

Anal. Calc'd for $C_{13}H_{20}N_6O_8$: C, 40.21; H, 5.15; N, 21.65. Found: C, 40.25; H, 5.13; N, 21.49.

1-(3-Methoxypropyl)-3-guanidinium sulfate had m.p. 113–114.5° after two crystallizations from 95% ethanol.

Anal. Calc'd for $C_{10}H_{28}N_6O_6S$: C, 33.33; H, 8.00; N, 23.33. Found: C, 33.30; H, 7.85; N, 23.60.

Picrate, m.p. 174–175° after one crystallization from 95% ethanol.

Anal. Calc'd for $C_{11}H_{16}N_6O_8$: C, 36.66; H, 4.44; N, 23.28. Found: C, 36.60; H, 4.51; N, 23.11.

1-(2-Methoxyethyl)-3-guanidinium sulfate had m.p. 122–123° after one crystallization from 95% ethanol.

Anal. Calc'd for $C_8H_{24}N_6O_6S$: C, 28.91; H, 7.22; N, 25.30. Found: C, 28.75; H, 7.15; N, 25.25.

1-(Alkoxyalkyl)-3-nitroguanidines. 1-(3-Methoxypropyl)-, 1-(3-isopropoxypropyl)-, and 1-(2-methoxyethyl)-3-nitroguanidine were prep'd. in this laboratory and have been previously reported.⁵

NITRATIONS

1-(3-Nitroxypropyl)-3-nitroguanidine. From 1-(3-alkoxypropyl)-3-nitroguanidine. 1-(3-Isopropoxypropyl)-3-nitroguanidine (1.0 g., 0.005 mole) was added portionwise with stirring, over a period of ten minutes, to a nitrating mixture consisting of 0.5 ml. of fuming nitric acid (98%) and 1.2 ml. of concentrated sulfuric acid. The nitration was performed at 0–5°. The resulting clear solution was poured onto 10 g. of ice; the white precipitate which formed was removed by filtration and washed with water and dilute sodium bicarbonate until free from acid. The crude product 1.0 g. (96.7%) melted at 119–120°. One crystallization from 95% ethanol (6 cc./g.) gave 0.94 g. (91%) of crystals melting at 121–122°. A mixture melting point with an authentic sample of 1-(3-nitroxypropyl)-3-nitroguanidine was undepressed. The nitration of 1.0 g. (0.0056 mole) of 1-(3-methoxypropyl)-3-nitroguanidine was carried out in an analogous manner and yielded 1.1 g. (98%) of 1-(3-nitroxypropyl)-3-nitroguanidine.

From 1-(3-alkoxypropyl)-3-guanidinium sulfate salts. The nitrating procedures used were identical to those described for the nitration of 1-(3-isopropoxypropyl)-3-nitroguanidine. The nitration of 1.0 g. (0.0024 mole) of 1-(3-isopropoxypropyl)- and 1.0 g. (0.0027 mole) of 1-(3-methoxypropyl)-3-guanidinium sulfate resulted in the formation of 1-(3-nitroxypropyl)-3-nitroguanidine in yields of 0.45 g. (90%) and 0.51 g. (92%) respectively. In both cases mixture melting points with authentic samples of 1-(3-nitroxypropyl)-3-nitroguanidine were undepressed. In addition, the product was characterized by cyclization in boiling *n*-butanol to 1-nitro-2-amino- Δ^2 -1,3-diazacyclohexene nitrate, which was identical to the cyclized derivative of an authentic sample of 1-(3-nitroxypropyl)-3-nitroguanidine.² The nitrations of both 1-(2-methoxyethyl)-3-guanidinium sulfate (1.0 g., 0.003 mole) and the nitroguanidine derivative (1.0 g., 0.006 mole) were performed in a similar manner to that described previously for 1-(3-isopropoxypropyl)-3-nitroguanidine. In the former case 0.43 g. (90%) of 1-(2-methoxyethyl)-3-nitroguanidine was obtained. The nitration of the latter led to the quantitative recovery of the starting compound.

