# Cycloaddition Reactions of Cycloimmonium Ylides with Triphenylcyclopropene [1]

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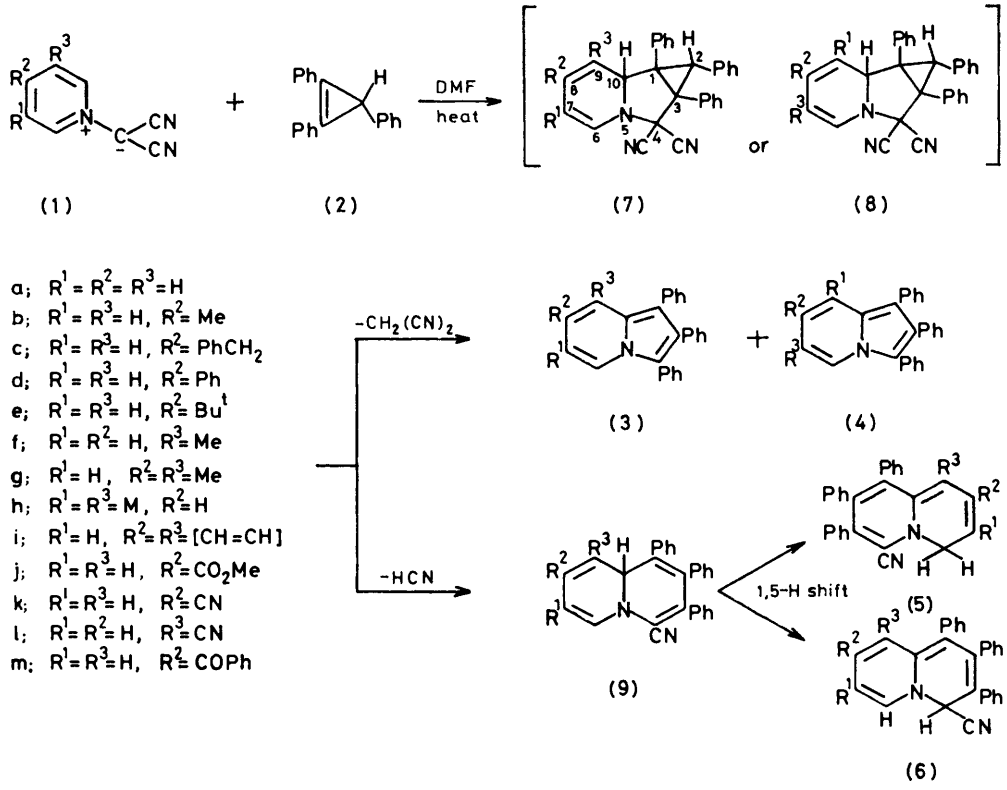
Cycloaddition reactions of 1,2,3-triphenylcyclopropene (TPP) with a variety of substituted pyridinium dicyanomethylides (1) give the corresponding 1,2,3-triphenylindolizines (3) [and (4)], 6-cyano-7,8,9-triphenyl-4*H*-quinolizines (5), 4-cyano-1,2,3-triphenyl-4*H*-quinolizines (6), and/or 1 : 1 adducts (7) [and (8)], depending on the substituents and their positions. The effect of substituents on the course of the reaction is discussed qualitatively. The pyrazinium dicyanomethylide (16) with TPP produces the 7-azaindolizine (19), whereas pyridazinium (17) and phthalazinium (18) dicyanomethylides give the primary adducts (20) and (21), respectively. Reaction of pyridinium bis(alkoxycarbonyl)methylides (22) with TPP gives, however, generally poor or no yield of the indolizines.

ADDITION reactions of substituted cyclopropenes (including cyclopropenones and heterocyclopropenes) to dienes, 1,3-dipoles, and related ylidic compounds can provide a synthetic entry into strained bicyclic systems in which a cyclopropane moiety is incorporated, as well as five-, six-, or seven-membered carbo- or hetero-cyclic systems.[2] The latter are generally formed with ring-opening of the former and/or by extrusion of such components as $H_2$, HX, $CH_2X_2$ (X = CN, $CO_2R$), C=Y (Y = O, S), and heteroaromatics, from the primary intermediates.

