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THE REACTION OF PHOSGENE WITH 2,6-DIMETHYL-4H-PYRAN-4-ONE

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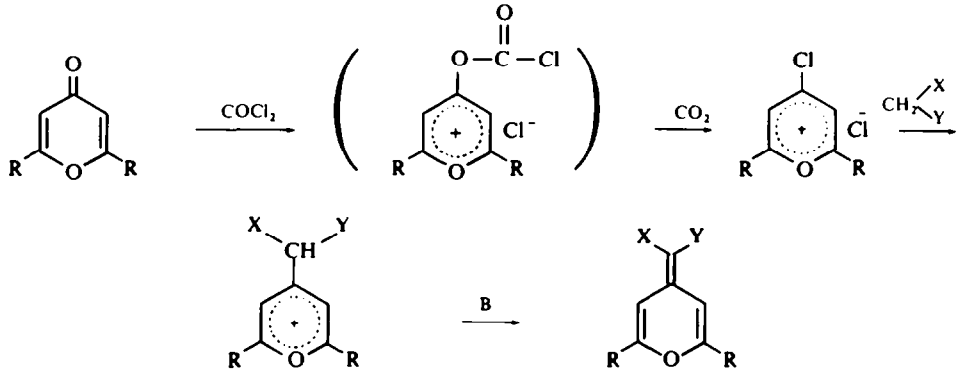
Abstract—Phosgene reacts with 2,6-dimethyl-4H-pyran-4-one at room temperature to yield 2,6-bis(4'-chloro-2',6'-dimethylphenyl)-4H-pyran-4-one (I), and 2-(4'-chloro-2',6'-dimethylphenyl)-6-methyl-4H-pyran-4-one (II). The structure assignment and the mechanism of formation is discussed. Some 4H-ylidene derivatives of I and II were prepared.

INTRODUCTION

OF THE SEVERAL METHODS available for the condensation of γ-pyrones with active methylene compounds one of choice consists of a two-step procedure in which γ-pyrones are first treated with phosgene yielding 4-chloropyrylium chlorides as intermediates, which, without isolation, are allowed to react in the second step with an active methylene compound in the presence of a suitable base (Scheme 1).[1,2]



X,Y = electron withdrawing groups: B = base

SCHEME 1

The presence of 4-chloropyrylium chlorides as intermediates in this reaction could be demonstrated in the case of γ-pyrone and 2,6-diphenyl-γ-pyrone, where it was possible, after carrying out the first step, to isolate and characterize these intermediates in the form of their hexachloroantimonates or perchlorates.[1] Not so, however, in the case of 2,6-dimethyl-γ-pyrone which could be condensed with active methylene compounds, by this method, in high yields,[1,2] but attempts to isolate its 4-chloropyrylium salts, when treated only with phosgene failed.[1,2]

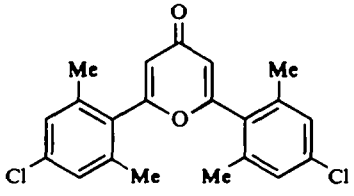
We believe that we are now able to explain this failure, as we have found that in the absence of active methylene compounds, the reaction between 2,6-dimethyl-γ-pyrone

and phosgene proceed further than the formation of 4-chloro-2,6-dimethylpyrylium chloride, and products derived from a formal condensation of two and three molecules of this intermediate are obtained.

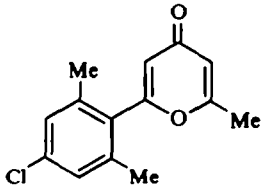
In the present paper we report the identification and characterization of two of these products.

RESULTS AND DISCUSSION

In a typical reaction between 2,6-dimethyl-γ-pyrone and phosgene, one equivalent of phosgene (20% solution in toluene) was treated with one equivalent of γ-pyrone for 24 hr at room temperature. Removal of solvent in vacuum left a dark solid which was subjected to a column chromatography, using EtOAc petrol–ether as eluents. A white solid, m.p. 222°, was obtained from the 20:80 v/v EtOAc petrol ether fraction and was identified as 2,6-bis (4′-chloro-2′,6′-dimethylphenyl)-4H-pyran-4-one (I).



