EXPERIMENTAL

dl-β-(3,4-Dihydroxyphenyl)alanine methyl ester hydrochloride. The compound, prepared according to the general method of Fischer,[5] was obtained as a crystalline product melting at 180–181°; yield 93%.

Anal. Calc'd for $C_{10}H_{13}NO_4 \cdot HCl$: C, 48.4; H, 5.6; N, 5.6. Found: C, 48.2; H, 5.44; N, 5.6.

dl-β-(3,4-Dihydroxyphenyl)alanine methyl ester. The ester hydrochloride (14 g.) was suspended in 50 ml. of chloroform and an equal volume of chloroform saturated with ammonia was added. After vigorous shaking and filtration to remove ammonium chloride, the chloroform was concentrated and petroleum ether was added; whereupon the ester crystallized at room temperature in quantitative yield. The ester melted at 126°, and was soluble in chloroform and carbon tetrachloride, but insoluble in petroleum ether, cold ethyl acetate, and water.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.1; N, 6.6. Found: C, 56.3; H, 5.8; N, 6.5.

Phthalyl glycine. This substance was prepared by the method of Sheehan and Frank[3] with one modification, which led to an increased yield. The modified procedure is as follows: Glycine (3.0 g.) and phthalic anhydride (5.9 g.) were suspended in *para*-cymene and the mixture was refluxed in an apparatus equipped with a Dean and Stark trap. When the theoretical amount of water had been collected, the *para*-cymene was removed under reduced pressure, and the residue was crystallized from water-alcohol. The product was obtained as fine needles (m.p. 192–194°) (reported 191–192°) in 90% yield after recrystallization from water-ethanol.

Phthalyl glycyl dl-β-(3,4-dihydroxyphenyl)alanine methyl ester. A slurry of 4.95 g. of Dopa methyl ester hydrochloride (0.02 mole) and 4.09 g. of triethylamine was mixed with 4.46 g. of phthalyl glycyl chloride[3] (0.02 mole) in chloroform. After stirring for three hours, the mixture was washed with water and the chloroform layer was dried over sodium sulfate. Evaporation of the solvent yielded a syrup which crystallized from chloroform and gave 4 g. (50%) of a compound melting at 196–197° (decomp.). This material gave a positive Arnow test indicating that both hydroxyl groups were free.

Anal. Calc'd for $C_{20}H_{18}N_2O_7$: C, 60.3; H, 4.6; N, 7.05. Found: C, 59.8; H, 4.7; N, 7.0.

Phthalyl glycyl dl-β-(3,4-dihydroxyphenyl)alanine methyl ester di-acetate. The diacetate of the above compound was prepared with acetic anhydride and glacial acetic acid according to the standard procedure. The product crystallized from methanol-water and melted at 174°. This substance gave a negative Arnow test (*loc. sit.*).

Anal. Calc'd for $C_{24}H_{22}N_2O_9$: C, 59.7; H, 4.6; N, 5.8. Found: C, 59.5; H, 4.7; N, 5.7.

The diacetate (2.5 g.) was dissolved in 50 ml. of methanol and was treated with 5 ml. of 2 *N* sodium hydroxide in a nitrogen atmosphere at room temperature. Upon acidification of the mixture, a precipitate which was insoluble in ether, alcohol, and petroleum ether was obtained. This material melted at 198° (decomp.) and showed no depression in melting point when melted mixed with the phthalyl glycyl Dopa methyl ester prepared above.

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(5) Fischer and Suzuki, *Ber.*, **37**, 2842 (1904).

