

detectable traces of the slow isomer (R_f 0.57) and two unknown, ninhydrin-positive compounds: $^1\text{H NMR}$ (D_2O) δ 2.2–2.9 (m, 2 H), 3.6–3.9 (m, 2 H), 4.1–4.6 (m, 3 H), 7.48 (s, 5 H). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{S}$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.22; H, 6.17; N, 6.05; S, 14.24.

S-Methylisothiazolidinium Nitrate (5). The reaction of 13.78 g (0.131 mol) of 3-(methylthio)propylamine with 31.73 g (0.125 mol) of iodine required 0.125 mol of NaOH. The product salts were converted to nitrates by use of Dowex-1 nitrate. Solvent was removed from the eluate and the residue was extracted with 100 mL of hot ethanol. Following decolorization with charcoal and filtration, the product readily crystallized to give 14.7 g (67% yield) of white needles which tested 96.5% pure. Crystallization was repeated until the sample was chromatographically and titrimetrically pure: $^1\text{H NMR}$ (D_2O) δ 1.9–2.9 (m, 2 H), 2.78 (s, 3 H), 3.4–4.1 (m, 4 H); $^{13}\text{C NMR}$ (D_2O) δ 53.7, 51.3, 32.9, 29.6. Anal. Calcd for $\text{C}_4\text{H}_{10}\text{NSNO}_3$: C, 28.90; H, 6.06; N, 16.86; S, 19.31. Found: C, 28.71; H, 6.00; N, 16.66; S, 19.09.

Titrimetric Assay for S-Substituted Isothiazolidinium Salts. To approximately 50 mg of compound dissolved in alcohol or water, 3 mL of 5 M KI and then 5 mL of 3 N HCl were added. The liberated iodine was titrated with standardized sodium thiosulfate. The best preparations of 1, 2, and 5 gave $99 \pm 1\%$ of the calculated amount of iodine in spite of the potentially competing hydrolysis reaction.

Thin-Layer Chromatography. Duplicate 20- μg samples were chromatographed on thin-layer cellulose plates, using acetonitrile–ethylene glycol–0.1 M ammonium acetate (70:15:15), pH 7.4, as the solvent. S-Alkylisothiazolidines were detected as brown spots formed immediately upon spraying with acidified potassium iodide. Duplicate chromatograms were sprayed with ninhydrin and developed at room temperature. Free amino acids gave purple spots within 1 h while the S-substituted isothiazolidinium salts gave purple spots after several days. Solvents containing acids or bases were avoided as they caused substantial decomposition of the S-alkylisothiazolidinium salts.

Optical Rotation Studies. Optical rotations were determined with 10 and 20 dm tubes, a Rudolph Model 325 polarimeter, and the D-line of sodium. The L-methionine as purchased had an $[\alpha]_{\text{D}}^{25}$ of $+23.5^\circ$ (5% solution in 1 N HCl) which is in satisfactory agreement with literature values. The diastereomers of 1 dissolved in water at a concentration of 2% gave $[\alpha]_{\text{D}}^{25}$ values of $+86$ and $+18^\circ$ for the 3(S),S(R) and 3(S),S(S) isomers, respectively. Rotations of the unhydrolyzed compounds were stable for at least 1 h. The samples were then diluted with an equal volume of 2 N HCl and the optical rotations of the resulting methionine sulfoxides gave the values reported in the text. Hydrolyses at room temperature were complete within 10 min.

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Registry No. 1, isomer 1, 70224-21-4; 1, isomer 2, 70266-80-7; 2, isomer 1, 70198-01-5; 2, isomer 2, 70198-02-6; 3, isomer 1, 70208-82-1; 3, isomer 2, 70198-03-7; 4, isomer 1, 70198-04-8; 4, isomer 2, 70198-05-9; (\pm)-5, 70198-07-1; L-methionine, 63-68-3; DL-ethionine, 67-21-0; S-phenyl-DL-homocysteine, 52162-05-7; S-benzyl-DL-homocysteine, 1017-76-1; 3-(methylthio)propylamine, 4104-45-4; α -methyl-DL-methionine, 2749-07-7; L-methionine amide, 4510-08-1; L-methionine methyl ester, 10332-17-9; L-methionine hydroxamate, 19253-87-3; L-methionylglycine, 14486-03-4; DL-methioninol, 16720-80-2; N-acetyl-DL-methionine, 1115-47-5; glycyl-L-methionine, 554-94-9; DL-methionine *dl*-sulfoxide, 4241-59-2; DL-methionine sulfone, 820-10-0; DL-methionine, 59-51-8; S-methyl-L-cysteine, 1187-84-4; S-benzyl-L-cysteine, 3054-01-1.

Alkyl Thioether Activation of the Nitro Displacement by Alkanethiol Anions. A Useful Process for the Synthesis of Poly[(alkylthio)benzenes]

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The reactions of *o*- and *p*-dinitrobenzenes, 2,4-dinitro-1-chlorobenzene, picryl chloride, and other simple halogenonitrobenzenes, with an excess of the sodium salt of the isopropanethiol, in HMPA, afforded the products of complete displacement of all the chloro and the nitro groups present in the molecule. These results indicated that the thioether function in the ortho or para positions activates the substitution of the nitro group by the alkanethiolate anion. The effect of the structure of the thiolate was examined by effecting the same reactions, in HMPA, with MeSNa , EtSNa , Me_3CSNa , and PhSNa . Reactions with Me_2CHSNa were also carried out in DMF and Me_2SO . It was observed that the reduction of the nitro group competes with the displacement process and that the relative importance of the two reactions depends on the structure of the aromatic substrate and of the thiolate as well as on the solvent employed. Complete and clean substitution reactions were obtained only with Me_2CHSNa in HMPA.

In the course of our researches in the field of homolytic aromatic ipso substitution reactions by alkyl radicals,¹ it was necessary to synthesize some poly(sulfonylbenzenes) and nitrosulfonylbenzenes in order to investigate the alkylsulfonation process. For this purpose, we employed

the procedure described by Kornblum and co-workers² consisting of the displacement of the nitro group in nitrobenzenes by the sodium salt of thiols in hexamethylphosphoramide (HMPA). While the reaction of *p*-dinitrobenzene with excess PhSNa afforded *p*-nitrophenyl phenyl sulfide, as reported in the literature,² the use of

(1) L. Testaferri, M. Tiecco, M. Tingoli, M. Fiorentino, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 93 (1978); L. Testaferri, M. Tiecco, and M. Tingoli, *J. Chem. Soc., Perkin Trans. 2*, in press.

