Department of Chemistry, Texas Woman's University

Cyclic Imides III.

A Study of the Hydroxy- and Methoxyphthalimidoacetic Acids and the Methyl Methoxyphthalimidoacetates (1,2)

Lyman R. Caswell and Patsey C. Atkinson (3)

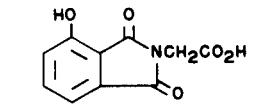
The hydroxy- and methoxyphthalimidoacetic acids and the methyl methoxyphthalimidoacetates have been synthesized. The ultraviolet absorption spectra of these compounds in 95% ethanol, aqueous acid, and aqueous base are discussed. Structures are suggested for the hydroxy- and methoxyphthalamate ions which are formed in basic solution. The Gabriel-Colman rearrangements of methyl 3- and 4-methoxyphthalimidoacetate give, respectively, 8-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VII) and 6-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VIII).

Phthalimide and its derivatives are rapidly saponified by aqueous base, to form salts of phthalamic acids. In earlier papers, we showed that the α-phthalimido acids are especially useful for spectrophotometric studies of this reaction, since their solubility in bases is not dependent upon their ability to saponify (4), and since the carboxyalkyl group has little effect upon the diagnostic absorption bands (4, 5). The esters of α-phthalimido acids are also of interest because of their ability to give the Gabriel-Colman rearrangement, in the presence of alcoholic sodium alkoxides, to form derivatives of 4-hydroxy-3-carbalkoxy-1(2*H*)-isoquinolone (6).

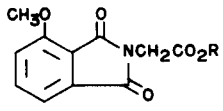
Our previous studies have dealt with the synthesis and ultraviolet absorption spectra of a series of α-phthalimido acids and the derived phthalamic acids (4), and of the nitro- and aminophthalimidoacetic acids and their methyl esters (5). We have extended these studies to the 3- and 4-hydroxyphthalimidoacetic acids (I and III), the 3- and 4-methoxyphthalimidoacetic acids (IIa and IVa), and the methyl 3- and 4-methoxyphthalimidoacetates (IIb and IVb).

The hydroxy- and methoxyphthalimidoacetic acids were easily made by the condensation of the hydroxy- and methoxyphthalic acids with glycine in hot nitrobenzene. The yields were, however, much lower than the yields of the nitrophthalimidoacetic acids prepared in nitrobenzene (5). Satisfactory syntheses of IIb and IVb were accomplished by passing anhydrous hydrogen chloride gas into solutions of IIa and IVa in absolute methanol.

In an earlier paper (7), we described the synthesis of 4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VI) by the Gabriel-Colman rearrangement of methyl phthalimidoacetate (V) in refluxing methanol. It has been found that significantly better yields of VI can be obtained if the reaction is carried out under pressure at a higher temperature. The rearrangements of IIb and IVb were therefore done under the latter conditions.



I



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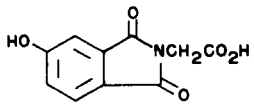

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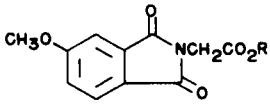
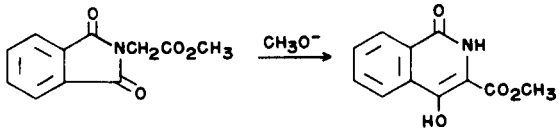


