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The Application of the Hofmann Reaction, etc. Part III.

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168. *The Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part III. Synthesis of 3-Alkyl-2 : 4-diketo-1 : 2 : 3 : 4-tetrahydroquinazolines from N-Alkylphthalamides.*

By F. S. SPRING and J. C. WOODS.

Application of the Hofmann reaction to a number of substituted phthalamides is described. Intramolecular reaction to give substituted 2 : 4-dihydroxyquinazolines was not observed in the cases of 4-nitro-, 3-nitro-, and 4-chloro-phthalamides, the only products isolated being the corresponding substituted anthranilic acids. In contrast to this behaviour treatment of *N-methylphthalamide* and *N-ethylphthalamide* with alkaline potassium hypobromite gives 3-methyl- and 3-ethyl-2 : 4-diketo-1 : 2 : 3 : 4-tetrahydroquinazolines respectively.

A remarkable reactivity of mono-*N*-alkylphthalamides is recorded. Treatment of phthalimide with excess aqueous methylamine or aqueous ethylamine gives *NN'-dimethylphthalamide* and *NN'-diethylphthalamide* respect-

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ively. These changes depend upon the facility with which *N*-methylphthalimide and *N*-ethylphthalimide (prepared by the action of dry alcoholic ammonia upon the corresponding *N*-alkylphthalimide) are converted into *N*-methylphthalimide and *N*-ethylphthalimide respectively; although the *N*-monoalkylphthalimides are relatively stable to heat treatment in absence of water, when a suspension in water is shaken at room temperature, they are quickly decomposed with formation of the corresponding *N*-alkylphthalimide and evolution of ammonia.

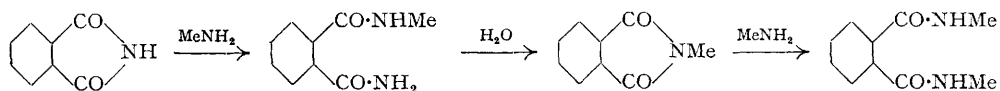
HOOGWERFF and VAN DORP (*Rec. Trav. chim.*, 1891, **10**, 4; 1896, **15**, 107) obtained 2:4-dihydroxyquinazoline by the interaction of equimolecular proportions of phthalimide and potassium hypobromite in alkaline solution. We have investigated the reaction of alkaline potassium hypobromite upon some substituted phthalimides.

When treated with one molecular proportion of potassium hypobromite in alkaline solution, 4-nitrophthalimide gives a mixture of 4- and 5-nitroanthranilic acids; the formation of 6- or 7-nitro-2:4-dihydroxyquinazoline was not observed. The behaviour of 4-nitrophthalimide does not correspond to that of phthalimide in similar circumstances, nor does it correspond to that of quinoxaline-2:3-dicarboxamide (Baxter and Spring, this vol., p. 229) since treatment of 4-nitrophthalimide with two molecular proportions of hypobromite also gives a mixture of 4- and 5-nitroanthranilic acids. Similar treatment of 3-nitrophthalimide and 4-chlorophthalimide gave 6-nitroanthranilic acid and 4-chloroanthranilic acid respectively.

So far as we are aware, the only example of the application of the Hofmann reaction to a *N*-monoalkyl or *N*-monoaryl substituted 1:2-dicarboxamide is that described by Hoogwerff and van Dorp (*Rec. Trav. chim.*, 1890, **9**, 42) who treated *N*-phenylsuccinamide with bromine and potassium hydroxide. After acidification with acetic acid an impure *N*-bromoamide was obtained which when heated with alkali gave β -(ω -phenylureido)propionic acid. 3-Phenyl-5:6-dihydrouracil was not isolated but its formation during the reaction sequence seems probable. We find that *N*-methylphthalimide and *N*-ethylphthalimide when treated with alkaline potassium hypobromite solution are converted into 3-methyl- and 3-ethyl-2:4-diketo-1:2:3:4-tetrahydroquinazoline respectively. In contrast to the smooth reaction observed in these cases an attempt to obtain 3-methyl-5:6-dihydrouracil from *N*-methylsuccinamide was unsuccessful.

