

m.p. 37–9°.

ANAL. Calcd. for $C_{11}H_{11}ClN_2$: Cl, 17.15; N, 13.56. Found: Cl, 17.25; N, 13.39.

5-Amino-2,6-dichloro-8-ethylquinoline. A solution of 2,6-dichloro-8-ethyl-5-nitroquinoline (5.0 g.) in absolute ethanol was subjected to hydrogenation at 40 p.s.i., with shaking, after having added Raney nickel catalyst. When hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate saturated with dry hydrogen chloride gas. A feathery-like, white solid amine hydrochloride formed; yield, 4.3 g.

5-Amino-2,6-dichloro-8-ethylquinoline hydrochloride (2.0 g.) yielded 5-amino-2,6-dichloro-8-ethylquinoline upon treatment with concentrated ammonium hydroxide; yield, 1.5 g.; m.p. 123–5°.

ANAL. Calcd. for $C_{11}H_{10}Cl_2N_2$: Cl, 29.41; N, 11.62. Found: Cl, 29.41; N, 11.71.

5-Acetamido-6-chloro-8-ethylquinoline and 5-Acetamido-2,6-dichloro-8-ethylquinoline. 5-Amino-6-chloro-8-ethylquinoline and 5-amino-2,6-dichloro-8-ethylquinoline were acetylated under essentially the same conditions as reported by Beasley, Brown, and Capps (2) for the acetylation of 5-amino-6-bromo-8-ethylquinoline. Melting points of 54–6° and 286° with decomposition were obtained, respectively.

ANAL. Calcd. for $C_{13}H_{14}ClN_2O$: Cl, 14.20; N, 11.22. Found: Cl, 14.38; N, 11.34.

ANAL. Calcd. for $C_{13}H_{13}Cl_2N_2O$: Cl, 25.04; N, 9.89. Found: Cl, 24.95; N, 9.77.

5-Benzamido-6-chloro-8-ethylquinoline. A mixture of 5-amino-6-chloro-8-ethylquinoline hydrochloride (2.0 g.), benzoyl chloride (10 ml.) and aqueous sodium hydroxide (20 ml.; 5%) was shaken vigorously. Additional aqueous sodium hydroxide was added occasionally to keep the system alkaline. When the odor of benzoyl chloride could

no longer be detected, the resulting solid was separated by filtration, washed with water, and finally recrystallized twice from hot 95% ethanol; yield, 1.35 g. (61%) of white solid; m.p. 242–4°.

ANAL. Calcd. for $C_{18}H_{15}ClN_2O$: Cl, 11.41; N, 9.01. Found: Cl, 11.35; N, 9.02.

5-Benzamido-2,6-dichloro-8-ethylquinoline. A mixture of 5-amino-2,6-dichloro-8-ethylquinoline (0.254 g.), benzoyl chloride (1 ml.) and aqueous sodium hydroxide (25 ml.; 5%) was shaken vigorously. Additional aqueous sodium hydroxide was added occasionally to keep the system alkaline. When the odor of benzoyl chloride could no longer be detected, the resulting solid was separated by filtration, washed with water and finally crystallized from ethanol and water solution; yield, 0.275 g. (75%) of feathery-like, white crystals; m.p. 202–3°.

ANAL. Calcd. for $C_{18}H_{14}Cl_2N_2O$: Cl, 20.54; N, 8.12. Found: Cl, 20.41; N, 8.14.

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Some Derivatives of Ethylbenzene

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2-Acetamido and 4-acetamidoethylbenzene yielded the corresponding 5-halo and 3-halo derivatives when brominated and when chlorinated. Nitration of the corresponding haloamines gave 4-nitro and 2-nitro derivatives that were acetylated. 2,4-Diacetamido-5-bromoethylbenzene was prepared from both 2-acetamido-5-bromo-4-nitroethylbenzene and 4-acetamido-5-bromo-2-nitroethylbenzene. Oxidation of 2,5-dibromoethylbenzene, 2,5-dichloroethylbenzene, 3,4-dichloroethylbenzene, and 3-chloro-4-nitroethylbenzene as derived from 2-amino-5-bromo-, 2-amino-5-chloro-, 4-amino-3-chloro-, and 2-amino-5-chloro-4-nitroethylbenzenes gave the corresponding benzoic acid derivatives. 2-Amino-4-nitro- and 2-amino-5-nitroethylbenzene, from the nitration of 2-acetamidoethylbenzene, were converted into 2-ethyl-4-nitro- and 2-ethyl-5-nitrobenzotrile, which were hydrolyzed to the corresponding benzoic acids. Modified Skraup ring closures on the properly substituted aminoethylbenzenes were accomplished with retention of all substituents to yield 8-bromo-, 8-bromo-5-nitro-, 8-chloro-, and 8-chloro-5-nitro- derivatives of 6-ethylquinoline. 6-Bromo-, 6-bromo-5-nitro-, 6-chloro-, 6-chloro-5-nitro-, 5-nitro-, and 6-nitro- derivatives of 8-ethylquinoline were also obtained in a similar manner. Methods of preparing authentic samples of benzene derivatives used in making structural comparisons were recorded. 4-Benzamido-3-bromoethylbenzene was also prepared.

MANY DERIVATIVES of ethylbenzene required for the synthesis of certain substituted quinolines are not described in the chemical literature, and studies were needed to verify the structures assigned to these intermediates. The results of some of these investigations are described.

A modification of the recommendations of Cline and

Reid (4) was used for the nitration of ethylbenzene, the conditions being more severe than those commonly used for the nitration of toluene. Quantities of unreacted ethylbenzene ranging from 12 to 22% were usually recovered and about equal amounts of ortho and para isomers were isolated, the ortho isomer predominating during certain

runs. The meta isomer, as indicated by Brown and Bonner (2), was collected in a rather impure state as a middle fraction during reduced pressure fractionation of the isomeric nitroethylbenzenes.

Both 2-nitroethylbenzene and 4-nitroethylbenzene were reduced catalytically in the presence of Raney nickel. Reduction of either 2-nitroethylbenzene or 4-nitroethylbenzene with mossy tin and hydrochloric acid usually resulted in lower yields of the corresponding amines accompanied by chloro-substituted amines, varying in amounts according to the rate of introduction of hydrochloric acid and the temperature of the reaction system. 2-Amino-5-chloroethylbenzene was obtained in 38% yield during one such reduction of 2-nitroethylbenzene with tin and hydrochloric acid. A lesser amount (4.7%) of 4-amino-3-chloroethylbenzene was obtained from 4-nitroethylbenzene under similar conditions. No 2-amino-5-bromoethylbenzene was isolated after reducing 2-nitroethylbenzene with mossy tin in the presence of hydrobromic acid.

Some difficulty was encountered during the isolation and purification steps after brominating 4-acetamidoethylbenzene. Relatively pure 4-acetamido-3-bromoethylbenzene was finally obtained after several alternate recrystallizations from acetic acid-water and methanol-water solutions. Kondo and Uyeo (10) had previously reported the bromination of 4-acetamidoethylbenzene without specifying the temperature of bromination.

A more desirable method for isolating relatively pure 4-acetamido-3-bromoethylbenzene involved selective precipitation of the crude material from a solution in glacial acetic acid by the careful addition of water, followed by the hydrolysis of the acetamido grouping, fractionation under reduced pressure, and then reacylation. When the precipitation from acetic acid by adding water was omitted, a vigorous reaction occurred in the still pot during distillation, accompanied by the liberation of a gas and the formation of a brittle solid.

Since samples of 4-acetamidoethylbenzene and 4-acetamido-3-bromoethylbenzene were prepared that melted at 93° to 94° C., some 4-amino-3-bromoethylbenzene was converted into 4-benzamido-3-bromoethylbenzene (m.p. 120.5° to 121.5° C.) by the Schotten-Baumann procedure. This served as a convenient reference material during the structural investigations upon 2-amino-5-bromo-4-nitroethylbenzene, as obtained when 2-amino-5-bromoethylbenzene was nitrated with sodium nitrate-sulfuric acid mixture. Deamination of 2-amino-5-bromo-4-nitroethylbenzene followed by reduction gave 4-amino-3-bromoethylbenzene that was converted into 4-benzamido-3-bromoethylbenzene. Thus 2-amino-5-bromoethylbenzene nitrated chiefly in the 4-position and hence meta with respect to the amino group.

2-Amino-5-bromoethylbenzene was obtained from the hydrolysis of 2-acetamido-5-bromoethylbenzene and also from the reduction of 5-bromo-2-nitroethylbenzene as derived from 4-amino-5-bromo-2-nitroethylbenzene. The nitration of 4-amino-3-bromoethylbenzene was used for the preparation of 4-amino-5-bromo-2-nitroethylbenzene.