(2) N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, 41, 1560 (1976).

Me_2CHSNa gave rise instead to the displacement of both nitro groups, affording $p\text{-C}_6\text{H}_4(\text{SCHMe}_2)_2$ in good yields. This unexpected result indicated that the isopropyl thioether function activates the displacement of the nitro group by isopropanethiol anion, and this was also confirmed by the formation of $p\text{-C}_6\text{H}_4(\text{SCHMe}_2)_2$ from the reaction of p -nitrophenyl isopropyl sulfide with Me_2CHSNa .

These results seemed of interest both from the synthetic and the mechanistic point of view and induced us to undertake a deeper investigation to explore applications of this reaction and gain information about the observed activation of the isopropylthio group and about the mechanism of the substitution. For this purpose, the reactions of Me_2CHSNa , in HMPA, with o - and p -chloronitrobenzenes, o -, m -, and p -dinitrobenzenes, 2,4-dinitro-1-chlorobenzene, and picryl chloride were investigated. Experiments were also carried out with other sodium alkanethiolates and with PhSNa with the aim of elucidating the effect of the RSNa structure. Finally, the reactions of some representative substrates were also run in DMF and Me_2SO to compare the results obtained in HMPA and to have some indications of the role of solvent.

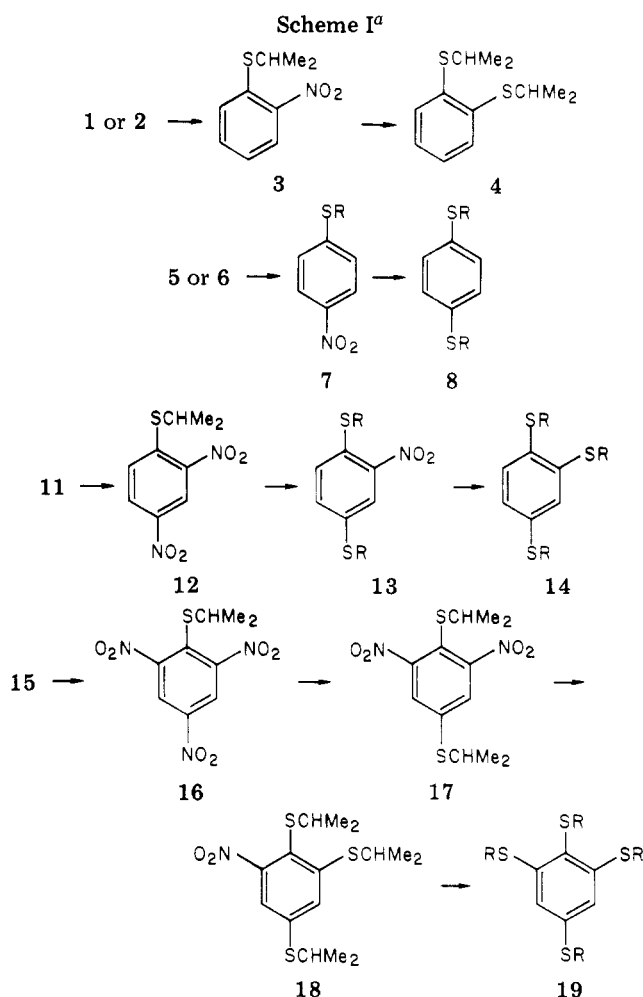
While this work was in its advanced stage of development,³ the results of a closely related investigation were reported by Beck and Yahner.⁴ These authors described the syntheses of several poly[(methylthio)benzenes] by displacement of chlorine and/or nitro group carried out with MeSH and lithium hydroxide in DMF. In this case also, evidence was obtained of the methyl thioether activation of the nitro displacement by the methanethiol anion. Several simple nitrobenzene derivatives, such as those investigated in the present work, failed to give the expected substitution products.

Results

Reactions with Me_2CHSNa in HMPA. The addition of an excess of Me_2CHSNa (2.4 mol) to a solution of o -chloronitrobenzene (1) (1 mol) in HMPA, at room temperature, gave rise to o -bis(isopropylthio)benzene (4) (30% yield); the same product (46.5%) was also obtained from o -dinitrobenzene (2). In a similar way, p -chloronitrobenzene (5) and p -dinitrobenzene (6) gave the p -bis(isopropylthio)benzene (8c) in 65 and 60% yields, respectively. The use of 1 molar equiv of Me_2CHSNa gave rise to the o -nitrophenyl isopropyl sulfide (3) (96.5%) from 2 and to the p -nitrophenyl isopropyl sulfide (7c) from 5 (70%) and from 6 (65%). Compounds 3 and 7c, when treated with Me_2CHSNa , were easily converted into 4 and 8c, respectively (Scheme I).

A different behavior was presented by m -dinitrobenzene (9). The reaction with 1 mol of Me_2CHSNa afforded the expected m -nitrophenyl isopropyl sulfide (10) (86%), but when an excess of thiolate was employed, a complex mixture of products was obtained, from which bis(isopropyl)disulfide could be isolated. Similarly, nitrobenzene gave rise to a mixture of products from which $\text{Me}_2\text{CHSSCHMe}_2$ and azobenzene were isolated; the presence of azoxybenzene was indicated by TLC.

Successful reactions were also obtained with 2,4-dinitro-1-chlorobenzene (11) and picryl chloride (15). Treatment of 11 with excess Me_2CHSNa gave 1,2,4-tris(isopropylthio)benzene (14c) (50%); the same compound (60%) was obtained likewise from the 2,4-dinitrophenyl



^a In compounds 7, 8, 13, 14, and 19, the groups R are identified by an alphabetical letter, as follows: a, R = Me; b, R = Et; c, R = Me_2CH ; d, R = Me_3C ; e, R = Ph.

isopropyl sulfide (12). In a similar way, the 1,2,4,6-tetrakis(isopropylthio)benzene (19c) was obtained from picryl chloride (69%) and from 2,4,6-trinitrophenyl isopropyl sulfide (16) (75%) (Scheme I).

