4 (t, 3 H, J = 7 Hz); mass spectrum (EI), m/e 351 (M^+), 306, 186, 159. Anal. Calcd for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88; N, 11.96; S, 9.13. Found: C, 51.11; H, 4.88; N, 12.10; S, 9.02.

Method B. A solution of 2-bromo-1-methyl-5-nitroimidazole[9] (40 mg, 0.2 mmol) and **4** (45 mg, 0.2 mmol) in dry DMF (5 mL) was treated with cuprous oxide (30 mg, 0.21 mmol) and heated at reflux temperature in an atmosphere of nitrogen for 4 h. The solution was cooled, filtered through a pad of Celite, and diluted with water (20 mL), and the precipitated product was recovered by centrifugation. Recrystallization from aqueous ethanol and then from toluene/hexane (1:4) gave yellow needles (mp 99.5–100 °C) identical with the product from method A above by TLC, mass spectrum, and mixture melting point.

Ethyl 4-[2-[(1-methyl-5-nitro-4-imidazolyl)thio]ethoxy]benzoate (13). A mixture of **8** (2.5 g, 10 mmol), **4** (2.5 g, 11 mmol), and cuprous oxide (1 g, 7 mmol) in dry DMF (100 mL) was heated at reflux temperature in a nitrogen atmosphere for 4 h. The solution was cooled, filtered through a pad of Celite, and poured into water (300 mL) with vigorous stirring. The product was filtered off and dried to give a yellow solid: 1.8 g (52%); mp 128–131 °C. Recrystallization from toluene/hexane (5:1) gave bright yellow plates: mp 133–134 °C, IR 3117, 3040–2850 (br), 2974, 1702, 1607, 1583 (sh), 1511, 1478, 1460, 1429, 1390, 1363, 1315, 1286, 1280–1230 (br), 1167, 1154, 1119, 1108, 1076, 1016, 999, 888, 849, 812, 763, 743 (w), 691, 672 (w) cm^{-1}; NMR ($CDCl_3$) δ 7.95 (d, 2 H, J = 9 Hz), 7.5 (s, 1 H), 6.95 (d, 2 H, J = 9 Hz), 4.3 (t, 2 H, J = 6 Hz, *and* q, 2 H, J = 7 Hz), 4.0 (s, 3 H), 3.6 (t, 2 H, J = 6 Hz), 1.3 (t, 3 H, J = 7 Hz); mass spectrum (EI), m/e 351 (M^+), 306, 186, 158. Anal. Calcd for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88, N, 11.96. Found: C, 51.28; H, 4.87; N, 12.01.

2-Deuterioimidazole. This compound was prepared by using a slightly modified form of the published procedure.[13] Imidazole (2 g) was heated under reflux for 17 h with deuterium oxide (50 mL; >99 atom % D), and the solvent was removed, giving a white crystalline solid (1,2-dideuterioimidazole) which was dried at ambient temperature under high vacuum, mp 86.5–88 °C; the deuterium–nitrogen bond is very labile, and exchange with atmospheric moisture rapidly occurs, giving 2-deuterioimidazole: NMR ($CDCl_3$) δ 7.13 (s); mass spectrum (EI), m/e 69 (M^+). The material contained >98 atom % D at C(2) (by NMR).

Reaction of 2-Deuterioimidazole with Iodine. A solution of iodine (3.60 g, 14.2 mmol) and sodium iodide (3.90 g, 26.0 mmol) in water (26 mL) was added over a period of 2 h with stirring to a solution of 2-deuterioimidazole (0.50 g, 7.25 mmol) and sodium carbonate decahydrate (4.50 g, 15.73 mmol) at ambient temperature. The mixture was then stirred for a further 2 h at ambient temperature and filtered, and the cream colored solid was washed with water (20 mL). Recrystallization from hot acetone/water (1:2 mixture; 150 mL) gave a white crystalline solid: 1.44 g; mp 192–193 °C dec; IR 3435 (br), 3060, 2960, 2900–2100 (br), 1785 (br), 1520, 1421, 1408, 1254, 1188 (sh), 1174, 994, 945, 910 (sh), 856, 638 (w), 548 cm^{-1}; NMR (Me_2SO-d_6) δ 11.9–13.4 (br, NH), 7.80 (trace residual protons at C2); mass spectrum (EI), m/e 321 (M^+). Anal. Calcd for $C_3H_2I_2N_2$: C, 11.26; H, 0.63; N, 8.76; I, 79.35. Found: C, 11.30; H, 0.69; N, 8.71; I, 79.31. The material contained >98 atom % D at C_2 (by NMR).

Back-Exchange of Labile Deuterium. A sample of the above product (877 mg) was heated under reflux for 20 h with water (250 mL), and the resulting clear, colorless solution was evaporated to dryness on a rotary evaporator at 40 °C, giving a cream-colored solid. Recrystallization from hot acetone/water (1:2 mixture, 70 mL) gave a white crystalline solid: 430 mg; mp 188–190 °C. This compound was identical in every respect with **16**.