Conversion of 5-bromo-2-nitroethylbenzene into 2-amino-5-bromoethylbenzene and hence into 2,5-dibromobenzoic acid via 2,5-dibromoethylbenzene is considered to be evidence that the nitro group in 4-amino-5-bromo-2-nitroethylbenzene really is meta with respect to the amino function and para with respect to the bromo function. Since values ranging from 151° to 153° C. have been reported for the melting point of 2,5-dibromobenzoic acid, and we obtained a product melting at 154° to 156° C., an authentic sample was prepared for comparison purposes from 4-amino-5-bromo-2-nitrotoluene (5) by the same sequence of chemical changes as used for converting 4-amino-5-bromo-2-nitroethylbenzene into 2,5-dibromobenzoic acid. The melting point of the authentic sample was

not depressed when mixed with the acid derived from 4-amino-5-bromo-2-nitroethylbenzene.

Attempts to oxidize 5-bromo-2-nitroethylbenzene to 5-bromo-2-nitrobenzoic acid were not successful. Ring-closure occurred under the conditions of a modified Skraup (5) procedure, however, yielding 6-bromo-8-ethylquinoline from the amine (2-amino-5-bromoethylbenzene) obtained when 5-bromo-2-nitroethylbenzene was reduced. Since the bromine was not removed during the ring-closure, the nitration product (4-amino-5-bromo-2-nitroethylbenzene) must contain the nitro group in either the 2-position with respect to the ethyl group and para with respect to the bromine, or the 3-position with respect to the ethyl group and meta with respect to the bromine. The fact that the nitration product (4-amino-5-bromo-2-nitroethylbenzene) gave 8-bromo-6-ethyl-5-nitroquinoline when subjected to the conditions of a modified Skraup (5) reaction rules out the possibility of the nitro group being in the 3-position with respect to the ethyl group.

2-Amino-5-bromo-4-nitroethylbenzene, the chief nitration product of 2-amino-5-bromoethylbenzene, was also converted into 6-bromo-8-ethyl-5-nitroquinoline via 2-acetamido-5-bromo-4-nitroethylbenzene and a modified Skraup (5) reaction. Nitration of 2-amino-5-bromoethylbenzene did not yield an ortho nitro-amine type as the chief nitration product under the conditions used for nitration, for the nitro group was retained during the ring-closure yielding the quinoline nucleus.

Acetylation of 2-aminoethylbenzene followed by bromination in glacial acetic acid with bromine or by bromination with bromide-bromate mixture in acidic alcohol-water medium, as used by Bogart and Hand (1) for the bromination of 2-acetamidotoluene, gave 2-acetamido-5-bromoethylbenzene, which was identical with the product obtained from 4-aminoethylbenzene via 4-acetamidoethylbenzene, 4-acetamido-3-bromoethylbenzene, 4-amino-3-bromoethylbenzene, 4-amino-2-nitro-5-bromoethylbenzene, 2-nitro-5-bromoethylbenzene, and finally 2-amino-5-bromoethylbenzene.

Further corroboration of the structures assigned 4-amino-5-bromo-2-nitroethylbenzene and 2-amino-5-bromo-4-nitroethylbenzene was achieved by changing both into the common derivative 2,4-diacetamido-5-bromoethylbenzene. The amino-bromo-nitroethylbenzenes were independently acetylated, reduced catalytically, and then acetylated again.

2-Acetamido-5-chloroethylbenzene was obtained when 2-acetamidoethylbenzene was chlorinated under conditions similar to those used by Reverdin and Cripieux (14) for the chlorination of 2-acetamidotoluene. 2-Amino-5-chloroethylbenzene resulted from the hydrolysis of 2-acetamido-5-chloroethylbenzene. Replacement of the amino group by chlorine according to the Sandmeyer procedure gave 2,5-dichloroethylbenzene, which yielded 2,5-dichlorobenzoic acid upon oxidation with potassium permanganate in aqueous sulfuric acid. Oxidation attempts, using either dilute nitric acid at atmospheric pressure or alkaline potassium permanganate, were not successful. Values for the melting point of 2,5-dichlorobenzoic acid are recorded in the chemical literature ranging from 150° to 154.4° C., and hence synthesis of an authentic sample for comparison was needed. 2-Amino-5-chlorotoluene, of known composition, was diazotized and subjected to the conditions of a Sandmeyer reaction prior to oxidizing the resulting 2,5-dichlorotoluene to 2,5-dichlorobenzoic acid with alkaline potassium permanganate under conditions similar to those reported (3) for such oxidations, except that a longer reflux time was used. Attempted oxidation with dilute nitric acid at atmospheric pressure was not successful.

The substance isolated after chlorinating 2-acetamidoethylbenzene with a mixture of sodium chlorate and hydrochloric acid was shown to contain chlorine in some other

position than that ortho to the acetamido group (3-position) by converting the chloroaminoethylbenzene derived from it into a chloroethylquinoline with no loss of chlorine.

2-Amino-5-chloro-4-nitroethylbenzene was prepared by nitrating 2-amino-5-chloroethylbenzene. Subjecting the 2-acetamido-5-chloro-4-nitroethylbenzene to modified Skraup conditions (15) gave 6-chloro-8-ethyl-5-nitroquinoline with retention of the chloro and nitro groupings; hence, meta rather than ortho nitration with respect to the amino group was indicated.

Deamination of 2-amino-5-chloro-4-nitroethylbenzene followed by oxidation of the resulting 3-chloro-4-nitroethylbenzene with acidic potassium permanganate yielded 3-chloro-4-nitrobenzoic acid. This was compared with an authentic sample prepared from 2-amino-5-chloro-4-nitrotoluene (8) by a similar sequence of chemical changes. Hence, the structure assigned 2-amino-5-chloro-4-nitroethylbenzene was further corroborated.

4-Acetamidoethylbenzene was chlorinated in acetic acid solution with sodium chlorate-hydrochloric acid mixture under conditions similar to those used by Reverdin and Crepieux (14) for the chlorination of 4-acetamidotoluene. The structure of 4-acetamido-3-chloroethylbenzene, as isolated from this chlorination, was ascertained by replacing the acetamido group with chlorine and oxidizing the resulting 3,4-dichloroethylbenzene, not characterized, with refluxing dilute nitric acid to 3,4-dichlorobenzoic acid. Since a sample of 4-acetamido-3-chlorotoluene (12) was available and since a wide range of melting points has been reported for 3,4-dichlorobenzoic acid, the 4-acetamido-3-chlorotoluene was subjected to the same sequence of changes that 4-acetamido-3-chloroethylbenzene had been subjected to, thus yielding an authentic sample of 3,4-dichlorobenzoic acid. The two samples of 3,4-dichlorobenzoic acid were shown to be identical, and the structure assigned 4-acetamido-3-chloroethylbenzene seems to be the correct one.

4-Amino-5-chloro-2-nitroethylbenzene resulted from the nitration of 4-amino-3-chloroethylbenzene. The amino group was removed by diazotizing in hot ethanol according to a procedure previously reported by Morton and McGooking (11) for such operations. Attempts to oxidize the resulting 5-chloro-2-nitroethylbenzene, not characterized, with neutral permanganate, acidic permanganate, and dilute nitric acid failed to yield the desired 5-chloro-2-nitrobenzoic acid. Catalytic reduction of 5-chloro-2-nitroethylbenzene, using Raney nickel, gave an amine which upon acetylation yielded 2-acetamido-5-chloroethylbenzene with properties identical to those of a compound previously prepared and characterized in this laboratory, thus further corroborating the structure assigned 4-acetamido-3-chloroethylbenzene and indicating the position taken by the nitro group during the nitration of 4-amino-3-chloroethylbenzene.

Acetylation of 4-amino-5-chloro-2-nitroethylbenzene gave 4-acetamido-5-chloro-2-nitroethylbenzene which yielded 8-chloro-6-ethyl-5-nitroquinoline when subjected to the conditions of a modified Skraup reaction (15). Since the nitro group was not ejected during the ring-closure operation, it would appear that it is placed meta to the amine function.

Horner (16) reported that the nitration of 2-acetamidoethylbenzene (*o*-ethylacetanilide) produced a mixture of the ortho and para isomers which he hydrolyzed and purified as the amine hydrochlorides. Attempts to duplicate this work indicated that the sulfuric-nitric acid mixture gave chiefly the meta and para isomers with respect to the acetamido group. Hence a source of 2-acetamido-4-nitroethylbenzene and 2-acetamido-5-nitroethylbenzene, as well as the corresponding amines, became available. This investigation was carried out before Hansch (6) reported upon the nitration of 2-acetamidoethylbenzene in glacial acetic acid solution with fuming nitric acid, yielding a

mixture of the 3-, 4-, and 5-nitro-2-acetamidoethylbenzenes. The conditions of nitration used by Hansch were rather severe, and Kirch and Orchin (9) reported some fume-offs while attempting to repeat the work of Hansch. The mixture obtained from the nitration with sulfuric-nitric acid solution was converted into the hydrochlorides of the corresponding amines and separated into 2-amino-4-nitroethylbenzene and 2-amino-5-nitroethylbenzene by taking advantage of the greater basicity of the 2-amino-4-nitroethylbenzene.

