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Cyclic Imides IV. The Reaction of Some N-Substituted

Nitrophthalimides with Sodium Methoxide (1,2)

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Treatment of methyl 4-nitrophthalimidoacetate (I) with sodium methoxide in refluxing methanol results in a Gabriel - Colman rearrangement to give 7 - nitro-4-hydroxy-3-carbomethoxy - 1(2H) - isoquinolone (II). Under the same conditions, N-substituted 3-nitrophthalimides (IV) yield N-substituted 3-methoxyphthalimides (V).

The mechanisms which have been proposed for the Gabriel-Colman rearrangement of α-phthalimido carbonyl compounds all require the attack of a nucleophile on the imide carbonyl at the more electron-deficient position of the benzene ring (4). An electron-attracting group on the benzene ring of the phthalimide moiety should activate toward nucleophilic attack the carbonyl group *ortho* or *para* to it, and thereby enhance the facility of the rearrangement. No examples of the Gabriel - Colman rearrangement of an α-phthalimido ester or ketone substituted with an electron-attracting group have been reported in the literature. However, excellent models for this situation exist in the rearrangements of the pyridinedicarboximidoacetic esters (5), in which the electronic effect of the hetero nitrogen atom of the pyridine ring may be roughly equivalent to the effect of a nitro group on the benzene ring (6). The products of both of these rearrangements have been unequivocally identified. Treatment of ethyl 2,3-pyridinedicarboximidoacetate with sodium methoxide yields 8-hydroxy - 7 - carbomethoxy-1,6-naphthyrid-5(6H)-one (5b); and ethyl 3,4-pyridinedicarboximidoacetate gives 4-hydroxy-3-carbomethoxy-2,7-naphthyrid-1(2H)-one (5a). These identifications are in agreement with the prediction that the α-carbon should rearrange to the carbonyl group at the position of lower electron density, *i.e.*, *ortho* or *para* to an electron-attracting group.

The familiar "textbook" reaction of aromatic nitro compounds with sodium alkoxides to produce azoxy compounds did not encourage an attempt at the Gabriel-Colman rearrangement of a nitrophthalimide derivative. However, a recent paper (7) reports the successful rearrangement of N-(p-nitrophenacyl)phthalimide to 4-hydroxy-3-(p-nitrobenzoyl)-1(2H)-isoquinolone. The survival of the nitro group in this reaction encouraged us to make the study.

In the previous paper of this series (8), we reported that the rearrangement of methyl phthalimidoacetate is more successful in a pressure flask at 120-125° than in refluxing methanol at atmospheric pressure. The opposite proved to be true in the case of the methyl nitrophthalimidoacetates. Treat-

ment of methyl 4 - nitrophthalimidoacetate (I) with sodium methoxide in absolute methanol in a pressure flask at 110-120° for three to six hours resulted in the formation of dark-brown powders. These materials blackened gradually without melting at temperatures above 250°, and were insoluble in all common solvents. The microanalytical data for these materials suggested that they were mixtures.

A very different product was obtained when I was treated with sodium methoxide in absolute methanol at reflux temperature. The ultraviolet absorption spectrum of this product was similar in form to the spectrum of 4-hydroxy - 3 - carbomethoxy-1(2H)-isoquinolone (9), though the maxima appeared at longer wave lengths. The product displayed a shift from 347 mμ in alcohol to 383 mμ in dilute sodium hydroxide, which was similar to the shift from 340 mμ to 368 mμ displayed by the latter compound (10). In order to determine if the product was an azoxy compound, 4,4'-azoxyphthalic acid (III) was prepared as a model, by reduction of 4-nitrophthalic acid

I

II

III

IV

a. $R = CH_2CO_2CH_3$

b. $R = \overset{CH_3}{\underset{CH_3}{C}}CO_2CH_3$

V
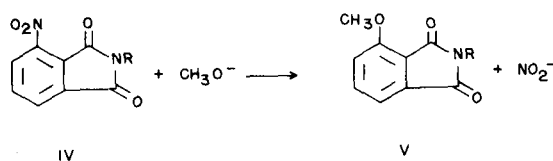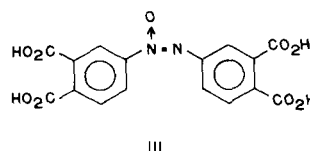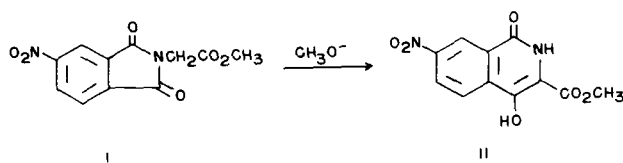
c. $R = CH_3$