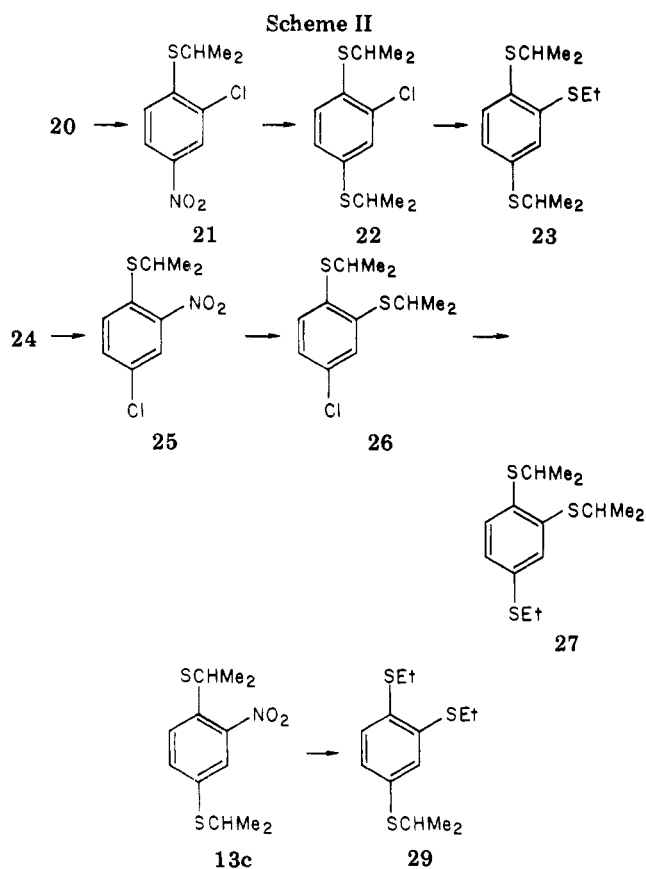
Experiments were then carried out with 11 and 15, using different amounts of Me_2CHSNa , in order to identify the products of partial substitution and obtain information about the selectivity of the process. Mixtures of products were obtained from these experiments, and the percent yields reported are based on isolated products after column chromatography.

Reaction of 2,4-dinitro-1-chlorobenzene (11) with Me_2CHSNa , using a 1:1 molar ratio, gave a 75% yield of a mixture of 12 and 13c (7:3); the use of 2 molar equiv of Me_2CHSNa led to a 73% yield of a mixture of 13c and 14c (8:2). Thus, the starting product and those deriving from partial substitution (12 and 13c) do not present substantial differences in reactivity and therefore, as the reaction proceeds, the products present in the reaction mixtures compete for the unreacted Me_2CHSNa . In the case of picryl chloride (15), more complex reaction mixtures were obviously observed. The following results in fact were obtained (molar ratios of 15 and Me_2CHSNa , yields, and reaction products and their ratios are given in order): 1/1, 40%, 16, 17, 18 (5:4:1); 1/2, 40%, 17, 18, 19c (3:6:1); 1/3, 61%, 18, 19c (3:7). The course of these reactions is indicated in Scheme I.

The reactions of 1,2-dichloro-4-nitrobenzene (20) and of 1,4-dichloro-2-nitrobenzene (24) with Me_2CHSNa were also performed in order to effect a comparison between

(3) The main findings in this paper were completed prior to the availability of ref 4 and were originally submitted in a manuscript received September 19, 1978—Editor.

(4) J. R. Beck and J. A. Yahner, *J. Org. Chem.*, 43, 2048 (1978).



the alkylthiodenitration and the alkylthiochlorination processes. In fact, the first products from these reactions will be 21 and 25, formed by displacement of the chlorine atoms activated by the *p*- or *o*-nitro groups; the next step will then involve either the chlorine atom or the nitro group. The reaction effected with 2 mol of Me_2CHSNa gave rise to 22 (62%) and 26 (58%) with no traces of products deriving from alkylthiochlorination (Scheme II). Similar findings were obtained from a competitive experiment between 7c and *p*-chlorophenyl isopropyl sulfide (28); the thiolate selectively consumed 7c to afford 8c, while 28 was quantitatively recovered.⁵ These observations are in agreement with the results of previous studies which demonstrated that the displacement of the aromatic nitro group by thiols occurs more easily than the displacement of the chlorine atom.^{6,7}

The reactions of 20 and 24 with excess Me_2CHSNa also gave rise to 22 and 26; if, however, the reaction temperature was raised to 80 °C, substitution of the chlorine atom occurred and compound 14c was obtained in 75 and 82% yields, respectively. The observed selectivity in the replacement of the various substituents in 20 and 24 can be used to synthesize compounds with different alkylthio groups. For instance, compounds 22 and 26 were easily formed at room temperature using 2 molar equiv of Me_2CHSNa ; addition of 1 mol of EtSNa and warming up of the reaction mixture to 80 °C afforded the trisubstituted compounds 23 (70%) and 27 (65.5%). Also reported in Scheme II is another example of the synthetic versatility of these reactions; treatment of 13c with an excess of EtSNa afforded the 1,2-bis(ethylthio)-4-(isopropylthio)benzene (29) (67%), resulting from the exchange of the

Table I. Percent Yields^a of the Sulfides 8, 14, and 19 Obtained from the Reaction of 5, 11, and 15 with an Excess of RSNa

R			
	8a-e	14a-e	19a-e
Me	7 ^b		6 ^b
Et	14 ^b	15 ^b	68
Me_2CH	65	50	69
Me_3C^c	44 ^d	44 ^e	33 ^f
Ph	g	34 ^h	37 ^f

^a Based on isolated products after column chromatography. ^b The RSSR were present in the reaction mixtures together with several unidentified products. ^c The reactions with Me_3CSNa required longer reaction times (8–15 h). ^d The presence of some unreacted 5 and of another unidentified product was indicated by TLC. ^e A 17% yield of 13d was also isolated. ^f The presence of another unidentified product was indicated by TLC. ^g The only product formed was 7e even with a large excess of PhSNa (6 mol) and long reaction times (30 h). ^h 13e (25%) and 1,2-bis(phenylthio)-4-nitrobenzene (30) (27%) were also isolated.

activated alkyl thioether function in the 1 position and from the displacement of the nitro group.

