Nitrosation of arenes with nitrosonium ethyl sulfate

N. V. Zyk, E. E. Nesterov, A. N. Khlobystov, and N. S. Zefirov*

Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (095) 939 0290. E-mail: zyk@org.chem.msu.su

Nitrosonium ethyl sulfate reacts with *O*-alkylphenols and *N,N*-dialkylanilines to give the corresponding 4-nitrosoarenes. The reaction is not accompanied by side processes characteristic of common nitrosating agents. Diazotization of primary aromatic amines with nitrosonium ethyl sulfate yields stable diazonium salts, which are promising reagents for organic synthesis.

Key words: nitrosonium ethyl sulfate, nitrosation, nitrosoarenes, diazotization, diazonium salts, azo coupling.

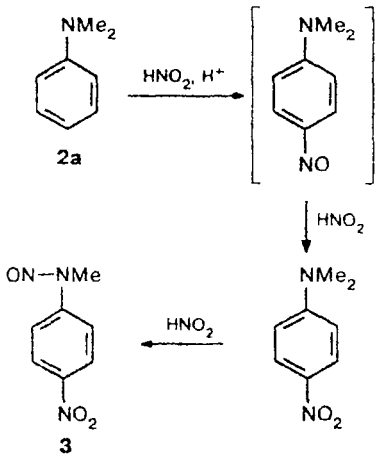
Nitrosoarenes are widely used in the production of organic intermediates and dyes, in the processing of elastomers, as reagents for analysis, *etc.* because of a variety of their chemical properties.[1] However, in contrast to aromatic nitration, nitrosation of arenes is much less well studied. First of all, this is due to the low electrophilicity of nitrosating agents such as HNO_2 or NOX (X = Hal, OR, OSO_3H, *etc.*). Thus, the activity of the NO^+ cation is 10^{14} times lower than that of NO_2^+.[2] In addition, it is often impossible to attain high concentrations of common nitrosating agents. A significant restriction that limits the potentialities of methods for the synthesis of nitrosoarenes is that they tend to react further with the nitrosating agent. That is why the search for new reagents for the synthesis of nitrosoarenes is still of current interest.[3]

Earlier,[4] we proposed to use nitrosonium ethyl sulfate as a highly reactive electrophilic nitrosating agent. This compound is easily generated in the reaction of EtONO with sulfur trioxide at −50 to −30 °C in CH_2Cl_2.

$$EtONO + SO_3 \longrightarrow EtOSO_2O^-(NO)^+$$
1

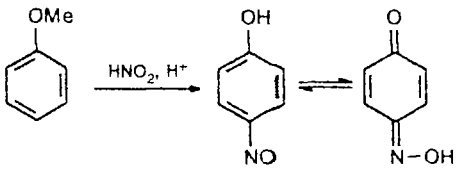
Being unstable at room temperature, compound **1** is introduced in further reactions *in situ*. We showed that it smoothly reacts with olefins following the electrophilic addition to give substituted ketones[5] and aldehydes.[6] Thus, the electrophilic addition of **1** at the C=C double bond may be considered as a convenient method for functionalization of olefins.

A study of electrophilic substitution in aromatic substrates is one of the most important steps in investigations of the properties of new reagents. This is all the more important because electrophilic nitrosation with common nitrosating agents is often accompanied by side reactions (first of all, oxidation of the nitroso group with an excess of the reagent and dealkylation of the substrate). For example, nitrosation of *N,N*-dimethylaniline (**2a**) with 10% HNO_2 yields 4-nitro-*N*-nitroso-*N*-methylaniline (**3**) as the main reaction product.[7]



3

Dealkylation is very often observed in the nitrosation of alkyl phenyl ethers, which usually results in 4-nitrosophenols.[2]



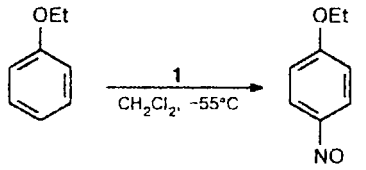
4 **5**

Hence, conventional nitrosation of arenes is nearly always accompanied by various side processes, which often gives unexpected products, thus strongly decreasing the synthetic value of the reactions.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*. No. 3, pp. 510—513, March, 1999.