I



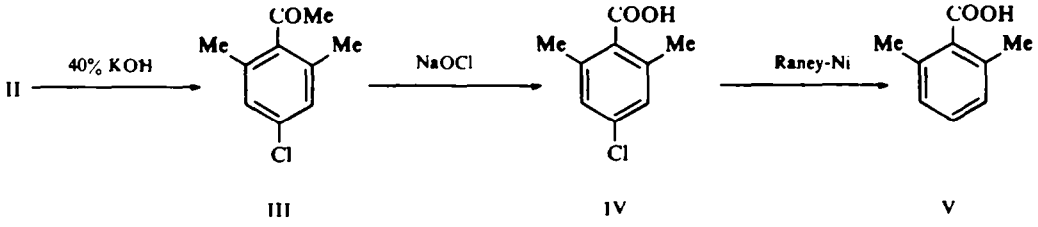
II

The structure assignment of I was based on the following evidence: Analytical data were in good agreement with a $C_{21}H_{18}Cl_2O_2$ formulation. The mass spectrum showed parent peaks at *m/e* 372, 374 and 376 (MW calc: 373·29) with relative intensities accountable for, on the basis of naturally occurring chlorine isotopes. The fragmentation pattern observed was in accord with the pathway suggested for fragmentations of molecules containing γ-pyrone nucleus.[3] The IR spectrum (KBr) exhibited strong absorptions at 1655 cm^{-1} and 1625 cm^{-1} which are characteristic to γ-pyrone systems.[4] The UV spectrum showed a maximum at $\lambda = 253$ nm ($\varepsilon = 22{,}600$). The NMR spectrum ($CDCl_3$) exhibited three singlets at δ 2·25 (Me's), 6·34 (pyrone protons) and 7·10 (aromatic protons) with area ratios of 6:1:2.

A second compound was obtained from the 40:60 v/v EtOAc petrol ether fraction, as a white solid, m.p. 105°. This compound was identified as 2-(4′-chloro-2′,6′-dimethylphenyl)-6-methyl-4H-pyran-4-one (II) on the basis of the following evidence: Analytical data were in good agreement with a $C_{14}H_{13}ClO_2$ formulation. The mass spectrum showed parent peaks at *m/e* 248 and 250 (MW calc. 248·71), with expected relative intensities. The fragmentation pattern observed was in accord with the pathway suggested for fragmentations of γ-pyrones[3]; IR (KBr) 1660 cm^{-1}, 1620 cm^{-1}; UV (MeOH), λ_{max} 250 nm ($\varepsilon = 19{,}200$). The NMR spectrum of II exhibited, quite unexpectedly, four singlets, at δ 2·23 (aromatic Me protons), 2·30 (pyrone Me protons), 6·20 (pyrone protons) and 7·11 (aromatic protons) with area ratios of 6:3:2:2. If the structure assignment for II is correct, the signal at 6·20, which had half intensity width

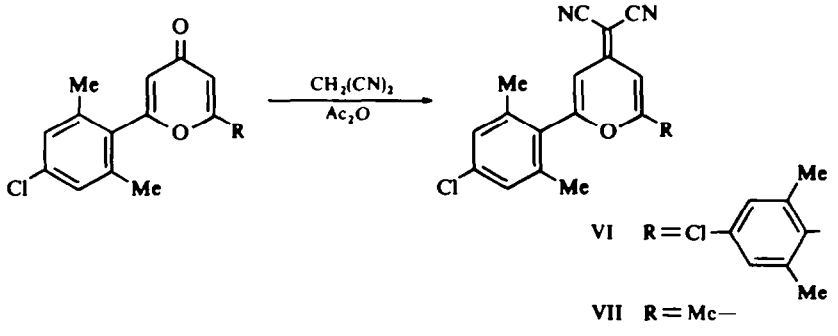
of 1·7 Hz, assigned to the two magnetically non equivalent protons on the pyrone ring, cannot be a "true singlet", but rather a coincidence of two signals, having the same chemical shift. Yet, this chemical shift equivalence persisted when the spectrum was taken in other solvents such as acetone-d_6, DMSO-d_6 or in $CDCl_3$ in the presence of $Eu(DPM)_3$. Separation of signals was, finally, achieved when the spectrum was taken in C_6F_6. The splitting pattern now observed fully supported the proposed structure. Thus the proton *cis* to the Ph group was coupled only by the proton *cis* to the Me group and appeared as a doublet at $\delta = 5{\cdot}97$ ($J = 2{\cdot}2$ Hz). The proton *cis* to the Me group was a doublet at $\delta = 5{\cdot}90$ ($J = 2{\cdot}2$ Hz), each part being a 1:3:3:1—quartet ($J = 0{\cdot}7$ Hz), due to allylic coupling with the Me protons.