Reactions with Other Thiolates in HMPA. In order to explore the field of application and the factors governing these substitution reactions, the effect of the structure of the sodium thiolate was investigated. For this purpose, the reactions of MeSNa , EtSNa , Me_3CSNa , and PhSNa with *p*-chloronitrobenzene (5), 2,4-dinitro-1-chlorobenzene (11), and picryl chloride (15) were carried out; these experiments were effected at room temperature and with an excess of RSNa , i.e., under the conditions in which Me_2CHSNa gave rise to the substitution of all the chlorine atoms and the nitro groups present in the aromatic substrate. The results are collected in Table I.

The same reactions were also carried out with 1,2-dichloro-4-nitrobenzene (20) at 80 °C. While MeSNa gave rise to a complex mixture of unidentified products, EtSNa afforded 14b in 65% yields and Me_3CSNa gave a mixture of 14d (21%) and of 1,4-bis(*tert*-butylthio)-2-chlorobenzene (31) (42%).

Reactions with Me_2CHSNa in DMF and Me_2SO . The role played by the solvent in the substitution reactions reported above was investigated by effecting the reactions of 5, 11, and 15 with an excess of Me_2CHSNa in DMF and Me_2SO , at room temperature. The reactions in Me_2SO were only examined by GLC, and the products were not isolated.

A fast chlorine displacement reaction occurred with 5; *p*-nitrophenyl isopropyl sulfide (7c) was obtained both in DMF and Me_2SO . However, substitution of the nitro group to afford 8c was not observed; rather, the reactions proceeded to give *p*-(isopropylthio)aniline (32), arising from the reduction of 7c. After 24 h, 7c (25%) and 32 (13%) were isolated from the reaction in DMF, while, in Me_2SO , 32 was the only reaction product detected by GLC.

In the case of 11, a complex mixture was formed in DMF and Me_2SO , and the reaction products could not be isolated. Small amounts of 14c were detected by GLC. The progress of the reaction of picryl chloride (15) and Me_2CHSNa was followed by GLC; no substantial differences were observed in the reactions carried out in DMF or in Me_2SO . The first formed product was the 1,4,6-tris(isopropylthio)-2-nitrobenzene (18); this was then slowly

(5) Displacement of halogen atoms can be easily effected at 80 °C by Me_2CHSNa in HMPA. This substitution is activated by a thioether function, accompanying paper.

(6) J. F. Bunnett and W. D. Merritt, *J. Am. Chem. Soc.*, **79**, 5967 (1957).

(7) G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, **10**, 125 (1977).

converted into 19c, but other products were also present.⁸ The results obtained with Me₂CHSNa induced us not to extend this kind of investigation to the other alkanethiolates.

Most of the sulfides obtained from the reactions described above were oxidized to the corresponding sulfones; the NMR spectra of these compounds were of great help in confirming the assigned structures.

Discussion

The reactions described in this paper have a remarkable synthetic utility because they make available, in one step, compounds not easily accessible in other ways, starting from very simple aromatic substrates. In this respect, the syntheses carried out in HMPA are of particular interest. At the same time, these reactions also have mechanistic relevance because they demonstrate that an alkylthioether function activates the displacements of nitro groups by an alkanethiol anion. Nucleophilic substitution of nitro groups ortho or para to an electron-withdrawing substituent can be easily effected in dipolar aprotic solvents; activation occurs in these cases also from the meta position.^{2,9} No examples were reported concerning the activating effect of an alkylthio substituent,¹⁰ and the present results, together with those reported by Beck and Yahner,⁴ represent the first examples of the nitro displacement activated by a thioether group; this effect is operative when the RS group is in the ortho or para position to the NO₂.

From the data reported under the Results section, it is observed that the interaction of an alkanethiol anion with an aromatic nitro compound can lead either to the displacement or to the reduction of the NO₂ depending on the nature of the aromatic substrate, the structure of the thiol anion, and the kind of solvent employed.

Let us first consider the reactions with Me₂CHSNa in HMPA. Successful alkylthiodenitration processes were obtained in every case with the exception of nitrobenzene and *m*-nitrophenyl isopropyl sulfide (10); the results are easily explained by assuming that these reactions represent examples of the classical addition-elimination mechanism, S_NAr, of nucleophilic aromatic substitution.¹¹ When the nitro group is not activated by the Me₂CHS function in the ortho or para positions, the reactions take a different course. In these cases it seems reasonable to suggest that an electron transfer occurs from the alkanethiol anion to the aromatic substrate to afford Me₂CHS· and ArNO₂⁻, as indicated by the formation of considerable amounts of (Me₂CHS)₂ from the reactions of 10 and nitrobenzene. The so formed radical anion is probably responsible for the formation of the reduction products, such as azoxy,¹² azo, or amino compounds (in DMF or Me₂SO). This interpretation of the experimental findings implicitly excludes that the substitution reactions can occur through the S_{RN}1

mechanism,¹³ which instead would require the fragmentation of the ArNO₂⁻ into aryl radicals and nitrite anions.

A quantitative estimation of the activating effect of the isopropylthiol group¹⁴ could not be effected in the systems employed in this work. However, in the case of the alkylthiodenitration reactions in HMPA, it has been determined that a *p*-Me₂CHS function activates the displacement of chlorine by the isopropanethiol anion by a factor of about 100;¹⁵ the result of the competitive experiment between 7c and 28, in agreement with previous kinetic investigations,^{6,7} indicates that the substitution of the nitro group occurs even more easily.

The structure of the thiolate has a great influence in the course of these nitro displacement reactions in HMPA. Electronic, steric, and solvation effects will play a different role with the various thiolates, and a rationalization of the observed reactivity is difficult. Although a clarification of this point would require an investigation which is beyond the scope of this work, some qualitative information can be gained from the available results.

