# The Structure of Some Methyl and Benzyl Malonate Derivatives of Pyrimidine



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Reaction of 2,4,6-trichloropyrimidine with sodium dibenzylmalonate in *p*-dioxane gave 4,6-dichloro-2-(dibenzylmalonyl)pyrimidine, while reaction of 2,4,6-trichloropyrimidine with sodium dimethylmalonate yielded both 4,6-dichloro-2-(dimethylmalonyl)pyrimidine and 2,2-bis-(4,6-dichloropyrimidin-2-yl)dimethylmalonate. Structural studies using nmr, ir and uv spectroscopy indicate that for the former two compounds in basic solvent, an equilibrium exists between the keto forms and resonance-stabilized enolate ions.

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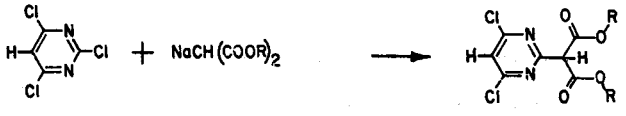
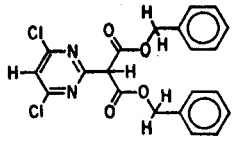
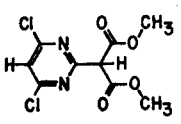
Unlike previous results showing the reaction of one, two or all three chlorine atoms of 2,4,6-trichlorotriazine with sodiomalonic ester in dioxane (1), reactions of 2,4,6-trichloropyrimidine with sodiomalonic ester at the boiling point of *p*-dioxane yielded only monosubstituted product. The 2-position of the pyrimidine ring is the reactive site, and the other two chlorines remain unreactive:



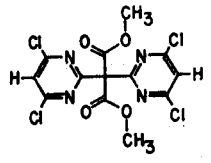
The nmr, ir and uv spectra of dichloropyrimidine monosubstituted with dibenzylmalonate or dimethylmalonate indicate the appropriate structures in non-polar solvents to be 4,6-dichloro-2-(dibenzylmalonyl)pyrimidine (I) and 4,6-dichloro-2-(dimethylmalonyl)pyrimidine (II). In addition to product II, when 2,4,6-trichloropyrimidine was added to sodium dimethylmalonate in dioxane, 2,2-bis(4,6-dichloropyrimidin-2-yl)dimethylmalonate (III) was also obtained. Product III can arise by the reaction of the anion of product II with another molecule of 2,4,6-trichloropyrimidine.



I.



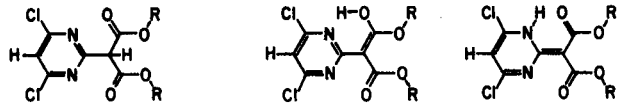
II.



III.

Figure I

Like the tautomerism of malonate derivatives of 2,4,6-trichlorotriazine (2), the malonate derivatives of pyrimidine I and II have the possibility of existing in several tautomeric forms. Shown below are the keto *A*, enol *B*, and enamine *C* forms. Compound III lacks the acidic malonate proton of compounds I and II, and therefore cannot exhibit tautomerism.



A B C

Infrared absorptions of compounds I, II and III are given in Table I. The same spectral bands were obtained for the pure compounds in nujol mulls, potassium bromide pellets or non-polar carbon tetrachloride and chloroform solvents. The spectra are all consistent with the keto structures shown in Figure I.

The ultraviolet spectra of the three compounds taken in chloroform and dimethylsulfoxide were quite revealing. As shown in Table II, compound III exhibited identical spectra in chloroform or DMSO as expected. In contrast, compounds I and II exhibited an extra band at 333-334 nm in DMSO solution in addition to the 263-265 nm band attributed to the keto tautomer present in chloroform or other low polarity solvent. This 333-334 nm band can be accentuated at the expense of the 263-265 nm band by adding a small amount of sodium hydroxide; or conversely, the 333-334 nm band can be depressed with a corresponding gain in the 263-265 nm band by adding a small amount of hydrochloric acid. Figure II shows the rise of the 334 nm band for compound I as the percentage of DMSO is increased in mixed chloroform/DMSO solutions. An isobestic point is evident at 277 nm indicating the wavelength at which the equilibrating species have equal absorptivities. From the measured absorptivities of the 263 nm band in chloroform ($\epsilon$ = 5500) and the 334 nm

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band in DMSO ($\epsilon$ = 7400), the approximate percent of keto form remaining in 100% DMSO is 64%.