Some interesting transformations were observed in preparing the *N*-monosubstituted dicarboxyamides required in this investigation. Treatment of succinimide with an excess of aqueous methylamine gave a quantitative yield of *N*-methylsuccinamide. On the other hand, treatment of phthalimide with excess aqueous methylamine gave a quantitative yield of *NN'*-dimethylphthalimide; using one molecular proportion of aqueous methylamine, a mixture of *NN'*-dimethylphthalimide and unchanged phthalimide was obtained. As an alternative approach to *N*-methylphthalimide, *N*-methylphthalimide was treated with aqueous ammonia. Instead of the required compound, this reaction gave ammonium *N*-methylphthalamate and thence *N*-methylphthalamic acid, which like its ammonium salt decomposes on heating and gives *N*-methylphthalimide. The required *N*-methylphthalimide was finally obtained by treatment of *N*-methylphthalimide with dry alcoholic ammonia.

The conversion of phthalimide into *NN'*-dimethylphthalimide probably involves the following steps:



In partial confirmation of this series of changes it was found that, when shaken with aqueous methylamine, *N*-methylphthalimide is converted into *NN'*-dimethylphthalimide and, as expected, similar treatment of *N*-methylphthalimide gives the same product. The unexpected stage in this reaction sequence is the postulated cyclisation of *N*-methylphthalimide at room temperature; an examination of the stability of this compound disclosed that this reaction occurs with great facility under certain conditions. *N*-Methylphthalimide can be crystallised from boiling acetone without decomposition. It is also reasonably stable when heated in the dry state. If it is maintained for a short time at its melting point, it decomposes smoothly to give *N*-methylphthalimide. When suspended in water and shaken at room temperature, *N*-methylphthalimide decomposes to yield *N*-methylphthalimide. The change is rapid and quantitative; it is accompanied by evolution of ammonia and an obvious change in crystalline form and it does not appear to be catalysed by traces of acids or alkalis. In contrast to the behaviour of *N*-methylphthalimide, phthalimide is not changed after prolonged shaking with water at room temperature. *NN'*-Dimethylphthalimide, however, is more akin to *N*-methylphthalimide; after shaking an aqueous suspension of the former compound for 20 minutes, methylamine can be detected. The reaction is not as rapid as the corresponding reaction of *N*-methylphthalimide, and the complete conversion of *NN'*-dimethylphthalimide into *N*-methylphthalimide occurs when its aqueous suspension is shaken for 1 hour at 25°.

An exactly analogous series of reactions was observed in the preparation of the *N*-ethylphthalimide, and *NN'*-diethylphthalimide. More particularly, simple shaking of an aqueous suspension of *N*-ethylphthalimide at room temperature for 20 minutes gave a quantitative yield of *N*-ethylphthalimide.

EXPERIMENTAL.

(M. p.s are uncorrected.)

4-Chlorophthalimide.—4-Chlorophthalimide (Rée, *Annalen*, 1886, **233**, 238) (7 g.) was dissolved in aqueous ammonia (200 c.c.; *d*, 0.88) with gentle warming. After standing overnight, the heavy crystalline mass of diamide was collected.

When crystallised from water, 4-chlorophthalimide was obtained in heavy prisms, m. p. 194—196° (decomp.) (yield, 75%) (Found : C, 48.4; H, 3.5; N, 13.6. $C_8H_5O_2NCl$ requires C, 48.4; H, 3.5; N, 14.1%). When heated for a short time at its melting point, the diamide decomposes to give 4-chlorophthalimide, m. p. and mixed m. p. 209—210°. Crystallisation of the diamide from water should not involve prolonged boiling of the solution since this treatment leads to considerable decomposition with formation of the imide.

