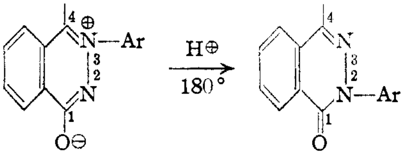
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

# The Rowe Rearrangement[1]

BY WYMAN R. VAUGHAN, DONALD I. MCCANE AND GILBERT J. SLOAN

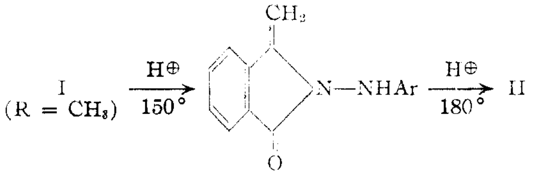
The ψ-phthalazone–phthalazone or Rowe rearrangement has been examined to determine whether or not the aryl group of the ψ-phthalazone structure migrates from one nitrogen to the other in the course of the rearrangement. A study of 3-(4′-nitrophenyl)-4-methyl-ψ-phthalazone with excess $N^{15}$ in the 2-position and 2-(4′-nitrophenyl)-4-methylphthalazone with excess $N^{15}$ in the 3-position indicates that treatment of a ψ-phthalazone enriched with $N^{15}$ at the 2-position with 1.2 *N* acid at 180° for 9 hours rearranges the molecule to a phthalazone enriched with $N^{15}$ at the 3-position. Thus no migration of the aryl group from one nitrogen to the other occurs. Implicit in these studies is additional support for the linear structure of diazonium ions.

The ψ-phthalazone[2]–phthalazone or Rowe[3] rearrangement involves the transformation of a ψ-phthalazone I into a phthalazone II in 1.2 *N* acid at 180°. The reaction requires approximately 9 hours to reach completion, and it has been established as intramolecular.[3] It is represented as



I II

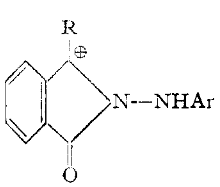
Rowe discarded a mechanism involving ring contraction to an isoindolone structure III even though he actually isolated such a compound in some of his studies[3]



III

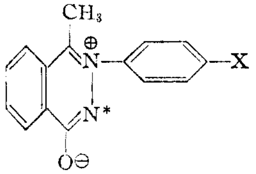
His reason for preferring to regard it as a shift of an aryl carbanion was that the rearrangement proceeds almost as well where the R group of I is hydrogen instead of methyl; obviously such a compound cannot yield an analog of III as an intermediate.

An alternative course of rearrangement has been proposed recently[4] and is closely related to Rowe's discarded mechanism, the difficulty of the intermediate structure being obviated by postulating a carbonium ion IV derived from the isoindolone instead of the isoindolone itself.

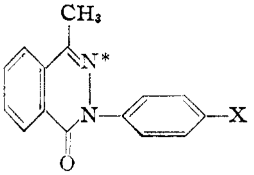


IV

In order to determine which course is taken, an actual shift of the aryl group from the nitrogen of the 3-position to the nitrogen of the 2-position, or an exchange of positions of the nitrogens of the two structures, the following compounds have been prepared with excess $N^{15}$ in the starred positions



I(a) X = $NO_2$
I(b) X = $NH_2$

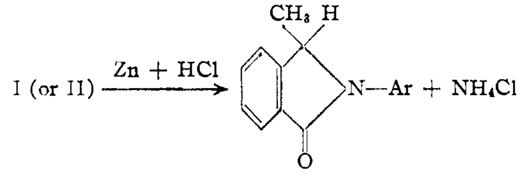


II(a) X = $NO_2$
II(b) X = $NH_2$
II(c) X = $NHCOCH_3$
II(d) X = H

If no migration occurs during the rearrangement, only position 3 of the rearranged product II(a) will contain enriched nitrogen, precisely as in II(a) prepared by synthesis.