From the data collected in Table I it emerges that the best results are obtained when Me₂CHSNa is employed. With MeSNa and 5 or 15, the desired substitution products, 8a or 19a, could be isolated in low yields. Electron transfer is very likely the dominant process occurring in these cases, and complex mixtures are obtained, probably consisting of the reduction products of nitro groups. Complex reaction mixtures were also obtained by Beck and Yahner⁴ with the same substrates and methanethiol anions; in that case, 8a and 19a were not observed at all, but the reactions were run in DMF, in which the substitution reactions are considerably slower² (see also below). An intermediate situation was observed with EtSNa. *p*-Nitrochlorobenzene and 2,4-dinitro-1-chlorobenzene gave rise to complex mixtures from which the substitution products, 8b and 14b, were isolated in yields slightly higher than in the case of MeSNa; the more reactive picryl chloride gave instead a clean substitution reaction affording 19b in good yields.

The reactions with Me₃CSNa were considerably slower than those with the other alkanethiolates; in the case of *p*-nitrochlorobenzene, for instance, some unreacted product was still present after 15 h. Moreover, with this bulky anion, steric restrictions to substitution came into play when 11 and 15 were used as substrates; thus, 2,4-dinitro-1-chlorobenzene afforded 14d in discrete yields, but the nitro derivative 1,4-bis(*tert*-butylthio)-2-nitrobenzene (13d) was also present. Similar results were obtained with PhSNa. The reaction with 5 gave 7e, but this remained unchanged after 30 h even in the presence of a large excess of the thiolate;¹⁶ similarly, when 11 was used as the substrate, the products of incomplete substitution, 13e and 30, were present in considerable amounts. This lower efficiency of the PhSNa in effecting the displacement of

(8) The reaction of 15 with Me₂CHSNa in DMF was worked up and 19c was isolated (20%). Two other products were also obtained. The first one was tentatively identified as the 3,4,5-tris(isopropylthio)nitrobenzene; on oxidation with H₂O₂ in acetic acid, in fact, a sulfone was obtained (mp 335 °C dec) which presented a singlet at δ 9.0. The second product presented absorption at 3360 and 3460 cm⁻¹ in the IR; its NMR spectrum showed an AB system, δ 6.55 (1 H) and 6.45 (1 H), and a broad absorption at δ 4.45 (2 H). Oxidation with H₂O₂ afforded the sulfone of compound 18. From these data, the structure of 2,3,5-tris(isopropylthio)aniline is suggested for this compound.

(9) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972); **38**, 4086 (1973); J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Yahner, *ibid.*, **39**, 1839 (1974); J. R. Beck and J. A. Yahner, *ibid.*, **39**, 3440 (1974). For a recent review, see J. R. Beck, *Tetrahedron*, **34**, 2057 (1978).

(10) Weak activation by *p*-methylthio has been observed in the methoxydechlorination of 1-chloro-2-nitro-4-methylthiobenzene when compared with *o*-chloronitrobenzene: J. Müller, *Aust. J. Chem.*, **9**, 61 (1956).

(11) J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12**, 1 (1958).

(12) G. A. Russell, *Science*, **161**, 433 (1968).

(13) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463, 7464 (1970).

(14) An experiment with *p*-nitrophenyl ethyl ether and Me₂CHSNa was carried out in order to compare the thioether with the ether function. Most of the starting product was recovered unchanged, and no *p*-ethoxyphenyl isopropyl sulfide could be found; the only reaction product obtained was 8c (15%) arising from 7c (also isolated in traces) through the substitution of the ethoxy group by the isopropanethiol anion.

(15) P. Cogolli, F. Maiolo, L. Testaferri, M. Tiecco, and M. Tingoli, accompanying paper.

(16) Similarly, the reaction of 7c with an excess of PhSNa does not proceed. On the contrary, from an experiment in which 7e was treated with an excess of Me₂CHSNa, compound 8c was obtained in 77% yields. Independently, it was demonstrated that 4-(isopropylthio)phenyl phenyl sulfide does not react with Me₂CHSNa. Thus the formation of 8c from 7e can be explained only assuming that the first step of this reaction is the replacement of the PhS by the Me₂CHS group to afford 7c.

Table II.^a Physical and NMR (CDCl₃) Data of Alkyl Aryl Sulfides Prepared in HMPA

