Cyclic Imides. VII. Carboxyphthalimidoacetic Acids (1,2)

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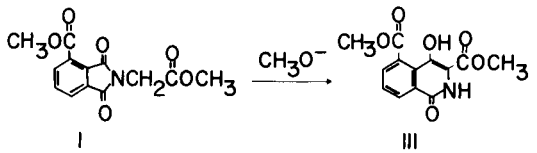
Previous papers in this series (4) have dealt with the syntheses and absorption spectra of nitro- and aminophthalimido acids (4b, g), hydroxy- and methoxyphthalimido acids (4d), and halogenated phthalimido acids (4f), and with the action of bases on these compounds and their esters (4a-f). We now report an extension of these studies to the carboxyphthalimidoacetic acids.

The carboxyphthaloylation of glycine was accomplished using the benzenetricarboxylic acids or their anhydrides in the phthaloylation method described earlier (4b,d). The ultraviolet absorption spectra of the carboxyphthalimidoacetic acids (Table I) were similar to the spectrum of phthalimidoacetic acid (4b,c). The peak in the vicinity of 240 mμ was, however, absent from the spectrum of 3-carboxyphthalimidoacetic acid. This suppression of the 240-mμ band has been observed in the spectra of other 3-substituted phthalimides (4b,d), in which this band usually appears as a shoulder. Since this suppression occurs with both electron-attracting and electron-donating groups in the 3-position, its cause is probably steric rather than electronic. Dissolving the carboxyphthalimidoacetic acids in basic solutions produced the hypsochromic shift and weakening of the maxima which are characteristic of phthalimides in basic solution, and which have been attributed to saponfication of the imide ring (4 b-d).

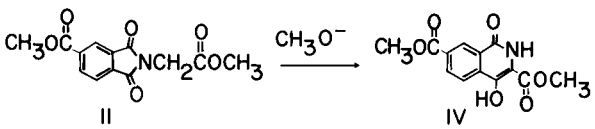
Esterification of the carboxyphthalimidoacetic acids by methanol gave methyl 3-carbomethoxyphthalimidoacetate (I) and methyl 4-carbomethoxyphthalimidoacetate (II). The absorption spectra of these esters (Table I) closely resembled those of the acids from which they were derived. The 240-mμ band was also missing from the spectrum of the 3-carbomethoxy ester. The esters showed the base-induced hypsochromic shift. The maxima of the basic solutions of the esters showed a time-related drift toward the maxima of the acids in basic solution. Such a time-related change in the spectrum has not been observed for other phthalimides. It probably derives from a slow saponification of the ester group on the ring.

The Gabriel-Colman rearrangements of I and II in hot, concentrated methanolic sodium methoxide solution proceeded nromally to form bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolones. These products resembled 3-carbomethoxy-4-hydroxy-1-2*H*-isoquinolone, the Gabriel-Colman product from methyl phthalimidoacetate (4a,5), in their extremely low solubilities, instability in basic solution, and especially in their ultraviolet absorption spectra in alcoholic and basic solutions (Table I). The extremely low solubilities of these products prevented accurate measurement of the regions of their spectra having molar absorbances less than 1000, and all spectra in acid solutions. Dissolving these compounds in basic solution produced a bathochromic shift, attributable to formation of an enolate ion. The basic solutions produced red precipitates within an hour after their preparation, and the spectral data for these solutions, although obtained as rapidly as possible, must therefore be considered approximate.

Although the spectral data are sufficient to identify these Gabriel-Colman products as derivatives of 3-carbomethoxy-4-hydroxy-1-2*H*-isoquinolone, the insolubility and instability of these compounds frustrated further structural studies. The rearrangement product from I may, however, be tentatively identified as 3,5-bis-(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (III), and the product from II as 3,7-bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (IV). The basis for these tentative assignments is the view that nucleophilic attack on substituted phthalimides should occur at the carbonyl group at the position of lower electron density (6). By either of the mechanisms proposed for the Gabriel-Colman rearrangement (6,7) this direction of attack will result in rearrangement of the α-carbon to the less electron-rich carbonyl. Thus, in a case where there is an electron-attracting group, such as the carbomethoxy group, on the