This paper deals with the [4 + 2]π cycloaddition–extrusion reaction of disubstituted cycloimmonium ylides with triphenylcyclopropene (TPP), which provides a new route to indolizines and quinolizines; this type of cycloaddition–extrusion reaction has not been well explored and furthermore the dipolarophilic capacity of TPP has been little examined,[3] although its Diels–Alder reactions are well known despite the expected large steric hindrance.[2a]




SCHEME 1

Reaction of pyridinium dicyanomethylide (1a) with TPP (2) in refluxing dimethylformamide (DMF) for 5 h gave two products, one of which had fluorescent character and was proven to be 1,2,3-triphenylindolizine (3a), being identical in all respects with authentic material prepared by the Chichibabin reaction.[4] The

other product was shown to be 6-cyano-7,8,9-triphenyl-4*H*-quinolizine (5a). The $^1$H n.m.r. signal for the protons at position 4 appeared at δ 3.98 as a singlet.* Indeed, a stereomodel of this compound shows that these two protons are at a 90° angle with the 3-proton. The equivalence of the 4-protons in the similar 4*H*-quinolizines has been discussed.[5] The $^{13}$C n.m.r. signal of the 4-carbon of the methyl derivative (5b) appeared at δ 13.5, which became a triplet upon partial proton decoupling.

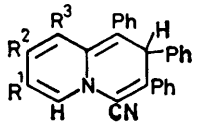
Similarly, 4-substituted pyridinium dicyanomethylides such as the 4-methyl-, 4-benzyl-, and 4-phenylpyridinium ylides (1b—d) underwent a cycloaddition–extrusion reaction to produce the corresponding indolizines (3b—d) and quinolizines (5b—d). From the t-butyl-substituted ylide (1e), the isomeric 4-cyano-1,2,3-triphenyl-4*H*-quinolizines (6e) was obtained as a major product. In all these cases, the formation of the quinolizine was predominant (Table 1).

TABLE 1

Products from reaction of dicyanomethylides (1) with 1,2,3-triphenylcyclopropene (2)

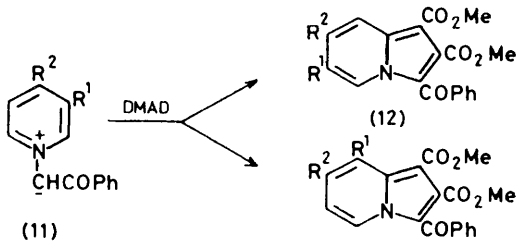
| | Dicyanomethylide | | | | Product and yield (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Reaction | (3) | | | (7) [and |
| | $R^1$ | $R^2$ | $R^3$ | time (h) | +(4) | (5) | (6) | (8)] |
| (1a) | H | H | H | 4 | 25 | 37 | | |
| (1b) | H | Me | H | 5 | 12 | 45 | | |
| (1c) | H | $CH_2Ph$ | H | 5 | 19 | 31 | | |
| (1d) | H | Ph | H | 5 | 18 | 43 | | |
| (1e) | H | Bu$^t$ | H | 6 | 15 | 22 | 34 | |
| (1f) | H | H | Me | 4 | 35 (9 : 1) | | 13 | |
| (1g) | H | Me | Me | 4 | 41 (3 : 1) | | 24 | |
| (1h) | Me | H | Me | 10 | 55 | | | |
| (1i) | H | $-[CH=CH]_2-$ | | 5 | 44 | | | |
| (1j) | H | $CO_2Me$ | H | 8 | 35 | | 4 | |
| (1k) | H | CN | H | 4 | 25 | | | 36 |
| | | | | 8 | 50 | | | |
| (1l) | H | H | CN | 5 | | | | 22 +35 |