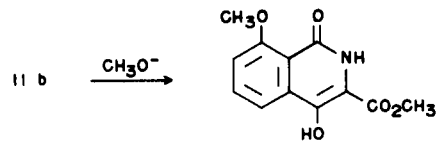
IV

a, R = H

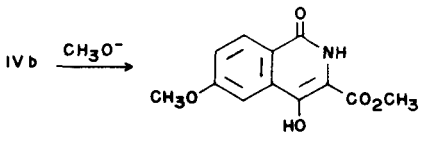
b, R = CH_3



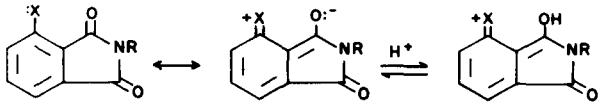
V VI



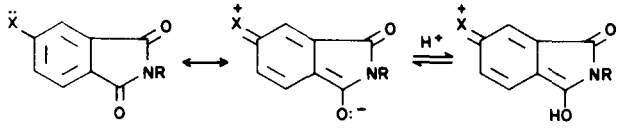
VII



VIII

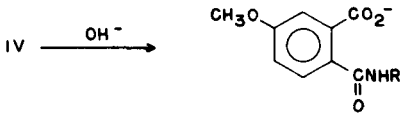


IX X

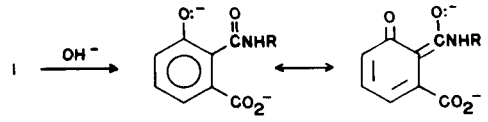


XI XII

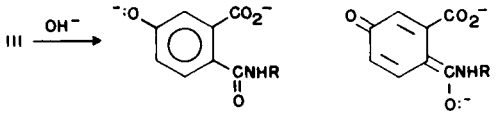
XIII



XIV



XV XVI



XVII XVIII

The ultraviolet absorption spectra of the hydroxy- and methoxyphthalimide derivatives are summarized in Table I. The spectra in 95% ethanol are nearly identical with those that have been reported (8) for the parent hydroxy- and methoxyphthalimides, except for the absence of a peak at 218-219 mμ in the case of some of the 3-isomers. The peak occurring at the longest wave length is the one of greatest interest. This peak is found at longer wavelengths than the corresponding peak of phthalimidoacetic acid (λ max, 292.5 mμ), but at shorter wave lengths than those found (5) for 3-aminophthalimidoacetic acid (λ max, 387 mμ) and 4-aminophthalimidoacetic acid (λ max, 372 mμ). The bathochromic shift from the spectrum of phthalimidoacetic acid is greater for a hydroxyl group than for a methoxyl group, and greater for a 3-substituent than for a 4-substituent. These results are interpretable in terms of contributions by quinoid resonance structures (IX and XI), the probabilities of which increase with the increasing ability of the substituent to donate electrons to the imide carbonyls (5, 8).

The spectra of the acid solutions showed small shifts from the spectra of the alcoholic solutions. Such shifts have not previously received comment. Review of earlier studies (5) showed similar shifts for other phthalimidoacetic acids, and a complete listing is provided in Table II. These shifts cannot be attributed to acid-catalyzed hydrolysis of the imide ring, since the spectra of the resultant phthalamic acids will in most cases be similar to the spectra of the phthalamate ions generated from the phthalimides in basic solution (4). They are, however, similar in magnitude to K-band solvent-effect shifts which are found in the comparison of spectra of aqueous and alcoholic solutions (9).

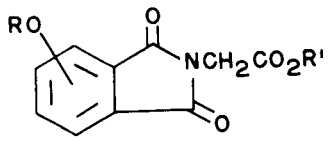
The bathochromism of the shifts decreases approximately with the increasing ability of the substituent to donate electrons, in agreement with earlier observations of such shifts (10). Since the excited states of aromatic compounds probably have quinoid structures (11), the acid-induced shifts observed with electron-donating substituents may be attributed to a lowering of the excitation energies as the result of stabilization of these quinoid structures by protonation of a carbonyl oxygen, giving structures X and XII.

The slight hypsochromic shifts of the aminophthalimidoacetic acids may result from protonation of the amino groups, which would raise the excitation energies. The remarkably small extent of these shifts is in agreement with earlier reports (5, 12) of the failure of aminophthalimides to show basic properties in aqueous media. In the case of 4-nitrophthalimidoacetic acid, the acid-induced stabilization of the excited state probably results from protonation of an oxygen atom in the nitro group.

