Evidence for $n_C \rightarrow \pi^*$ Transition in N-Malonic Esters of Heterocyclic Compounds[1]

John C. Nnadi and Shih Yi Wang[2,3]

Contribution from the Department of Biochemistry,
School of Hygiene and Public Health, The Johns Hopkins University,
Baltimore, Maryland 21205. *Received November 20, 1969*

Abstract: In aqueous solutions, the uv spectra of N-malonic ester-substituted uracils, phthalimide, pyridone, and aniline have been determined from pH 1 to 12.8. For the uracils, carbanion formation at higher pH is accompanied by a two- to sixfold hyperchromicity. But for phthalimide, pyridone, and aniline, carbanion formation leads to a new intense peak at the 240–260-nm region in addition to those observed for the undissociated molecules. In acetonitrile, the uv spectra of the sodium salts of these compounds show the same hyperchromicity and the appearance of new peaks when compared with those of the initial compounds. The effects are rationalized in terms of an electronic transition from the nonbonding p orbital of carbanions (n_C) to the π^* orbital of the aromatic system, overlapped on normal uracil spectra in the case of uracil derivatives but completely distinct (although in the same region as for uracil derivatives) for phthalimido-, pyridono- and anilinomalonic esters. Using these effects, the dissociation constants (pK_a) of these compounds studied have been obtained.

For our study of the effects of substitution, pH, and media on the rates of photohydration of uracils,[4–6] diethyl uracil-1-malonate (I) and didiethyl uracil-1,3-dimalonate (II) were synthesized (among many other uracil derivatives). A surprising observation was that these two compounds showed a 20% hyperchromicity in pH 7 buffered solution as compared to that in H_2O (pH 6.5). This finding not only pointed out the necessity for exact pH control for reproducible absorbancy measurements but also prompted us to undertake a detailed study in order to understand the nature of these effects. The results of this study are the subject of this paper.

Results and Discussion

In aqueous solutions, the uv spectra of I from pH 1 to 6.5 are the same (Figure 1a), with λ_{max} 259 nm. From pH 6.5 to 10, the ϵ_{max} increases 2.5-fold with a hypsochromic or blue shift of the λ_{max} to 255 nm. Although there is no further increase in ϵ_{max} at pH >11, a 5-nm bathochromic or red shift in λ_{max} is noted. The observed pH dependent absorbancy increase seems to suggest that ionization of the tertiary proton of the malonate moiety may occur and may initiate interactions responsible for the hyperchromicity. This proton is triply activated by a pyrimidine ring and two carboethoxy groups, and may be ionized at pH >6.5. At pH >10, the ionization[7] of N_3H might be responsible for the red shift.

To test these possibilities, the uv spectra of II were determined under similar conditions. If ionization of protons is associated with the hyperchromic effect, then additional spectral changes would be expected for II having two such tertiary protons. As seen in Figure 1b, the expected 2.5-fold hyperchromicity similar to that of I is observed; however, a second distinct yet overlapping hyperchromicity is clearly evident from those spectra at pH >10. This results in an additional 2.5fold, or a total of sixfold, absorbancy increase for spectra at pH 12.5. On the other hand, no red shift at pH >10 was observed since this compound has substituents on both N_1 and N_3 and the ionization of N_3H is not possible.

Further support came from the study of the uv spectra of diethyl uracil-1-dicarboethyoxymonocarbomethoxymethide-3-malonate (III, Figure 1c). In the absence of the tertiary proton on the N_1-methide group, very little hyperchromicity was observed up to pH 7, further suggesting that carbanion formation at N_1 is probably associated with the hyperchromic effect at pH >6.5. At higher pH, a gradual increase in absorbancy up to sixfold at pH 12.5 was observed, indicating that carbanion formation at N_3 is possibly responsible.

To strengthen the case, the uv spectra of related compounds were studied. For diethyl phthalimidomalonate (IV) (Figure 2), a new absorption peak at 254 nm, in addition to those observed at low pH, appears at pH 7 and increases from pH 7 to 10. However at pH >10, the spectra of IV show no maxima in the uv region. The appearance of the new intense peak for IV led us to suspect that the effects observed for I, II, and III could be due to an accidental coincidence of the absorption of a malonate and a pyrimidine moiety (see below, structure VII). But at tenfold, the concentration used above, no increases in absorption in the 220–290-nm region were observed at basic pH for diethyl acetamidomalonate or diethyl ethylmalonate, thus ruling out the above suspicion.