Compounds I(a) and (b) were prepared according to Rowe's directions[2,5] while II(a) was prepared from 2-acetobenzoic acid and β-$N^{15}$-enriched 4-nitrophenylhydrazine, obtained by the usual alkaline sodium sulfite reduction of 4-nitrobenzene diazonium chloride[6] in which the β-nitrogen came from $N^{15}$-enriched potassium nitrite. Compound II(b) was prepared by stannous chloride–hydrochloric acid reduction of II(a); II(c), by acetylation of II(b); and II(d), by the elegant deamination procedure of Kornblum[7] applied to II(b).

Reduction of either ψ-phthalazones[5] or phthalazones[8] affords chiefly an N-substituted isoindolone and ammonium chloride



If the reaction releases the unsubstituted nitrogen as ammonium ion, the ammonium chloride produced on reduction of I or II should contain the excess $N^{15}$ of the potassium nitrite used in their preparation. The assay for excess $N^{15}$ in ammo-

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[1] (a) This work was assisted by a grant from the Michigan Memorial Phoenix Project; (b) presented before the Division of Organic Chemistry at the 117th Meeting of the American Chemical Society at Philadelphia, April 13, 1950.

[2] F. M. Rowe, E. Levin, A. C. Burns, J. S. H. Davies and W. Tepper, *J. Chem. Soc.*, 690 (1926).

[3] F. M. Rowe, D. A. W. Adams, A. T. Peters and A. E. Gillam, *ibid.*, 90 (1937).

[4] W. R. Vaughan, *Chem. Revs.*, **43**, 447 (1948).

[5] F. M. Rowe, E. Levin and A. T. Peters, *J. Chem. Soc.*, 1067 (1931).

[6] E. Bamberger and E. Kraus, *Ber.*, **29**, 1824 (1896); W. Davies, *J. Chem. Soc.*, **121**, 715 (1922).

[7] N. Kornblum and D. C. Iffland, THIS JOURNAL, **71**, 2137 (1949), Procedure I, p. 2140.

[8] S. Racine, *Ann.*, **239**, 78 (1887); *cf.* ref. 2 and 4.

nium chloride is based on the reaction

$$NH_4{}^*Cl + KNO_2 \longrightarrow NN^* + 2H_2O + KCl$$

This reaction is also used to determine the excess $N^{15}$ in the potassium nitrite from which I(a) and II(a) are made; here, however, the ammonium chloride contains no excess $N^{15}$.[9]

The direct reduction of I(a) or II(a) was not feasible, and while the reduction of I(b) afforded the expected[5] products, all attempts to reduce the isomeric II(b) ended with essentially quantitative recovery of II(b). Reduction of II(c) yielded ammonium chloride which proved to be contaminated with *p*-phenylenediamine dihydrochloride as shown by spot tests.[10,11] While correction for this was possible, the difficulty is avoided if II(d) is reduced instead of II(c), but aniline is now produced. However, aniline hydrochloride is readily separated from ammonium chloride by extraction with absolute ethanol.

The following table summarizes the results of mass-spectrometric analysis. The values in column 5 represent conversion of those in column 4 to excess atom per cent. $N^{15}$ enrichment in the inorganic compound listed; and by reason of the source of the ammonium chloride, they also represent the excess atom per cent. enrichment at the starred positions of I(a) or II(a). The per cent. of the expected value of enrichment observed (last column) is obtained by division of the values for the numbered samples by the values for the lettered samples (standard potassium nitrite) preceding each series.

TABLE I

ISOTOPE ANALYSIS[12]

| Sample | Compound | Source | Excess atom $N_2$ | % $N^{15}$ in Compound | % Expected excess $N^{15}$ |
|---|---|---|---|---|---|
| A | $KNO_2$ | .... | 2.28 | 4.56 | Standard |
| 1 | $NH_4Cl$[a] | II(d)[b] | 2.23 | 4.46 | 98 |
| B | $KNO_2$ | .... | 0.943 | 1.89 | Standard |
| 2 | $NH_4Cl$[c] | I(b) | .758 (0.892)[f] | 1.52 (1.78)[g] | 81 (95)[g] |
| 3 | $NH_4Cl$[c] | II(c)[d] | .856 (0.893)[f] | 1.71 (1.79)[g] | 91 (95)[g] |
| 4 | $NH_4Cl$[c] | II(c)[d] | .836 (0.909)[f] | 1.67 (1.82)[g] | 89 (96)[g] |
| 5 | $NH_4Cl$[a] | II(d)[d] | .920 | 1.84 | 98 |
| B′ | $NH_4Cl$[i] | .... | .946 | 1.89 | Standard |
| C | $KNO_2$ | .... | ... | 1.39[h] | Standard |
| 6 | $NH_4Cl$[a] | II(d)[b] | .681 | 1.36 | 98 |
| 7 | $NH_4Cl$[a] | II(d)[e] | .683 | 1.37 | 98 |