The ultraviolet absorption spectra of the basic solutions of the phthalimides are the spectra of the phthalamate ions resulting from the saponification of the phthalimides (4). The structures of these ions, and of the Gabriel-Colman rearrangement

TABLE I

Ultraviolet Absorption Spectra of

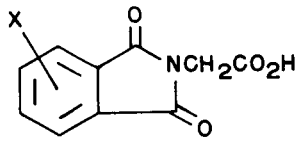


Compound	Position of Substitution	R	R'	in 95% EtOH λ max, mμ	in 95% EtOH log ε max	in dil. HCl λ max, mμ	in dil. HCl log ε max	in dil. NaOH λ max, mμ	in dil. NaOH log ε max
I	3	H	H	---	----	220	4.76	---	----
				243 (a)	3.97	243 (a)	3.96	276	4.17
				339	3.81	340	3.80	396	2.62
IIa	3	CH_3	H	242 (a)	3.91	242 (a)	3.89	---	----
				336	3.72	342	3.72	287	3.47
IIb	3	CH_3	CH_3	218	4.84	220	4.69	---	----
				242 (a)	3.89	243 (a)	3.88	---	----
				338	3.76	342	3.75	289	3.54
III	4	H	H	232	4.72	233	4.68	---	----
				288 (a)	3.42	280 (a)	3.36	322	3.75
				330	3.51	333	3.50	394	3.37
IVa	4	CH_3	H	232	4.69	235	4.60	---	----
				284	3.25	---	----	---	----
				321	3.42	330	3.42	246 (a)	3.97
IVb	4	CH_3	CH_3	232	4.69	234	4.61	---	----
				284	3.25	284	3.25	---	----
				321	3.42	332	3.44	248 (a)	3.97

(a) Inflection.

TABLE II

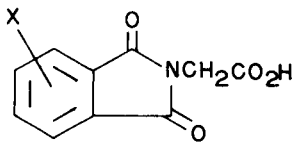
Solvent-Effect Shifts for



X	λ max (EtOH), mμ	λ max (dil. HCl), mμ	Δ λ max (dil. HCl-EtOH), mμ
4-NO_2 (a)	278 (b)	288.5	10.5
4-CH_3O	321	330	9
3-CH_3O	336	342	6
H (a)	292.5	297	4.5
4-OH	330	333	3
3-OH	339	340	1
3-NH_2 (a)	388	387	-1
4-NH_2 (a)	372	368	-4

(a) Reference 5. (b) Inflection.

TABLE III



Compound	X	Yield, %	M.p., °C	Analyses Calcd. C	H	N	Found C	H	N
I	3-OH	50	216-218	54.31	3.19	6.33	54.06	3.17	6.25
IIa	3-CH_3O	35	237-239	56.17	3.86	5.96	55.97	3.81	5.78
III	4-OH	51	221-222	54.31	3.19	6.33	54.03	3.29	6.65
IVa	4-CH_3O	51	221-222	56.17	3.86	5.96	56.02	4.09	5.94

products, are tentatively assignable on the basis of the following considerations. The mechanisms of the saponification of phthalimide derivatives and of the Gabriel-Colman rearrangement of α-phthalimido esters both involve the attack of a nucleophile on one of the imide carbonyls. In the saponification, the nucleophile is the hydroxide ion, and the carbonyl which it attacks becomes the carboxylate group of the resulting phthalamate ion (13). In the Gabriel-Colman rearrangement, the nucleophile may be either the alkoxide ion (6b) or the carbanion formed by removal of a proton from the α-carbon (14). The carbonyl carbon atom which the nucleophile attacks becomes the carbon atom at position 4 of the resulting derivative of 1(2*H*)-isoquinolone.