For N^1-(diethyl malonate)-2-pyridone (V), a new absorption peak at 257 nm began to appear at pH 8 and reached a maximal level at pH 12.5 (Figure 3). The absorbancy maximum at 290 nm, due to the pyridone moiety, was unchanged from pH 1 to 12. This observation strongly argues against the possibility that the observed hyperchromicity is due to the enhancement of the $n \rightarrow \pi^*$ or the $\pi \rightarrow \pi^*$ transition of the pyridone moiety. Rather, it clearly indicates a distinct

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[3] Author to whom all correspondence should be addressed.

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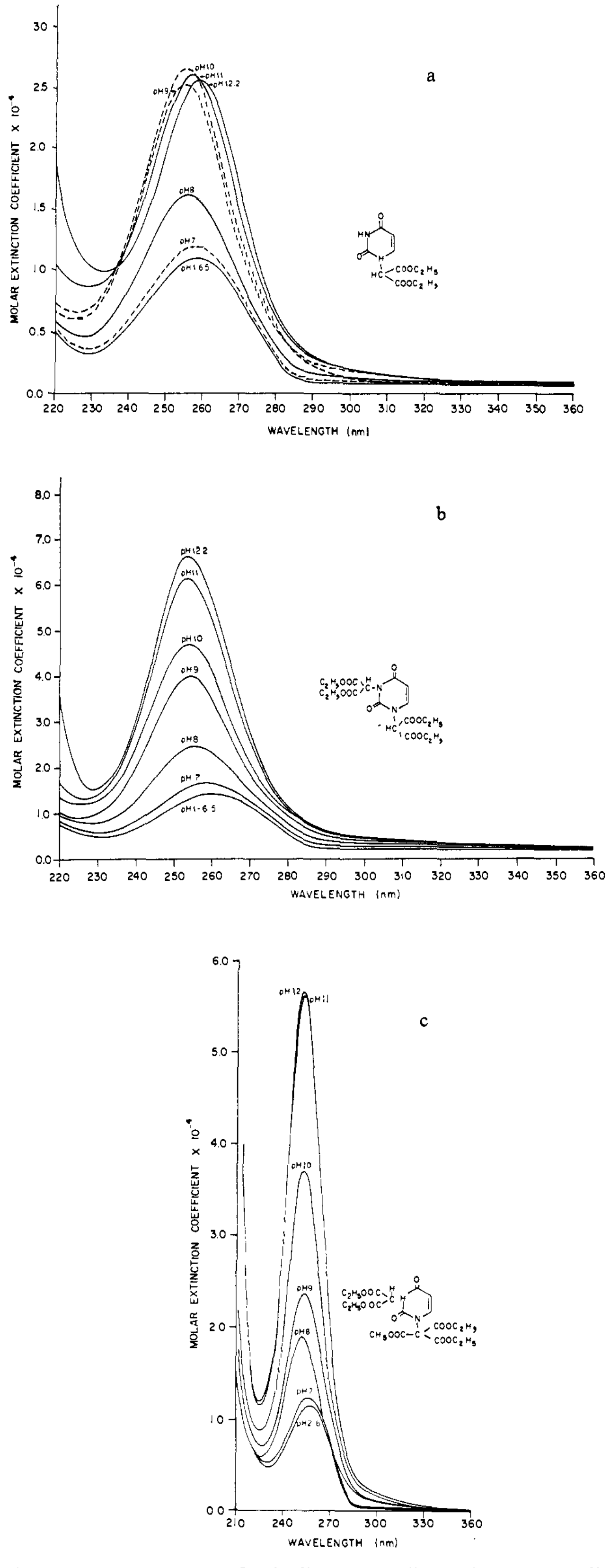

Figure 1. Uv spectra of (a) diethyl uracil-1-malonate, (b) didiethyl uracil-1,3-dimalonate, and (c) diethyl uracil-1-dicarboethoxymonocarbomethoxymethide-3-malonate in aqueous solutions.

and newly recognized transition involving the promotion of nonbonding electrons of the carbanion to the π^* orbital of the aromatic moieties. (No such effects were observed for the alkylmalonic esters.)