4-Iodoimidazole (22). This compound was prepared by the published procedure[16] (for **17**) and was recrystallized from water: mp 137–138 °C (lit.[16] mp 135–136 °C); IR 3440 (br), 3142 (w), 3090, 2992, 2940–2200 (br), 1820 (br), 1655 (w), 1535, 1475 (w), 1435, 1318 (w), 1290, 1240 (w), 1218, 1167, 1070, 956, 948 (sh), 908 (sh), 833, 772, 761, 664, 660 (sh), 622 619 cm^{-1}; NMR (Me_2SO-d_6) δ 7.23 (d, 1 H, J = 1.1 Hz), 7.60 (d, 1 H, J = 1.1 Hz); mass spectrum (EI), m/e 194 (M^+). Anal. Calcd for $C_3H_3N_2I$: C, 18.57; H, 1.56; N, 14.44; I, 65.42. Found: C, 18.55; H, 1.55; N, 14.45; I, 65.40.

4-Bromo-5-iodoimidazole (24). The procedure of Pauly[16] (for the preparation of **18**) was modified as follows. A solution of **22** (1.94 g, 10.0 mmol) in chloroform (200 mL) was added dropwise to a solution of bromine (5 g) in chloroform (500 mL). After 10 min, the precipitated product was filtered off and dried to give **23** as orange-yellow crystals, mp 214–215 °C (lit.[16] mp 215.5 °C).

A suspension of **23** (127 mg, 0.359 mmol) in water (20 mL) was titrated against 0.1 M sodium hydroxide solution by using a Radiometer TTT2 automatic potentiometric titrator; 3.5 mL of 0.1 M sodium hydroxide was required for neutralization (calcd 3.59 mL). The white product was filtered off, dried, and further purified by preparative TLC (silica; 10% MeOH/$CHCl_3$) and recrystallization from aqueous methanol to give white crystals: mp 182.5–183 °C dec; IR 3157, 3100–2500 (br), 1639 (br), 1558 (br), 1508, 1454 (w), 1434, 1289, 1214 (sh), 1198, 1148 (sh), 1145, 966, 951, 928, 865, 808, 769 cm^{-1} NMR (Me_2SO-d_6) δ 7.88 (s); mass spectrum (EI), m/e 274 + 272 (M^+). Anal. Calcd for $C_3H_2BrIN_2$: C, 13.20; H, 0.74; N, 10.27; Br, 29.28; I, 46.51. Found: C, 13.23; H, 0.79; N, 10.25; Br, 29.18; I, 46.67.

2-Iodo-1-methyl-4-nitroimidazole (12). 2-Iodo-1-methylimidazole[19] (2 g, 9.6 mmol) was added with stirring to concentrated nitric acid (10 mL) at 0 °C. Concentrated sulfuric acid (20 mL) was added slowly, and the cooling bath was removed. After being stirred for 3 h at ambient temperature, the solution was poured onto ice (120 g), and the product was filtered, washed with saturated sodium sulfite solution (2 × 20 mL), dried, and recrystallized from DMF/water (1:2) to give off-white crystals: 730 mg (30%); mp 243–244 °C (a 1:1 intimate mixture with **10** had a melting point of 198 °C); IR 3150, 1656, 1639, 1573, 1544, 1498, 1447, 1413, 1400, 1382 (sh), 1345, 1301 (sh), 1286, 1144, 1121 (sh), 1094, 1050, 992, 817, 746, 688, 655 cm^{-1}; NMR (Me_2SO-d_6) δ 8.44 (s, 1 H), 3.62 (s, 3 H); mass spectrum (EI), m/e 253 (M^+). Anal. Calcd for $C_4H_4IN_3O_2$: C, 18.99; H, 1.59; N, 16.61; I, 50.16. Found: C, 18.80; H, 1.61; N, 16.56; I, 49.65.

4-Bromo-5-nitroimidazole (29). A suspension of **9** (1 g, 5.2 mmol) in hydrobromic acid (48%, 10 mL) was heated under reflux

for 20 min, during which period a heavy sublimate of iodine collected in the condenser. The solution was cooled and poured into water (50 mL), and the product was filtered off, washed with water (3 × 10 mL), and dried to give off-white crystals: 653 mg (81%); mp 281–282 °C dec (lit.[17b] mp 279 °C); NMR (Me_2SO-d_6) δ 7.92 (s); mass spectrum (EI), m/e 191 + 193 (M^+).

5-Bromo-1-methyl-4-nitroimidazole (30). A solution of **29** (160 mg, 0.83 mmol) in aqueous sodium hydroxide (1 M, 3 mL) was treated with dimethyl sulfate (100 μL, 1.05 mmol) and stirred at ambient temperature for 20 min. The product was filtered off, washed with ice-water (2 × 1 mL), and dried to give a white solid: 120 mg (70%); mp 175–178 °C (lit. mp (a)[24]180 °C, (b)[25] 178 °C; lit.[25] mp (2-bromo-1-methyl-4-nitroimidazole) 155 °C); NMR ($CDCl_3$) δ 7.60 (s, 1 H), 3.70 (s, 3 H); mass spectrum (EI), m/e 205 + 207 (M^+).