Additional support to the proposed structure for II was obtained by chemical degradation (Scheme 2).

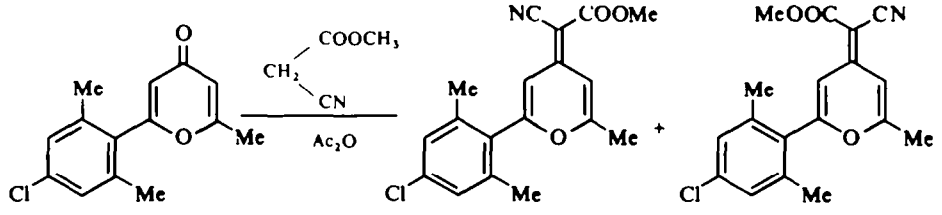


SCHEME 2

On heating II with 40% KOH for 24 hr, 4-chloro-2,6-dimethylacetophenone (III) was obtained, which on treatment with NaOCl afforded 4-chloro-2,6-dimethylbenzoic acid (IV). Dechlorination of IV with Raney Nickel in aqueous NaOH yielded the known 2,6-dimethylbenzoic acid (V). Compound I was much more resistant to base degradation and could be recovered almost quantitatively after 48 hr of reflux in 40% KOH. Nevertheless, we could detect traces of III as a degradation product of I (IR, TLC).



The structure of I and II being now established, we, next, turned our attention to the preparation of some of their derivatives. Both compounds did not yield the corresponding γ-pyridones when treated with methylamine in boiling EtOH. This is expected in the case of I where the two bulky substituents in positions 2 and 6 hinder any nucleophilic attack on these carbons. As a result, I is stable even in hot alkali. In compound II nucleophilic attack can take place on the less hindered 6-position, but apparently more drastic conditions are needed to affect reaction with amines. Both compounds did, however, react with active methylene compounds in a similar way to other 2,6-substituted γ-pyrones.[5] Treatment of I or II with malononitrile in boiling Ac_2O gave VI, m.p. 274° and VII, m.p. 180° respectively. Analysis and spectral properties of both compounds were in accord with their proposed structures.



VIII IX

It is noteworthy that the NMR spectrum of VII in $CDCl_3$ was very similar to that of II exhibiting a "singlet" at δ 6·57 for the two magnetically non equivalent protons on the pyrone ring. In C_6F_6 the signals were separated giving rise to the same splitting pattern observed in II. Treatment of II with methyl cyanoacetate in boiling Ac_2O afforded a product m.p. 105–117°, one spot on TLC whose NMR spectrum indicated it to be an approximate 2:1 mixture of two geometrical isomers. Separation of the two isomers was affected by careful recrystallization from EtOAc petrol ether, affording an isomer, m.p. 154°, assigned as VIII and the second one, m.p. 139° assigned as IX.

The structure of the two isomers was easily deduced from their NMR spectra (Fig 1 and 2). Owing to the difference in the anisotropy of the cyano and carbomethoxy groups, the two signals of the protons H_A and H_B of the pyrone ring are separated by *ca.* 1·3 p.p.m. From the splitting pattern observed, it is concluded that H_A is the proton *cis* to the Ph group and H_B is *cis* to the Me group. When comparing the spectra to those of VI and VII it is also evident that the signals at δ 6·70 are those of the protons *cis* to the cyano group, and the more deshielded ones at δ 8·0 are those of the protons *cis* to the carbomethoxy group.