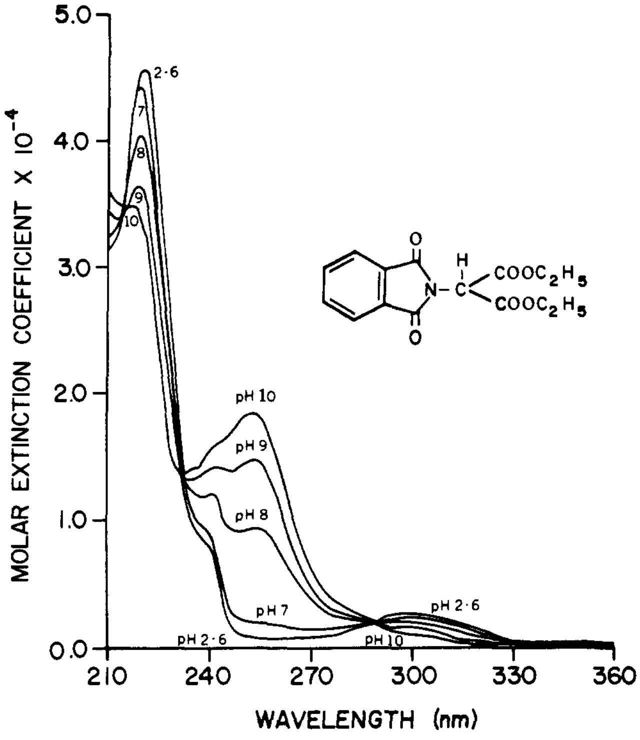

Figure 2. Uv spectra of diethyl phthalimidomalonate in aqueous solution.

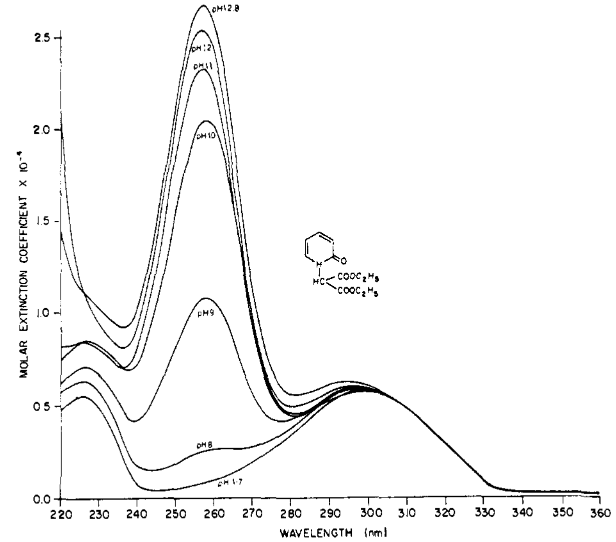

Figure 3. Uv spectra of N^1-(diethyl malonate)-2-pyridone in aqueous solution.

The general relevancy of this effect was shown by our preliminary study with malonic esters substituted on the heteroatoms N, S, and O, as well as C of several aromatic compounds.[8] One example, diethyl N-methylanilinomalonate (VI), displayed a new intense peak at 238 nm (Figure 4). This peak is comparable to those observed in the compounds discussed above and is characteristic of this new type of transition.

Using unbuffered NaOH solutions (1 m*M*), hyperchromic and hypsochromic effects can be reversed by acidification to pH <6.5. Interestingly, in D_2O (pH 6.9), a 20% hyperchromicity and a 2-nm blue

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[8] Unpublished results.

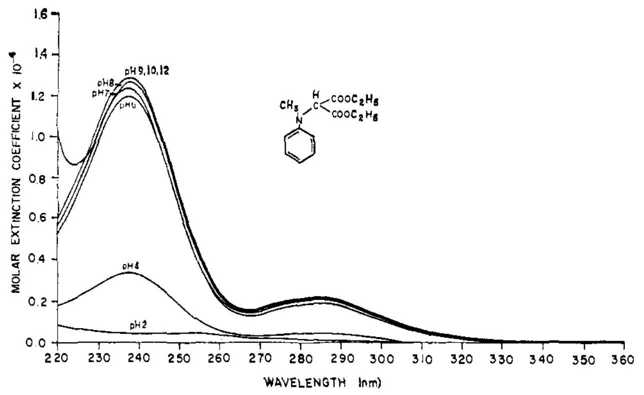


Figure 4. Uv spectra of diethyl N-methylanilinomalonate in aqueous solution.