When there is a substituent on the benzene ring of the phthalimide moiety, the nucleophile may be expected to attack the carbonyl group at the position on the ring having the lower electron density. The attack should therefore occur on the carbonyl *ortho* or *para* to an electron-attracting group, or *meta* to an electron-donating group. This expectation has been confirmed in most cases for which the product has been unequivocally identified (15). Thus, the Gabriel-Colman rearrangement of ethyl 4-ethoxyphthalimidoacetate in the presence of ethanolic sodium ethoxide gives the expected 6-ethoxy-4-hydroxy-3-carbethoxy-1(2*H*)-isoquinolone; in the presence of sodium methoxide, 6-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VIII) is obtained (16). The Hofmann rearrangement of 4-hydroxyphthalimide gives 5-hydroxyanthranilic acid, which could have been formed only by way of intermediate formation of the 5-hydroxyphthalamate ion (17). The results of the Hofmann rearrangements of the methoxyphthalamides are especially indicative of the susceptibility of the carbonyl *meta* to the methoxyl group to attack by base. On treatment with two moles of sodium hypochlorite for each mole of the methoxyphthalamide, 3-methoxyphthalamide gave only 8-methoxy-2, 4(1*H*, 3*H*)-quinazolinedione, and 4-methoxyphthalamide gave only 6-methoxy-2,4(1*H*,3*H*)-quinazolinedione (18). We can, therefore, with some certainty assign structure VII, 8-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone, to the Gabriel-Colman product from IIb, and structure VIII, 6-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone, to the product obtained from IVb. The 3-methoxyphthalimides must yield the 3-methoxyphthalamate ions (XIII) in aqueous base, and 5-methoxyphthalamate ions (XIV) are obtained by saponification of the 4-methoxyphthalimides. Finally, the saponification of I must give XV, and III must give XVII.

The ultraviolet absorption spectra of the basic solutions of the methoxyphthalimidoacetic acids and their esters show the hypsochromic shifts, from the spectra of the alcoholic solutions, that usually accompany saponification of the imide ring (5,19). These shifts probably result from excitation-energy increases occurring when the quinoid-stabilizing effect of the imide ring is lost. On the other hand, the hydroxyphthalimidoacetic acids show bathochromic shifts in basic solution. These shifts are readily explained by the fact that the hydroxyphthalamate ions, XV and XVII, are also phenoxide ions, which will have comparatively low energies of excitation to the quinoid structures XVI and XVIII.

EXPERIMENTAL (20)

3-Methoxyphthalic Acid.

To a solution of 3.64 g. (0.02 mole) of 3-hydroxyphthalic acid (21) and 3.0 g. of sodium hydroxide in 40 ml. of water was added 7.56 g. of dimethyl sulfate and 20 ml. of 20% sodium hydroxide. The mixture was refluxed with stirring for one hour, cooled, acidified to *p*H 3 with 10% hydrochloric acid, and continuously extracted with 500 ml. of ether for 24 hours. The ether extract was concentrated to an oil. A solution of 5 g. of sodium hydroxide in 25 ml. of water was added, and the mixture was heated on a steam cone for two hours. Acidification to *p*H 3 with 10% hydrochloric acid gave 2.1 g. (54%) of 3-methoxyphthalic acid, m.p. 169-173°; reported (22) m.p. 173-174°.

4-Methoxyphthalic Acid.

To a solution of 9.1 g. (0.05 mole) of 4-hydroxyphthalic acid (23) and 6 g. of sodium hydroxide in 20 ml. of water was added dropwise 6.3 g. of dimethyl sulfate. Then 5 ml. of 20% sodium hydroxide was added, and the mixture was refluxed for 30 minutes. The solution was acidified to *p*H 4 with concentrated hydrochloric acid and cooled. The resulting precipitate was dissolved in 100 ml. of hot water. The

solution was acidified with concentrated hydrochloric acid to *p*H 1, heated two hours on a steam cone, and refrigerated for two days, giving 7.2 g. (73%) of 4-methoxyphthalic acid, m.p. 160-165°; reported (23) m.p. 170°.

Hydroxy- and Methoxyphthalimidoacetic Acids (I, IIa, III, and IVa). General Procedure.

Equimolar portions of glycine and the phthalic acid were ground in a mortar, then placed in one-necked flasks with magnetic stirrer slugs. Five milliliters of nitrobenzene was added for each gram of the phthalic acid in each mixture. The mixtures were heated under reflux with stirring for one hour. The hot mixtures were filtered through heated funnels. The filtrates were cooled to room temperature and filtered. The lumpy precipitates were broken up, washed with 5 ml. of cold benzene for each gram of phthalic acid used, dried in a vacuum oven at 100° for 24 hours, and recrystallized from water. The yields, melting points, and microanalytical data for the products are summarized in Table III.

Methyl Methoxyphthalimidoacetates (IIb and IVb). General Procedure.