[a] Purified by extraction with absolute ethanol (Procedure A in Experimental). [b] Prepared synthetically from 2-acetobenzoic acid and 4-nitrophenylhydrazine, etc. [c] Purified by treatment with hot dilute $H_2O_2$ and Norit (Procedure B in Experimental). [d] Prepared by rearrangement. [e] Synthetic sample subjected to conditions of rearrangement before reduction and deamination. [f] Values in parentheses corrected for dilution using factors from column 6 of Table III in equation: excess % $N^{15} = E \div X/W_2$, where $E$ is excess % $N^{15}$ observed. [g] Values in parentheses from "corrected" values of column 4. [h] Value calculated from dilution of sample A with $KNO_2$ of known purity. [i] Check standard prepared by quantitative reduction of sample B.[13]

## Discussion of Results

An examination of the data for samples 1 and 6 (Table I) shows that where II(d) is obtained from II(a) prepared synthetically, 98% of the expected excess $N^{15}$ is present in the ammonium chloride formed upon zinc–hydrochloric acid reduction. Furthermore, the data for sample 7 indicate that where similarly prepared II(a) is subjected to the rearrangement conditions prior to reduction and deamination, the relative positions of the aryl group and the nuclear nitrogens remain unaltered.

Accordingly, since II(d) prepared by rearrangement (sample 5) yields ammonium chloride in which 98% of the expected excess $N^{15}$ is present, the nitrogen in the 3-position (unsubstituted) of this sample was the enriched nitrogen Since the ψ-phthalazone, I(a), from which the II(d) was prepared by rearrangement, contained excess $N^{15}$ in the 2-position (unsubstituted), as shown by the method of synthesis and confirmed by the mass spectrometric data for I(b), sample 2, it must follow that in both I(a) and II(a) the 4-nitrophenyl group is attached to the same (unenriched) nitrogen. Hence no migration of the aryl group occurs during rearrangement.

It follows that the nitrogen of the 2-position in the ψ-phthalazone and in the 3-position of the phthalazone is the same (enriched) nitrogen. Contraction to a structure such as IV followed by subsequent expansion to give the phthalazone is thus a not unreasonable course for the rearrangement. It is consistent with this evidence and with such evidence as is offered by Rowe.[3]

The data for samples 3 and 4, II(c), which like sample 5, II(d), were prepared from I(a) by rearrangement, support the arguments of the preceding paragraphs. The reasons for failure to observe 100% of the expected excess $N^{15}$ in any of the samples is undoubtedly due to contamination of the reduction products with spurious ammonium chloride, or less probably aniline hydrochloride, whose origin constitutes a separate problem which is under investigation along with a study of the reduction reaction.

In conclusion, it should be pointed out that these studies provide new evidence for the view that the nitrogens of diazonium ions are non-equivalent. This is implicit in the work of Allen[14] on the Fischer indole synthesis and has been explicitly demonstrated by Holt and Bullock.[15]

## Experimental[16]

**$N^{15}$-Enriched Potassium Nitrite.**—A sample of $N^{15}$-enriched potassium nitrate (Eastman Kodak Co., 31%) was mixed with sufficient reagent grade potassium nitrate to effect approximately 6-fold dilution of the excess $N^{15}$. The resulting mixture was heated with about 20% more than twice its weight of lead at 420° for 2.25 hours, with vigorous stirring. After cooling and extraction with water, there was obtained about 64% of the theoretical yield of potassium nitrite (as shown by titration of an aliquot with standard potassium permanganate). The solid potassium nitrite obtained upon crystallization was shown to be 90% pure by similar titration (sample A, Table I). Subsequently, a second preparation of enriched nitrite was prepared by dilution of the original with reagent potassium nitrite of known

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(9) W. R. Vaughan, W. T. Boyd, D. I. McCane and G. J. Sloan, *Anal. Chem.*, **23**, 508 (1951); *cf.* also samples B and B′, Table I.