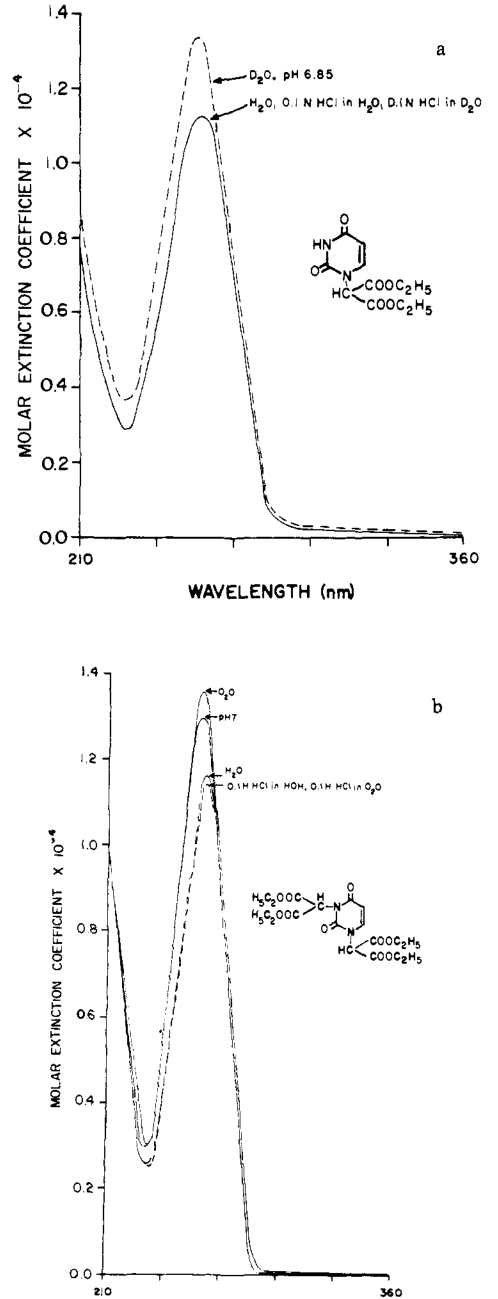


Figure 5. Effects of D_2O on the uv spectra of (a) diethyl uracil-1-malonate and (b) didiethyl uracil-1,3-dimalonate.

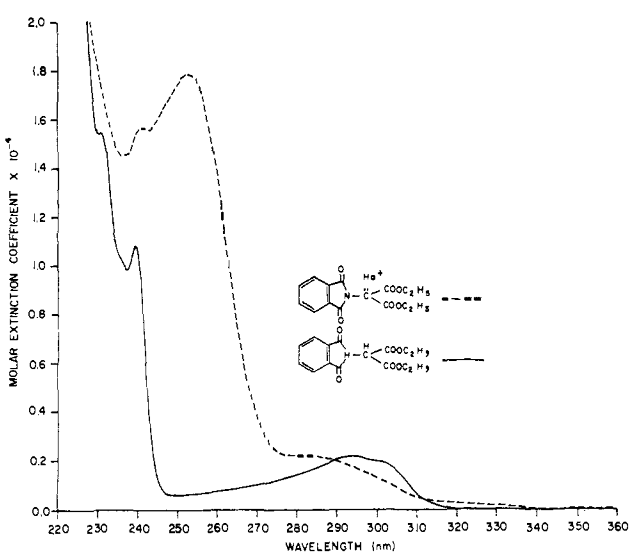


Figure 6. Uv spectra of monosodium salt of phthalimidomalonate in acetonitrile.

shift were observed (Figure 5a, 5b), but these effects were no longer exhibited in cases where the D_2O solutions were 0.1 *N* in DCl or HCl. As indicated in Figures 1 and 5, similar hyperchromic changes occurred in D_2O and pH 7 buffered solutions. In all the above experiments, uracil-1-malonic acids behaved exactly like their esters. These observations would tend to rule out the possibility that the observed spectral changes might be due to irreversible reactions occurring during spectral determination. Most probably they imply that reversible dissociations of protons are directly associated with these changes.

If, indeed, the carbanion formation at high pH is responsible for the hyperchromicity or the additional intense peaks observed in the uv spectra of these malonic esters, their sodium salts would be expected to have spectra in aprotic solvents similar to those observed for the parent esters at high pH. In acetonitrile, only qualitative comparison could be made with the sodium salts of pyrimidine malonic esters (I, II, III) because of their limited solubilities. The spectra of these salts showed both hyperchromicity and hypsochromicity conforming to those of the parent esters at high pH. However, quantitative comparison was possible with IV. As seen in Figure 6, the spectrum of the sodium salt of phthalimidomalonic ester exhibited the same new and intense peak as its parent compound at alkaline pH.