Solutions of IIa and IVa in absolute methanol, containing 5 ml. of methanol for each gram of acid, were placed in one-liter, three-necked flasks equipped with reflux condensers and stirring bars. Anhydrous hydrogen chloride gas was passed through these solutions for 20-30 minutes with stirring. The solutions were then chilled in an ice-salt bath and to each was added 10 ml. of saturated sodium bicarbonate solution for each gram of IIa or IVa, followed by addition of enough solid sodium bicarbonate to raise the *p*H to 8. The mixtures were filtered and the precipitated esters were washed on the filter with ice water until the washings were neutral. The esters were recrystallized from methanol, giving a 66% yield of methyl 3-methoxyphthalimidoacetate (IIb), m.p. 147-149°, and a 77% yield of methyl 4-methoxyphthalimidoacetate (IVb), m.p. 145-146°. Both products were white powders.

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found for IIb: C, 57.50; H, 4.57; N, 5.53. Found for IVb: C, 57.89; H, 4.54; N, 5.59.

4-Hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VI) (24).

To a solution of 1.6 g. of sodium in 40 ml. of absolute methanol in a 250 ml. pressure flask was added 7.2 g. (0.033 mole) of methyl phthalimidoacetate (V) (7) and 40 ml. of absolute methanol. The flask was sealed and placed in an oil bath which had been preheated to 120°, and was maintained at 120-125° for three hours. The flask was cooled to room temperature and opened. The bright-green contents were mixed with 200 ml. of water, forming a dark-green solution, and 0.1 *N* of hydrochloric acid was added slowly until the color had turned pinkish gray and no more precipitate formed. The mixture was filtered, and the precipitate was washed with 300 ml. of hot water, then recrystallized from 600 ml. of methanol, giving 75-81% yields of 4-hydroxy-3-methoxy-1(2*H*)-isoquinolone (VI), fine, rose-pink needles, m.p. 222-223°; reported (6a) m.p. 221-222°.

8-Methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VII).

A solution of 0.5 g. of sodium in 10 ml. of absolute methanol was added to 2.0 g. (0.008 mole) of IIb in 10 ml. of absolute methanol in a 250 ml. pressure flask. The flask was sealed and heated in an oil bath at 105° for three hours. The flask was cooled and opened, and the dark, greenish-brown contents were mixed with 50 ml. of water, forming a dark-brown solution. This solution was acidified to *p*H 5 with 5% hydrochloric acid, which gave a deep-red color. The solution was warmed at 50° for two hours, during which precipitation of small, shiny, beige flakes slowly occurred. The mixture was cooled and filtered. The precipitate was washed with a few milliliters of cold water, then dried at 100° and 127 mm. for 24 hours, giving 0.2 g. (10%) of 8-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VII), m.p. 187-189°.

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.76; H, 4.71; N, 5.59.

6-Methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VIII).

A solution of 0.4 g. of sodium in 10 ml. of absolute methanol was added to 1.8 g. (0.007 mole) of IVb in 10 ml. of absolute methanol in a 250 ml. pressure flask. The flask was sealed and heated in an oil bath at 105° for three hours. The flask was cooled and opened, and the gelatinous, dark-green mass was dissolved in 50 ml. of water, forming a dark-green solution. To this solution was slowly added 10% hydrochloric acid until precipitation ceased and the solution had a pale-pink color. The mixture was filtered and the precipitate was recrystallized from methanol and dried for 24 hours at 100° and 127 mm., giving 1.6 g. (89%) of 6-methoxy-4-hydroxy-3-carbomethoxy-1(2*H*)-isoquinolone (VIII), pale-pink powder, m.p. 242-245° to form a red liquid; reported (16) m.p. 248°.

Ultraviolet Absorption Spectra.

The ultraviolet absorption spectra were determined with a Cary Model 15 recording spectrophotometer, using 1 cm. cylindrical cells and concentrations of 10^{-5} to 10^{-2} mole per liter. The acidic and basic solutions were prepared by diluting 10^{-2} molar stock solutions in 95% ethanol with 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide.

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(2) The authors gratefully acknowledge the financial support of this work by The Robert A. Welch Foundation, through Research Grant M-101.

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