Introduction of a methyl group at position 3 caused formation of the indolizines (3f and g) and (4f and g) predominantly as mixtures of isomers in the ratios 9 : 1 and 3 : 1 (n.m.r.), respectively, in which the 8-methylindolizines (3f and g) were the major products. Instead of the 6-cyano-4*H*-quinolizine (5), the 4-cyano-isomer (6) was isolated. The alternative structures for the



(10)

quinolizine such as the 9a*H*-quinolizine (9) and the 2*H*-quinolizine (10) can be ruled out since the signals of the 6-, 7-, 8-, and 9-protons in the 9a*H*-quinolizines have been known to appear at higher field than those of the corresponding protons in the 4*H*-quinolizine [6] and the signal of the proton at the 2-position in the 2*H*-quinolizine should appear at higher field than 5.8 p.p.m.[5] The decreased regioselectivity (from 9 : 1 to 3 : 1) in the formation of the dimethylindolizines (3g) and (4g) may be due to the buttressing effect through the 4-methyl group. This effect seems also to be reflected in the increased formation of the quinolizine (6g). This type of steric effect was observed in a more amplified fashion in the reaction of the pyridinium phenacylide (11) with dimethyl acetylenedicarboxylate (DMAD); [7] a mixture of the 6,7-dimethylindolizine (12b) and the 7,8-dimethylindolizine (13b) was obtained, in the ratio 2 : 1, from (11b), whereas a mixture of the 6-methyl (12a) and 8-methyl (13a) isomers was obtained, in the ratio 1 : 2.5, from (11a).




| | (12) | (13) |
|---|---|---|
| a; $R^1$=Me, $R^2$=H | 1 | 2.5 |
| b; $R^1$=$R^2$=Me | 2 | 1 |

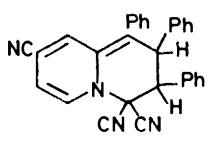
SCHEME 2

The reaction of 3,5-dimethylpyridinium dicyanomethylide (1h) and isoquinolinium dicyanomethylide (1i) with TPP gave the corresponding indolizines (3h) and (3i), with this time no quinolizine being isolated. The cycloaddition of isoquinolinium ylides has been reported to occur exclusively at the 1-position.[8] Thus, when the position next to the reaction centre in the pyridine ring is substituted, no quinolizine formation was observed. This result again suggests that the formation of quinolizine is more sensitive to steric effects than that of indolizine.

4-Methoxycarbonylpyridinium dicyanomethylide (1j) with TPP produced the indolidine (3j) along with a small amount of the 4*H*-quinolizine (6j). The crude indolizine was contaminated, probably with the 1 : 1 adduct (n.m.r.). In the analogous reaction of 4-cyanopyridinium dicyanomethylide (1k) with TPP was obtained the primary adduct (7k) with an unestablished configuration, in addition to the indolizine (3k). The $^1$H n.m.r. spectrum of (7k) displayed a singlet due to the triphenylcyclopropyl proton [3a,9] at δ 3.40 and a doublet due to the 10-proton at δ 5.21 ($J$ 2.5 Hz); its $^{13}$C n.m.r. spectrum exhibited a signal due to the 2-carbon at 30.8 with a $^{13}$C–H coupling constant of $J$ 157 Hz. Thus structures such as (14) and (15) can be excluded. Prolonged heating (8 h) of the reaction mixture yielded only the indolizine (3k)

* Details of $^1$H and $^{13}$C n.m.r. spectra are given in Tables 1, 2, and 3 of Supplementary Publication No. SUP 22893 (5 pp.); for details of the Supplementary Publications scheme see Notice to Authors No. 7, *J.C.S. Perkin I*, 1979, Index issue.

in 50% yield. In contrast, 3-cyanopyridinium dicyanomethylide (1l) with TPP produced the isomeric 1 : 1 adducts (7l) and (8l) in 22 and 35% yields, respectively, where no indolizine was formed even on prolonged heat-