substrate	sulfide	mp or bp (torr), °C	¹ H NMR, δ (CDCl ₃) ^b	ref
2	3			
1	4 ^d	164-5 (18)	7.3-7.15 (AA'BB', 4 H), 3.45 (spt, 2 H), 1.3 (d, 12 H)	r
5	7c ^e	46-7	8.05 (m, 2 H), 7.3 (m, 2 H), 3.6 (spt, 1 H), 1.4 (d, 6 H)	
5	8c ^f	167-9 (18)	7.22 (s, 4 H), 3.3 (spt, 2 H), 1.25 (d, 12 H)	s
9	10	108-10 (1)		
11	14c ^g	208-9 (18)	7.35-7.0 (m, 3 H), 3.45 (spt, 1 H), 3.4 (spt, 1 H), 1.3 (d, 12 H), 1.25 (d, 6 H)	t
15	19c ^h		7.0 (s, 2 H), 3.55 (spt, 2 H), 3.45 (spt, 1 H), 3.4 (spt, 1 H), 1.35 (d, 6 H), 1.25 (d, 6 H)	
11	12 ^j	93-4		
11	13c ^k	153-5 (1)	8.0 (m, 1 H), 7.45 (m, 2 H), 3.55 (spt, 1 H), 3.45 (spt, 1 H), 1.35 (d, 6 H), 1.25 (d, 6 H)	u
15	16 ^l	30-2	8.6 (s, 2 H), 3.45 (spt, 1 H), 1.25 (d, 6 H)	
15	17 ^m	87-9	7.35 (s, 2 H), 3.45 (spt, 1 H), 3.4 (spt, 1 H), 1.4 (d, 6 H), 1.25 (d, 6 H)	
15	18 ⁿ		7.25 (d, 1 H), 7.15 (d, 1 H), <i>J</i> = 1.5 Hz, 3.5 (spt, 1 H), 1.3 (d, 6 H), 1.25 (d, 6 H)	
20	22	146-7 (1)	7.35-7.0 (m, 3 H), 3.45 (spt, 1 H), 3.3 (spt, 1 H), 1.3 (d, 6 H), 1.25 (d, 6 H)	
24	26	113-4 (1)	7.22 (d, <i>J</i> = 2 Hz, H ₃), 7.2 (d, <i>J</i> = 9 Hz, H ₆), 7.0 (dd, H ₅), 3.45 (spt, 1 H), 3.4 (spt, 1 H), 1.3 (d, 6 H), 1.25 (d, 6 H)	
20	23	146-8 (1)	7.35-6.9 (m, 3 H), 3.45 (spt, 1 H), 3.3 (spt, 1 H), 2.9 (q, 2 H), 1.3 (t, 3 H), 1.25 (d, 6 H)	
24	27	214-5 (18)	7.35-6.9 (m, 3 H), 3.45 (spt, 1 H), 3.4 (spt, 1 H), 2.9 (q, 2 H), 1.3 (d, 6 H), 1.25 (d, 6 H), 1.25 (t, 3 H)	
13c	29		7.4-7.0 (m, 3 H), 3.3 (spt, 1 H), 2.9 (q, 4 H), 1.3 (t, 6 H), 1.25 (d, 6 H)	
5	8a	80-2	7.2 (s, 4 H), 2.4 (s, 6 H)	v
5	8b	46-7	7.25 (s, 4 H), 2.9 (q, 4 H), 1.35 (t, 6 H)	w
5	8d	112-3	7.45 (s, 4 H), 1.3 (s, 18 H)	
5	7e	53-4		
11	14b ^o	172 (1)	7.3-7.05 (m, 3 H), 2.9 (q, 6 H), 1.3 (t, 3 H), 1.25 (t, 6 H)	x
11	13d and 14d ^p	163-4 (1)	8.0-7.0 (m, 3 H), 1.3 (s, 18 H)	
11	13e and 14e and 30	78-80 84-5	7.8 (d, <i>J</i> = 2 Hz, H ₃), 7.55 (d, <i>J</i> = 9 Hz, H ₆), 7.0 (dd, H ₅), 1.4 (s, 18 H), 1.35 (s, 9 H)	
15	19a		8.0 (d, <i>J</i> = 2 Hz, H ₃), 7.4 (s, 5 H), 7.25 (s, 5 H), 7.05 (dd, H ₅), 6.7 (d, <i>J</i> = 9 Hz, H ₆)	
15	19b		7.2-6.8 (m)	
15	19d		7.85 (d, <i>J</i> = 2 Hz, H ₃), 7.73 (dd, H ₅), 7.4 (s, 5 H), 7.3 (s, 5 H), 6.85 (d, <i>J</i> = 9 Hz, H ₆)	
15	19e		6.7 (s, 2 H), 2.5 (s, 3 H), 2.4 (s, 6 H), 2.3 (s, 3 H)	
20	31 ^q		6.8 (s, 2 H), 2.8 (m, 8 H), 1.3 (m, 12 H)	
			7.8 (s, 2 H), 1.35 (s, 27 H), 1.3 (s, 9 H)	
			7.25 (s, 10 H), 7.2 (s, 5 H), 7.15 (s, 5 H), 6.2 (s, 2 H)	
			7.65 (d, <i>J</i> = 2 Hz, H ₃), 7.5 (d, <i>J</i> = 9 Hz, H ₆), 7.3 (dd, H ₅), 1.4 (s, 9 H), 1.35 (s, 9 H)	

^a The reaction products are reported in this table in the order in which they are presented under the Results section. Satisfactory elemental analyses ($\pm 0.4\%$ for C, H, N) were obtained for all new compounds. ^b The vicinal coupling constant in the isopropyl and ethyl groups was 7 Hz in every case. ^c Bp or mp not determined. See Table III for the mp of the sulfone. ^d Also obtained from 2 and 3. ^e Also obtained from 6. ^f Also obtained from 6 and 7c. ^g Also obtained from 12, 20, and 24. ^h Also obtained from 16. ⁱ Viscous oil. ^j Isolated from the mixture with 13c. ^k Isolated from the mixture with 14c. ^l Isolated from the mixture with 17 and 18. ^m Isolated from the mixture with 16 and 18. ⁿ Isolated from the mixture with 17 and 19c. ^o Also obtained from 20. ^p Also obtained from 20 together with 31. ^q Isolated from the mixture with 14d. ^r Reference 20, 44.5 °C. ^s Reference 22, 94.5 °C. ^t Reference 1, 30-2 °C. ^u Reference 23, 85 °C. ^v Reference 24, 46.5 °C. ^w Reference 2, 52.5-53 °C.