d. $R = C(CH_3)_3$

e. $R = C_6H_5$

with sodium arsenite. The absorption spectrum of III was quite different from that of the product, and was essentially unaltered by base. We can therefore conclude that a Gabriel-Colman product has been obtained. On the basis of the model provided by the rearrangement of ethyl 3,4-pyridinedicarboximidoacetate (5a), we can tentatively assign to this product the structure of 7-nitro-4-hydroxy-3-carbomethoxy-1(2H)-isoquinolone (II).

Treatment of methyl 3-nitrophthalimidoacetate (IVa) with sodium methoxide in refluxing absolute methanol resulted in displacement of the nitro group and formation of methyl 3-methoxyphthalimidoacetate (Va). The identification of this product was confirmed by its failure to depress the melting point of authentic Va, and by comparison of its ultraviolet and infrared absorption spectra with those of Va. The acidified reaction mixture turned potassium iodide-starch paper blue, indicating the presence of nitrite. A nucleophilic displacement of the nitro group had therefore occurred.

Four other N-substituted 3-nitrophthalimides (IVb-e) were prepared and subjected to similar reaction conditions. Displacement of the nitro group occurred in all cases. The absorption spectra of the products with aliphatic N-substituents (Vb-d) were identical, or nearly identical, with the spectrum of Va; and the spectrum of the product obtained from IVe was similar to the spectrum reported (11) for Ve.

These nucleophilic displacements of imide-activated groups from a benzene derivative appear to be unique examples. Activation by the anhydride group has, however, been observed, but only at elevated temperatures in the absence of a solvent. For example, 3-nitrophthalic anhydride can be converted to 3-chlorophthalic anhydride by prolonged heating with phosphorus pentachloride (12); and 3-chlorophthalic anhydride has been converted to 3-fluorophthalic anhydride by fusion with anhydrous potassium fluoride (13). The conversion of molten 3-nitrophthalic anhydride to 3-chlorophthalic anhydride by the action of elemental chlorine (14) is a related case, but probably involves a radical mechanism, rather than an ionic one.

No displacement occurred in aqueous media. Solutions of IVa in dilute sodium hydroxide gave negative tests for nitrite even after prolonged boiling. This result is in accord with extreme ease with which the imide ring is cleaved by aqueous base (15), with accompanying loss of activating effect. The rather low yields of the displacement products are probably the result of competing solvolytic or saponification reactions occurring during both the reaction and work-up periods. This conclusion is demonstrated by the isolation of a small amount of N-phenyl-6-nitrophthalamic acid, one of the more stable and less soluble of the phthalamic acids (16), as a by-product of the conversion of IVe to Ve.

EXPERIMENTAL (17)

Attempted Gabriel-Colman Rearrangement of Methyl 4-Nitrophthalimidoacetate (I).

A solution of 0.5 g. of sodium in 25 ml. of absolute methanol was added to 2.4 g. (0.009 mole) of I (18) in 15 ml. of absolute methanol in a 250-ml. pressure flask. The flask was sealed and placed in a pre-heated oil bath at 110° and maintained at this temperature for 3.5 hours with magnetic stirring. After cooling, the dark-brown mixture was dissolved in 100 ml. of water and acidified with 1 N hydrochloric acid. The brown precipitate weighed 0.45 g. and melted at 235-237° with decomposition. Repeated extractions of this material with methanol ultimately gave a dark-brown residue which gradually blackened without melting as the temperature was raised above 250°. Comparable results were obtained from six similar runs. The microanalytical results do not yield an empirical formula.

Anal. Found: C, 52.49; H, 3.89; N, 9.64.

7-Nitro-4-hydroxy-3-carbomethoxy-1(2H)-isoquinolone (II).