1066-5285/99/4803-0506 $22.00

We studied nitrosonium ethyl sulfate as a possible agent for nitrosation of some aromatic substrates. Anisole, phenetole, and *N,N*-dialkylanilines were chosen as the subjects of investigation. In the case of phenetole (**6**), 4-nitrosophenetole (**7**) was obtained in 30% yield.

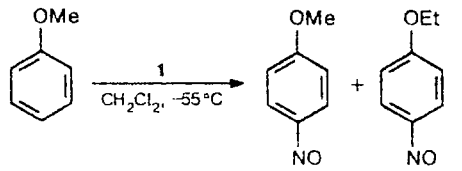


6 **7**, 30%

Initially, in order to avoid oxidation of nitroso compound with excess reagent, we carried out the reaction at a substrate : reagent ratio of 1 : 1. However, it turned out that the reaction proceeds very slowly (phenetole is converted only slightly upon stirring of the reaction mixture for 3 h). In addition, heating to room temperature often initiated oxidation of the nitrosation product into the nitro compound. That is why we modified the initial procedure. The reaction was carried out with a fivefold excess of compound **1**, but this excess was eliminated by addition of an aqueous solution of EtOH prior to heating of the reaction mixture in order to avoid oxidation. Such a modification resulted in virtually pure nitroso compound **7**, and the reaction was not accompanied by dealkylation or oxidation.

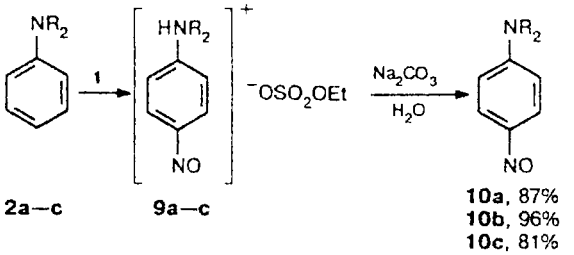
The reaction of **1** with anisole (**4**) unexpectedly yielded a mixture of 4-nitrosoanisole (**8**) and 4-nitrosophenetole (**7**).

Product **7** is a result of transalkylation of anisole. The mechanism of this process is still obscure, but it is quite probable that the transalkylation involves diethyl sulfate formed in the reaction of **1** with EtOH, which is added in order to decompose the excess of **1**. However, small amounts of product **7** are also formed when compound **1** is decomposed by addition of pure water rather than ethanol. Moreover, the presence of **7** is detected in the reaction mixture by TLC before the completion of the reaction. Apparently, the transalkylation can occur owing to the ethyl group contained in the anionic part of nitrosonium ethyl sulfate proper. Nevertheless, here too, the main reaction product is 4-nitrosoanisole **8**.



4 **8** major product **7** minor product

The reaction of **1** with *N,N*-dialkylanilines proceeds easily to give 4-nitrosophenyl(dialkyl)ammonium ethyl sulfates **9a—c**.



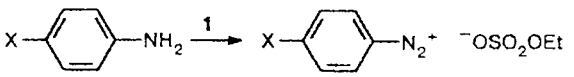
2a—c **9a—c**

10a, 87%
10b, 96%
10c, 81%

R = Me (**a**), Et (**b**), Pr^i (**c**)

Because these salts are insoluble in CH_2Cl_2, they precipitate and can be readily isolated from the reaction mixture. The amine nitrogen atom is protonated with participation of ethylsulfuric acid formed upon electrophilic substitution for the hydrogen atom of the aromatic ring. Subsequent treatment of salts **9a—c** with an aqueous solution of Na_2CO_3 allows one to obtain the corresponding 4-nitroso-*N,N*-dialkylanilines **10a—c** in the form of free bases. Note that the overall yield of thus obtained nitroso compounds **10a—c** is quite high. The absence of oxidation and dealkylation products is a significant advantage of nitrosonium ethyl sulfate compared to common nitrosating agents, although there are limitations here, too. Thus, an attempt to carry out the reaction with *N*-benzyl-*N*-methylaniline resulted in a mixture mainly composed of *N*-nitrosoamines. In this case, dealkylation is probably due to the fact that the intermediate benzylium cation is more stable than alkyl analogs.