Both 2-amino-5-nitroethylbenzene and 2-amino-4-nitroethylbenzene were diazotized and converted into the corresponding nitriles under conditions similar to those used by Hodgson and Heyworth (7) for such conversions. These nitriles were hydrolyzed to the previously reported corresponding benzoic acid derivatives. This served to establish the structures of these aminonitroethylbenzenes and the corresponding acetamido derivatives. The fact that both of the 2-acetamido-nitroethylbenzenes could be changed into nitroethylquinolines by a modified Skraup (15) reaction further indicated that meta and para isomers were isolated from the nitration mixture rather than ortho and para isomers.

Conversion of 2-amino-4-nitroethylbenzene into 4-acetamidoethylbenzene further corroborated the structure assigned the meta nitration isomer. This was accomplished by the removal of the amino group (11) giving 4-nitroethylbenzene which was reduced with stannous chloride and hydrochloric acid mixture to yield 4-aminoethylbenzene that was in turn acetylated.

An additional study was made upon 2-amino-5-nitroethylbenzene that related it to 4-acetamidoethylbenzene. Deamination gave 3-nitroethylbenzene, not characterized, which was reduced to the amine and acetylated. The resulting 3-acetamidoethylbenzene did not crystallize. This was not particularly surprising for a melting point of 24° to 25° C. had been reported for this compound while 2-acetamidoethylbenzene and 4-acetamidoethylbenzene as prepared in our laboratory melted at 112° to 113° C. and 93° to 94° C., respectively. Bromination of 3-acetamidoethylbenzene gave colorless needles, after recrystallization from 95% ethanol, that melted at 145° to 146° C. When mixed with a sample of 2-acetamido-5-bromoethylbenzene (m.p. 146° to 147° C.) a definite depression of melting range was observed.

4-Amino-3-nitroethylbenzene was then prepared by essentially the same procedure as used by Noyes (13) for the preparation of 4-amino-3-nitrotoluene. After deaminating, reducing catalytically, acetylating and brominating, a product was obtained that was similar to that prepared from 2-amino-5-nitroethylbenzene and melting at 145° to 146° C. No depression of melting range was observed for a mixture of the two substances.

EXPERIMENTAL

Nitration of Ethylbenzene. A mixture of nitric acid (sp. gr. 1.42; 512.2 ml.) with sulfuric acid (sp. gr. 1.84; 525 ml.) was added slowly, with vigorous stirring, to ethylbenzene (1155 ml.) at 32° to 40° C. (8 hours). Stirring was continued for 4 more hours prior to increasing the temperature to 40° C. for 3 hours and 95° C. for 2 hours. After cooling to room temperature spontaneously, the oil layer was separated, washed with water (3 times), 2.5% aqueous sodium hydroxide and finally water. The washed oil was steam distilled (superheated steam), dried over anhydrous calcium sulfate and stripped of ethylbenzene (223 grams, 22.3%) by atmospheric distillation. Fractionation gave 2-nitroethylbenzene (333 grams, 23.4%; b.p. 112° to 115° C./15 mm.) and 4-nitroethylbenzene (319.5 grams, 22.4%; b.p. 125° to 127° C./15 mm.).

4-Nitroethylbenzene. 2-Amino-4-nitroethylbenzene (3.0 grams; 0.018 mole), commercial grade absolute ethanol (10 ml.), sulfuric acid (0.7 ml.; sp. gr. 1.84) were mixed

together and brought to reflux temperature. Finely ground sodium nitrite (2.42 grams; 0.035 mole) was added in small portions followed by ethanol (4.0 additional ml.). When the evolution of gas ceased, 8 ml. of alcohol was collected by distillation and 20 ml. of water added. Distillation was continued with intermittent return of water-rich distillate phase until 1.5 ml. of 4-nitroethylbenzene had been collected.

2-Aminoethylbenzene. 2-Nitroethylbenzene (52.7 grams; 0.348 mole), dissolved in the minimum amount of absolute ethanol, was hydrogenated at 40 p.s.i.g. in the presence of Raney nickel at 71° C. (2 hours). The cooled mixture was filtered, the filtrate was acidified with 1:1 hydrochloric acid, and the ethanol distilled. The residue was neutralized with cold 40% sodium hydroxide, and the mixture extracted with ether. The extract was dried over sodium hydroxide pellets, concentrated and the residue distilled; yield 32.2 grams (69.6%), b.p. 98° to 99° C./13 mm.

Hydrochloric acid (1300 ml.; sp. gr. 1.19) was added to a mixture of 2-nitroethylbenzene (368 grams; 300 ml.) with mossy tin (550 grams) at such a rate as to maintain reflux. Heat was then applied to maintain reflux (1 more hour). Later (12 hours) sodium hydroxide (900 grams) dissolved in water was added prior to distilling with steam (superheated). The distillate was extracted with ether and the extract dried over sodium hydroxide pellets prior to concentrating. Fractionation of the residue gave 2-aminoethylbenzene (112.4 grams; 38.1%; b.p. 103° to 105° C./17 to 18 mm.) and 2-amino-5-chloroethylbenzene (113 grams; 34.6%; b.p. 140° to 142° C./18 to 19 mm.).

2-Nitroethylbenzene (24 grams) was reduced with a mixture of mossy tin (45 grams) and hydrobromic acid (115 ml.; 48%) under conditions similar to those when using hydrochloric acid to give 2-aminoethylbenzene; yield 12 grams (63%), b.p. 80° to 84° C./6 mm.

4-Aminoethylbenzene. 4-Nitroethylbenzene (250 grams) was hydrogenated under conditions similar to those used for the hydrogenation of 2-nitroethylbenzene; yield 191 grams (93.5%), b.p. 102° to 104° C./12 to 13 mm.

4-Nitroethylbenzene (160 grams) was hydrogenated in a copper bronze cylinder (1400 p.s.i.g., 105° to 108° C.) and the 4-aminoethylbenzene recovered under conditions similar to those described for hydrogenation of 2-nitroethylbenzene; yield 118 grams (92%).

4-Nitroethylbenzene (184 grams) was reduced with a mixture of mossy tin (275 grams) and hydrochloric acid (750 ml.; sp. gr. 1.19) under conditions similar to those described for reducing 2-nitroethylbenzene; yield of 4-aminoethylbenzene 96 grams (65%), b.p. 102° to 104° C./13 mm.; yield of 4-amino-3-chloroethylbenzene 4.7%, b.p. 117° to 119° C./12 mm.

4-Nitroethylbenzene (1.5 ml.) was dissolved in 95% ethanol (20 ml.) and stannous chloride dihydrate (8.35 grams) contained in hydrochloric acid (20 ml.; sp. gr. 1.19) was slowly added at 60° to 70° C. with shaking. After 20 minutes, a few pieces of tin metal were added, and a temperature of 60° to 70° C. maintained for 10 minutes. Upon cooling, conc. NaOH-water solution was added with cooling until most of the solid matter had dissolved. The amine was extracted with ethyl ether and recovered.

2-Acetamidoethylbenzene. Acetic anhydride (60 ml.) was added slowly with shaking and cooling to 2-aminoethylbenzene (60.6 grams). One hour later, the residue was dissolved in hot water prior to treating with decolorizing carbon. Crystals formed upon cooling; yield 62 grams, m.p. 112° to 113° C. and 6 grams, m.p. 111.5° to 112° C.

4-Acetamidoethylbenzene. 4-Aminoethylbenzene (from reduction of 1.5 ml. of 4-nitroethylbenzene), glacial acetic acid (5 ml.) and acetic anhydride (2 ml.) were mixed and heated at reflux for 0.5 hour. Repeated recrystallizations (including decolorizing carbon treatments) of the crude 4-acetamidoethylbenzene (as recovered by the usual procedure) from water containing a small amount of ethanol gave needle-like crystals; m.p. 93° to 94° C.; transition of air dried crystals occurred at 87° to 88° C. but the solid that formed after heating to 120° C. and cooling melted at 93° to 94° C.

2-Acetamido-5-bromoethylbenzene. A mixture of 2-aminoethylbenzene (60.0 grams), glacial acetic acid (153 ml.)

and acetic anhydride (63 ml.) was refluxed for 0.5 hour. Bromine (30 ml.) was added dropwise 55° to 65° C., while stirring, before solidification occurred. The solid was transferred, with stirring, to ice-water mixture (1500 ml.) containing sodium metabisulfite (15 grams). The resulting solid (12 hours later) was collected by filtration, washed with water, and recrystallized from hot 95% ethanol; dense white (colorless) needles; m.p. 146° to 147° C.; yield 97.3 grams (80.8%).