The pK_a's of these malonic esters were determined (Table I) according to the method of Stenstrom and

Table I. pK_a Values of Substituted Malonic Ester Protons and Uv Absorbancy Maxima of Their Corresponding Carbanions

Substituted diethyl malonates	pK_a	λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$
N-Methylanilino- (VI)	4.82	238	13.0
Uracil-1- (I)	8.32	253	26.5
Uracil-1,3- (II)	8.32, 10.39	253	66.3
Uracil-1-dicarboethoxy-monomethoxymethide-3- (III)	10.27	253	56.5
2-Pyridone (V)	9.10	257	26.6
Phthalimido- (IV)	9.17	254	18.5

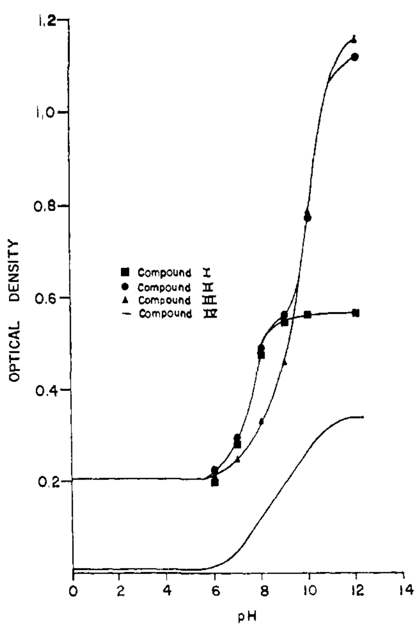


Figure 7. Plots of the absorbancy maxima of several malonate derivatives *vs.* pH.

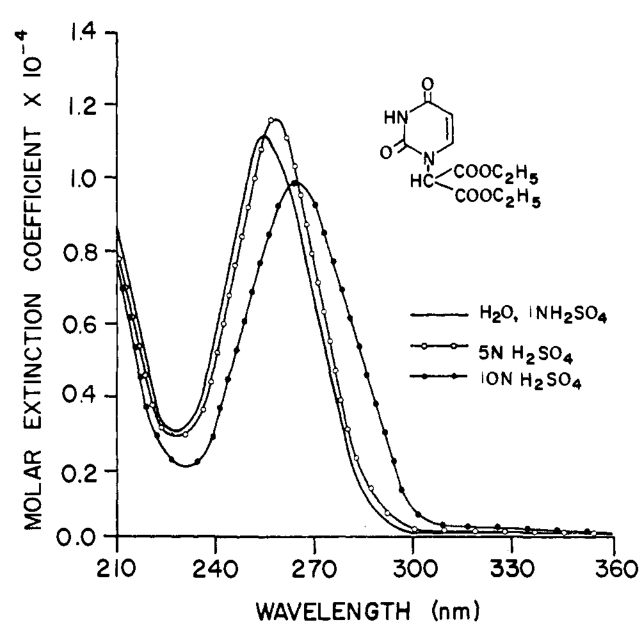
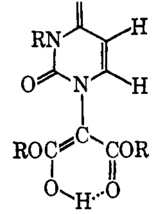


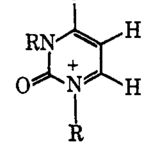
Figure 8. Uv spectra of diethyl uracil-1-malonate in strong acidic media.

Goldsmith.[9] The pK_a of anilinomalonic ester (VI) is the lowest of all the compounds studied and falls in the range observed for aniline derivatives. It may be noted that the pK_a of the proton of N_1-malonic ester (I) is lower than that of N_3- (II, III), a fact which is consistent with the reactivities of the ground-state molecules.[10] Similar pK_a values should be expected for the malonic ester proton of the two imides, phthalimide (IV) and N_3- of uracil (II or III), if no additional effects are operating from the aromatic moieties. The lower pK_a value for IV than for II or III indicates that the benzoyl group exerts a stronger electron withdrawal effect than does the pyrimidine ring. The proton of pyridonomalonic ester (V) had a pK_a of 9.10 which is in accord with that of the pyrimidine malonic esters (Figure 7).