One of the important processes in organic chemistry that includes nitrosation in the principal stage is diazotization of aromatic amines. We studied the reaction of nitrosonium ethyl sulfate (**1**) with aniline and some of its 4-substituted derivatives **11a—c**. It turned out that, when the ratio of compound **1** to aromatic amine is equal to 1 : 1, the reaction proceeds smoothly to give diazonium salts **12a—c** in almost quantitative yield.



11a—c

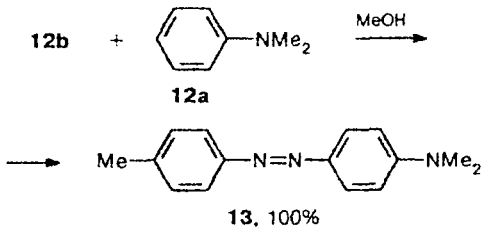
12a, 73%
12b, 95%
12c, 96%

X = H (**a**), Me (**b**), COMe (**c**)

Diazonium salts **12a—c** are white crystalline compounds that are resistant to heating and mechanical actions. For example, *p*-toluyldiazonium ethyl sulfate (**12b**) begins to decompose only at 107 °C and can be stored without moisture access at room temperature for a few months. These salts are well soluble in water and insoluble in most organic solvents, which is additional evidence in favor of their ionic structure. Aqueous solutions of diazonium salts **12a—c** are rather unstable. After several hours transparent solutions grow turbid, gas

bubbles are evolved, and a yellowish precipitate of the corresponding phenol is formed. However, their solutions in water-acetone and water-alcohol mixtures are much more stable.

Because diazonium salts **12a—c** are stable in storage and easy to handle, they can be successfully used in laboratory practice, in particular, for azo coupling. The synthesis of an azo dye in quantitative yield can be cited as an example:



13, 100%

Thus, nitrosonium ethyl sulfate **1** is a convenient reagent for electrophilic nitrosation of arenes. In some cases, it has obvious advantages for the synthesis of nitrosoarenes against other nitrosating agents because its reactions with arenes are not accompanied by side processes such as oxidation or dealkylation. The reactions of **1** with aromatic amines yield stable diazonium salts, which are convenient reagents for a wide range of synthetic transformations.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian XR-400 instrument (400 and 100 MHz, respectively). Chemical shifts are given with respect to tetramethylsilane as the internal standard. IR spectra were recorded on a UR-20 instrument.

The course of reactions and the purity of reaction products were monitored by TLC on silica gel (Silufol plates). Reaction products were separated by column chromatography (silica gel L 40/100 μm or Silpearl 25/40 μm).

Melting points of compounds were measured in a box with an open capillary. Uncorrected melting points are given.

All solvents used were purified according to the standard procedures. Ethyl nitrite was synthesized as in Ref. 8. Sulfuric anhydride was obtained by removal from 60% oleum followed by repeated distillation in a glass setup. Freshly distilled SO_3 was weighed and dissolved in CH_2Cl_2 to use in reactions in the form of a solution.

Reaction of nitrosonium ethyl sulfate (1) with phenetole (6). A solution of EtONO (1.85 g, 24.7 mmol) in 25 mL of CH_2Cl_2 was added dropwise with vigorous stirring under argon to a solution of SO_3 (0.79 g, 9.9 mmol) in 30 mL of CH_2Cl_2 cooled to −45 °C. The reaction mixture was stirred for 45 min. Further, a solution of compound **6** (0.41 g, 3.4 mmol) in 10 mL of CH_2Cl_2 was added to the thus obtained solution of compound **1** over 20 min so that the temperature was no higher than −35 to −40 °C. Stirring was continued at this temperature for 3 h, and then EtOH (2 mL) was gradually added. The reaction mixture was slowly heated to ~20 °C, washed with water (4×20 mL), dried with Na_2SO_4, concentrated on a rotary evaporator to 5 mL, diluted with 20 mL of heptane, and concentrated again to 5 mL. The residue separated into two immiscible layers, the lower one being diethyl sulfate Et_2SO_4. The upper layer was separated. Removal of the solvent on a rotary evaporator and of the unreacted phenetole *in vacuo* (oil pump, water bath, ~40 °C) gave 4-nitrosophenetole **7** (0.15 g, 30%) as a dark green oil that slowly crystallizes upon storage, m.p. 30—32 °C (from Et_2O) (Ref. 9: m.p. 33—34 °C (from petroleum ether)). ^1H NMR ($CDCl_3$), δ: 1.45 (t, 3 H, CH_3, J = 7.0 Hz), 4.16 (q, 2 H, CH_2, J = 7.0 Hz), 6.97 (d, 2 H, HC arom., J = 8.0 Hz), 7.86 (br.s, 2 H, HC arom.).