2-Acetamidoethylbenzene (0.5 grams) was converted into 2-acetamido-5-bromoethylbenzene under conditions similar to those used by Bogert and Hand (1) for the conversion of 2-acetamidotoluene into 2-acetamido-5-bromotoluene. Fine colorless (white) needles were obtained from 95% ethanol, m.p. 146° to 147° C.

4-Amino-5-bromo-2-nitroethylbenzene (37 grams) was dissolved in absolute ethanol (88 ml.) prior to adding sulfuric acid (5.7 ml.; sp. gr. 1.84) cautiously with mixing and cooling. Finely ground sodium nitrite (20.2 grams; 0.293 mole) was then added in small portions as the alcoholic solution refluxed. The alcohol was removed by distillation after the evolution of gas had ceased. Water was then added to the residue and the 2-nitro-5-bromoethylbenzene distilled with steam. An ethyl ether solution of the 2-nitro-5-bromoethylbenzene as obtained by extraction was dried over anhydrous calcium sulfate before evaporating the ether.

Some of the 2-nitro-5-bromoethylbenzene (1 ml.) was dissolved in absolute ethanol (30 ml.) and hydrogenated (Raney nickel; 40 p.s.i.g.). The catalyst was removed by filtration and the filtrate acidified with hydrochloric acid (sp. gr. 1.19). After concentrating by distilling some alcohol, crystals of the hydrochloride formed. These were dissolved in water (35 ml.) prior to adding acetic anhydride (2 ml.) followed immediately by saturated sodium acetate-water solution. Solid 2-acetamido-5-bromoethylbenzene, as recovered by filtering and washing with water, was recrystallized from 95% ethanol; m.p. 146° to 147° C.

2-Amino-5-bromoethylbenzene. 2-Acetamido-5-bromoethylbenzene (20 grams) was dissolved in ethanol (95%; 160 ml.) and hydrochloric acid (55 ml.; sp. gr. 1.19) was added. The mixture was refluxed for 3 hours, and then most of the alcohol was removed by distillation. After cooling, the residue was poured into 300 ml. of water and sodium hydroxide solution added until the system was basic. The 2-amino-5-bromoethylbenzene was extracted with ethyl ether and the resulting extract dried with sodium hydroxide pellets. The ether was removed by distillation, and the crude amine was fractionated; yield 15.6 grams (95%), b.p. 125° to 130° C./8 to 10 mm.

See preparation of 2-acetamido-5-bromoethylbenzene for reduction of 2-nitro-5-bromoethylbenzene.

2-Amino-5-bromo-4-nitroethylbenzene. The amine resulting from the hydrolysis of 2-acetamido-5-bromoethylbenzene (10.0 grams; 0.0413 mole) was dissolved in sulfuric acid (60.0 ml.; sp. gr. 1.84) prior to cooling to -5° C. and adding a solution of sodium nitrate (3.5 grams; 0.057 mole) in sulfuric acid (27 ml.; sp. gr. 1.84) at such a rate that the temperature did not increase above 0° C. Mechanical agitation was used and continued for 3 hours with the cooling bath removed. An orange solid formed upon pouring into cracked ice-water mixture (620 ml.). The crude material (3.7 grams), collected by filtration, washed and dried in air, was recrystallized from 95% ethanol as yellow needles; yield 1.8 grams (18%), m.p. 98° to 99° C.

Anal. Calcd. for $C_8H_9BrN_2O_2$: Br, 32.61; N, 11.43. Found: Br, 32.82; N, 11.60.

2-Acetamido-5-bromo-4-nitroethylbenzene. 2-Amino-5-bromo-4-nitroethylbenzene (16.0 grams; 0.06 mole) was dissolved in glacial acetic acid (60 ml.) and acetic anhydride (10.0 ml.; 0.107 mole) added. After refluxing for 0.5 hour, cooling and pouring into cracked ice-water mixture, a solid was collected on a filter and washed with water. Recrystallization from 95% ethanol gave pale-green needles; yield 13.1 grams (70%), m.p. 192° to 194° C.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_3$: Br, 27.84; N, 9.76. Found: Br, 27.66; N, 9.28.

4-Amino-3-bromoethylbenzene. A mixture of 4-amino-

ethylbenzene (234 grams; 1.93 mole), glacial acetic acid (590 ml.) and acetic anhydride (200 ml.; 2.12 mole) was refluxed for 0.5 hour. While agitating mechanically, bromine (106 ml.; 2.00 mole; 55° to 60° C.) was added dropwise. The temperature was controlled at 50° to 55° C. for 3 additional hours and finally allowed to decrease to that of the room for 8 hours. The resulting solution was poured into cracked ice-water mixture (4000 ml.) containing 40 grams of sodium bisulfite. Stirring was continued until all lumps were broken up and the excess bromine had been destroyed. The solid was collected, washed with water, dried and dissolved in hot glacial acetic acid prior to pouring into cold water that was being mechanically agitated. Again the crude acetamidobromoethylbenzene was collected, washed with water, and sucked reasonably dry.

Hydrolysis was accomplished by refluxing with ethanol (95%; 300 ml.) and hydrochloric acid (300 ml.; sp. gr. 1.19) for 3 hours. Most of the ethanol was removed by distillation before diluting the residue with water and liberating the amine from its salt with sodium hydroxide (25° C. or less). The amine was extracted with ethyl ether and the extract washed with water prior to drying over sodium hydroxide pellets. The dried extract was concentrated and the residue rapidly distilled from a Claisen flask at reduced pressure. Fractionation through a packed column then yielded 200 to 300 grams of 4-amino-3-bromoethylbenzene, b.p. 116° to 118° C./7 to 8 mm.

4-Acetamido-3-bromoethylbenzene. Various attempts to purify the crude 4-acetamido-3-bromoethylbenzene, prepared by the bromination of 4-acetamidoethylbenzene, using crystallization techniques resulted in considerable loss of material. Crystals melting at 93° to 94° C. were obtained after subjecting solutions in hot ethanol (95%) to decolorizing carbon treatments. Crystals were also obtained from methanol-water solution that melted at 92° to 93° C. The preferred method of preparation involved acetylation of the carefully fractionated amine followed by recrystallization from ethanol.

4-Benzamido-3-bromoethylbenzene. 2-Amino-5-bromo-4-nitroethylbenzene (10 grams), dissolved in commercial absolute ethanol (24 ml.) and sulfuric acid (1.54 ml.; sp. gr. 1.84) having been added, was brought to reflux temperature of the solvent. Finely powdered sodium nitrite (5.46 grams) was added in small portions and refluxing continued until gas evolution seemed to cease. Ethanol (20 ml.) was removed by distillation and the residue poured into 100 ml. of water. The 4-nitro-3-bromoethylbenzene was extracted with benzene and the benzene extract was washed three times with water prior to drying over anhydrous calcium sulfate.

The low boiling components were distilled at atmospheric pressure followed by the reduced pressure distillation of the residue. Approximately 3 ml. of distillate was obtained, about one-third of which crystallized. The yellow crystals were dissolved in absolute ethanol and hydrogenated (Raney nickel; 40 p.s.i.g.). The catalyst was separated and the filtrate was acidified with sulfuric acid before distilling the alcohol. Sodium hydroxide solution was added to make the residue basic and 0.5 ml. of benzoyl chloride was introduced accompanied by shaking. The solid that formed was separated, washed with water and repeatedly crystallized from 95% ethanol until a product was obtained melting at 120° to 121° C.

4-Acetamido-3-bromoethylbenzene (0.4 gram) was mixed with 95% ethanol (5 ml.) and hydrochloric acid (5 ml.; sp. gr. 1.19) prior to refluxing the mixture for 4 hours. The alcohol was distilled and the residue taken up in water. After making basic by the addition of sodium hydroxide solution, the residue was benzoylated and the impure 4-benzamido-3-bromoethylbenzene purified. The resulting sample melted at 120° to 121° C. and the melting point of the sample prepared from 2-amino-5-bromo-4-nitroethylbenzene was not depressed when mixed with part of this sample.

4-Amino-5-bromo-2-nitroethylbenzene. 4-Amino-3-bromoethylbenzene (20.0 grams; 0.10 mole) was nitrated under essentially the same conditions as described for the preparation of 2-amino-5-bromo-4-nitroethylbenzene; yield

16.5 grams (67.5), m.p. 78° to 79° C.; yellow-reddish, small plates.

Anal. Calcd. for $C_8H_8BrN_2O_2$: N, 11.43. Found: N, 11.63.

4-Acetamido-5-bromo-2-nitroethylbenzene. Acetic anhydride (3.12 ml.; 0.0334 mole) was added to a solution of 4-amino-5-bromo-2-nitroethylbenzene (5.0 grams; 0.0205 mole) in glacial acetic acid (20 ml.), and the resulting solution was refluxed for 0.5 hour. A solid separated upon pouring with stirring into ice-water mixture (400 ml.); pale-green to yellow needles from 95% ethanol; yield 5.1 grams (89%), m.p. 124° to 125° C.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_3$: Br, 27.84; N, 9.76. Found Br, 27.54; N, 9.79.