To a solution of 0.2 g. (0.0087 mole) of sodium in 200 ml. of absolute methanol in a 500-ml. flask was added 1.8 g. (0.0068 mole) of I. A reflux condenser and drying tube were attached and the mixture was refluxed with magnetic stirring for three hours. When the cooled, dark-red mixture was acidified with 1 N hydrochloric acid, it turned golden yellow and a precipitate formed. Filtration of the chilled mixture gave 0.27 g. (15%) of a yellow powder, m.p. 278-280°. This material was recrystallized from ethyl acetate, which raised the melting point to 284-285.5°. It was finally extracted with methanol, which left 7-nitro-4-hydroxy-3-carbomethoxy-1(2H)-isoquinolone (II), bright orange powder, m.p. 290-291.5°, λ max, 253, 347 mμ (95% ethanol); 272, 383 mμ (dilute NaOH).

Anal. Calcd. for $C_{11}H_8N_2O_6$: C, 50.01; H, 3.05; N, 10.60. Found: C, 50.31; H, 3.31; N, 10.86.

4,4'-Azoxyphthalic Acid (III) (19).

A solution of 12.7 g. (0.06 mole) of 4-nitrophthalic acid in 100 ml. of 5% sodium hydroxide solution was placed in a 500-ml. round-bottom three-necked flask fitted with a reflux condenser. A magnetic stirrer slug was added and a thermometer was inserted. A solution of 17 g. of arsenious oxide and 21 g. of sodium hydroxide in 175 ml. of water was added. The brown mixture was gradually warmed, with stirring, to 70°, and was kept at this temperature for one hour. The cooled solution was acidified with 3 N hydrochloric acid. The orange precipitate was recrystallized from a 3:1 mixture of glacial acetic acid and concentrated hydrochloric acid, giving 3.45 g. (31%) of 4,4'-azoxyphthalic acid (III), pale pinkish orange powder, m.p. 255-257°, λ max 330-333 mμ (95% ethanol), 333-334 mμ (dilute NaOH).

Anal. Calcd. for $C_{16}H_{10}N_2O_9$: C, 51.35; H, 2.69; N, 7.48. Found: C, 51.34; H, 2.95; N, 7.49.

Methyl α-(3-Nitrophthalimido)isobutyrate (IVb).

Anhydrous hydrogen chloride gas was passed for 30 minutes into a solution of 10 g. (0.036 mole) of α-(3-nitrophthalimido)isobutyric acid (20) in 65 ml. of absolute methanol in a 250-ml. two-necked round-bottom flask fitted with a reflux condenser. The reaction vessel was chilled in an ice bath and the pH was raised to 8 by addition of 5% sodium carbonate solution. The mixture was filtered and the precipitate was washed on the filter with cold distilled water until the washings were neutral. Recrystallization of the precipitate from methanol gave 1.05 g. (10%) of methyl α-(3-nitrophthalimido)isobutyrate (IVb), white, shiny plates, m.p. 123-124°, featureless ultraviolet absorption spectrum in 95% ethanol, inflection at 273 mμ in dilute sodium hydroxide.

Anal. Calcd. for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.38; H, 4.29; N, 9.55.

Acidification of the alkaline filtrates from this synthesis precipitated 6 g. (60%) of the starting material. An attempt to prepare IVb by esterification of α-(3-nitrophthalimido)isobutyric acid in the presence of concentrated sulfuric acid resulted in a yield of only 0.5%.

N-(t-Butyl)-3-nitrophthalimide (IVd).

A mixture of 0.026 mole each of 3-nitrophthalic anhydride and t-butylamine was heated to 180°, then allowed to cool to room temperature. The solidified mass was dissolved in boiling 95% ethanol, filtered, and diluted, while still hot, with enough water to cause appearance of cloudiness. Chilling yielded 2.1 g. (33%) of N-(t-butyl)-3-nitrophthalimide (IVd), m.p. 78-81°. Recrystallization from 1:1 ethanol-water raised the melting point to 80.5-82.5°. Ultraviolet absorption spectrum, inflections at 264 and 293 mμ in 95% ethanol, and at 253 and 273 mμ in dilute sodium hydroxide.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.28; H, 4.74; N, 11.32.

Methyl 3-Methoxyphthalimidoacetate (Va).