Reaction of 1 with anisole (4) was carried out as described above (the sole difference was that the excess of reagent was decomposed with the use of water rather than EtOH). The reaction of SO_3 (0.89 g, 11.1 mmol) in 25 mL of CH_2Cl_2, EtONO (1.67 g, 22.3 mmol) in 25 mL of CH_2Cl_2, and compound **4** (0.4 g, 3.7 mmol) in 10 mL of CH_2Cl_2 yielded a green oil (0.19 g) that was a mixture of nitroso derivatives **8** and **7** in the ratio 7 : 2 (^1H NMR). Additional chromatographic purification (hexane—AcOEt (1 : 1) as the eluent) gave 4-nitrosoanisole **8** (0.15 g, 30%) as blue green crystals, R_f 0.65, m.p. 23—24 °C (Ref. 10: m.p. 23 °C). ^1H NMR ($CDCl_3$), δ: 3.80 (s, 3 H, CH_3), 6.88 (d, 2 H, HC arom., J = 7.8 Hz), 7.65 (br.s, 2 H, HC arom.).

Reaction of 1 with *N,N*-dimethylaniline (2a). A solution of EtONO (0.86 g, 11.5 mmol) in 25 mL of CH_2Cl_2 was added dropwise with vigorous stirring under argon to a solution of SO_3 (0.37 g, 4.6 mmol) in 20 mL of CH_2Cl_2 cooled to −40 °C. The reaction mixture was then stirred for 1 h, whereupon the temperature was lowered to −75 °C, and a solution of **2a** (0.56 g, 4.6 mmol) in 5 mL of CH_2Cl_2 was added dropwise for 5 min. Then the resulting solution was slowly (for 1 h) heated to ~20 °C. The abundant crystalline precipitate that began to form at ~0 °C was filtered off, washed with CH_2Cl_2, and dried in an desiccator over P_2O_5 to give 4-nitrosophenyl(dimethyl)ammonium ethyl sulfate **9** (1.24 g, 94%) in the form of an orange-red crystalline powder that is readily soluble in water and other polar solvents, decomp.p. 166 °C. IR, ν/cm^{-1}: 3180—2615 (N^+—H). ^1H NMR (CD_3COCD_3/D_2O, 1 : 4 v/v, 62 °C), δ: 1.20 (t, 3 H, CH_3, J = 7.2 Hz), 3.74 (s, 6 H, $N(CH_3)_2$), 3.97 (q, 2 H, OCH_2, J = 7.2 Hz), 7.39 (d, 2 H, HC arom., J = 9.5 Hz), 7.77 (d, 2 H, HC arom., J = 9.5 Hz). Found (%): C, 43.23; H, 5.60; N, 10.17. $C_{10}H_{16}N_2O_5S$. Calculated (%): C, 43.47; H, 5.84; N, 10.14.

To obtain **4-nitroso-*N,N*-dimethylaniline (10a)**, a solution of salt **9a** (0.5 g, 1.8 mmol) in 5 mL of EtOH was added dropwise to 10 mL of a 0.4 *M* ethanolic solution of KOH; the initial red solution turned green. The reaction mixture was passed through a column with silica gel (height 3 cm), and the ethanol was removed on a rotary evaporator to give compound **10a** (0.24 g, 87%) in the form of blue green crystals, m.p. 92 °C (from Et_2O) (Ref. 11: m.p. 92—94 °C). ^1H NMR ($CDCl_3$), δ: 2.95 (s, 6 H, $N(CH_3)_2$), 6.20 (d, 2 H, HC arom., J = 8.5 Hz), 7.35 (br.s, 2 H, HC arom.).