4- and 5-Nitroanthranilic Acids from 4-Nitrophthalimide.—4-Nitrophthalimide (2.1 g.) was treated with an ice-cold solution of potassium hypobromite (28 c.c.; prepared as described in *J.*, 1945, 231) diluted with water (22 c.c.). The diamide dissolved rapidly with evolution of ammonia. The solution was heated at 80° for 20 minutes and, after cooling, acidified with dilute hydrochloric acid. The solid was collected, dried (1.2 g.) and extracted with boiling xylene. The insoluble portion formed a pale yellow solid freely soluble in aqueous bicarbonate with effervescence and when crystallised from aqueous acetic acid gave 5-nitroanthranilic acid (0.7 g.) as bright yellow felted needles, m. p. 276° (decomp.) both alone and when mixed with an authentic specimen (Found : C, 46.2; H, 3.6; N, 15.6. Calc. for $C_7H_5O_4N_2$: C, 46.15; H, 3.3; N, 15.4%). The acid was further characterised by conversion into 5-nitro-acetylanthranil which formed pale yellow needles from acetic anhydride, m. p. 161° (Bogert and Cook, *J. Amer. Chem. Soc.*, 1906, 28, 1451, give m. p. 161—162° corr.) and thence into 5-nitro-acetylanthranilic acid which formed pale yellow needles from water, m. p. 220° (Ullmann and Uzbachian, *Ber.*, 1903, 36, 1797, give m. p. 221°). Evaporation of the xylene extract followed by crystallisation of the deep orange coloured residue from aqueous alcohol gave 4-nitroanthranilic acid as orange-yellow needles, m. p. 269° (0.4 g.) both alone and when mixed with an authentic specimen (Found : C, 46.0; H, 3.3; N, 15.7%). The acid was further characterised by conversion into 4-nitro-acetylanthranil which separated as prisms from acetic anhydride, m. p. 140—141° (Bogert and Seil, *J. Amer. Chem. Soc.*, 1907, 29, 530, give m. p. 137—138° corr.) and thence into 4-nitro-acetylanthranilic acid which formed pale yellow needles from water, m. p. 216—217° (Chapman and Stephen, *J.*, 1925, 1791, give m. p. 217°).

Repetition of this experiment using two molecular proportions of potassium hypobromite in excess potassium hydroxide solution gave a mixture of 4- and 5-nitroanthranilic acids in 90% yield. The ratio 5-nitro-acid : 4-nitro-acid was approximately 3 : 2.

6-Nitroanthranilic Acid from 3-Nitrophthalimide.—Using the method described above, treatment of 3-nitrophthalimide with either one or two molecular proportions of potassium hypobromite gave a 30—40% yield of 6-nitro-anthranilic acid. The product formed yellow needles from alcohol, m. p. 184°, and was characterised by conversion into 6-nitro-acetylanthranil which separated in pale yellow needles from acetic anhydride, m. p. 154° (Bogert and Chambers, *J. Amer. Chem. Soc.*, 1905, 27, 649 give m. p. 155—156° corr.), and thence into 6-nitro-acetylanthranilic acid which separated as prisms from water, m. p. 212° (Bogert and Chambers, *loc. cit.*, give m. p. 212—214°).

4-Chloroanthranilic Acid from 4-Chlorophthalimide.—Using the procedure described above, treatment of 4-chlorophthalimide with two molecular proportions of potassium hypobromite in alkaline solution gave a 70% yield of 4-chloroanthranilic acid; the acid separated in light brown needles from acetic acid, m. p. 235° (Found : C, 48.6; H, 3.5; N, 7.9. Calc. for $C_7H_5O_2NCl$: C, 49.0; H, 3.5; N, 8.2%). The acid was characterised by conversion into 4-chloro-acetylanthranil, pale yellow needles from acetic anhydride, m. p. 144° (Heller and Hessel, *J. prakt. Chem.*, 1928, 120, 71, give m. p. 145°), and thence into 4-chloro-acetylanthranilic acid, needles from water, m. p. 210° (Heller and Hessel, *loc. cit.* give m. p. 213°).