Mechanism

The main feature of this reaction is the formation of a benzene ring *via* a condensation of a 4-chloro-2,6-dimethylpyrylium chloride molecule with the Me group of another molecule. Dimroth and Wolf have reported that under basic conditions pyrylium salts condense with a CH-acidic compound to yield benzene derivatives.[6] We believe

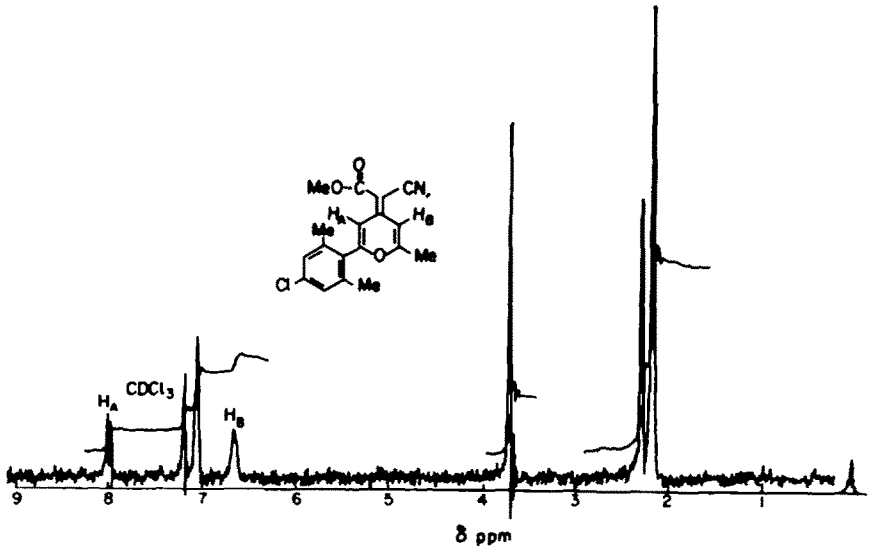


FIG 1. NMR spectrum of IX ($CDCl_3$)

