[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF PURDUE UNIVERSITY]

The Reaction of Dihaloanisoles with Sodium Amide in Liquid Ammonia

BY ROBERT A. BENKESER AND GENE SCHROLL

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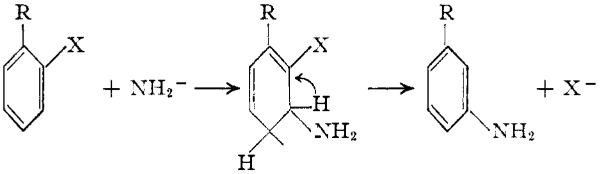
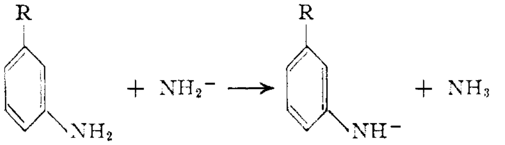
Various isomeric dihaloanisoles were treated with sodium amide in liquid ammonia. In every case only monohaloamines were isolated which would be predicted by a nucleophilic displacement mechanism. 2,6-Dibromoanisole and 2,5-dichloroanisole gave good yields of 4-bromo-*m*-anisidine and 4-chloro-*m*-anisidine, respectively, as the sole products. 2,4-Dichloroanisole under similar conditions gave a mixture of haloamines from which were identified 5-chloro-*o*-anisidine, 6-chloro-*m*-anisidine and 4-chloro-*m*-anisidine.

Previous reports indicate that ortho halogenated anisoles,[1] trifluoromethylbenzenes,[2] thioanisoles[3] and phenylmethyl sulfones[3] react with sodium amide in liquid ammonia to give the meta aryl amine in each case with the elimination of the halogen atom.[4] It has been established that if the halogen atom of a methylhaloanisole is similarly replaced by an amino group, the latter enters the ring only at the position ortho to the halogen atom.[5]

It is difficult to reconcile these findings into a single all-inclusive mechanism, consistent with modern concepts. However, a nucleophilic amide ion attack[4] accompanied by a synchronous intramolecular hydrogen shift and halide ion elimination is attractive from certain standpoints.

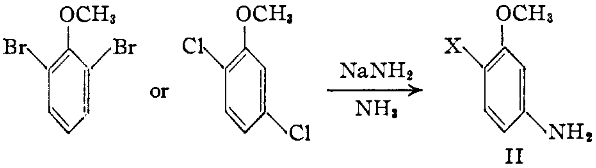


The aryl amine produced in this fashion would react immediately with excess amide ions since the latter are more basic than anilide ions.

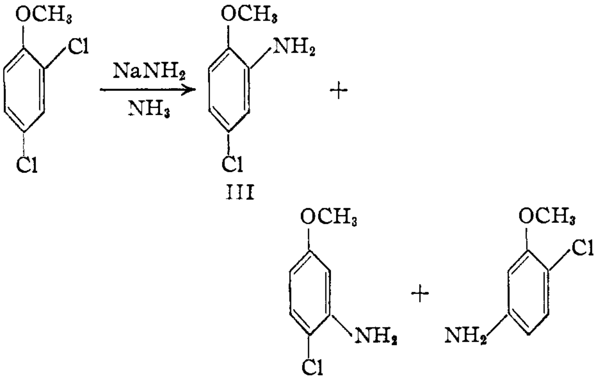


As a partial test of this mechanism various isomeric dihaloanisoles were treated with sodium amide in liquid ammonia. It would be predicted that only monoamines should be formed since (a) simultaneous attack by two amide ions would involve an unlikely termolecular collision and (b) attack by a second negative amide ion, in a stepwise sequence, should be greatly inhibited by the presence of *two* strong electron donors like -OCH$_3$ and -NH$^-$.

Accordingly, 2,6-dibromoanisole and 2,5 dichloroanisole gave good yields of 4-bromo-*m*-anisidine (II) and 4-chloro-*m*-anisidine (II), respectively, as the sole products. 2,4-Dichloroanisole under similar conditions gave a mixture of monohaloamines from which were identified 5-chloro-*o*-anisidine (III), 6-chloro-*m*-anisidine (IV) and 4-chloro-*m*-anisidine (V).



II



III IV V

It seems not unlikely that trace amounts of 3-chloro-*p*-anisidine and 2-chloro-*m*-anisidine might also have been formed in the latter reaction. The proof of the structure of all the compounds isolated was established by comparing them with samples made by independent syntheses.