N-Methylphthalamic Acid.—N-Methylphthalimide (5 g.) was shaken with aqueous ammonia (d 0.88; 80 c.c.) for 30 minutes when solution was complete. The clear yellow-green solution was evaporated to dryness under reduced pressure and the product crystallised from aqueous alcohol to give ammonium N-methylphthalamate in prismatic needles, m. p. 118—119° (decomp.), in quantitative amount (Found : C, 55.1; H, 5.9; N, 14.1. $C_9H_{12}O_3N_2$ requires C, 55.1; H, 6.1; N, 14.3%). The ammonium salt dissolves in cold 3N sodium hydroxide with liberation of ammonia; it is very hygroscopic. This salt was dissolved in the minimum volume of cold water and the solution acidified by the addition of cold dilute hydrochloric acid. The precipitated acid was collected and purified by solution in ether, removal of a small quantity of undissolved phthalic acid followed by evaporation of the ethereal solution. N-Methylphthalamic acid was obtained in prisms, m. p. 134° undepressed when mixed with a specimen prepared by the following method.* Phthalic anhydride (3 g.) was treated with aqueous methylamine (33%; 10 c.c.), solution occurring with considerable evolution of heat. The solution was cooled and carefully acidified, with cooling, with cold concentrated hydrochloric acid. After standing, the crystalline mass was collected and shaken with cold N-sodium hydroxide. The insoluble portion was removed and shown to be N-methylphthalimide (m. p. and mixed m. p.). The alkaline solution was cooled with ice-water and acidified with concentrated hydrochloric acid. On standing N-methylphthalamic acid separated as prisms, m. p. 138°, totally soluble with effervescence in sodium bicarbonate solution (yield, 80%). For analysis the acid was repeatedly washed with cold distilled water and dried at room temperature under reduced pressure over potassium hydroxide (Found : C, 60.2; H, 4.9; N, 7.85. $C_9H_9O_2N$ requires C, 60.3; H, 5.0; N, 7.8%). When maintained at its melting point for 5 minutes, the acid is converted into N-methylphthalimide and the same change occurred during an attempt to recrystallise the acid from acetone.

N-Methylphthalimide.—N-Methylphthalimide (5 g.) was shaken with an alcoholic solution of ammonia (80 c.c. saturated at 0°) for 24 hours when solution was complete. After standing at 0° for 2 days, the separated solid was collected and crystallised from acetone to give N-methylphthalimide in prismatic needles, m. p. 181° (decomp.). When mixed with NN'-dimethylphthalimide the m. p. was depressed. A further amount of the product was obtained by evaporation (reduced pressure) of the alcoholic mother liquor; total yield, 90% (Found : C, 60.5; H, 5.6; N, 15.5. $C_9H_{10}O_2N_2$ requires C, 60.7; H, 5.6; N, 15.7%).

NN'-Dimethylphthalimide.—(a) Powdered phthalimide (50 g.) was shaken with aqueous methylamine (33%; 75 c.c.). Solution was complete in ca. 5 minutes and the product began to separate with evolution of heat. When reaction was complete the crystalline solid was collected and recrystallised from acetone from which NN'-dimethylphthalimide separated in needles, m. p. 185° (decomp.) (yield, 95%) (Found : C, 62.8; H, 6.4; N, 14.5. $C_{10}H_{12}O_2N_2$ requires C, 62.5; H, 6.25; N, 14.6%). (b) A suspension of N-methylphthalimide (16 g.) in water (50 c.c.) was shaken with aqueous methylamine (33%, 16 c.c.) until solution was complete (2 hours). The solution was concentrated under reduced pressure until crystallisation commenced. NN'-Dimethylphthalimide separated in needles, m. p. 184° (decomp.) either alone or when mixed with the specimen described above (yield, 90%). (c) Powdered N-methylphthalimide (0.5 g.) was shaken at room temperature with aqueous methylamine (2 c.c.). After 1 minute the mixture set to a homogeneous stiff paste. After 6 minutes the solid was collected and identified as NN'-dimethylphthalimide, m. p. 183—184° (decomp.) (yield, nearly quantitative).

N-Methylphthalimide.—(a) NN'-Dimethylphthalimide (4 g.) was maintained at 185—190° for 10 minutes; considerable evolution of methylamine occurred. When cold, the reaction product was crystallised from aqueous alcohol giving N-methylphthalimide as fine needles, m. p. 133° (yield, 3 g.) (Found : N, 8.7. Calc. for $C_9H_7O_2N$: N, 8.7%).

* The preparation of N-methylphthalamic acid, m. p. 130—135°, is mentioned without detail or analysis by Hoogewerff and Van Dorp, *Rec. Trav. chim.*, 1894, 13, 98 (footnote).

(b) Powdered *N*-methylphthalimide (1.5 g.) was shaken with distilled water (2 c.c.). The evolution of ammonia was detected after a few minutes and the suspended solid changed into fine needles. After 20 minutes the solid was collected and shown to be *N*-methylphthalimide, m. p. and mixed m. p. 133° (yield, nearly quantitative). (c) A suspension of powdered *NN'*-dimethylphthalimide (1.5 g.) in water (2 c.c.) was shaken at 15°. After a short time the evolution of methylamine was detected but after 4 hours' shaking the suspended solid had m. p. 126—170° (decomp.). When the *NN'*-dimethylphthalimide was shaken with water for 1 hour at 25°, decomposition was complete, the suspended solid then forming fine needles, m. p. 132°, undepressed when mixed with *N*-methylphthalimide.