Table III.^a Physical and NMR (CDCl₃) Data of Alkyl Aryl Sulfones

starting sulfide	mp, °C	sulfone product ^b	¹ H NMR, δ (CDCl ₃) ^d	ref
3	57-8			e
4	153-4		8.4-7.8 (AA'BB', 4 H), 4.3 (spt, 2 H), 1.3 (d, 12 H)	
7c	113-4		7.45 (m, 2 H), 7.1 (m, 2 H), 3.3 (spt, 1 H), 1.35 (d, 6 H)	f
8b	191-2		8.05 (s, 4 H), 3.2 (q, 4 H), 1.3 (t, 6 H)	
8c	163-4		8.1 (s, 4 H), 3.3 (spt, 2 H), 1.35 (d, 12 H)	
8d	308-10		8.05 (s, 4 H), 1.4 (s, 18 H)	
13c	164-5		8.25 (s, 3 H), 3.95 (spt, 1 H), 3.3 (spt, 1 H), 1.4 (d, 6 H), 1.35 (d, 6 H)	
13e	158-9		8.35 (d, J = 9 Hz, H ₆), 8.2 (dd, H ₅), 8.1 (d, J = 2 Hz, H ₃), 8.0-7.7 (m, 2 H), 7.6-7.4 (m, 3 H)	
14b	159-60		8.7 (d, J = 2 Hz, H ₃), 8.4 (d, J = 9 Hz, H ₆), 8.25 (dd, H ₅), 3.65 (q, 4 H), 3.2 (q, 2 H), 1.3 (t, 9 H)	
14c	220-2		8.6 (d, J = 2 Hz, H ₃), 8.4 (d, J = 9 Hz, H ₆), 8.2 (dd, H ₅), 4.3 (spt, 2 H), 3.25 (spt, 1 H), 1.3 (d, 18 H)	
14e	202-3			
17	206-8		8.2 (s, 2 H), 4.1 (spt, 1 H), 3.35 (spt, 1 H), 1.55 (d, 6 H), 1.35 (d, 6 H)	
18	194-6		8.8 (d, J = 2 Hz, 1 H), 8.15 (d, 1 H), 4.5 (spt, 1 H), 4.3 (spt, 1 H), 3.3 (spt, 1 H), 1.45 (d, 6 H), 1.35 (d, 6 H), 1.3 (d, 6 H)	
19b	204-6		8.8 (s, 2 H), 4.1 (q, 1 H), 3.8 (q, 2 H), 3.25 (q, 1 H), 1.55 (t, 3 H), 1.45 (t, 6 H), 1.35 (t, 3 H)	
19c	229-30		8.95 (s, 2 H), 4.5 (spt, 3 H), 3.35 (spt, 1 H), 1.55 (d, 12 H), 1.40 (d, 12 H)	
22	145-7		8.2 (d, J = 9 Hz, H ₃), 7.9 (d, J = 2 Hz, H ₃), 7.8 (dd, H ₂), 3.8 (spt, 1 H), 3.25 (spt, 1 H), 1.3 (d, 12 H)	
23	193-5		8.65 (d, J = 2 Hz, H ₃), 8.4 (d, J = 9 Hz, H ₆), 8.25 (dd, H ₅), 4.3 (spt, 1 H), 3.7 (q, 2 H), 3.3 (spt, 1 H), 1.35 (d, 12 H), 1.3 (t, 3 H)	
26	137-9		8.2 (d, J = 2 Hz, H ₃), 8.15 (d, J = 9 Hz, H ₆), 7.75 (dd, H ₅), 4.3 (spt, 1 H), 4.25 (spt, 1 H), 1.35 (d, 12 H)	
27	185-6		8.65 (d, J = 2 Hz, H ₃), 8.4 (d, J = 9 Hz, H ₆), 8.25 (dd, H ₅), 4.3 (spt, 2 H), 3.2 (q, 2 H), 1.3 (d, 12 H), 1.3 (t, 3 H)	
29	170-1		8.65 (d, J = 2 Hz, H ₃), 8.4 (d, J = 9 Hz, H ₆), 8.25 (dd, H ₅), 3.7 (q, 4 H), 3.3 (spt, 1 H), 1.35 (d, 6 H), 1.3 (t, 6 H)	
30	208-10			

^a Satisfactory elemental analyses ($\pm 0.4\%$ for C, H, N) were obtained for all new compounds. ^b Yields were in the range of 80-90%. ^c After crystallization from ethanol. ^d The vicinal coupling constant in the isopropyl and ethyl group was 7 Hz in every case. ^e Reference 25, 59.5 °C. ^f Reference 20, 115.3 °C.

the nitro group is very likely the result of its lower nucleophilicity in respect to the alkanethiolates.¹⁷ The fact that products like 13d, 7e, 13e, and 30 could be isolated from reaction mixtures in which an excess of the thiol anions was still present indicates that with Me₃CSNa and PhSNa, in HMPA, the reduction process is not so important as with MeSNa and EtSNa.

Finally, the results obtained from the reactions of 5, 11, and 15 with Me₂CHSNa in different solvents demonstrated that HMPA is a solvent superior to DMF or Me₂SO in the nucleophilic displacement of nitro groups by thiolate anions. In fact, only in HMPA is the rate of the desired substitution reaction enhanced to the point that it proceeds faster than reduction; thus, 5, 11, and 15 smoothly afford the products of complete replacement of the chlorine atom and of all the nitro groups present in the aromatic substrate. On the contrary, in DMF or Me₂SO, the displacement easily takes place until it is activated by a nitro group, then competition with the reduction process is observed.¹⁸ In fact, 5 and 15 gave a fast reaction with Me₂CHSNa to afford *p*-nitrophenyl isopropyl sulfide (7c) and 1,4,6-tris(isopropylthio)-2-nitrobenzene (18), respectively; then the reaction went on slowly and only the reduction product, 32, was obtained from 7c, whereas a mixture of compounds arising from reduction and substitution was formed from the more reactive product, 18. The substantially different reactivity presented by 5 and 15 in the various solvents can be used fruitfully to direct the synthesis toward the products of extensive substitution (in HMPA) or toward those of partial substitution (in DMF or Me₂SO).

Experimental Section¹⁹

Sodium thiolates were prepared from thiols and sodium ethoxide in ethanol. Evaporation of the solvent left a solid residue which was washed with ether, filtered, and dried under vacuum.

General Procedure Powdered Me₂CHSNa (1.2 molar equiv for each group to be displaced in the aromatic substrate) was added, under nitrogen, to a stirred solution of the nitro compound (0.01 mol) in HMPA (50 mL), at room temperature. The progress of the reaction was monitored by TLC or GLC; most of the reactions were complete a few minutes after the addition of the thiolate.

After 1 h, the dark red reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and dried, and the solvent was evaporated. The residue was chromatographed on silica gel using a mixture of light petroleum (bp 40-60 °C) and ethyl ether as eluent. The products were purified by distillation or crystallization.

Details on the reaction conditions and on the products formed in the various reactions are given under the Results section. Physical and NMR data are collected in Table II; IR spectra confirmed the presence of the Me₂CH group (1380 and 1360 cm⁻¹) and the NO₂.

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(18) Interestingly, if *p*-nitrochlorobenzene is allowed to react with Me₂CHSNa in ethanol, the reduction of the nitro group is even faster than the alkylthiochlorination; from this reaction in fact very small amounts of 7c were formed, the main product being the 4,4'-dichloroazoxybenzene (70%). Similar results were reported for the reaction of 5 with MeSNa (H. H. Hodgson and F. W. Handley, *J. Soc. Chem. Ind., London*, 46, 435T (1927)). However, if the Me₂CHSNa is formed in the presence of both excess thiol and aromatic substrate, 7c is produced in 93% yields (E. H. Gold, V. Piotrowski, and D. Z. Weiner, *J. Org. Chem.*, 42, 554 (1977)).