2,5-Dibromobenzoic Acid. 2-Acetamido-5-bromoethylbenzene (12.5 grams; 0.057 mole) was hydrolyzed and the resulting amine extracted with ethyl ether under conditions described in 2-amino-5-bromoethylbenzene preparation. The residue obtained after distilling the ether was dissolved in sulfuric acid (5.8 ml.; sp. gr. 1.84)-water (45.2 ml.) solution and cooled to -5° C. A solution of sodium nitrite (3.87 grams; 0.049 mole) in water (6.45 ml.) was added dropwise (below 0° C.).

Previously a solution of copper (I) bromide had been prepared from copper (II) sulfate. The solution of $CuSO_4 \cdot 5H_2O$ (16 grams in water (7.8 ml.) was divided into two equal parts. Zinc dust (2.1 grams) was added to the first part and the resulting copper washed twice with dilute sulfuric acid solution by decantation. This copper metal, potassium bromide (15.4 grams), and sulfuric acid (1.94 ml.; sp. gr. 1.84) were then added to the second portion of copper sulfate solution and stirred well.

The copper (I) bromide solution was heated to boiling and the diazotized amine solution added dropwise. Steam distillation of the resulting mixture gave 2,5-dibromoethylbenzene (4 ml.), which was washed once with dilute sodium hydroxide-water solution and twice with water.

After refluxing the resulting oil with dilute nitric acid (1 part, sp. gr. 1.42, to 3.5 parts of water by volume) for two days, crystals formed upon cooling. These were collected, washed with water and recrystallized from dilute water-ethanol solutions; m.p. 154° to 156° C. More dilute nitric acid solution was added to the filtrate and it was refluxed for another day. A solid mixture resulted upon cooling that was subjected to further oxidation with hot alkaline permanganate, yielding some additional 2,5-dibromobenzoic acid; m.p. 154° to 155° C.

4-Amino-5-bromo-2-nitrotoluene, previously prepared and studied in this laboratory, was converted into 2-amino-5-bromotoluene and thence into 2,5-dibromotoluene under essentially the same conditions that 4-amino-5-bromo-2-nitroethylbenzene was converted into 2,5-dibromoethylbenzene.

2,5-Dibromotoluene was refluxed with dilute nitric acid of the same concentration as used for the oxidation of 2,5-dibromoethylbenzene for 60 hours. The crystals that formed upon cooling were collected and dried; m.p. 152° to 153° C. A mixture of these with those prepared from 4-amino-5-bromo-2-nitroethylbenzene also melted at 152° to 153° C.

2,4-Diacetamido-5-bromethylbenzene. 2-Acetamido-5-bromo-4-nitroethylbenzene (0.5 gram; 0.0017 mole) dissolved in absolute ethanol (50 ml.) was hydrogenated (3 grams Raney nickel; 40 p.s.i.g.). The catalyst was separated and the filtrate concentrated by distilling some of the alcohol under reduced pressure. Slightly impure 2-acetamido-4-amino-5-bromoethylbenzene separated upon cooling as almost colorless rosettes; m.p. 143° to 145° C.

2-Acetamido-5-bromo-4-nitroethylbenzene (1.0 gram; 0.0035 mole) was reduced under similar conditions but the filtrate was acidified with hydrochloric acid prior to distilling the alcohol. The residue was made basic with sodium hydroxide solution and extracted with ethyl ether. After drying the extract over sodium hydroxide pellets, the ether was removed by distillation and the residue dissolved in glacial acetic acid (8 ml.). Acetic anhydride (1.25 ml.) was added and the solution refluxed for 0.5 hour. Upon pouring into cracked ice-water mixture (50 ml.), a white solid formed. This was collected, washed with water and recrystallized. The 2,4-diacetamido-5-bromoethylbenzene formed as white needles from 95% ethanol upon cooling

slowly and as rosettes when cooled rapidly; m.p. 221° to 222° C.

4-Acetamido-5-bromo-2-nitroethylbenzene was dissolved in a minimum amount of absolute ethanol, reduced catalytically and then acetylated under conditions similar to those used for the reduction and acetylation of 2-acetamido-5-bromo-4-nitroethylbenzene; m.p. 221° to 222° C. No depression of melting point was observed when products derived from 2-acetamido-5-bromo-4-nitroethylbenzene and 4-acetamido-5-bromo-2-nitroethylbenzene were mixed together.

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2$: Br, 26.71; N, 9.36. Found: Br, 26.91; N, 9.18.

2-Amino-5-chloroethylbenzene. 2-Acetamidoethylbenzene (65.3 grams) was dissolved in glacial acetic acid (200 ml.) and hydrochloric acid (80 ml.; sp. gr. 1.19) was added. After cooling in an ice bath, a solution of sodium chlorate (26.4 grams) in water (120 ml.) was added dropwise (15° C.) with stirring. The resulting mixture was poured into water (1000 ml.) containing sodium bisulfite (60 grams). The solid resulting was collected, washed with water, and then subjected to the action of refluxing ethanol (95%; 126 ml.) mixed with hydrochloric acid (126 ml.; sp. gr. 1.19) for 4 hours. The solvent was removed by distillation before dissolving the residual amine hydrochloride in water. This solution was made basic by adding sodium hydroxide-water solution and was then extracted with ethyl ether. The extract was dried over sodium hydroxide pellets and the ether distilled. Distillation of the residual amine from a Claisen flask under reduced pressure was followed by fractionation through a packed column; yield 31.5 grams (50.7%), b.p. 140° to 142° C./ 18 to 19 mm.

Anal. Calcd. for $C_8H_{10}ClN$: N, 9.00; Cl, 22.79. Found: N, 9.02; Cl, 22.73.

See part of preparation of 2-aminoethylbenzene by the reduction of 2-nitroethylbenzene with tin and hydrochloric acid.

4-Amino-5-chloro-2-nitroethylbenzene (6 grams) was dissolved in absolute ethanol to which sulfuric acid (1.4 ml.; sp. gr. 1.84) had been added. Sodium nitrite (4.6 grams) was then added at the reflux temperature, the excess solvent removed, water added and the 5-chloro-2-nitroethylbenzene distilled with steam under conditions similar to those reported in part of the 4-nitroethylbenzene preparation; yield 3 ml.

The 5-chloro-2-nitroethylbenzene was reduced catalytically in absolute ethanol under essentially the same conditions as reported for the reduction of 5-bromo-2-nitroethylbenzene. The amine was converted into 2-acetamido-5-chloroethylbenzene for characterization.

2-Acetamido-5-chloroethylbenzene. 2-Amino-5-chloroethylbenzene (134.5 grams) was treated with acetic anhydride (105 ml.) by adding it slowly with shaking and cooling. After standing for 1 hour at room temperature, the resulting solid was dissolved in a hot mixture of ethanol and water and given a decolorizing carbon treatment. Long, colorless (white) needles formed; yield 145.5 grams (90.9%), m.p. 137° C. to 138° C.

Smaller size batches were acetylated by refluxing acetic acid-acetic anhydride solutions with similar results.

2,5-Dichloroethylbenzene. A solution of sodium bisulfite (5.86 grams) and sodium hydroxide (3.9 grams) in water (43.5 ml.) was added to a hot solution of $CuSO_4 \cdot 5H_2O$ (27.2 grams) in water (87 ml.). After cooling to room temperature the precipitated copper (I) chloride was separated by decantation and washed with water prior to dissolving in a solution of hydrochloric acid (29.3 ml.; sp. gr. 1.19) in water (10.8 ml.) and placing in a cooling bath until the diazotization of 2-amino-5-chloroethylbenzene had been effected.

2-Amino-5-chloroethylbenzene (13.5 grams) was dissolved in a warm solution of hydrochloric acid (55 ml.; sp. gr. 1.19) in water (10.8 ml.). This solution was cooled to 0° C. with stirring forming a suspension before adding dropwise with stirring a solution of sodium nitrite (5.07 grams) in water (17.3 ml.) (below 5° C.).

The diazonium solution was then added dropwise with stirring to the previously cooled copper (I) chloride solution (below 0° C.). The cooling bath was removed after 10 minutes and warming to room temperature permitted.

2,5-Dichloroethylbenzene was then removed by steam distillation and extracted from the distillate with ethyl ether. Anhydrous calcium sulfate was used to dry the extract before distilling the ether and fractionating the residual oil; yield 10 to 11 grams, b.p. 108° to 110° C./ 23 mm.