The Acid Cleavage of 1-(3-Alkoxypropyl)-3-Guanidines and Nitroguanidines[1]

LAWRENCE FISHBEIN AND JOHN A. GALLAGHAN

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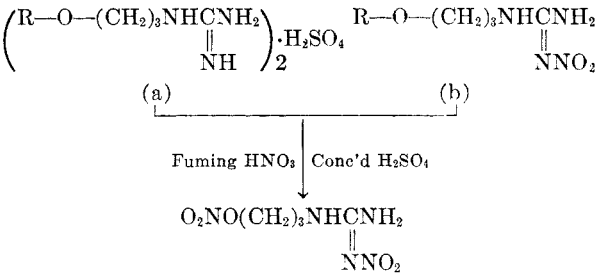
In the nitration of 1-(3-alkoxypropyl)-3-guanidinium sulfate salts and 1-(3-alkoxypropyl)-3-nitroguanidine, a unique ether cleavage occurred giving excellent yields of 1-(3-nitroxypropyl)-3-nitroguanidine. The nitrations were performed at 0–5° with a nitrating mixture consisting of fuming nitric acid and concentrated sulfuric acid.



R = CH_3; $(CH_3)_2CH$

The infrared spectra of the product formed from both reactions (a) and (b) were found to be identical with an authentic sample of 1-(3-nitroxypropyl)-3-nitroguanidine prepared earlier by the authors.[2]

The mechanism of this reaction is somewhat obscure in that attempts to nitrate 1-(2-methoxyethyl)-3-guanidinium sulfate under the same conditions failed to give ether cleavage and resulted in the formation of the normal 1-(2-methoxyethyl)-3-nitroguanidine. Attempts to cleave 1-(2-methoxyethyl)-3-nitroguanidine by an analogous nitrating procedure resulted in the recovery of the starting material. The elucidation of the course of this reaction is being investigated.

EXPERIMENTAL[3]

1-(Alkoxyalkyl)-3-guanidinium sulfate salts. 1-(2-Methoxyethyl)-, 1-(3-methoxypropyl)-, and 1-(3-isopropoxypropyl)-3-guanidinium sulfate were prepared according to the procedure of Rathke,[4] utilizing 2-methyl-2-thiopseudouronium sulfate and the corresponding alkoxyalkylamine.

1-(3-Isopropoxypropyl)-3-guanidinium sulfate had m.p. 135–137° after one crystallization from 95% ethanol.

Anal. Calc'd for $C_{14}H_{36}N_6O_6S$: C, 40.38; H, 8.67; N, 20.19. Found: C, 40.30; H, 8.70; N, 20.33.

Picrate, m.p. 178–180° after one crystallization from 95% ethanol.

(1) Publication approved by the Bureau of Ordnance, Navy Department. The opinions expressed are those of the authors.

(2) Fishbein and Gallaghan, *J. Am. Chem. Soc.*, **76**, 3217 (1954).

(3) All melting points are corrected.

(4) Rathke, *Ber.*, **17**, 297 (1884); Schoeller and Schotte, German Patent 455,682 (June 23, 1931).

Anal. Calc'd for $C_{13}H_{26}N_6O_8$: 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 prepd. 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 Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954); McKay and Milks, *J. Am. Chem. Soc.*, **72**, 1616 (1950).

The Reaction of Haloanisoles with Lithium Dimethylamide

ROBERT A. BENKESER AND CHARLES E. DEBOER

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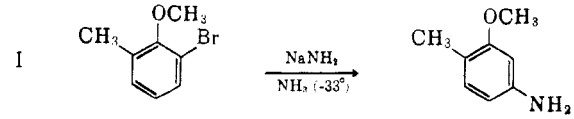
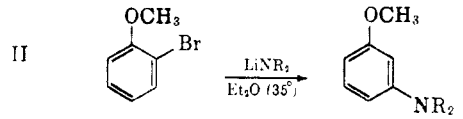
Benkeser and Buting[1] investigated the reactions of sodium amide with three of the isomeric methyl-*o*-bromoanisoles and found that the amide ion enters only in the position adjacent to the displaced bromide ion. Thus 2-bromo-6-methylanisole reacts with sodium amide in liquid ammonia to form 6-methyl-*m*-anisidine 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 analgous 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, Crounse, Massie, Benkeser, and Spatz, *J. Am. Chem. Soc.*, **67**, 2106 (1954).