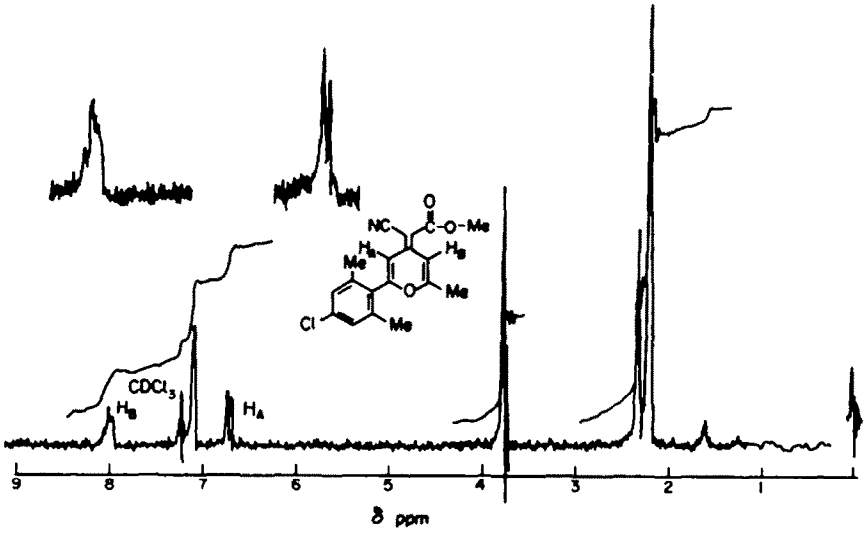
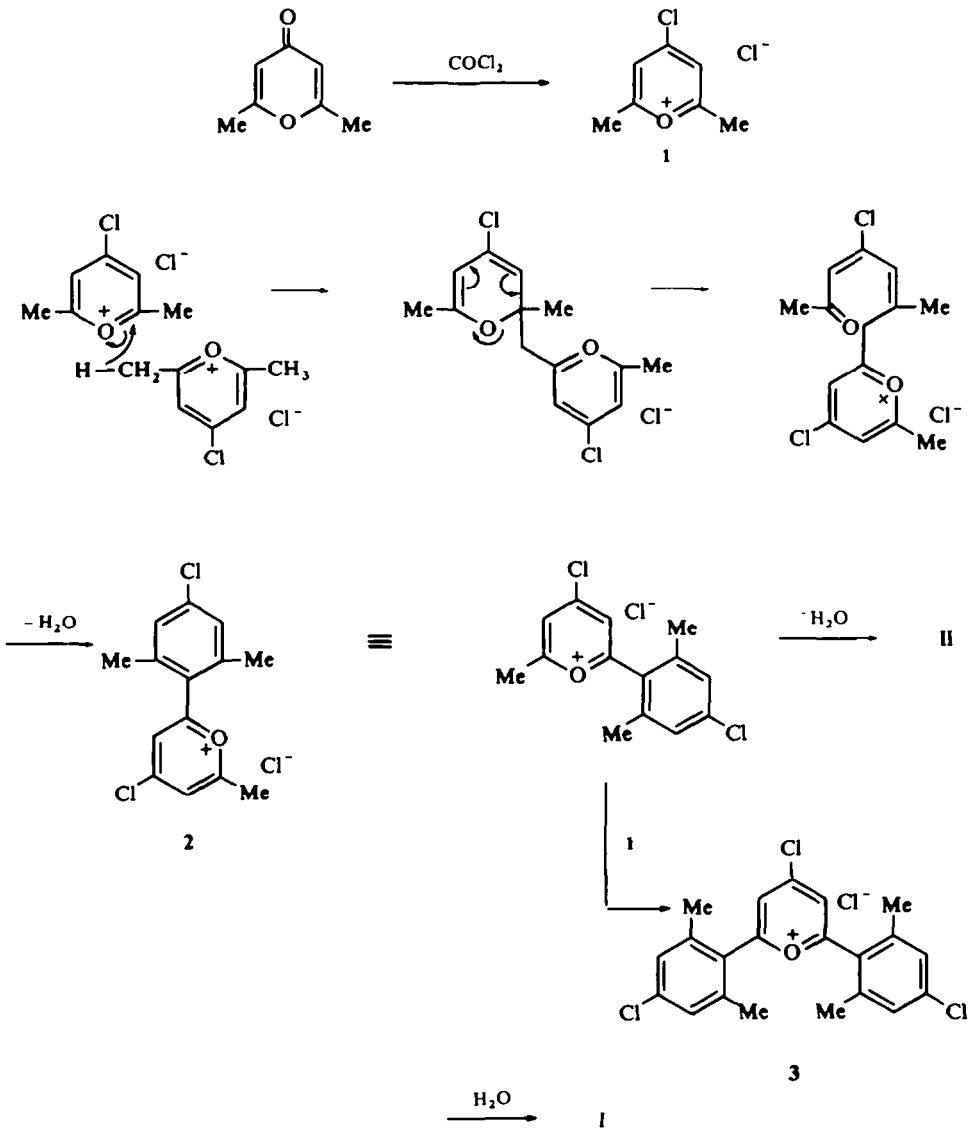


FIG 2. NMR spectrum of VIII ($CDCl_3$)

that this reaction proceeds along a similar path, although under acidic rather than basic conditions, and we propose the following:



The first step, the formation of 4-chloro-2,6 dimethylpyrylium chloride (**1**), is probably the fastest one, as could be judged from the disappearance of free phosgene (IR, the disappearance of 1800 cm^{-1} band), soon after its complete addition. The condensation, therefore, takes place between two molecules of **1** rather than between **1** and a molecule of γ-pyrone.

EXPERIMENTAL

M.ps were determined on a Thomas Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer grating spectrometer model 337. UV spectra were recorded on a Perkin–Elmer 137UV spectrometer. NMR spectra were taken on a Varian HA-100 spectrometer and on a Jeol JNM-C-60HL spectrometer with TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin–Elmer RMU-6 instrument, the samples being introduced directly into the ion source through a vacuum-lock, electron energy 70 eV.