Reaction of 1 with *N,N*-diethylaniline (2b) was carried out as described above. The reaction of SO_3 (0.8 g, 10.0 mmol) in 70 mL of CH_2Cl_2, EtONO (0.9 g, 12.0 mmol) in 30 mL of CH_2Cl_2, and **2b** (1.49 g, 10.0 mmol) in 30 mL of CH_2Cl_2 yielded 4-nitroso-*N,N*-diethylaniline **10b** (1.72 g, 96%) in the form of green crystals, m.p. 82—84 °C (from Et_2O) (Ref. 12: m.p. 83 °C).

Reaction of 1 with *N,N*-diisopropylaniline (2c) was carried out as described above. The reaction of SO_3 (1 g, 12.5 mmol) in 80 mL of CH_2Cl_2, EtONO (1.2 g, 16.0 mmol) in 30 mL of CH_2Cl_2, and **2c** (2.2 g, 12.4 mmol) in 30 mL of CH_2Cl_2 yielded 4-nitroso-*N,N*-diisopropylaniline **10c** (2.1 g, 81%) in the form of green lamellar crystals, m.p. 71—72 °C (from

petroleum ether). ^{1}H NMR ($CDCl_3$), δ: 1.33 (d, 12 H, 4 CH_3, J = 6.8 Hz), 3.45 (septet, 2 H, 2 CH, J = 6.8 Hz), 6.51 (d, 2 H, HC arom., J = 8.5 Hz), 7.52 (d, 2 H, HC arom., J = 8.5 Hz). Found (%): C, 69.72; H, 8.74; N, 13.51. $C_{12}H_{18}N_2O$. Calculated (%): C, 69.85; H, 8.80; N, 13.59.

Reaction of 1 with *p*-toluidine (11b). A solution of EtONO (1.09 g, 14.5 mmol) in 25 mL of CH_2Cl_2 was added dropwise with stirring under argon to a solution of SO_3 (0.47 g, 5.8 mmol) in 25 mL of CH_2Cl_2 cooled to −45 °C. Stirring was continued for 45 min, and then a solution of **11b** (0.63 g, 5.8 mmol) in 6 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for an additional 45 min and slowly heated to −20 °C. The crystals that formed were filtered off, and the mother liquor was concentrated *in vacuo*. After a while, the residual heavy dark oil began to crystallize intensely. The crystals that formed were washed from the oil with cold acetone. The acetone solution was concentrated again, the crystals that formed were separated, and the procedure was repeated. All crystals were combined and dried in an desiccator over P_2O_5 to give *p*-toluyldiazonium ethyl sulfate **12b** (1.26 g, 90%) in the form of colorless lamellar crystals that are well soluble in water and water—acetone mixtures, decomp.p. 107 °C. IR, ν/cm^{-1}: 2295 ($N^+{\equiv}N$). ^{1}H NMR (CD_3COCD_3/D_2O, 1 : 4 v/v), δ: 1.13 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.1 Hz), 2.58 (s, 3 H, CH_3), 3.91 (q, 2 H, $\underline{OCH_2}$, J = 7.1 Hz), 7.76 (d, 2 H, HC arom., J = 8.6 Hz), 8.55 (d, 2 H, HC arom., J = 8.6 Hz). ^{13}C NMR (CD_3COCD_3/D_2O, 1 : 4 v/v), δ: 14.93 (CH_3), 22.75 (CH_3), 64.08 (OCH_2), 111.17, 132.90 (2 C), 133.04 (2 C), 156.18 (C arom.). Found (%): C, 44.31; H, 4.85; N, 11.50. $C_9H_{12}N_2O_4S$. Calculated (%): C, 44.25; H, 4.96; N, 11.48.