(19) NMR spectra were recorded, in CDCl₃ solutions, on a 60 MHz Jeol C60HL instrument; IR spectra were recorded, in CH₂Cl₂ solutions, on a Beckman Acculab TM5 spectrometer; and GLC analyses were performed on a Hewlett-Packard 5830A chromatograph with a 20 in. 10% UCW 982 column.

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Reactions with other sodium thiolates were carried out under the same experimental conditions described above for the Me_2CHSNa .

Sulfones were obtained by oxidation with H_2O_2 in acetic acid; the solution was warmed on a water bath for 2 h and then poured into ice. The solid was filtered and crystallized from ethanol. The IR spectra of the sulfones presented the characteristic absorptions at 1320–1300 and 1150 cm^{-1} . Physical and NMR data of the products obtained are reported in Table III.

The NMR spectra of the sulfones were particularly useful to confirm the assigned structures. It was in fact observed that when two RSO_2 groups are in the ortho position, the protons linked to the α carbon in R are considerably deshielded; for instance, while the septet of the isopropyl groups in the sulfone of **8c** is found at δ 3.3, that of the sulfone **4** resonates at δ 4.3.

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Registry No. 1, 88-73-3; 2, 528-29-0; 3, 70415-85-9; 3 sulfone, 70415-86-0; 4, 70398-84-4; 4 sulfone, 70415-87-1; 5, 100-00-5; 6, 100-25-4; 7c, 7205-63-2; 7c sulfone, 7205-84-7; 8a, 699-20-7; 8b, 17661-83-5; 8b sulfone, 70415-88-2; 8c, 70398-85-5; 8c sulfone, 70398-99-1; 8d, 25752-95-8; 8d sulfone, 25752-71-0; 9, 99-65-0; 10, 70415-89-3; 11, 97-00-7; 12, 66923-41-9; 13c, 70415-90-6; 13c sulfone, 70415-91-7; 13d, 70415-92-8; 13e, 67745-29-3; 13e sulfone, 70415-93-9; 14b, 4115-57-5; 14b sulfone, 70415-94-0; 14e, 70415-95-1; 14c sulfone, 70415-96-2; 14d, 70415-97-3; 14e, 3379-34-8; 14e sulfone, 70415-98-4; 15, 88-88-0; 16, 70415-99-5; 17, 70416-00-1; 17 sulfone, 70416-01-2; 18, 70416-02-3; 18 sulfone, 70416-03-4; 19a, 70416-04-5; 19b, 70416-05-6; 19b sulfone, 70416-06-7; 19c, 70416-07-8; 19c sulfone, 70416-08-9; 19d, 70416-09-0; 19e, 70416-10-3; 20, 99-54-7; 22, 70416-11-4; 22 sulfone, 70416-12-5; 23, 70416-13-6; 23 sulfone, 70416-14-7; 24, 89-61-2; 26, 70416-15-8; 26 sulfone, 70416-16-9; 27, 70416-17-0; 27 sulfone, 70416-18-1; 29, 70416-19-2; 29 sulfone, 70416-20-5; 30, 67745-30-6; 30 sulfone, 70416-21-6; 31, 70416-22-7; MeSNa , 5188-07-8; EtSNa , 811-51-8; Me_3CSNa , 29364-29-2; PhSNa , 930-69-8; Me_2CHSNa , 20607-43-6; 3,4,5-tris(isopropylsulfonyl)nitrobenzene, 70416-23-8; 2,3,5-tris(isopropylthio)aniline, 70416-24-9.

Nucleophilic Aromatic Substitution Reactions of Unactivated Aryl Halides with Thiolate Ions in Hexamethylphosphoramide

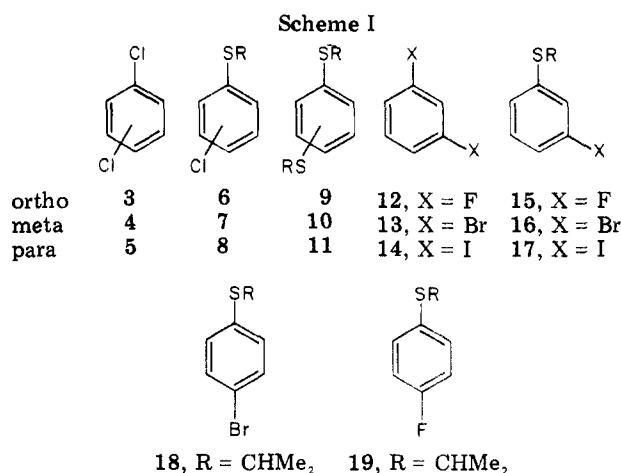
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A simple, high-yields method for the synthesis of aryl thioethers via nucleophilic displacement of unactivated aryl halides by the sodium salts of thiols in hexamethylphosphoramide (HMPA) is reported. The reactions are proceeding by the bimolecular displacement mechanism $\text{S}_{\text{N}}\text{Ar}$. Competitive experiments showed that the four halogenobenzenes presented comparable reactivities toward isopropanethiol anions; the relative halogen mobility was $\text{I} > \text{F} > \text{Br} > \text{Cl}$. The effect of some substituents on the reactivity of chlorobenzene has also been measured.

In a previous paper,¹ we discussed the nucleophilic displacement of aromatic nitro groups, which were activated by an ortho or para alkyl thioether function, by sodium thiolates; the best results were obtained when these alkylthiodenitration reactions were carried out in hexamethylphosphoramide. It has been observed recently that unactivated aryl halides react with sodium methoxide in HMPA to afford methyl aryl ethers in good yields,² and we report in this paper that several aryl halides easily give alkylthiodenitration reactions when treated with sodium alkanethiolates in HMPA. Few examples of nucleophilic substitutions of unactivated aryl halides are reported in the literature. Reactions can be performed with aryl thiolates in refluxing quinoline or DMF, but yields are generally low with simple halogenobenzenes;³ successful substitutions were obtained with PhSNa and aryl dihalides in dimethylacetamide at 170–5 °C⁴ and with butyl mercaptide and bromo- or fluoronaphthalene in Me_2SO at 80 °C.⁵ Because of the simple procedure and



of the high yields obtained, the results described in this paper represent an improvement of the previously reported methods. Kinetic experiments were also carried out to clarify the mechanism of these alkylthiodenitration

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