Reaction of 2,6-*dimethyl-γ-pyrone with phosgene.* Phosgene (0·01 mole, 5 ml of 20% solution in toluene) was added dropwise at room temperature, under dry N_2, into a stirred solution of 1·24 g (0·01 mole) of 2,6-dimethyl-γ-pyrone in 30 ml of toluene. Stirring was continued for 24 hr. Removal of the toluene left a dark solid which was subjected to column chromatography on Kieselgel (0·05–0·2 mm) using EtOAc pet. ether as eluents. The 20:80 v/v EtOAc pet. ether fraction contained 0·23 g of I, m.p. 220°. Analytical sample was obtained by sublimation in high vacuum (180°/0·1 mm), m.p. 222°; MS (%) 376, 374, 372 (7, 41, 60, M^+), 344 (10·5), 208 (23·5), 164 (31), 129 (100), 128 (58), 127 (30), 103 (37), 77 (38); (Found: C, 67·59; H, 4·86; Cl, 19·51. $C_{21}H_{18}Cl_2O_2$ requires: C, 67·57; H, 4·86; Cl, 19·00%).

From the 40:60 v/v EtOAc pet. ether fraction 0·35 g of II were obtained, m.p. 105° after sublimation in vacuum (100°/0·1 mm): MS (%) 250, 248 (19·2, 57, M^+), 166 (33), 165 (12), 164 (100), 129 (61), 128 (28), 127 (16), 77 (14); (Found: C, 67·63; H, 5·35; Cl, 14·15. $C_{14}H_{13}ClO_2$ requires: C, 67·61; H, 5·26; Cl, 14·26%).

4-*Chloro*-2,6-*dimethylacetophenone* (III). A solution of 1·24 g (5 mmole) of II in 25 ml of 40% KOH in 60% EtOH was refluxed for 24 hr. 50 ml of water were added, and the product was extracted with ether. Removal of the ether and vacuum distillation afforded 0·69 g (76%) of III, b.p. 136–7°/22 mm; $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; NMR ($CDCl_3$) (δ) 2·22 (6H, s), 2·43 (3H, s), 6·96 (2H, s); MS (%), 184, 182 (10·2, 30·7, M^+), 169 (33), 167 (100), 141 (15), 139 (43·5), 103 (25), 77 (23); (Found: C, 66·08; H, 5·78; Cl, 19·51. $C_{10}H_{11}ClO$ requires: C, 65·76; H, 6·08; Cl, 19·41%).

4-*Chloro*-2,6-*dimethylbenzoic acid* (IV). To a 0·2 g of III in 20 ml of 10% NaOCl solution, few ml of MeOH were added until an homogeneous solution was obtained. The solution was heated at 70–80° for 24 hr with occasional addition of 5 ml portions of NaOCl. The mixture was washed with ether, the aquous layer acidified, yielding 0·16 g (79%) of IV, m.p. 183° after recrystallization from EtOAc pet. ether: ν_{max}^{KBr} 3050–2850 cm^{-1} (broad, OH), 1695 cm^{-1}, 1595 cm^{-1}; NMR ($CDCl_3$) (δ), 2·38 (6H, s), 7·02 (2H, s), 8·60 (1H, broad s); MS (%) 186, 184 (19, 57, M^+), 168 (34), 166 (100), 141 (9·5), 139 (28), 103 (57), 77 (47); (Found: C, 58·50; H, 4·67; Cl, 19·48. $C_9H_9ClO_2$ requires: C, 58·55, H, 4·92; Cl, 19·26%).

2,6-*Dimethylbenzoic acid* (V). A solution of 0·1 g of IV in 15 ml of 5% NaOH containing 0·1 g of Raney Nickel powder was refluxed for 5 hr. Filtration and acidification afforded 0·05 g (61%) of V m.p. 116° (lit. 116°[7]) after recrystallization from EtOAc; MS, M^+ 150; MW calc. 150·18.

Reaction of I *with* KOH. A solution of 0·1 g of I in 25 ml of 40% KOH in 60% EtOH was refluxed for 48 hr and then 100 ml of water added. The solid that separated was dissolved in ether, and the water extracted with ether. Evaporation of the combined ether solutions, and recrystallization from pet. ether afforded 0·9 g (90%) of I. The pet. ether filtrate was evaporated in vacuum. The residue was dissolved in $CHCl_3$. The IR spectrum ($CHCl_3$) exhibited besides absorptions of I a carbonyl absorption at 1690 cm^{-1}. TLC of the residue showed, besides a spot for I, a spot with a R_f similar to that of III.