(10) O. Heim, *Ind. Eng. Chem., Anal. Ed.*, **7**, 146 (1935).

(11) H. E. Cox, *Analyst*, **54**, 694 (1929).

(12) The authors are indebted to Mr. Worthy T. Boyd who made the mass spectrometric analyses on the Consolidated-Nier instrument, model 21-201, of the Department of Chemical and Metallurgical Engineering of the University of Michigan. Values are correct to ±0.5% of the recorded figures.

(13) O. Baudisch and P. Mayer, *Biochem. Z.*, **107**, 1 (1920).

(14) C. H. F. Allen, THIS JOURNAL, **65**, 611 (1943).

(15) P. F. Holt and B. I. Bullock, *J. Chem. Soc.*, 2311 (1951).

(16) Melting points are corrected.

purity. This sample (B, Table I), was calculated to be 2.25 atom %$N^{15}$, and mass spectrometric analysis showed it to be 2.248 atom %$N^{15}$. A sample of this salt was converted to silver nitrite, washed free of nitrate, dissolved in potassium hydroxide, and after filtration from silver oxide was reduced quantitatively to ammonium chloride by boiling with ferrous hydroxide[13] (sample B′). A third sample was prepared by similar dilution, and similar calculation gave 1.75 atom %$N^{15}$. The latter sample (C, Table I) was not analyzed in the mass spectrometer.

**3-(4′-Nitrophenyl)-4-methyl-ψ-phthalazone Sulfate.**—This substance was prepared according to Rowe's directions[2,5] from sodium 2-naphthol-1-sulfonate[17] and 4-nitroaniline diazotized with $N^{15}$-enriched potassium nitrite equivalent to the sodium nitrite used by Rowe.[2] The following intermediates were obtained in essentially the same yields and with the same melting points as reported by Rowe[2]: 3-(4′-nitrophenyl)-3,4-dihydrophthalazinyl-4-sodium acetate-1-sodium sulfonate[2]; 1-hydroxy-3-(4′-nitrophenyl) 3,4-dihydrophthalazinyl-4-acetic acid.[2] The 3-(4′-nitrophenyl)-4-methyl-ψ-phthalazone sulfate[5] was used for the preparation of the free base and for the rearrangement. It corresponded entirely with Rowe's product,[5] similarly prepared.

**3-(4′-Nitrophenyl)-4-methyl-ψ-phthalazone I(a).**—The free base was prepared from the preceding sulfate (5.0 g.) by addition to 20 ml. of water containing 2.5 g. of sodium acetate. The solution was boiled with good stirring for 1 minute or until all brown material had become yellow. After cooling, the mixture was filtered, and there was thus obtained 2.42 g. (65%) of the free base, m.p. 251–252° (dec.), Rowe[5] gives 251°.

**3-(4′-Aminophenyl)-4-methyl-ψ-phthalazone I(b).**—A hot solution of 18 g. of sodium sulfide in 18 ml. of water was used to reduce 2.3 g. of the nitro-ψ-phthalazone just described to the desired amino-ψ-phthalazone according to Rowe's directions[5] to yield 1.55 g. (76%), m.p. 277° (dec.), Rowe[5] gives 277°.

**2-(4′-Nitrophenyl)-4-methylphthalazone (by rearrangement) II(a).**—Rowe's best procedure[8] (1.2 *N* acid at 180° for 9 hours) was followed with the following modifications: the sulfate (2.5 g. samples) of the ψ-phthalazone was used in place of the free base in order to minimize mechanical losses, and sulfuric acid (36 ml. of 1.2 *N* acid for each sample) was used in place of hydrochloric. The solutions were sealed in glass tubes and heated at 180 ± 3° for 9 hours. The yield of II(a) based on the sulfate was 56–60%; based on the amount of free base actually available (65%) in the sulfate, the yield was 86–91% 2-(4′-nitrophenyl)-4-methylphthalazone, m.p. 215.5–216.5° after recrystallization from acetic acid–water. Rowe gives 214°.[18] Samples 3 and 5 (Table II) were prepared from the same rearrangement product obtained from a double-sized run, while sample 4 was prepared from the product of a separate rearrangement.