Experimental

Reaction of 2,6-Dibromoanisole with Sodium Amide in Liquid Ammonia.[6]—A mixture of 18.6 g. (0.07 mole) of 2,6-dibromoanisole (m.p. 14.5°)[7] and 30 cc. of petroleum ether (b.p. 35–40°) was added over a period of 15 minutes to 0.53 mole of sodium amide[8] in 500 cc. of liquid ammonia in a one-liter, three-necked flask equipped with a stirrer, dropping funnel and a Dry Ice condenser. Stirring was continued for four hours before 35 g. of ammonium chloride was added. Fifty cc. of benzene was stirred into the mixture and the ammonia was permitted to evaporate. The benzene solution was filtered and then extracted with 0.5 *N* hydrochloric acid. The chilled acid extract was made basic with concentrated sodium hydroxide and 13 g. (92%) of a tan solid melting at 97–99° was filtered off. The benzoyl derivative melted at 131°. Mixed melting points of the amine and its benzoyl derivative with authentic samples of 4-bromo-*m*-anisidine and 4′-bromo-*m*-benzaniside, respectively, showed no depressions[9]; the authentic samples were derived from 2-bromo-5-nitrophenol[10] by methylation and catalytic reduction.

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[1] H. Gilman and S. Avakian, THIS JOURNAL, **67**, 349 (1945).

[2] R. A. Benkeser and R. G. Severson, *ibid.*, **71**, 3838 (1949).

[3] H. Gilman and G. A. Martin, *ibid.*, **74**, 5317 (1952).

[4] See J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 382 (1951) for a discussion of these "cine-substitution" reactions.

[5] R. A. Benkeser and W. E. Buting, THIS JOURNAL, **74**, 3011 (1952).

[6] This was the general procedure used in all the reactions with sodium amide and was an adaptation from the work of R. A. Benkeser and W. E. Buting, ref. 5.

[7] F. G. Pope and A. S. Wood, *J. Chem. Soc.*, **101**, 1823 (1912).

[8] T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

[9] R. H. Griffith and E. Hope, *J. Chem. Soc.*, **127**, 990 (1925), list the melting point of 4-bromo-*m*-anisidine at 90.5° and the melting point of the benzoyl derivative as 124°. Our authentic samples melted at 95–96° and 130–131°, respectively.

[10] R. V. Henley and E. E. Turner, *ibid.*, 928 (1930).

Anal. Calcd. for C_7H_8ONBr: N, 6.93. Found: N, 6.87.

In another instance where 0.14 mole of 2,6-dibromoanisole and 0.56 mole of sodium amide reacted over a period of 2.5 hours, a 62% yield of 4-bromo-*m*-anisidine was obtained.

Reaction of 2,5-Dichloroanisole with Sodium Amide in Liquid Ammonia.—A solution of 27.6 g. (0.156 mole) of 2,5-dichloroanisole (m.p. 22°)[11] in 40 cc. of petroleum ether (b.p. 35–40°) was added to 0.624 mole of sodium amide in 500 cc. of liquid ammonia over a period of 40 minutes. Stirring was continued for 3.5 hours. After isolation and two crystallizations from ethanol, 19 g. (78%) of an amine melting at 79–81°[12] was obtained. The acetyl derivative melted at 123–124°.[12] Mixed melting points of the amine and its acetyl derivative with authentic samples of 4-chloro-*m*-anisidine and 4-chloro-*m*-acetaniside, respectively, showed no depression.

Reaction of 2,4-Dichloroanisole with Sodium Amide in Liquid Ammonia.—A solution of 2,4-dichloroanisole (m.p. 24°)[11] in 40 cc. of petroleum ether (b.p. 35–40°) was added to sodium amide in 500 cc. of liquid ammonia. After the desired reaction time, the excess sodium amide was neutralized with ammonium chloride. The amine was isolated and vacuum distilled so as to remove the accompanying tars. The following table summarizes a number of trials.

Trial	2,4-Dichloranisole, moles	Sodium amide, moles	Reaction time, min.	Yield, g.
1	0.1	0.45	30	2
2	.1	.2	45	5
3	.1	.25	75	8
4, 5, 6	.156	.624	250	19 (av.)

The material obtained in trials 4, 5 and 6 was placed in a 25° constant temperature bath and the clear, oily needles (m.p. 40–43°) that formed were filtered off and washed with petroleum ether. The acetyl derivative of the needles melted at 103–104° after two crystallizations from a water-ethanol solution and was identified as 5-chloro-*o*-acetaniside[12] by a mixed melting point with an authentic sample prepared from 4-chloro-2-nitroanisole.

The remaining, liquid portion of the combined products from trials 4, 5 and 6 was distilled with a Todd wire spiral column. A representative fraction (b.p. 136.5–137° at 9 mm., $n^{25.5}D$ 1.5853) was converted into the benzoyl derivative which melted at 106–107° after repeated crystallizations from ethanol (95%). The benzoyl derivative was identified as 6′-chloro-*m*-benzaniside by a mixed melting point with an authentic sample whose preparation is described below.