Reaction of 1 with aniline (11a) was carried out as described for compound **11b**. The reaction of SO_3 (0.47 g, 5.9 mmol) in 30 mL of CH_2Cl_2, EtONO (0.91 g, 12.1 mmol) in 30 mL of CH_2Cl_2, and **11a** (0.55 g, 5.9 mmol) in 5 mL of CH_2Cl_2 yielded phenyldiazonium ethyl sulfate **12a** (0.99 g, 73%) in the form of colorless crystals, decomp.p. 86 °C. IR, ν/cm^{-1}: 2313 ($N^+{\equiv}N$). ^{1}H NMR (CD_3COCD_3/D_2O, 1 : 4 v/v), δ: 1.15 (t, 3 H, CH_3, J = 7.0 Hz), 4.00 (q, 2 H, OCH_2, J = 7.0 Hz), 8.11 (t, 2 H, HC arom., J = 8.2 Hz), 8.32 (t, 1 H, HC arom., J = 8.2 Hz), 8.83 (d, 2 H, HC arom., J = 8.2 Hz).

Reaction of 1 with 4-aminoacetophenone (11c) was carried out as described for compound **11b**. The reaction of SO_3 (0.5 g, 6.2 mmol) in 30 mL of CH_2Cl_2, EtONO (0.7 g, 9.3 mmol) in 30 mL of CH_2Cl_2, and **11c** (0.84 g, 6.2 mmol) in 5 mL of CH_2Cl_2 yielded 4-acetylphenyldiazonium ethyl sulfate **12c** (1.62 g, 96%) in the form of an orange oil. IR, ν/cm^{-1}: 2356 ($N^+{\equiv}N$). ^{1}H NMR (CD_3COCD_3/D_2O, 1 : 4 v/v), δ: 1.18 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.1 Hz), 2.75 (s, 3 H, $\underline{CH_3}CO$), 4.03 (q, 2 H, OCH_2, J = 7.1 Hz), 8.43 (d, 2 H, HC arom., J = 8.8 Hz), 9.07 (d, 2 H, HC arom., J = 8.8 Hz).

Reaction of compound 12b with *N,N*-dimethylaniline (2a). A solution of **2a** (0.13 g, 1.2 mmol) in 25 mL of AcOEt was added with stirring under argon at −20 °C to a solution of **12b** (0.3 g, 1.2 mmol) in 25 mL of MeOH. The reaction mixture was stirred for 6 h and then passed through a column with a thin layer of silica gel. Removal of the solvent *in vacuo* gave 4-(dimethylamino)-4′-methylazobenzene **13** (0.27 g, 100%) in the form of blue crystals, m.p. 172—173 °C (from MeOH) (Ref. 13: m.p. 171—171.5 °C).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-32570).

References

1. *The Chemistry of Nitro and Nitroso Groups, Part 1*, Ed. H. Feuer, Interscience, New York, 1969.
2. B. C. Challis, R. J. Higgins, and A. J. Lowson, *J. Chem. Soc., Perkin Trans. 1*, 1972, **12**, 1831.
3. D. L. H. Williams, *Nitrosation*, Cambridge University Press, Cambridge, 1988, 214.
4. N. S. Zefirov, Yu. A. Lapin, E. E. Nesterov, and N. V. Zyk, *Zh. Org. Khim.*, 1993, **29**, 1489 [*Russ. J. Org. Chem.*, 1993, **29** (Engl. Transl.)].
5. N. S. Zefirov, N. V. Zyk, Yu. A. Lapin, E. E. Nesterov, and B. I. Ugrak, *J. Org. Chem*, 1995, **60**, 6771.
6. N. V. Zyk, E. E. Nesterov, A. N. Khlobystov, and N. S. Zefirov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1322 [*Russ. Chem. Bull.*, 1996, **45**, 1259 (Engl. Transl.)].
7. H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, 1941, **8**, 470.
8. *Organic Synthesis, Collect., Vol. 2*, Ed. A. Blatt, Wiley, New York, 1946.
9. K. Lutz and J. B. Lytton, *J. Org. Chem.*, 1937, **2**, 68.
10. P. Ramart-Lucas and M. M. Martynoff, *Bull. Soc. Chim. France*, 1949, 53.
11. Dtsch. Reichspatent No. 3 253 306, 1920.
12. B. V. Gidaspov and E. Yu. Belyaev, *Aromaticheskie nitrozosoedineniya* [*Aromatic Nitroso Compounds*], Khimiya, Leningrad, 1991, 106 (in Russian).
13. J. D. Piper and W. R. Brode, *J. Am. Chem. Soc.*, 1935, **57**, 135.

Received July 27, 1998