**2-(4′-Nitrophenyl)-4-methylphthalazone (by Synthesis) II(a).**—$N^{15}$-Enriched 4-nitrophenylhydrazine was prepared by diazotizing 4-nitroaniline with $N^{15}$-enriched potassium nitrite and reducing the diazonium salt with alkaline sodium sulfite.[19] The enriched 4-nitrophenylhydrazine (2.0 g.) was dissolved in the minimum quantity of 95% ethanol to give a saturated solution on the steam-bath. To this solution there was added a similarly warmed solution of 4.0 g. of 2-acetobenzoic acid[20] in 10 ml. of 95% ethanol. The resulting solution was treated, without isolation of the hydrazone, with a drop of 10% hydrochloric acid to effect cyclization. An almost colorless precipitate was formed immediately, and the mixture was kept on the steam-bath for 15 minutes. The crude product (3.5 g., 95% yield), m.p. 211–212°, obtained on filtration of the cooled reaction mixture was used in subsequent reactions. Recrystallization from acetic acid–water yielded a product identical with that from the rearrangement, m.p. and mixed m.p. 215.5–216.5°; reported 214°.[18]

**2-(4′-Aminophenyl)-4-methylphthalazone II(b).**—Nitrophthalazone, II(a), (2.00 g.) was reduced by treatment with 10 g. of stannous chloride dihydrate in 30 ml. of concd. hydrochloric acid with shaking at room temperature until solution was nearly complete, during which time (about 15 minutes) some heat was evolved. The mixture was then allowed to stand on the steam-bath for 1 hour whereupon a beautiful, crystalline precipitate appeared. After cooling to 5°, the mixture was poured, with external cooling, into a solution of 30 g. of sodium hydroxide in 45 ml. of water (precooled to 5°). After filtration and thorough washing with water there was obtained 1.79 g. (quantitative yield) of 2-(4′-aminophenyl)-4-methylphthalazone, m.p. 211–212°. Rowe obtained a somewhat less pure sample, m.p. 206–207°,[21] by reduction with sodium sulfide.

**2-(4′-Acetamidophenyl)-4-methylphthalazone II(c).**—The corresponding aminophthalazone, II(b) (1.72 g.) was acetylated in boiling 3 *N* hydrochloric acid (34 ml.) by adding 8.5 g. of anhydrous sodium acetate and 4 ml. of acetic anhydride with good stirring, to yield 2.0 g. (quantitative) of II(c), m.p. 257.5–259°. Rowe reports 252°.[21]

**2-Phenyl-4-methylphthalazone II(d).**—A 1.72-g. sample of 2-(4′-aminophenyl)4-methylphthalazone, II(b), was treated in 22.5 ml. of 25% hypophosphorous acid with 0.52 g. of sodium nitrite[7] in 2.3 ml. of water. The mixture was stirred at 5° for 0.5 hr. and then at room temperature for 4 hr. The resulting precipitate was filtered off and dried in air to yield 1.54 g. (95%), m.p. 97–98° of 2-phenyl-4-methylphthalazone. Upon careful recrystallization from ethanol–water the product was found to give no melting point depression with an authentic sample, m.p. and mixed m.p. 101.5–102.5°, prepared from 2-acetobenzoic acid and phenylhydrazine according to Roser who reports 102°.[22]