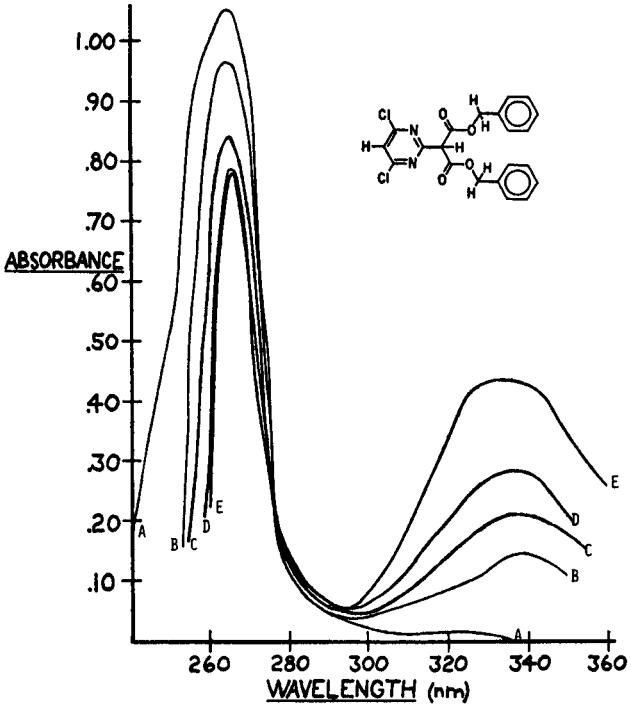


Figure II. Ultraviolet spectra of Compound I in $CHCl_3$/DMSO mixtures. Concentrations are $1.9 \times 10^{-4}$ M. A: 100% $CHCl_3$, B: 75% $CHCl_3$, C: 50% $CHCl_3$, D: 25% $CHCl_3$, E: 0% $CHCl_3$.

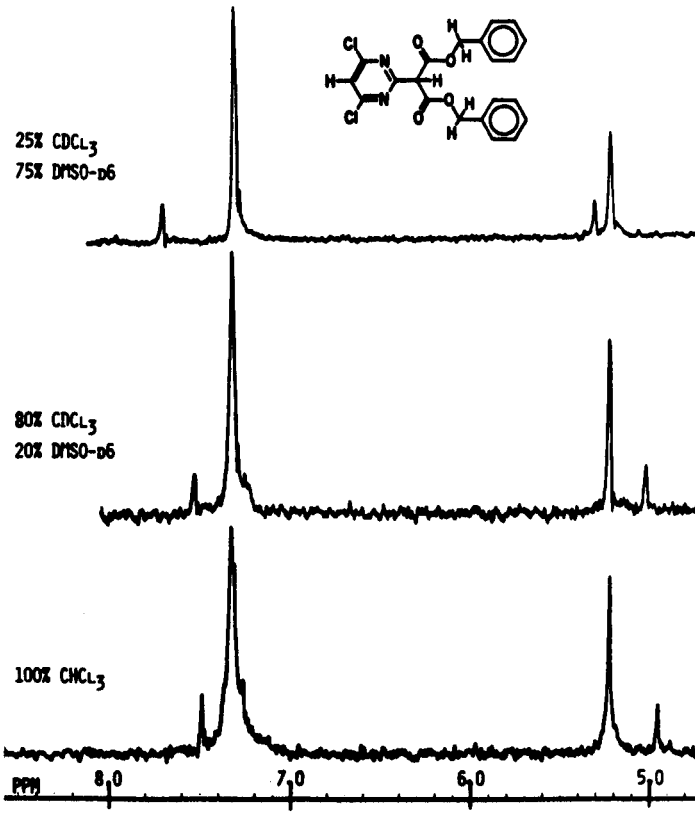


Figure III. 100 MHz pmr spectra of Compound I in $CDCl_3$ and $CDCl_3$/DMSO-$d_6$ mixtures.