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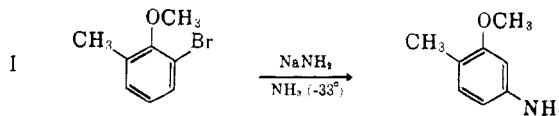
(5) Fishbein and Gallagher, *J. Am. Chem. Soc.*, **76**, 1877 (1954); McKay and Milks, *J. Am. Chem. Soc.*, **72**, 1616 (1950).

The Reaction of Haloanisoles with Lithium Dimethylamide

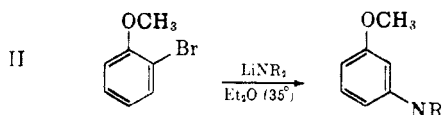
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Received November 3, 1955

Benkeser and Buting¹ investigated the reactions of sodium amide with three of the isomeric methyl-*o*-bromoanisoles and found that the amide ion enters only in the position adjacent to the displaced bromide ion. Thus 2-bromo-6-methylanisole reacts with sodium amide in liquid ammonia to form 6-methyl-*m*-anisidine as the only amine product.



A seemingly analogous reaction occurs between lithium dialkylamides and the haloanisoles in diethyl ether, since a "cine"² type dialkylated amine is obtained.³



It will be noted, however, that the solvent is quite different in the two cases as well as the reaction temperature. Also, significant quantities of anisole have been reported as a by-product in the dialkylamide-ether reactions, while such reduction products have not been noted in the amide-ammonia system. In view of these differences it seemed advisable to examine the dialkylamide-ether reactions more closely to decide whether the hitherto tacit assumption that they are analogous to the sodium amide-ammonia reactions is really valid.

Again the isomeric methyl-*o*-bromoanisoles were employed to determine the exact position of entry of the dialkylamino group. The only amine product isolated from the reaction of 2-bromo-6-methylanisole with lithium dimethylamide was 3-methoxy-4-methyldimethylaniline. The absence of 3-methoxy-2-methyldimethylaniline indicated that in this system, like the sodium amide-ammonia system, substitution can occur only at the position adjacent to the bromine atom. The high yield of 5-methoxy-2-methyldimethylaniline obtained from the reaction of 2-bromo-4-methylanisole with lithium dimethylamide indicated little steric interference to-

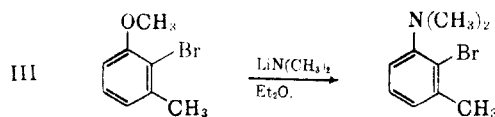
(1) Benkeser and Buting, *J. Am. Chem. Soc.*, **74**, 3011 (1952).

(2) The term "cine" substitution was introduced by Bunnett [*Chem. Revs.*, **49**, 382 (1951)] to designate those aromatic nucleophilic substitution reactions in which the entering group does not take the same position in the ring as the displaced group.

(3) Gilman, Crouse, Massie, Benkeser, and Spatz, *J. Am. Chem. Soc.*, **67**, 2106 (1954).

ward entry of a dimethylamide ion at a position adjacent to a methyl group. Therefore, the failure to obtain products of substitution *para* to the bromine atom cannot be ascribed to steric hindrance.

Surprisingly, 2-bromo-3-methylanisole, in which the position adjacent to the bromine atom is substituted with a methyl group, did give an amine product on reaction with lithium dimethylamide. This amine contained bromine, and when its Grignard reagent was prepared and hydrolyzed, *N,N*-dimethyl-*m*-toluidine was obtained. The original amine was therefore 2-bromo-*N,N*-dimethyl-*m*-toluidine, which must have arisen from displacement of methoxide by the dimethylamide ion.



This result is contrary to that observed in the amide-ammonia system. When 2-bromo-3-methylanisole was treated with sodium amide in liquid ammonia, the bromo compound was recovered unchanged.¹ Further evidence of this displacement was obtained when it was found that anisole gave *N,N*-dimethylaniline in low yield when treated with lithium dimethylamide in either ethyl ether or anisole as solvent.