If, in solution, the malonic ester moiety exists in the enol form with the six-membered H-bonded structure (VII), the malonic ester protons should have much lower pK_a than those given in Table I and the positions of the chemical shifts in the nmr spectra should be much further downfield than the signals at δ 6.28 and 6.19, respectively, for protons of N_1- and N_3-malonate groups determining in $(CD_3)_2SO$. In highly acidic media, the pyrimidine ring is protonated, leading to the structure of type (VIII)[10] which absorbs at a longer wavelength with reduced intensity. These characteristics were observed for I at 5 *N* and 10 *N* H_2SO_4 (Figure 8). Thus, neither the structure of VII nor that of VIII contributes significantly to the ground state of these compounds in the pH 1–14 region.

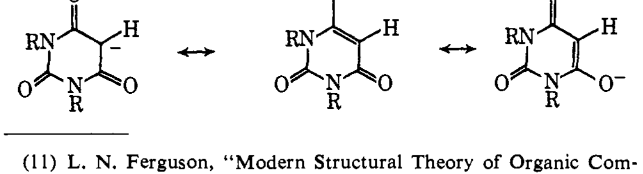


VII



VIII

Resonance and inductive interactions alter the energies of the ground and excited states of molecules and consequently contribute to observed uv spectra.[11,12] Since the uv spectra of the undissociated malonic esters are the same as those of other alkyl pyrimidines, the effects of these interactions are presumably insignificant. Upon ionization, however, the carbanions, capable of delocalizing the electron pairs, are expected to approach sp^2–p or trigonal hybridization.[13] Such a configuration maximizes the overlap between the p orbital of the carbanion and those of the pyrimidine ring, allowing the charge-transfer transition.[14] Such a transition results in absorbancy of high intensity which is presumably manifested as the observed hyperchromicity. These observations are similar to those reported for charge resonance transition of pyrimidines[10] and triphenylmethanes.[15] However, unlike these instances, the spectral shifts observed were minimal. In the case of barbituric acid,[16] the π-electron system of the pyrimidine ring is restored by charge delocalization in the ionized form. Consequently this form has the spectrum of substituted uracil but with increased intensity.



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In summary, it is suggested that the spectral changes observed for the anionic forms of these compounds might be due to transitions involving the excitation of nonbonding p electrons on carbanions (n_C) to π^*-orbitals of the aromatic rings. If this newly identified transition, $n_C \rightarrow \pi^*$, does actually occur, then its excitation energy would be expected to depend on the relative stability of the carbanions and the extent of the π system.

Experimental Section

General Procedures. Melting points are uncorrected and were taken on a Fisher-Jones apparatus. Ultraviolet and infrared (KBr pellets) absorption spectra were recorded on a Cary recording spectrophotometer, Model 14, and a Perkin-Elmer Infrared spectrophotometer, Model 21, respectively. Nuclear magnetic resonance spectra were obtained on a Varian HR-60 spectrometer using tetramethylsilane as an internal standard (TMS = 0.0 ppm). Aliquots (0.10–0.50 ml) of 10 m*M* ethanol solutions of various compounds were diluted to 10.0 ml with various buffers for uv spectra (see Table I). Elemental analyses were performed by Mr. J. Walter of The Johns Hopkins University and at Mobil Research and Development Corp., Paulsboro, N. J.

Diethyl Uracil-1-malonate (I). Pulverized potassium salt of uracil (U-1-K, 5 g) was allowed to boil (air condenser) for 30 min, while being stirred, in 100 ml of dimethylformamide (DMF). It was cooled to 100° and 5 ml of bromodiethylmalonate (BDEM) was slowly introduced. A vigorous reaction set in and the mixture turned dark brown. After being kept at 100–110° for 60 min, the solvent was removed by distillation under reduced pressure and nitrogen. The residue was extracted several times with absolute ethanol resulting in a 70% yield of the crude product. It was recrystallized from absolute ethanol to a constant melting point 118–120°.

Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.88; H, 5.18; N, 10.37. Found: C, 48.81; H, 5.09; N, 10.37; mol wt 270 (mass spectrum).

Didiethyl Uracil-1,3-dimalonate (II). Pulverized U-1-K (5 g) was triturated with BDEM (5 ml) in an erlenmeyer flask. After heating at 100° for 60 min, the resulting brown paste was extracted several times with 20-ml portions of benzene–chloroform. The combined extracts were allowed to evaporate until dry and the residue was redissolved in 10 ml of absolute ethanol. It was placed in a refrigerator overnight and a total of 2.5 g (>20%) of pale greenish crystals, mp 90–93°, was collected. Recrystallization from absolute ethanol gave 2.1 g of colorless crystals, mp 95°.