N-Ethylphthalimide obtained by the action of dry alcoholic ammonia on *N*-ethylphthalimide, separated in fine needles from acetone, m. p. 150° (yield, 90%) (Found: C, 62.6; H, 6.2; N, 14.3. $C_{10}H_{12}O_2N_2$ requires C, 62.5; H, 6.25; N, 14.6%).

NN'-Diethylphthalimide was obtained from phthalimide and aqueous ethylamine as described in method (a) for *NN'*-dimethylphthalimide. It was also obtained by shaking *N*-ethylphthalimide with aqueous ethylamine. In both cases the yield was nearly quantitative. *NN'*-Diethylphthalimide separates from acetone in soft felted needles, m. p. 162—163° (decomp.) (Found: C, 65.8; H, 7.3; N, 12.7. $C_{12}H_{16}O_2N_2$ requires C, 65.5; H, 7.3; N, 12.7%).

N-Ethylphthalimide.—(a) *NN'*-Diethylphthalimide was heated for 10 minutes at 170°. The cold reaction product was crystallised from aqueous alcohol from which the imide separated in needles, m. p. 78° (Found: N, 8.0. Calc. for $C_{10}H_8O_2N$: N, 8.0%). (b) A suspension of powdered *N*-ethylphthalimide (1 g.) was shaken at room temperature with distilled water (2 c.c.) for 20 minutes. Ammonia was evolved and the form of the solid changed to a mass of felted needles, m. p. 78° undepressed when mixed with *N*-ethylphthalimide.

3-Methyl-2 : 4-diketo-1 : 2 : 3 : 4-tetrahydroquinazoline.—A solution of potassium hypobromite (28 c.c., prepared as described in this vol., p. 231) was diluted with water (22 c.c.) and added to *N*-methylphthalimide (1.78 g.). The diamide dissolved immediately with considerable evolution of heat and the mixture was heated at 80° for 15 minutes and cooled. The solution was saturated with carbon dioxide and the flocculent precipitate collected and crystallised twice from alcohol to give 3-methyl-2 : 4-diketo-1 : 2 : 3 : 4-tetrahydroquinazoline in fine felted needles, m. p. 236—238°, in 45% yield. It is insoluble in acid but soluble in 3*N* alkali, the solution showing a blue fluorescence [Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2062, give m. p. 237—238° (corr.) for this compound] (Found: C, 61.6; H, 4.8; N, 15.9. Calc. for $C_9H_8O_2N_2$: C, 61.4; H, 4.55; N, 15.9%).

3-Ethyl-2 : 4-diketo-1 : 2 : 3 : 4-tetrahydroquinazoline was obtained by similar treatment of *N*-ethylphthalimide. It separates from aqueous alcohol as needles, m. p. 196° (yield, 53%). Stewart (*J. prakt. Chem.*, 1894, [2], **49**, 318) gives m. p. 195—196° (Found: C, 63.4; H, 5.3; N, 14.5. Calc. for $C_{10}H_{10}O_2N_2$: C, 63.2; H, 5.3; N, 14.7%).

N-Methylsuccinamide.—Succinimide (10 g.) was shaken with aqueous methylamine (25 c.c.; 33%) until solution was complete. On standing, the solution deposited a crystalline solid (13 g.) which was collected and recrystallised from alcohol to give *N*-methylsuccinamide in prisms, m. p. 159—161° (Found: C, 46.3; H, 8.0; N, 21.7. $C_5H_{10}O_2N_2$ requires C, 46.15; H, 7.7; N, 21.5%). The *N*-methylamide melts without obvious decomposition. After maintaining a specimen at its m. p. for 15 minutes, the m. p. of the product was 110—130°. When heated at 200° for 4 hours, *N*-methylsuccinamide gave a small sublimate of *N*-methylsuccinimide, m. p. 68—70° (Wheeler, *Amer. Chem. J.*, 1900, **23**, 148, gives m. p. 68—70°).

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THE UNIVERSITY, MANCHESTER.

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