Table I

Infrared Absorptions for Compounds I, II and III

| Compound | Absorptions ($cm^{-1}$) |
|---|---|
| I | 1170-1310, 1540, 1570, 1755, 3145-3150 |
| II | 1170-1310, 1530, 1560, 1750, 3145 |
| III | 1185-1300, 1525, 1545, 1750, 3145 |

Table II

Ultraviolet Spectral Data in Chloroform and Dimethylsulfoxide

| Compound | Solvent | $\lambda$ max (nm) |
|---|---|---|
| I | Chloroform | 263 |
| | DMSO | 263, 334 |
| II | Chloroform | 265 |
| | DMSO | 265, 333 |
| III | Chloroform | 265 |
| | DMSO | 265 |

Table III

Pmr Chemical Shifts ($\delta$) and Integrated Areas (all peaks are singlets)

| Compound | Solvent | Shifts and Areas |
|---|---|---|
| I | Chloroform-*d* | 4.93 (1H), 5.21 (4H), 7.32 (10H), 7.48 (1H) |
| | DMSO-$d_6$ | 5.25 (4H), 5.56 (1H), 7.35 (10H), 7.91 (1H) |
| II | Chloroform-*d* | 3.83 (6H), 4.89 (1H), 7.61 (1H) |
| | DMSO-$d_6$ | 3.75 (6H), 5.40 (1H), 7.92 (1H) |
| III | Chloroform-*d* | 3.89 (6H), 7.97 (2H) |
| | DMSO-$d_6$ | 3.86 (6H), 7.99 (2H) |

The nmr results also show the effect of proton equilibria in DMSO or other basic solvent as shown in Table III. The chemical shifts of both the 2-malonate proton [$\delta$ (chloroform) = 4.93 for compound I, and 4.89 for compound II] and the pyrimidine ring proton [$\delta$ (chloroform) = 7.48 for compound I, and 7.61 for compound II] are very sensitive to the amount of DMSO present in chloroform/DMSO-$d_6$ solutions, while the benzyl protons of compound I and the methyl protons of compound II are not. Figure III il-

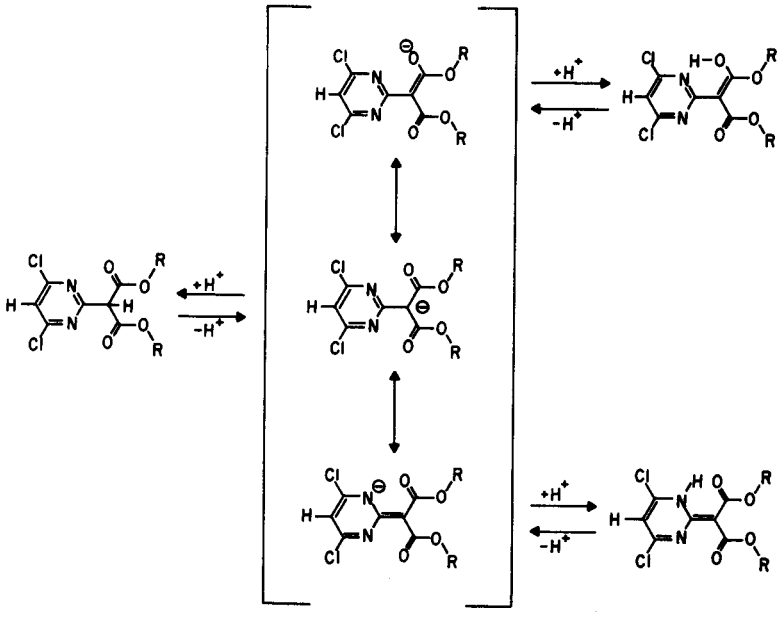

Figure IV

lustrates the downfield shift of both the 2-malonate proton and the pyrimidine ring proton for compound I as the percent of DMSO is increased. The magnitude of this downfield shift can be increased by adding a small amount of base to the solution, and this downfield shift caused by adding base can be reversed by adding a small amount of acid.