Anal. Calcd for $C_{18}H_{24}N_2O_{10}$: C, 50.46; H, 5.60; N, 6.54. Found: C, 50.72; H, 5.63; N, 6.27; mol wt 428 (mass spectrum).

Monosodium Salt of I. To a solution of 0.23 g of Na in 10 ml of absolute ethanol at 60°, 2.7 g of I was added, and the resulting solution was allowed to stand for *ca.* 2 min. Upon cooling in an ice bath, crystalline material separated and was collected. After washing twice with 10 ml of anhydrous ether, it was desiccated to constant weight of 2.7 g (*ca.* 90%).

Anal. Calcd for $C_{11}H_{13}N_2O_6Na$: C, 45.25; H, 4.50; N, 9.59. Found: C, 45.20; H, 4.60; N, 9.80.

Diethyl Uracil-1-dicarboethoxymonomethoxymethide-3-malonate (III). The above prepared Na salt (4.2 g) was mixed with 5 ml of methyl chloroformate and was refluxed for 3 hr under anhydrous conditions. After removing the excess methyl chloroformate, the light brown residue weighed 4.8 g. It was extracted three times with 10 ml of absolute ethanol and the combined extracts were concentrated to 5 ml. A pastelike precipitate (4.5 g, 85%) was obtained upon the addition of 10 ml of petroleum ether (bp 30–60°). This process was repeated several times. Finally, it was crystallized from absolute ethanol–petroleum ether (3:1) to a material with constant mp at 77–78°.

Anal. Calcd for $C_{20}H_{26}N_2O_{12}$: C, 49.45; H, 5.35; N, 5.75. Found: C, 49.60; H, 5.26; N, 5.94; mol wt, *m/e* 486 (mass spectrum).

Disodium Salt of II. To a solution of 0.23 g of Na in 10 ml of absolute ethanol at 60°, 2.3 g of II was added. The resulting solution was heated to 70° for *ca.* 2 min and then cooled in an ice bath. Colorless crystalline material formed and was collected. After washing twice with 10 ml of anhydrous ether, it was desiccated to a constant weight of 2.5 g (*ca.* 95%).

Anal. Calcd for $C_{18}H_{22}N_2O_{10}Na_2$: C, 45.80; H, 4.65; N, 5.93. Found: C, 45.65; H, 4.73; N, 5.71.

Diethyl Phthalimidomalonate (IV). Samples were obtained from Chemical Procurement Lab. Inc. They were recrystallized to constant mp 73–74° (lit.[17] 74°).

Monosodium Salt of IV. This was prepared by a method similar to the procedure described above. From 3.0 g of IV, 3.1 g of the salt was obtained.

Anal. Calcd for $C_{15}H_{14}NO_6Na$: C, 54.90; H, 4.28; N, 4.28. Found: C, 54.82; H, 4.35; N, 4.50.

N^1-Diethyl Malonate-2-pyridone (V). A solution of 9.5 g of 2-pyridone was allowed to react with 2.35 g of Na dissolved in 100 ml of absolute ethanol as described above. The salt obtained weighed 11.0 g. BDEM (12.0 g) was used to react with 5.9 g of the salt. When these were mixed, a vigorous reaction set in. After heating at 60–80° for 1 hr, 50 ml of absolute ethanol was introduced. The precipitate, mainly NaBr, was filtered and was washed with 25 ml of hot absolute ethanol. The combined washings and filtrate were concentrated to 10 ml. Upon addition of 10 ml of petroleum ether, 6.0 g (48%) of the product was precipitated. It was recrystallized from absolute ethanol–petroleum ether, mp 78–79°.

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.75; H, 5.98; N, 5.67; mol wt, *m/e* 253 (mass spectrum).

Diethyl N-Methylanilinomalonate (VI). N-Methylaniline (10.7 g) was used for the preparation according to the method for V. The compound was recrystallized from absolute ethanol–petroleum ether with mp 105–106°.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.60; H, 7.03; N, 5.40; mol wt, *m/e* 265 (mass spectrum).

Acknowledgment. The authors wish to express thanks to Dr. A. W. Peter of Mobil Research for very helpful discussions and the determinations of the mass spectra.

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