The pot residue from the distillation yielded, after extensive purification, a small amount of an amine melting at 68–71°. This amine was converted into its acetyl derivative (m.p. 122–124°)[12] which was identified as 4-chloro-*m*-acetaniside by a mixed melting point with an authentic sample.

4-Chloro-2-nitroanisole.—A mixture of 8.1 g. of nitric acid (70%) and 30 cc. of glacial acetic acid was added to a cooled mixture of 12.8 g. (0.09 mole) of *p*-chloroanisole and 10 cc. of glacial acetic acid. The acid mixture was diluted with water after refluxing for four hours, and the precipitate was collected and crystallized twice from ethanol. The liquor from the crystallizations was diluted with water and steam distilled, yielding more product after the initial distillation of unreacted *p*-chloroanisole. A 16% yield of the desired product was obtained; m.p. 96–98°.[12]

6-Chloro-*m*-anisidine.—Catalytic reduction of 4-chloro-3-nitroanisole (m.p. 43.2–45°)[13] obtained from 2-nitro-*p*-anisidine[14] by means of a Sandmeyer reaction, gave a 92% yield of the amine; b.p. 136–137° (10 mm.), $n^{25.5}D$ 1.5848.

Anal. Calcd. for C_7H_8ONCl: C, 53.4; H, 5.12. Found: C, 54.01; H, 5.44.

Benzoylation of 6-chloro-*m*-anisidine yielded 6′-chloro-*m*-benzaniside melting at 106–107°.

Anal. Calcd. for $C_{14}H_{12}O_2NCl$: C, 64.3; H, 4.03; N, 5.35. Found: C, 64.22; H, 4.31; N, 5.31.

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[11] A. F. Holleman, *Rec. trav. chim.* **37**, 96 (1917).

[12] F. Reverdin and F. Eckhard, *Ber.*, **32**, 2622 (1899).

[13] H. van Erp, *J. prakt. Chem.*, **127**, 20 (1930).

[14] P. E. Fanta and D. S. Tarbell, *Org. Syntheses*, **25**, 79 (1945).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Synthesis and Reactions of 1-Methyl-2-vinyl-4-hydroxycyclohexene

BY GILBERT STORK, S. S. WAGLE AND P. C. MUKHARJI

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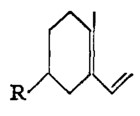
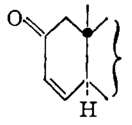
Pure 1-methyl-2-vinyl-4-hydroxycyclohexene, 1-methyl-2-vinylcyclohexene and 6-methyl-1-vinylcyclohexene have been prepared for the first time. The first two substances do not take part in the Diels–Alder reaction and previously described adducts of the second substance are in reality derived from the third.

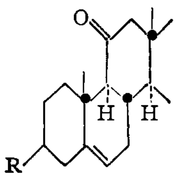
One of the attractive synthetic schemes for the elaboration of C-10 methylated steroids of the cortical hormone type consists of the union of two halves of the steroid molecule by means of a Diels–Alder reaction between a suitable derivative of 1-methyl-2-vinylcyclohexene (I) and a dienophile of the general type shown in II.[1] This might be expected to furnish adducts possessing not only the desired structural arrangement, but also presumably the natural steroid stereochemistry shown in III.[2]



I , R = H
Ia, R = OH



II



III

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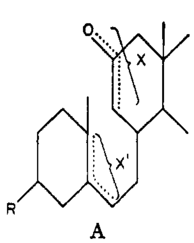
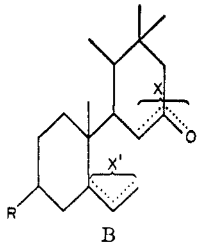
[1] (a) A. B. Meggy and R. Robinson, *Nature*, **140**, 282 (1937); (b) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938); (c) P. A. Robins and J. Walker, *ibid.*, 642 (1952). Since this paper was written, a further paper by Robins and Walker has appeared in which they reach conclusions which are to a large extent in agreement with our own (*ibid.*, 1610 (1952)).

[2] After base isomerization at C_9 of the initially *cis* adduct. The structural anticipation follows from a consideration of the four possible formal transition states that can be written for the addition of I to II. The charges associated with the two halves in the transition state are here denoted by x, which in the case under consideration is either one electron or negative, and by x′ which here must be either one electron or positive. Only the two transition states illustrated by A and B need be considered since the alternate mode of addition to the dienophile would result in much less stabilization for x. Of these



A



B