**Zinc–Hydrochloric Acid Reductions.**—The same general procedure was used throughout. From 1 to 2 g. of the phthalazone, II(c) or (d), or ψ-phthalazone, I(b), was dissolved in a mixture of 8 ml. of 95% ethanol and 16 ml. of concentrated hydrochloric acid at the boiling point. There was then added 3.3 g. of 30 mesh zinc in four equal portions (approximately four times the theoretical quantity), each successive portion being added as soon as the vigorous foaming from the preceding portion had subsided. After 1 hour at the reflux temperature all of the zinc dissolved, whereupon the flask was fitted with a dropping funnel and a downward condenser whose delivery tube dipped beneath the surface of 5 ml. of concentrated hydrochloric acid in a glass evaporating dish. Through the dropping funnel was added 20 g. of sodium hydroxide in 35 ml. of water at such a rate as to maintain vigorous boiling. When the boiling showed signs of diminishing in vigor, heat was supplied, and the distillation was generally continued until the distilling vapors were no longer alkaline to moist litmus. The strongly acid distillate was then evaporated to dryness on the steam-bath and baked at 90° for one hour, during which process the initially white residue darkened. The yields of crude ammonium chloride so obtained are given in column 4 of Table II. Samples 5, 6 and 7 were subjected to more extensive distillation (until no further oily drops were noticed) with the result that considerably more aniline hydrochloride was obtained from the distillates.

TABLE II

YIELDS OF $NH_4Cl$ FROM REDUCTION OF ORGANIC COMPOUNDS

| Sample | Compound | Weight in grams: Compound | Weight in grams: $NH_4Cl$, crude | Weight in grams: $N^*H_4Cl$ | Yield, % |
|---|---|---|---|---|---|
| 1 | II(d) | 1.69 | 0.40 | 0.33[a] | 86 |
| 2 | I(b) | 1.20 | .15 | .086[b] | 34 |
| 3 | II(c) | 2.00 | .30 | .24[b] | 66 |
| 4 | II(c) | 2.00 | .32 | .23[b] | 63 |
| 5 | II(d) | 1.50 | .51[c] | .20[a] | 59 |
| 6 | II(d) | 1.20 | .55[c] | .20[a] | 74 |
| 7 | II(d) | 1.20 | .55[c] | .20[a] | 74 |

[a] After extraction of crude product with five 1-ml. portions of absolute ethanol. [b] Value from Table III ÷ 0.99. [c] Distillation of alkaline mixture continued until no oily droplets observed (approximately twice the volume of distillate previously collected).

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(17) Kindly supplied by the Hilton-Davis Chemical Co., Cincinnati, Ohio, a Division of Sterling Drugs.

(18) F. M. Rowe and A. T. Peters, *J. Chem. Soc.*, 1918 (1931).

(19) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd Ed., Longmans, Green and Co., London, 1948, p. 387; *cf.* ref. 6.

(20) H. L. Yale, THIS JOURNAL, **69**, 1547 (1947).

(21) F. M. Rowe, G. M. Heath and C. V. Patel, *J. Chem. Soc.*, 311 (1936).

(22) W. Roser, *Ber.*, **18**, 803 (1885).

**Reduction By-products.**—Samples 2, 3 and 4 all yielded distillates in which the presence of *p*-phenylenediamine could be demonstrated by spot tests.[10,11] Samples 1, 5, 6 and 7 [II(d)] all contained aniline hydrochloride in the distillates. A reduction of 1.2 g. of unenriched II(d) yielded 0.56 g. of crude ammonium chloride upon evaporation of the distillate. Extraction of this with five 1-ml. portions of absolute ethanol left 0.32 g. of ammonium chloride, and evaporation of the ethanolic extracts followed by solution of the dark residue in 5 ml. of water left 0.05 g. of black tarry material. The aqueous solution was brought to boiling and treated with 0.25 g. of anhydrous sodium acetate and 0.35 ml. of acetic anhydride, and on cooling there separated 0.19 g. of slightly grayish plates of acetanilide, m.p. 112–113°. After recrystallization from water the material did not depress the melting point of authentic acetanilide, m.p. and mixed m.p. 113–114°. The almost quantitative yield of acetanilide indicates that the ethanol-soluble material was almost entirely aniline hydrochloride.