2,5-Dichlorobenzoic Acid. 2,5-Dichloroethylbenzene was refluxed with sulfuric acid-water solution (50% by volume) while solid potassium permanganate was added from time to time until the color of excess permanganate persisted. The hot solution was filtered and ethanol added to the filtrate to destroy the permanganate. Crystals formed upon cooling that were separated, washed with water and dried; m.p. 148° to 149° C. Upon dissolving the crystals in dilute sodium hydroxide solution, treating with decolorizing carbon, filtering, and acidifying the filtrate with dilute sulfuric acid, crystals formed that were again separated and washed with water; m.p. 153° to 154° C.

An authentic sample of 2-amino-5-chlorotoluene was prepared from 2-aminotoluene and converted into 2,5-dichlorotoluene under essentially the same conditions as recorded for the conversion of 2-amino-5-chloroethylbenzene into 2,5-dichloroethylbenzene. Refluxing the 2,5-dichlorotoluene with dilute nitric acid failed to give 2,5-dichlorobenzoic acid.

2,5-Dichlorotoluene (1 gram), potassium permanganate (2.33 grams) and water (28 ml.) were refluxed and stirred together for 20 hours prior to distilling unreacted 2,5-dichlorotoluene (0.5 to 0.6 ml.) along with water. Water was added from time to time to replace that distilled. Filtration of the pot residue while hot followed by treatment of the filtrate with decolorizing carbon, coagulation with filter aid, filtering and making the final filtrate acidic with sulfuric acid, gave a white (colorless) solid contaminated with inorganic salts. This solid was dissolved in dilute sodium hydroxide solution, treated with decolorizing carbon, filtered, and dilute sulfuric acid was added to the filtrate. Crystals formed that melted at 152° to 153° C. during first heating and 154° to 155° C. after solidification. No depression of the melting range was observed when these crystals were mixed with those prepared from 2,5-dichloroethylbenzene.

2-Amino-5-chloro-4-nitroethylbenzene. A cooled solution of anhydrous sodium nitrate (4.8 grams) in sulfuric acid (37 ml.; sp. gr. 1.84) was added dropwise with stirring to a solution of 2-amino-5-chloroethylbenzene (8.7 grams) in sulfuric acid (80 ml.; sp. gr. 1.84) (below 5° C.). Upon warming to room temperature and after 3 hours, the solution was poured with stirring into cracked ice-water mixture (750 ml.). Sodium carbonate was added to neutralize the acid, the precipitate was collected and washed with water, and it was then recrystallized from 95% ethanol; yield 6.7 grams (60%), m.p. 83° to 85° C.

Anal. Calcd. for $C_8H_9ClN_2O_2$: Cl, 17.68; N, 13.97. Found: Cl, 17.82; N, 13.92.

2-Acetamido-5-chloro-4-nitroethylbenzene. 2-Amino-5-chloro-4-nitroethylbenzene was acetylated under essentially the same conditions as used for the acetylation of 2-amino-5-bromo-2-nitroethylbenzene; m.p. 165.5° to 166.5° C.

3-Chloro-4-nitrobenzoic Acid. 2-Amino-5-chloro-4-nitroethylbenzene (3.0 grams) was converted into 3-chloro-4-nitroethylbenzene (1 to 1.5 ml.) under conditions similar to those used to convert 4-amino-5-chloro-2-nitroethylbenzene into 5-chloro-2-nitroethylbenzene and reported as part of 2-amino-5-chloroethylbenzene preparation.

Some 3-chloro-4-nitroethylbenzene was oxidized under conditions similar to those used for the oxidation of 2,5-dichloroethylbenzene and reported in preparation of 2,5-dichlorobenzoic acid. Two crystallizations by dissolving in dilute sodium hydroxide solution, subjecting to decolorizing carbon treatments and then acidifying the hot filtrates with dilute sulfuric acid gave crystals melting at 183° to 184° C.

An authentic sample of 2-amino-5-chloro-4-nitrotoluene was given essentially the same treatment as 2-amino-5-chloro-4-nitroethylbenzene yielding a comparable amount of 3-chloro-4-nitrobenzoic acid. A mixture of the two samples of 3-chloro-4-nitrobenzoic acid showed no depression in melting range.

4-Amino-3-chloroethylbenzene. 4-Aminoethylbenzene (182 grams), acetic acid (456 ml.) and acetic anhydride (156 ml.) were refluxed together for 1.5 hours; after which time, the solution was cooled to 10° C. and hydrochloric acid (495 ml.; sp. gr. 1.19) was slowly added. Vigorous stirring was begun, and sodium chlorate (49.5 grams) dissolved in water (130 ml.) was added dropwise (15° to 20° C.). Stirring was continued for 6 hours before pouring the reaction mixture into a cracked ice-water mixture (2000 ml.). A heavy, viscous oil separated that was washed several times with cold water and cooled below 0° C., but it would not solidify. This was hydrolyzed and purified as indicated for 2-amino-5-chloroethylbenzene; yield 100 grams (41.2%), b.p. 115° to 117° C./10 mm. and 109° C./6 mm. (analytical sample).

Anal. Calcd. for $C_8H_{10}ClN$: Cl, 22.79; N, 9.00. Found: Cl, 22.97; N, 9.13.

4-Acetamido-3-chloroethylbenzene. 4-Amino-3-chloroethylbenzene (6 grams) was dissolved in water (97 ml.) containing hydrochloric acid (4.5 ml.; sp. gr. 1.19), and the solution was treated with decolorizing carbon and filtered. The solution was then heated to 50° C., and acetic anhydride (4.7 ml.) was added, followed by the rapid addition of sodium acetate (6.5 grams) dissolved in water (20 ml.). On cooling the solution deposited fine, colorless needles; yield 6.0 grams (79%); m.p. 81° to 82° C.

Anal. Calcd. for $C_{10}H_{11}ClNO$: Cl, 18.03; N, 7.12. Found: Cl, 17.89; N, 7.15.

3,4-Dichloroethylbenzene. 4-Amino-3-chloroethylbenzene (16.6 grams) was subjected to conditions similar to those used for changing 2-amino-5-chloroethylbenzene into 2,5-dichloroethylbenzene except that the crude product was washed with sodium hydroxide solution and water before being oxidized to 3,4-dichlorobenzoic acid, rather than extracting with ether and fractionating; yield 14 grams.

3,4-Dichlorotoluene. An authentic sample of 4-acetamido-3-chlorotoluene (9.8 grams) was hydrolyzed and the resulting amine extracted with ethyl ether according to the conditions described in preparation of 2-amino-5-bromoethylbenzene. The crude 4-amino-3-chlorotoluene was then converted into 3,4-dichlorotoluene (3 grams) by the application of conditions similar to those reported for the preparation of 3,4-dichloroethylbenzene.

3,4-Dichlorobenzoic Acid. 3,4-Dichloroethylbenzene was refluxed for 49 hours in dilute nitric acid (14 ml. of water and 4 ml. of nitric acid; sp. gr. 1.42). On cooling, short needles separated. Repeated crystallizations from benzene and from water gave colorless needles melting at 204° to 205° C.

3,4-Dichlorotoluene was oxidized exactly as described for the oxidation of 3,4-dichloroethylbenzene to give colorless needles; m.p. 204° to 205° C. No depression of melting range was observed when the sample of 3,4-dichlorobenzoic acid as obtained from 3,4-dichloroethylbenzene was mixed with the sample obtained from 3,4-dichlorotoluene.

4-Amino-5-chloro-2-nitroethylbenzene. 4-Amino-3-chloroethylbenzene (15.5 grams) was nitrated under somewhat similar conditions to those used for the nitration of 2-amino-5-chloroethylbenzene. Orange-yellow crystals formed from ethanol-water solution (1:1); yield 13.3 grams (66.5%), m.p. 60° to 61° C.

Anal. Calcd. for $C_8H_9ClNO_2$: Cl, 17.68; N, 13.97. Found: Cl, 17.70; N, 13.99.

4-Acetamido-5-chloro-2-nitroethylbenzene. 4-Amino-5-chloro-2-nitroethylbenzene (10 grams), acetic acid (38.5 ml.) and acetic anhydride (7.7 ml.) were refluxed together for 1 hour. After cooling to room temperature, the mixture was poured into a cracked ice-water mixture (500 ml.). The solid which formed was collected and recrystallized from 95% ethanol as pale-yellow plates; yield 10.6 grams (96.8%); m.p. 127° to 128° C.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3$: Cl, 14.61; N, 11.54. Found: Cl, 14.68; N, 11.64.

2-Acetamido-4- and 5-nitroethylbenzenes. 2-Acetamidoethylbenzene (26 grams) was dissolved in sulfuric acid (47 ml.; sp. gr. 1.84) at 0° C. good mechanical agitation being used; nitric acid (10.7 ml.; sp. gr. 1.42) was added dropwise (0° to 5° C.). After remaining in the cold bath for 4 hours, the resulting solution was poured with stirring into a cracked ice-water mixture. A colorless (white) solid

formed which was separated and washed with cold 2N sodium hydroxide solution followed by cold water.