To a solution of 0.2 g. (0.0087 mole) of sodium in 20 ml. of an-

hydrous methanol in a 100-ml. round bottom flask was added 0.9 g. (0.0034 mole) of IVa (18). A reflux condenser surmounted by a drying tube was attached to the flask, and the red mixture was refluxed for seven hours (21) with magnetic stirring. The reaction mixture was cooled to room temperature and acidified with 1 N hydrochloric acid, giving 0.38 g. (46%) of Va, m.p. 146-148°, reported (8) m.p. 147-149°. The product did not depress the melting point of an authentic sample of Va, and its ultraviolet absorption spectrum was identical with that of Va (8). The infrared absorption spectra (17d) were also identical, with the major bands appearing at 1005, 1057, 1085, 1174, 1257-1290, 1488, 1710, 1750, 2960, and 3420 cm^{-1}.

A 21% yield of Va was obtained from the action of methanolic sodium methoxide on IVa in a pressure flask at 115° for four hours. The product was contaminated with dark-colored unidentified materials resembling those obtained from I under similar conditions.

Methyl α-(3-Methoxyphthalimido)isobutyrate (Vb).

To a solution of 0.2 g. (0.0087 mole) of sodium in 15 ml. of absolute methanol was added 0.857 g. (0.00293 mole) of IVb, and the mixture was refluxed with stirring for seven hours. No color changes occurred during the reaction. The cooled solution was acidified with 1 N hydrochloric acid and chilled overnight in a freezer, giving small, white needles. The mother liquor was concentrated until an oil separated. This oil was dissolved in a minimum of methanol, and the solution was chilled and seeded with crystals from the first crop, giving additional crystals. The combined product was 0.0827 g. (10%) of methyl α-(3-methoxyphthalimido)isobutyrate (Vb), m.p. 104-105° after recrystallization from methanol, λ max (95% ethanol), 218, 244 (inflection), and 338 mµ, λ max (dil. NaOH), 287 mµ.

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.49; H, 5.40; N, 5.16.

N-Methyl-3-methoxyphthalimide (Vc).

To a solution of 0.6 g. (0.026 mole) of sodium in 50 ml. of absolute methanol was added 2.1 g. (0.01 mole) of N-methyl-3-nitrophthalimide (IVc) (22). The mixture was refluxed seven hours, cooled, and acidified with 1 N hydrochloric acid. The mixture was chilled and gave 0.76 g. (40%) of N-methyl-3-methoxyphthalimide (Vc), m.p. after recrystallization from methanol, 146.5-148°, reported (22b) m.p. 147°. Ultraviolet absorption spectrum, λ max, (95% ethanol), 219, 243, and 336 mµ, λ max, (dilute NaOH), 287 mµ.

N-(t-Butyl)-3-methoxyphthalimide (Vd).

A solution of 0.4 g. (0.017 mole) of sodium and 1.7 g. of IVd in 30 ml. of absolute methanol was refluxed for 24 hours. Acidification with 1 N hydrochloric acid and chilling gave 0.126 g. (8%) of N-(t-butyl)-3-methoxyphthalimide, m.p. 113-114° after recrystallization from methanol. Ultraviolet absorption spectrum, λ max, (95% alcohol), 220 and 333 mµ, λ max (dil. NaOH), 286 mµ.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.14; H, 6.56; N, 6.11.

N-Phenyl-3-methoxyphthalimide (Ve).

To a solution of 0.2 g. (0.0087 mole) of sodium in 20 ml. of absolute methanol was added 0.9 g. (0.034 mole) of N-phenyl-3-nitrophthalimide (IVe) (12a). The mixture was refluxed with stirring for one hour, then cooled, acidified with 1 N hydrochloric acid, and chilled. The precipitate was recrystallized from 95% ethanol to give 0.225 g. (27%) of N-phenyl-3-methoxyphthalimide (Ve), m.p. 190-192°, reported (23) m.p. 188.5-190°. Ultraviolet absorption spectrum, λ max (95% ethanol), 222 and 339 mµ, λ max (dilute NaOH), inflections at 223 and 291 mµ, reported (11) λ max, (95% ethanol), 226 and 336 mµ.

The mother liquor was concentrated on a steam cone until precipitation commenced. Chilling gave 0.121 g. (15%) of N-phenyl-6-nitrophthalamic acid, m.p. 173-176° with bubbling; reported (16) m.p.

185°. A repetition of the melting-point determination on the same sample gave 132°; the reported (12a) m.p. of N-phenyl-3-nitrophthalimide is 137°.

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