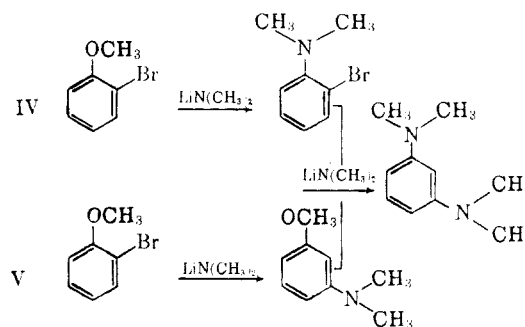
The fact that displacement of a methoxyl group occurred rather than substitution at any other ring position clearly demonstrated that unless the position adjacent to the halogen atom is available for substitution, cine substitution will not occur. Since no such displacement of a methoxyl group has been observed with sodium amide in ammonia, the reaction temperature must be the important factor. The fact that a somewhat higher yield of dimethylaniline is obtained in refluxing anisole rather than in refluxing ether is further proof of this point.

We had previously observed high-boiling amines from the reaction of lithium dimethylamide with *o*-bromoanisole and therefore repeated the reaction on a large scale to see if these products were resulting from displacement of a methoxyl group. When the reaction was carried out in ether, two previously unobserved products, *N,N*-dimethyl-*o*-anisidine (7%) and *N,N,N',N'*-tetramethyl-*m*-phenylenediamine (2%) were isolated.

The formation of the diamine must have occurred either by displacement of a methoxyl group giving *o*-bromodimethylaniline which then underwent cine substitution (Equation IV), or by displacement of the methoxyl group from *N,N*-dimethyl-*m*-anisidine (Equation V).

Equation IV seems the more reasonable since the inductive effect of the halogen appears to favor such a displacement. Thus we observed considerably more methoxyl displacement in the case of 2-bromo-3-methylanisole than in the reaction of anisole itself. In addition *o*-bromodimethylaniline

has been reported to undergo "cine substitution" with lithium diethylamide.⁴ When *N,N*-dimethyl-*m*-anisidine and lithium dimethylamide in ether were refluxed for 20 hours, none of the diamine



could be isolated. This demonstrated that only a fraction, if any, of the observed diamine was formed by this reaction sequence (Equation V).

EXPERIMENTAL

The methyl-o-bromoanisoles. The isomeric 4- and 6-methyl-*o*-bromoanisoles were prepared following the directions of Benkeser and Buting.¹ The 2-bromo-3-methylanisole was prepared following the directions of Huston and Peterson.⁵

Lithium dimethylamide. The lithium dimethylamide used in all reactions was prepared by condensation of dimethylamine into an ether solution of *n*-butyllithium. A slight excess of amine was always added. All of the reactions with lithium dimethylamide were carried out in an atmosphere of nitrogen.

Lithium dimethylamide and 2-bromo-4-methylanisole. A mixture of 20.1 g. (0.1 mole) of 2-bromo-4-methylanisole and 0.12 mole of lithium dimethylamide in ether was refluxed with stirring for 24 hours and then was hydrolyzed with dilute hydrochloric acid. This gave 0.6 g. (5%) of *p*-methylanisole⁶ and 13.3 g. (81%) of 5-methoxy-2-methyldimethylaniline; b.p. 60.5° (1 mm.), n_D^{20} 1.5315.

Anal. Calc'd for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.78.

5-Methoxy-2-methyldimethylaniline. Following the directions of Benkeser and Buting,¹ 6-methyl-*m*-anisidine was prepared from 2-bromo-4-methylanisole and sodium amide. This was methylated by preparation of the quaternary methiodide and subsequent decomposition at reduced pressure. The product was treated with acetic anhydride and distilled, yielding 5-methoxy-2-methyldimethylaniline; b.p. 60-60.5° (1 mm.), n_D^{20} 1.5312.

Lithium dimethylamide and 2-bromo-6-methylanisole. A mixture of 20.1 g. (0.1 mole) of 2-bromo-6-methylanisole and 0.12 mole of lithium dimethylamide in ether was refluxed with stirring for 21 hours and hydrolyzed with dilute hydrochloric acid. This gave: 1.45 g. (13%) of *o*-methylanisole;⁶ 3.9 g. (19%) of recovered 2-bromo-6-methylanisole; and 10.3 g. (63%) of 3-methoxy-4-methyldimethylaniline, b.p. 88-89° (2 mm.), n_D^{20} 1.5508.