2-Amino-4- and 5-nitroethylbenzenes. The mixture of 2-acetamido 4- and 5-nitroethylbenzenes was treated with hydrochloric acid (100 ml.; sp. gr. 1.19) and heated under reflux for 2 hours. The crystals that formed upon standing overnight were collected on a sintered glass-type funnel. The filtrate was concentrated yielding a second crop of crystals. These two crops of crystals were combined and washed with a small amount of ethyl ether. When they were mixed with about 10 times their volume of water and carefully warmed to 50° C., a dark-brown oil separated. This oil was collected by gravity filtration before it solidified. Recrystallizations from ethanol-water solutions gave 2-amino-5-nitroethylbenzene; yield, 4 grams (15.6%); m.p. 86° to 87.5° C.

Anal. Calcd. for $C_8H_{10}N_2O_2$: N, 16.85. Found: N, 16.45.

The filtrate, resulting when the oily 2-amino-5-nitroethylbenzene was separated, was neutralized with sodium hydroxide solution causing the precipitation of 2-amino-4-nitroethylbenzene as yellow needles, provided the temperature was kept low and the base was added slowly. The crude 2-amino-4-nitroethylbenzene was crystallized again from hydrochloric acid (sp. gr. 1.19) as the hydrochloride prior to converting into the amine again by adding sodium hydroxide solution; yield 13 grams (49%); m.p. 60° to 61° C.

Anal. Calcd. for $C_8H_{10}N_2O_2$: N, 16.85. Found: N, 16.65.

2-Acetamido-5-nitroethylbenzene. 2-Amino-5-nitroethylbenzene (2 grams) was dissolved in a mixture of glacial acetic acid (8 ml.) and acetic anhydride (4 ml.) along with 1 drop of sulfuric acid (sp. gr. 1.84), and the resulting solution was refluxed for 1.5 hours. This mixture was then poured with stirring into an ice-water mixture (100 ml.). Colorless (white) needles separated upon neutralizing by adding sodium hydroxide-water solution. These needles were collected, washed with water, and recrystallized from 10% ethanol-water solution after being subjected to a decolorizing carbon treatment; yield 1.75 grams (70%); m.p. 157° to 158° C.

2-Ethyl-4-nitrobenzoic Acid. The method of Hodgson and Heyworth (7) was used for converting 2-amino-5-nitroethylbenzene (2 grams) into 2-ethyl-4-nitrobenzonitrile (0.7 gram, 32.8%); m.p. 76° to 77° C.

2-Ethyl-4-nitrobenzonitrile (0.3 gram) was mixed with sulfuric acid (20 ml.; 30% by volume in water; sp. gr. 1.84) and heated under reflux (24 hours). The long, colorless needles that formed upon cooling were dissolved by adding 10% sodium hydroxide solution. The resulting mixture was extracted with ethyl ether and then filtered. A pale-yellow solid formed upon acidifying the filtrate with hydrochloric acid. This was separated and washed with water prior to recrystallizing from water; yield 0.1 gram (30.3%); m.p. 125.5° to 126.5° C.

2-Ethyl-5-nitrobenzoic Acid. 2-Amino-4-nitroethylbenzene (2 grams) was converted into 2-ethyl-5-nitrobenzonitrile (1.2 grams, 56.5%; m.p. 69° to 70° C.) and 2-ethyl-5-nitrobenzoic acid under essentially the same conditions that 2-amino-5-nitroethylbenzene was changed into 2-ethyl-4-nitrobenzoic acid; yield 0.3 gram (54.2%) from 0.5 gram of nitrile; m.p. 164° to 165° C.

4-Amino-3-nitroethylbenzene. 4-Acetamidoethylbenzene (7.5 grams) was nitrated under conditions similar to those used by Noyes (13) for the nitration of 4-acetamidotoluene; yield 3 grams (43%) after crystallizing from 95% ethanol, with cooling in an ice bath; m.p. 44° C.

3-Acetamidoethylbenzene Bromo Derivative. 4-Amino-3-nitroethylbenzene (3 grams) was deaminated under the same conditions as reported for the deamination of 2-amino-4-nitroethylbenzene under part of 4-nitroethylbenzene preparation; yield 1.5 ml. of 3-nitroethylbenzene. The 3-nitroethylbenzene was dissolved in absolute ethanol and hydrogenated (Raney nickel, 38 p.s.i.g., 50° C.). Sulfuric acid was used to acidify the filtrate after removing the catalyst and prior to distilling most of the ethanol. After making the residue basic by adding sodium hydroxide solution, it was extracted with ethyl ether, and the ether extract was dried over sodium hydroxide pellets. The ether was removed by distillation under reduced pressure and a mixture of glacial acetic acid (20 ml.) with acetic anhydride

(3 ml.) was added to the residue. This was refluxed for 20 minutes and cooled to 50° C. before adding bromine dropwise until the bromine color persisted on standing. Upon pouring into water (200 ml.) with stirring, filtering, washing the solid with water, and recrystallizing from 95% ethanol, colorless (white) needles formed; m.p. 145° to 146° C.

2-Amino-5-nitroethylbenzene (2.0 grams) was deaminated, reduced, and acetylated under conditions similar to those reported in part of 4-nitroethylbenzene, part of 4-aminoethylbenzene, and the 4-acetamidoethylbenzene preparations respectively. The liquid 3-acetamidoethylbenzene was dissolved in glacial acetic acid and brominated under the above conditions; m.p. 145° to 146° C. A mixture of crystals, prepared as above, with these also melted at 145° to 146° C.

8-Bromo-6-ethylquinoline. 4-Amino-3-bromoethylbenzene (135.5 grams) was converted into 8-bromo-6-ethylquinoline under modified Skraup conditions similar to those used by Richter and Smith (15) for such ring-closures. The crude quinoline was extracted from the reaction mixture with ethyl ether, the ether solution was dried over anhydrous sodium sulfate, and the ether was removed by distillation. Fractionation of the residue yielded a yellow oil; 91.7 grams (57.4%), b.p. 179° to 184° C./13 to 14 mm. During another preparation by another worker 70.4 grams of amine gave 39.5 grams of quinoline distilling at 170° to 174° C./8 mm. This quinoline darkened rapidly on standing in air. The picrate melted at 157° to 158° C.

Anal. Calcd. for $C_{11}H_{13}BrN_2O_2$: Br, 17.18; N, 12.04. Found: Br, 16.97; N, 12.20.

8-Bromo-6-ethyl-5-nitroquinoline. 4-Acetamido-5-bromo-2-nitroethylbenzene (5.0 grams; 0.0174 mole), dry glycerol (6.5 ml.; 0.0835 mole), arsenic pentoxide (4.0 grams; 0.0174 mole) and acetic anhydride (3.0 ml.; 0.0418 mole) were mixed together, and sulfuric acid (6.0 ml.; sp. gr. 1.84) was added dropwise to the mixture accompanied by mechanical stirring. After the addition of the acid, the temperature of the oil bath which was used as a source of heat was increased to 130° C. and maintained for approximately 0.5 hour prior to increasing it to 165° to 170° C. The mechanical stirring was discontinued when the reaction mixture started to reflux. When 3 hours had elapsed the source of electrical energy (used to heat the oil bath) was disconnected, and the contents of the flask allowed to cool slowly by keeping the flask immersed in the oil bath overnight. The reaction mixture was diluted with an equal volume of water, stirred and filtered. The residue *A* on the filter paper was washed with water. Filtrate *A* was subjected to a decolorizing carbon treatment, and concentrated aqueous sodium hydroxide solution was added slowly and with stirring to the resulting filtrate. Residue *B* was collected on a filter paper and washed with water. The filtrate along with wash water was again treated with decolorizing carbon, followed by filtration and addition of sodium hydroxide solution to the resulting filtrate. In a similar manner residues *C*, *D*, and *E* were collected before the filtrate and wash liquid was finally made basic.

Residues *A*, *B*, *C*, *D*, and *E* were extracted independently with boiling 95% ethanol. Resulting alcoholic solutions were treated with decolorizing carbon and concentrated. Upon cooling, the extracts obtained from residues *A* and *B* deposited crystals. Further purification of these by additional decolorizing carbon treatments in 95% ethanol and concentration finally resulted in long, dense, pale-yellow to colorless needles; yield 0.68 gram (14%), m.p. 89° to 90° C.

Anal. Calcd. for $C_{11}H_9BrN_2O_2$: C, 46.83; H, 3.22; Br, 28.44; N, 9.94. Found: C, 46.83; H, 3.57; Br, 28.63; N, 10.01.

6-Bromo-8-ethylquinoline. 2-Acetamido-5-bromoethylbenzene (14.85 grams) was converted into 6-bromo-8-ethylquinoline under conditions similar to those used to prepare 8-bromo-6-ethylquinoline; yield 9.8 grams (67.7%), b.p. 141° to 146° C./7 to 8 mm.