Thus, both the uv and nmr results for compounds I and II in DMSO or other basic solvent are consistent with an equilibrium between the keto form (Figure IV, left) and the resonance stabilized enolate ions (Figure IV, center). The removal of a proton results in a uv shift to the red as expected for the conjugated enolate ions. Also, the nmr shift of the pyrimidine ring proton to lower field would be expected since the increased pi electron circulation in the ring of the ions would cause greater deshielding of this proton. The existence of a neutral enol or enamine form (Figure IV, right) was not detected. The hydrogen bonded enol OH or enamine NH proton should have a proton chemical shift in the 8-11 ppm range (3), but only an averaged proton shift of 5-6 ppm was observed for the 2-malonate proton in DMSO-$d_6$ solutions at the probe temperature employed in this study (28°).

## EXPERIMENTAL

The nmr spectra were recorded on a Varian HA-100 spectrometer using TMS as an internal reference in all cases. The deuteriochloroform and DMSO-$d_6$ were Stohler Isotope Chemical spectrometric grade and were used as received. The ir spectra were recorded on a Perkin-Elmer 735B recording spectrophotometer. The solvents for the solution ir and uv spectra were all dried and distilled reagent grade. The uv spectra were recorded on a scanning Beckman DB-G spectrophotometer with a chart recorder. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Michigan Technological University Microanalytical Laboratory.

4,6-Dichloro-2-(dibenzylmalonyl)pyrimidine (I).

Sodium dibenzylmalonate was prepared by adding 8.8 g. (0.039 mole) of dibenzylmalonate to 1 g. of sodium metal in *p*-dioxane near the boiling point. Then 7.1 g. (0.039 mole) of 2,4,6-trichloropyrimidine was added as rapidly as possible maintaining a temperature of 85-90°. This temperature was maintained for two hours before the solution was cooled and filtered. Evaporation of excess solvent resulted in a viscous orange oil which was dissolved in diethyl ether and extracted with water. The ether solutions were extracted with *p*H 10 ammonium hydroxide solutions repeatedly until hplc showed a marked decrease of the product in the ether layer. The ammonium hydroxide extracts were then acidified with acetic acid and the product was extracted back into an ether solution. Pale yellow crystals were obtained from both ether and ethanol solutions at about −20°. At room temperature these crystals slowly converted to an oil. About 3 g. of purified 4,6-dichloro-2-(dibenzylmalonyl)-pyrimidine was obtained by recrystallization from ethanol.

*Anal.* Calcd. for $C_{21}H_{16}Cl_2N_2O_4$: C, 58.48; H, 3.74; N, 6.50. Found: C, 58.62; H, 3.59; N, 6.41.

4,6-Dichloro-2-(dimethylmalonyl)pyrimidine (II) and 2,2-bis(4,6-Dichloropyrimidin-2-yl)dimethylmalonate (III).

Sodium dimethylmalonate was prepared by adding 7.3 g. (0.055 mole) of dimethylmalonate to 1.4 g. of sodium metal in *p*-dioxane near the boiling point. 10.0 g. (0.055 mole) of 2,4,6-trichloropyrimidine was added maintaining a temperature of 50-65°. After two hours the reaction was stopped and some of the dioxane solution was evaporated at room temperature with forced air and the cool mixture filtered. The remainder of the dioxane solution was evaporated to an oil and chromatographed in portions on a silica gel column. The most active sites on the silica were deactivated by eluting the column with acetic acid in dichloromethane, then the reaction product was eluted with heptane/carbon tetrachloride/dichloromethane. Compound III was eluted first followed by compound II. Compound III was a white crystalline material (m.p. 141-142°) and compound II was a viscous yellow oil at room temperature.

About 4 g. of pure compound II oil was obtained and about 5 g. of pure white crystals of compound III was obtained by recrystallization from methanol. All attempts to replace more than one chlorine of trichloropyrimidine by reacting it with excess sodium dimethylmalonate were unsuccessful.

*Anal.* (II) Calcd. for $C_9H_8Cl_2N_2O_4$: C, 38.73; H, 2.89; N, 10.04. Found: C, 38.71; H, 2.76; N, 10.41.

*Anal.* (III) Calcd. for $C_{13}H_8Cl_4N_4O_4$: C, 36.65; H, 1.89; N, 13.15. Found: C, 36.76; H, 1.84; N, 13.25.

Acknowledgment.

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