I III



II IV

TABLE I

Ultraviolet Absorption Spectra

Compound	In Methanol		In Dilute HCl		In Dilute NaOH	
	λ max, mμ	log ε max	λ max, mμ	log ε max	λ max, mμ	log ε max
Phthalimidoacetic Acid (a)	239.5 (b)	4.22	240	4.10	---	---
	292.5 (b)	3.38	297	3.48	269	3.04
3-Carboxyphthalimidoacetic Acid	289	3.03	289	2.97	275	2.90
Methyl 3-Carbomethoxyphthalimidoacetate (I)	287	3.10	295	3.13	277 (c)	2.92 (c)
4-Carboxyphthalimidoacetic Acid	244 (d)	4.41	244.5 (d)	4.11	245 (d)	4.00
	298	3.47	303	3.50	278 (d)	3.20
Methyl 4-Carbomethoxyphthalimidoacetate (II)	244 (d)	4.33	243.5	4.13	246 (c,d)	2.99 (c)
	298	3.42	300	3.47	280 (c,d)	3.20 (c)
3-Carbomethoxy-4-hydroxy-1-2*H*-isoquinolone (e)	272 (b)	3.71	270	3.69	---	---
	335 (b)	4.10	335	4.13	365	4.11
	340 (b)	4.11	340	4.11		
3,5-Bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (III)	272	3.69	(f)	---	---	---
	345	4.10	(f)	---	375 (c)	4.04 (c)
3,7-Bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (IV)	277.5	3.75	(f)	---	---	---
	353	3.94	(f)	---	375 (c)	4.00 (c)

(a) Reference 4b. (b) In 95% ethanol. (c) Approximate value. (d) Shoulder. (e) Reference 4a. (f) Insoluble.

ring, rearrangement should occur to the carbonyl *ortho* or *para* to this substituent. This orientation of a Gabriel-Colman rearrangement has been confirmed in the cases of the pyridinedicarboximidoacetic esters (8). A related example of this orienting effect by an electron-attracting group is found in the formation of *N*-phenyl-6-nitrophthalamic acid by saponification of *N*-phenyl-3-nitrophthalimide (9).

EXPERIMENTAL (10)

Carboxyphthalimidoacetic Acids.

Mixtures of 0.1 mole each of glycine (7.5 g.) and either hemimellitic acid (21 g.) or trimellitic anhydride (11) (19.2 g.) were condensed in 100 ml. of hot (170-175°) nitrobenzene, following the phthaloylation method of Caswell and Atkinson (4b). Crude yields were 91-100%. The products were thrice recrystallized by dissolving them in 100-200 ml. of boiling water, filtering the hot solutions through 1-2 g. activated charcoal, and chilling, to give 3-carboxyphthalimidoacetic acid, m.p. 208-208.5°, and 4-carboxyphthalimidoacetic acid, m.p. 272-273°.

Anal. Calcd. for $C_{11}H_7NO_6$: C, 53.02; H, 2.83; N, 5.62. Found for 3-carboxyphthalimidoacetic acid: C, 53.38; H, 2.90; N, 5.45. Found for 4-carboxyphthalimidoacetic acid: C, 52.95; H, 2.96; N, 5.61.

Methyl Carbomethoxyphthalimidoacetates (I and II).

The carboxyphthalimidoacetic acids were esterified by passing gaseous hydrogen chloride through stirred solutions of 2.49 g. (0.01 mole) of the acids in 50 ml. of methanol for 30-60 minutes. To the chilled mixtures were added 150 ml. of saturated sodium bicarbonate solution and enough solid sodium bicarbonate to raise the *p*H to 8. The esters precipitated in yields of 76-84%. Two recrystallizations from methanol gave methyl 3-carbomethoxyphthalimidoacetate (I), m.p. 109-110°, and methyl 4-carbomethoxyphthalimidoacetate (II), m.p. 125-126°.

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found for I: C, 56.22; H, 4.20; N, 5.44. Found for II: C, 56.66; H, 4.20; N, 5.33.

Gabriel-Colman Rearrangement of Methyl Carbomethoxyphthalimidoacetates.

In dry, 200-ml. pressure flasks were placed 20 ml. of absolute methanol, 2.8 g. (0.01 mole) of I or II, and 10-20 ml. of absolute methanol in which 0.46 g. (0.02 mole) of sodium had been dissolved. The sealed flasks were placed in an oil bath at 110-120° for three hours. After cooling, the flasks were opened, and the gelatinous contents of each flask were mixed with 50 ml. of water and enough 0.1 *N* hydrochloric acid to reduce the *p*H to 5. The resulting gray-green suspensions were heated to boiling and filtered. The precipitates were washed with 100 ml. of hot water. The products were 67% 3,5-bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (III), light-tan powder, m.p. 194-196° with decomposition; and 52-72% 3,7-bis(carbomethoxy)-4-hydroxy-1-2*H*-isoquinolone (IV), greenish-white powder, m.p. 246-248° with decomposition.

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found for III: C, 56.38; H, 4.15; N, 5.13. Found for IV: C, 56.11; H, 4.00; N, 5.05.

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} *M*, or 10^{-6} to 10^{-3} *M* for III and IV. The acidic and basic solutions were prepared by dilution of methanolic stock solutions with 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide. The *p*H values of the acidic and basic solutions were approximately 1 and 12, respectively. The spectra are summarized in Table I.

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(1) Part IV of a series dealing with Derivatives of 1-2*H*-Isoquinolone. For Part III, see reference 4e.

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(3) Abstracted in part from the M. S. Theses of R. A. H. (now Mrs. R. A. Burks) and D. C. Y. (now Mrs. N. y. Lee).

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(11) A research sample of trimellitic anhydride was generously donated by the Amoco Chemicals Corp.

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