Anal. Calcd. for $C_{11}H_{10}BrN$: N, 5.93. Found: N, 5.96.

6-Bromo-8-ethyl-5-nitroquinoline. 2-Acetamido-5-bromo-4-nitroethylbenzene (5.0 grams) was subjected to the same

modified Skraup conditions as reported under the preparation of 8-bromo-6-ethyl-5-nitroquinoline. A solid formed when the reaction mixture was poured into water (300 ml.). This solid was collected, washed with water and then extracted with sulfuric acid-water solution (1:1 by volume). After applying a decolorizing carbon treatment to the extract and filtering, the filtrate was nearly neutralized by adding sodium hydroxide solution. The pale-colored solid that formed was separated and recrystallized from 95% ethanol to which a few drops of water was added to induce crystallization; m.p. 86° to 87° C. Satisfactory analyses were obtained for derivatives of this nitroquinoline.

6-Chloro-8-ethylquinoline. 2-Amino-5-chloroethylbenzene (24.2 grams) was subjected to the same conditions as reported under preparation of 8-bromo-6-ethylquinoline; yield 20.5 grams (68.8%); b.p. 139.5° to 142.5°/6 to 7 mm. Anal. Calcd. for $C_{11}H_{10}ClN$: Cl, 18.50; N, 7.31. Found: Cl, 18.7; N, 7.45.

6-Chloro-8-ethyl-5-nitroquinoline. Sulfuric acid (7 ml.; sp. gr. 1.84) was added to a mixture of 2-acetamido-5-chloro-4-nitroethylbenzene (7.0 grams), arsenic pentoxide (5.55 grams) and anhydrous glycerol (10.2 ml.) prior to increasing the temperature to 135° to 140° C. and maintaining it for several hours. After cooling, the mixture was poured into water with stirring before heating to boiling, decolorizing, and filtering. The filtrate was made basic by adding sodium hydroxide solution and extracted with ethyl ether. Distillation was used to remove the ether, after drying the solution, and the residue was crystallized from 95% ethanol; m.p. 55.5° to 56.5° C.

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: Cl, 14.99; N, 11.84. Found: Cl, 15.11; N, 11.84.

8-Chloro-6-ethylquinoline. 4-Amino-3-chloroethylbenzene (24.2 grams) was subjected to same conditions as reported under preparation of 8-bromo-6-ethylquinoline; yield 11 grams (36.9%), b.p. 175° to 177° C./8 mm.

Anal. Calcd. for $C_{11}H_{10}ClN$: Cl, 18.50; N, 7.31. Found Cl, 18.50; N, 7.26.

8-Chloro-6-ethyl-5-nitroquinoline. 4-Acetamido-5-chloro-2-nitroethylbenzene (9 grams), arsenic pentoxide (7.3 grams), anhydrous glycerol (13.1 ml.), and sulfuric acid (9 ml.; sp. gr. 1.84) were heated together in an oil bath at 130° C. for 8 hours; mechanical stirring was used. After cooling to room temperature and pouring into water (600 ml.), the insoluble material was collected. This was mixed with decolorizing carbon and extracted with refluxing 95% ethanol. Two additional decolorizing treatments were applied to the filtrate before it was concentrated by distillation. Short, pale yellow needles formed; yield 1.8 grams (20.3%), m.p. 81° to 82° C.

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: Cl, 14.99; N, 11.84. Found: Cl, 14.87; N, 11.99.

8-Ethyl-5-nitroquinoline. The conditions reported by Richter and Smith (15) for accomplishing Skraup type ring-closures were applied to 2-acetamido-4-nitroethylbenzene (3.1 grams). The final heating bath temperature was 160° C. and was maintained for 4 hours before pouring into cracked ice-water mixture (100 ml.) and adding sodium hydroxide solution. A cloudy distillate obtained from distilling with steam deposited crystals of 8-ethyl-5-nitroquinoline (1 gram; 31.2%); m.p. 45° to 46° C.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.85. Found: N, 13.85.

8-Ethyl-6-nitroquinoline. 2-Acetamido-5-nitroethylbenzene (4.5 grams) was subjected to essentially the same modified-Skraup conditions as 2-acetamido-4-nitroethylbenzene except that the final temperature of the bath was 175° C. and a solid was isolated directly upon pouring into water and neutralizing. This solid was recrystallized three times from 95% ethanol; yield 2 grams (40%), m.p. 99° to 100° C.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.85. Found: N, 13.20.

In view of the fact that derivatives of 8-ethyl-6-nitroquinoline were also prepared, we feel that this analysis is incorrect.

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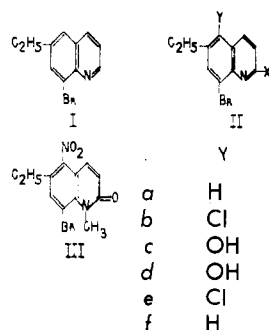
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8-Bromo-6-Ethylquinoline and Some Derivatives

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Hydrolysis of 8-bromo-2-chloro-6-ethylquinoline, as obtained by the oxidation of 8-bromo-6-ethyl-1-methylquinolinium salt to 8-bromo-6-ethyl-2-quinolone and treatment with phosphorus pentachloride-phosphoryl chloride mixture, gave 8-bromo-6-ethyl-2-quinolinol. Nitration of 8-bromo-, 8-bromo-2-chloro-, and 8-bromo-2-hydroxyderivatives of 6-ethylquinoline resulted in the formation of the 5-nitro compounds which were compared with authentic samples prepared by alternate routes. Oxidation of 8-bromo-6-ethyl-1-methyl-5-nitroquinolinium iodide, as obtained from 8-bromo-6-ethyl-5-nitroquinoline, gave 8-bromo-6-ethyl-1-methyl-5-nitro-2-quinolone that was converted by phosphorus pentachloride-phosphoryl chloride mixture into 8-bromo-2-chloro-6-ethyl-5-nitroquinoline; this product hydrolyzed to 8-bromo-6-ethyl-5-nitro-2-quinolinol. Amines resulting from the reduction of 8-bromo-6-ethyl-5-nitroquinoline and 8-bromo-2-chloro-6-ethyl-5-nitroquinoline were acetylated and benzoylated.

SOME NEW derivatives of 8-bromo-6-ethylquinoline (I) are recorded. Various derivatives (II) were prepared.



The 2-chloro compounds (II *b*, *e*) were made (from I, II *a*) by quaternizing the quinoline compound with methyl sulfate, oxidizing with alkaline ferricyanide or with alkaline peroxide, and finally treating with a mixture of phosphoryl chloride and phosphorus pentachloride. Acid hydrolysis of the 2-chloro compounds yielded the 2-quinolinols (II *c*, *d*). Other reactions used were conventional: reduction of nitro to amino and acylation or arylation of amino to amido.

Nitroquinolines (II *a*, *d*, and *e*). Cold solutions of nitric acid (24.5 ml., 0.57 ml., and 0.8 ml.; sp. gr. 1.42) in sulfuric acid (35 ml., 0.8 ml., and 1.2 ml.; sp. gr. 1.84) were added dropwise with stirring independently at 0°C. or less to solutions of I (35.0 grams), II *b* (0.8 gram), and II *c* (1.2 grams) in sulfuric acid (35 ml., 1.2 ml., and 0.8 ml.; respectively; sp. gr. 1.84). These solutions were kept overnight at 25°C. before heating to 70°C. for 5 minutes. After cooling, these solutions were poured into cracked ice and water mixtures causing the formation of solids that were collected, washed with water, and crystallized from 95% ethanol after applying decolorizing carbon treatments; yield is 29.0 grams (70%) of pale-yellow almost colorless needles (II *a*; m.p. 89° to 90°C.), 0.35 gram (II *e*; m.p. 168° to 169.5°C.), and 1.2 grams (85%) (II *d*; m.p. 198° to 199°C.). Attempts to oxidize II *a* to the corresponding CQOH acid with potassium dichromate-sulfuric acid mixture failed. Anal. Calcd. for C₁₁H₉ClBrN₂O₂: (Cl + Br), 36.56; N, 8.88. Found: (Cl + Br), 36.33; N, 8.59.

Calcd. for C₁₁H₉BrN₂O₃: Br, 26.90; N, 9.43. Found: Br, 27.13; N, 9.15.

2-Chloroquinolines (II *b*, *e*). QUATERNIZATIONS. Compound I (9.5 grams) and methyl sulfate (14.3 ml.) were heated together in an oil bath maintained at 125°C. for 2 hours. Water (50 ml.) was added before extracting with ethyl ether three times (25-15-10 ml.).

Compound II *a* (20.0 grams) and methyl sulfate (30 ml.) were heated together in an oil bath maintained at 120°C. for 2 hours. Water (90 ml.) was added, after cooling, followed by two extractions with ethyl ether (50-30 ml.).