Crystallographic Data and X-ray Structure Analysis. A plate-shaped crystal (1.04 × 0.80 × 0.02 mm) of 4-[2-[(1-methyl-5-nitro-2-imidazolyl)thio]ethoxy]benzoic acid sodium salt was used for the X-ray structure analysis. Cell parameters were determined by a Philips PW1100 diffractometer using Mo Kα (λ = 0.7107 Å) radiation. Crystal data: $C_{13}H_{12}N_3O_5SNa$ monoclinic; space group $C2/c$; a = 50.547 (8) Å, b = 6.235 (5) Å, c = 9.318 (4) Å, β = 95.80 (3)°; V = 2921.6 Å^3; Z = 8; M = 345.31; ρ_{calcd} = 1.569 g cm^{-3}. Intensity data were measured by using Mo Kα radiation (λ = 0.7107 Å, θ_{max} = 25°). A total of 2499 reflections was collected; of these, 1685 which had $F > 6\,\sigma(F)$ were used in the analysis. The structure was solved by direct methods[26] and refined by full-matrix, least-squares procedures to R_1 = 0.067 and R_2 = 0.064. As a test that the atoms in the imidazole ring were correctly assigned, refinement was repeated by assuming N(2) to be carbon and C(12) to be nitrogen (see Figure 1 for numbering scheme); the apparent temperature factors then changed markedly to values substantially different from those of the other atoms and in a direction which shows that the original assignment was correct. In addition, the hydrogen atom on C(12) which did not appear clearly in the final synthesis was shown to be present in a difference synthesis using the low-angle reflections only (calculated by multiplying all the observed structure factors by exp|−2.31 sin^2 θ|). The bond lengths and angles obtained are, in general, closely similar to those found in related compounds.

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Registry No. **1**, 53869-36-6; **2**, 13369-87-4; **3**, 17024-47-4; **4**, 76529-46-9; **5**, 41386-38-3; **8**, 76529-47-0; **9**, 76529-48-1; **10**, 35681-63-1; **11**, 13369-81-8; **12**, 13369-86-3; **13**, 76529-49-2; **14**, 19198-80-2; **16**, 15813-09-9; **17**, 3034-62-6; **18**, 76529-50-5; **22**, 71759-89-2; **23**, 76529-51-6; **24**, 72946-56-6; **29**, 6963-65-1; **30**, 933-87-9; 2-iodo-1-methylimidazole, 37067-95-1; 4-[2-[(1-methyl-5-nitro-2-imidazolyl)thio]ethoxy]benzoic acid sodium salt, 64444-68-4.

Supplementary Material Available: Tables I–III listing positional parameters, thermal parameters, and bond lengths and angles with their estimated standard deviations, respectively (6 pages). Ordering information is given on any current masthead page.

Conformations of the 3,4-Dichloro- and 3,4-Dibromo-2,5-dimethylhexanes. A Test of the Gauche-Gauche′ C-C-C-C-X Steric Exclusion

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The 3,4-dichloro- and 3,4-dibromo-2,5-dimethylcyclohexanes provide a good test case of the gauche–gauche′ steric exclusion in C–C–C–C–X chain segments, analogous to established exclusions in five-carbon chains and in 1,3-dihalogenated three-carbon chains. If the exclusion holds, there should be only one conformation for the meso form and at most two for the (±) form. The two forms have very different dipole moments and NMR spectra, consistent with the conformations predicted. The vibrational spectra indicate the presence of only one conformation in each case, and the infrared–Raman coincidences, Raman polarizations, and frequency differences between symmetric and antisymmetric C–X stretches are consistent with the proposed exclusion. The data are shown to be inconsistent with several alternative possibilities for conformational mixtures.

In the study of the conformations of molecules undergoing internal rotation, steric effects have had an important place. In Pitzer's classic treatment of saturated noncyclic hydrocarbons[1] using tetrahedral angles and threefold barriers, he assumed that one type of five-carbon, four-bond segment was so unfavorable that it occurred only in those highly branched molecules where no alternative conformation existed. This steric exclusion, sometimes called the pentane effect, applies to that combination of two adjacent gauche rotations in which the first and fourth bonds would lie parallel, like opposite sides of a chair-form cyclohexane ring. The two terminal carbons of the segment are then separated by only 2.5 Å. Pitzer assigned such conformations an infinite conformational energy and was able to make accurate and useful predictions of thermodynamic properties on this basis.

In halogen-substituted alkanes, two possible extensions of the pentane effect (hereafter called the C_5 exclusion) might occur: those involving C–C–C–C–X and X–C–C–C–X segments. These will be called the C_4X and C_3X_2 exclusions, respectively. Thompson and co-workers showed that the zero dipole moment of pentaerythrityl chlorides, bromides, and iodides[2] could be explained by using the C_3X_2 exclusion and that the assumption was useful in treating other small halocarbons as well.[3] Many

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