2,6-*Bis*(4′-*chloro*-2′,6′-*dimethylphenyl*)-4H-*pyran*-4-*ylidenemalononitrile* (VI). A solution of 0·187 g (0·5 mmole) of I and 0·04 g (0·6 mmole) of malononitrile in 7 ml Ac_2O was refluxed for 72 hr. The Ac_2O was removed at low pressure and the residue subjected to column chromatography on Kieselgel (0·05–0·20 mm) employing EtOAc pet. ether as eluents. From 5:95 v/v EtOAc pet. ether fraction 0·05 g (24·4%) of VI were obtained, m.p. 274°, after recrystallization from pet. ether: ν_{max}^{KBr} 2200 cm^{-1}, 2180 cm^{-1}, 1645 cm^{-1}, 1595 cm^{-1}; NMR ($CDCl_3$) (δ), 2·23 (12H, s), 6·70 (2H, s), 7·04 (4H, s); (Found: C, 68·32; H, 4·15; N, 6·47. $C_{24}H_{18}Cl_2N_2O$ requires: C, 68·42; H, 4·30; N, 6·65%).

2-(4′-*Chloro*-2′,6′-*dimethylphenyl*)-6-*methyl*-4H-*pyran*-4-*ylidenemalonitrile* (VII). A solution of 0·2 g (0·8 mmole) of II and 0·06 g (0·9 mmole) of malononitrile in 7 ml of Ac_2O was refluxed for 60 hr. The Ac_2O was removed in vacuum, and the residue subjected to column chromatography on Kieselgel (0·05–0·20 mm) using EtOAc pet. ether as eluents. The 15:85 v/v EtOAc pet. ether fraction contained 0·07 g (29%) of VII, m.p. 180° after recrystallization from EtOAc pet. ether; ν_{max}^{KBr} 2200 cm^{-1}, 2190 cm^{-1} (sh.), 1650 cm^{-1}, 1595 cm^{-1}; NMR ($CDCl_3$) (δ), 2·17 (6H, s), 2·32 (3H, s), 6·57 (2H, s), 7·05 (2H, s), (C_6F_6) (δ) 2·13 (6H, s), 2·33 (3H, s), 6·58 (1H, 2q), 6·67 (1H, d), 6·94 (2H, s); (Found: C, 68·43; H, 4·65; N, 9·24. $C_{17}H_{13}ClN_2O$ requires: C, 68·80; H, 4·41; N, 9·44%).

Methyl 2-(4'-chloro-2'6'-dimethylphenyl)-6-methyl-4H-pyran-4-ylidenecyanoacetate (VIII + IX). A solution of 0·2 g (0·8 mmole) of II and 0·13 g (1·2 mmole) of methyl cyanoacetate in 6 ml Ac_2O was refluxed for 24 hr. The Ac_2O was removed at low pressure, and the residue was subjected to column chromatography on Kieselgel (0·05–0·20 mm) using EtOAc pet. ether as eluents. From the 15:85 v/v EtOAc pet. ether fraction 0·125 g (49%) of a mixture of VIII and IX was obtained, m.p. 105–117°; ν_{max}^{KBr} 2195 cm^{-1}, 1700 cm^{-1}, 1645 cm^{-1}, 1595 cm^{-1}, 1505 cm^{-1}; NMR ($CDCl_3$) (δ), 2·20 (6H, s), 2·32 (3H, s), 3·72, 3·75 (3H, 2s), 6·65 (1H, m), 7·05 (2H, s), 8·00 (1H, m): (Found: C, 65·69; H, 5·12; N, 3·97. $C_{18}H_{16}ClNO_3$ requires: C, 65·50; H, 4·90; N, 4·25%).

The mixture (100 mg) was dissolved in 40 ml of hot 15:85 v/v EtOAc petrol ether. The solution was allowed to cool slowly to room temperature, and left for 2 days, whereupon 50 mg of orange crystals of VIII, m.p. 154°, separated and were collected. The filtrate was kept at 0° for 2 hr, and 15 mg of product, m.p. 121°–127°, separated and were collected. On keeping the filtrate at 0° for 2 days, 30 mg of yellow crystals of IX were obtained, m.p. 139°.

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