**Treatment of Ammonium Chloride Samples.**—**Procedure A** for samples contaminated with aniline hydrochloride involved only careful washing with 5 or more 1-ml. portions of absolute ethanol. The residue insoluble in this solvent is essentially pure ammonium chloride (see Table III); the samples thus washed were converted to nitrogen.[9]

**Procedure B** for samples contaminated with *p*-phenylenediamine dihydrochloride involved solution of the crude residue, obtained upon evaporation of the acidic distillate, in 20 ml. of water to which was added 5 ml. of 3% hydrogen peroxide solution. The resulting solution was boiled for 5 minutes, during which time a brownish precipitate separated. There was then added 0.5 g. of Norit, and the mixture was boiled for an additional 5 minutes and then was filtered, the residue being washed with liberal quantities of hot water. The colorless filtrate and washings were combined and evaporated to dryness on the steam-bath. The residue no longer responded to spot tests for *p*-phenylenediamine. The weights of ammonium chloride obtained by this procedure are given for samples 2, 3 and 4 in column 4 of Table III. The approximate weights of the ammonium chloride actually produced by the reduction of these organic compounds are given in column 5 of Table III. They are calculated, using the values for *a* and *b* obtained in the following experiment, by means of the equation

$$X = W_2 - \frac{W_1b - W_2}{(M_1b/2M_2a) - 1}, \text{ which reduces to } X = W_2 - 0.31\ (0.99W_1 - W_2)$$

$M_1$ is mol. wt. of *p*-phenylene dihydrochloride; $M_2$ is mol. wt. of ammonium chloride.

TABLE III

CORRECTIONS FOR DILUTION OF $NH_4Cl$ BY "PURIFICATION" WITH $H_2O_2$ AND NORIT

| | | Weight in grams | | | |
|---|---|---|---|---|---|
| Sample | Source | Crude $NH_4Cl$ ($W_1$) | Purified $NH_4Cl$ ($W_2$) | $N^*H_4Cl$ ($X$) | $X/W_2$ |
| 2 | I(b) | 0.15 | 0.10 | 0.085 | 0.85 |
| 3 | II(c) | .30 | .25 | .24 | .96 |
| 4 | II(c) | .32 | .25 | .23 | .92 |

The purified (and thus diluted) ammonium chloride samples were converted to nitrogen as in Procedure A.[9]

**Conversion of *p*-Phenylenediamine Dihydrochloride to Ammonium Chloride (a).**—Samples of *p*-phenylenediamine (0.20 g.) were treated in the following manner. The base was dissolved in excess concd. hydrochloric acid and the resulting solution was evaporated to dryness to yield the dihydrochloride which was then treated as in the preceding Procedure B using the same quantities of reagents. The colorless filtrate was evaporated to dryness on the steam-bath to yield 0.079 ± 0.001 g. of ammonium chloride (40% or $a = 0.40$).

**(b).**—A blank determination carried out as in (a), on pure ammonium chloride (0.400 g.) showed that 0.396 g. of the pure salt, or 99% ($b = 0.99$) is recoverable after this oxidation procedure.

**(c).**—Mixtures of *p*-phenylenediamine (0.25 g., 0.20 g.) and ammonium chloride (0.15 g., 0.20 g.) were dissolved in concentrated hydrochloric acid and treated as in (a). There was obtained pure ammonium chloride (0.30 g., 0.27 g.), the weight loss in each case being chiefly due to loss in conversion as shown by (a) and (b). From these data it may be concluded that any ammonium chloride (*i.e.*, the enriched salt) originally present in a mixture with *p*-phenylenediamine dihydrochloride will be essentially unaffected by such treatment.

**N-4′-Acetamidophenyl-3-methylisoindolone.**—The process of distilling the ammonia from the strongly alkaline reaction mixture after completion of the reductions of I(b) or II(c) rendered the isolation of the organic reduction product extremely difficult, since much of it turned to a tar during the distillation.[23] However, by dissolving most of the tarry matter in dilute hydrochloric acid and treating the dark solution with Norit at the boiling temperature, a brownish-yellow solution could be obtained. From this, on addition of sodium acetate and acetic anhydride, there separated a crystalline product. When the original reaction involved 2-(4′-acetamidophenyl)-4-methylphthalazone, the acetylation product was accompanied by an intensely purple-blue pigment which could only be removed by liberal use of Norit during successive recrystallizations from acetic acid–water. This pigment was not encountered when the ψ-phthalazone was reduced. The same product, as shown by mixed melting point determination, was obtained from both reductions by the process just described. It proved to be the expected N-4′-acetamidophenyl-3-methylisoindolone, m.p. 250–251°. Rowe reports 250°.[5]

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[23] Milder conditions, however, yielded the expected isoindolone as previously reported.[5]