Anal. Calc'd for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.31. A picrate of this amine melted at 160-161°.

Anal. Calc'd for $C_{16}H_{18}N_4O_7$: N, 14.21. Found: N, 14.33.

3-Methoxy-4-methyldimethylaniline. Following the directions of Benkeser and Buting,¹ 4-methyl-*m*-anisidine was

(4) Gilman, Kyle, and Benkeser, *J. Am. Chem. Soc.*, **68**, 143 (1946).

(5) Huston and Peterson, *J. Am. Chem. Soc.*, **55**, 3880 (1933).

(6) Anisole and the methylanisoles were identified by preparation of nitro derivatives and subsequent mixture melting points with authentic samples.

prepared from 2-bromo-6-methylanisole and sodium amide. This was converted to the quaternary methiodide which was decomposed at reduced pressure. The product was treated with acetic anhydride and distilled, giving 3-methoxy-4-methyldimethylaniline; b.p. 67.5° (1 mm.), n_D^{20} 1.5514. A *picrate* melted 160.5–161°.

Lithium dimethylamide and 2-bromo-3-methylanisole. A mixture of 20.1 g. (0.1 mole) of 2-bromo-3-methylanisole and 0.12 mole of lithium dimethylamide in ether was refluxed with stirring for 22.5 hours and hydrolyzed with dilute hydrochloric acid. This gave: 1.5 g. (12%) of *m*-methylanisole;⁶ 7.6 g. (38%) of recovered 2-bromo-3-methylanisole; and 6.0 g. (28%) of a bromine-containing amine, boiling at 64–66° (1 mm.), n_D^{20} 1.5664 (Second run, n_D^{20} 1.5690). A *picrate* of this material melted 145–145.5°.

Anal. Calc'd for $C_{15}H_{15}BrN_4O_7$: C, 40.66; H, 3.41; N, 12.64. Found: C, 40.46; H, 3.68; N, 12.77.

To 1.5 g. of magnesium in 50 ml. of ether was added a solution of 7.4 g. of the amine in 50 ml. of ether. After spontaneous refluxing ceased, the mixture was refluxed for one hour and then was hydrolyzed with 100 ml. of water. This gave 2.45 g. (53%) of *N,N*-dimethyl-*m*-toluidine; b.p. 52.5° (1.5 mm.), n_D^{20} 1.5497.⁷

A *picrate* melted at 126–127.5°⁸ and a *trinitrobenzene derivative* at 105–106°.⁷ These did not depress the melting points of authentic samples.

Lithium dimethylamide and anisole. A mixture of 53.5 g. (0.5 mole) of anisole and 0.6 mole of lithium dimethylamide in 200 ml. of ether was refluxed with stirring for 20 hours and hydrolyzed with water. This gave 1.1 g. (2%) of *N,N*-dimethylaniline.

When the reaction was carried out in anisole as solvent, at the reflux temperature, a 7% yield of *N,N*-dimethylaniline was isolated. The product was identified by a *picrate* melting at 158.5–159.5°,^{9,10} which did not depress the melting point of an authentic sample.

Lithium dimethylamide and o-bromoanisole. A mixture of 93.5 g. (0.5 mole) of *o*-bromoanisole and 0.9 mole of lithium dimethylamide in 500 ml. of ether was refluxed with stirring for 19 hours and then was hydrolyzed with water. This gave: 5.0 g. (7%) of *N,N*-dimethyl-*o*-anisidine, n_D^{20} 1.5420, *picrate* m.p. 141–142°;¹¹ 24.1 g. (32%) of *N,N*-dimethyl-*m*-anisidine, n_D^{20} 1.5579, *picrate* m.p. 142.5–143.5°; 9.3 g. (17%) of anisole;⁹ 16.5 g. (18%) of recovered *o*-bromoanisole; 1.5 g. (2%) of *N,N,N',N'*-tetramethyl-*m*-phenylenediamine, *trinitrobenzene derivative* m.p. 122–123°;¹² and 2.7 g. of material, b.p. 110.5–111° (1.5 mm.), n_D^{20} 1.5480, which was not identified. The mixture melting points of the derivatives with authentic samples were not depressed. The *picrate* of the *ortho* isomer depressed the melting point of the *picrate* of the *meta* isomer. The *trinitrobenzene derivative* was analyzed.

Anal. Calc'd for $C_{16}H_{19}N_5O_6$: C, 50.92; H, 5.07; N, 18.56. Found: C, 50.92; H, 5.25; N, 18.74.

Lithium dimethylamide and N,N-dimethyl-m-anisidine. A mixture of 30.2 g. (0.2 mole) of *N,N*-dimethyl-*m*-anisidine and 0.2 mole of lithium dimethylamide in 200 ml. of ether was refluxed with stirring for 20 hours and then was hydrolyzed with 100 ml. of water. Nothing other than 28.0 g. (93%) of starting material could be isolated.

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(7) Ley and Pfeiffer, *Ber.*, **54**, 363 (1921).

(8) Groenewoud and Robinson, *J. Chem. Soc.*, 1692 (1934).

(9) Rascanu, *Ann. sci. univ. Jassy*, **Pt. I**, **25**, 395 (1939); *Chem. Abstr.*, **34**, 394 (1940).

(10) Hodgson and Kershaw, *J. Chem. Soc.*, 277 (1930).

(11) Fahim and Galaby, *J. Chem. Soc.*, 3529 (1950).

(12) Van Romburgh, *Rec. trav. chim.*, **7**, 1 (1888).

The Dissociation Constants and Infrared Spectra of Some Nitroacids¹

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Received November 3, 1955

In connection with a general program on the chemistry of organic nitrates, it was of interest to obtain some idea of the electrical effect of the nitrate ester function. Accordingly, several nitrocarboxylic acids were synthesized and their dissociation constants and infrared spectra were obtained. α -Nitroacids have previously been prepared by nitration of the corresponding hydroxyacids, but in several cases the acids were reported as unstable yellow oils. For this work the nitroacids were all prepared by reaction of silver nitrate in acetonitrile² with the corresponding bromo- or iodoacids. The acids obtained in this way were quite stable and could readily be purified by distillation. The physical properties of the nitroacids along with the yields obtained are summarized in Table II. The acids were all colorless solids or liquids, and the close correspondence of their neutral equivalents with the theoretical values is indicative of their high purity.

Freezing point measurements³ and infrared spectra⁴ have shown that carboxylic acids exist largely as monomers in polar solvents and as dimers in nonpolar solvents. Accordingly, the infrared spectra of the nitroacids were measured in carbon tetrachloride solution and the carbonyl frequencies of the acids so were established. The dimer frequency was preferred since the carbonyl frequency of the monomer is strongly dependent on solvent. The dimer frequencies of the nitroacids along with those of the bromoacids and the unsubstituted acids, as a standard of comparison, are summarized in Table I. The acid strengths of the nitroacids were also determined and their *pK* values along with those of the bromo and unsubstituted acids⁵ are tabulated in Table I. No hydrolysis of the nitrate ester function occurred during the titration of the nitroacids. This was indicated by the sharp end points obtained, and also by the fact that a 10⁻⁴M solution of nitroacetic acid did not change in conductance over a several hour period.

As might be anticipated α -nitroacids are somewhat stronger acids than the corresponding bromoacids, and a fairly constant difference of 0.60 in *pK* value is actually observed. According to accepted theory this difference is due to electrostatic repul-

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) Ferris, McLean, Marks, and Emmons, *J. Am. Chem. Soc.*, **75**, 4078 (1953).

(3) Lassette, *Chem. Revs.*, **20**, 277 (1937).

(4) Flett, *J. Chem. Soc.*, 962 (1951).

(5) Washburn, Editor, *International Critical Tables*, Vol. VI, McGraw-Hill, New York, N. Y., 1929, p. 259 ff.