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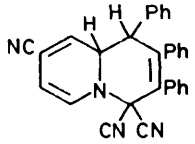
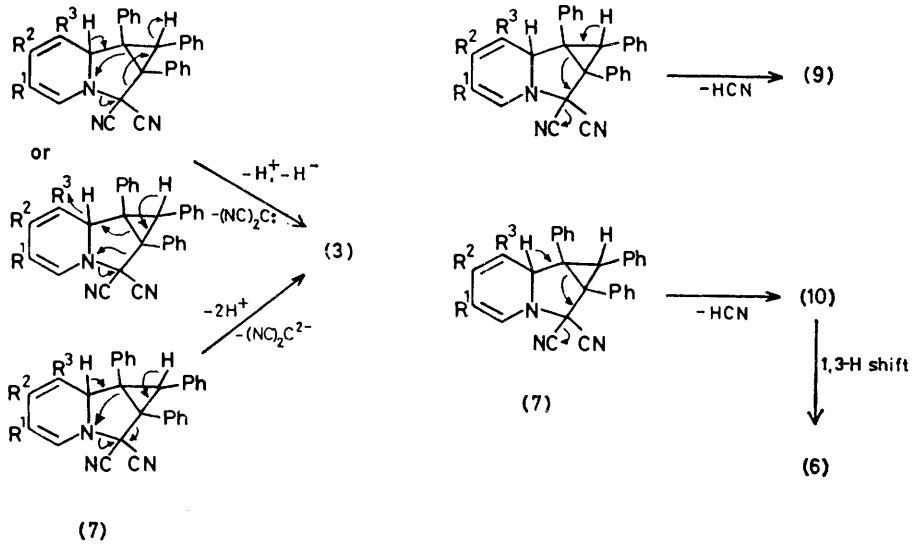


(15)

ing of the reaction mixture. These isomeric assignments were based upon $^1$H n.m.r. spectral analysis of the ring protons; the signal due to the 7-proton of the 9-cyano-isomer (7l) appeared at δ 5.42 as a double doublet, while the 8- and 9-protons of the 7-cyano-isomer (8l) absorbed at δ 5.20 and 6.05 as an AB quartet. It is interesting that the primary adducts could be isolated, since little is known on the isolation of primary adducts in 1,3-dipolar cycloadditions of cycloimmonium ylides with cycloalkenes.[3]

The influence of substituents and their positions on the product distribution is summarized in Table 1, which may serve as a preparative guide. In the case of 4-alkyl- and 4-aryl-substituted ylides, the formation of 6-cyano-4*H*-quinolizine (5) is predominant. When a methyl group is introduced at the 3-position, the formation of the indolizines (3) and (4) predominates. In this case, formation of 4-cyano-4*H*-quinolizine (6) arises from attack at the 6-position of (1). When the position adjacent to the reaction centre is occupied by a substituent, the indolizine (1) is the sole isolable product. Dicyanomethylides having an electron-withdrawing substituent such as cyano or methoxycarbonyl groups at the 4-position gives the indolizine through a discrete formation of the primary 1 : 1 adduct. However, in the 3-cyano-ylide (1l), the primary adduct was too stable under the reaction conditions to be converted into the indolizine.

A possible mechanism for the formation of the indolizines (3) or (4) involves a 1,3-dipolar addition of the ylide (1) to TPP to give an initial adduct (7) or (8), followed by ring opening of the cyclopropane and formal extrusion of malononitrile. This process can occur in either of two fashions; the dicyanomethyl group cleaving to form either dicyanocarbene or dicyanocarbodianion. For either of these mechanisms, the presence of an electron-withdrawing group, especially at the 3-position, or the replacement of the ring α-carbon with nitrogen (see later) in the pyridine ring would disfavour



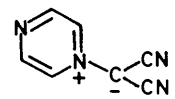
SCHEME 3

cleavage of the C–N bond by virtue of its resonance or inductive effect, respectively, thus stabilizing the 1 : 1 adduct. The quinolizine (5) or (6) could be formed by opening of the three-membered ring and elimination of hydrogen cyanide, followed by a 1,5-hydrogen shift. The alternative route to (6) is possibly formation of the 2*H*-quinolizine (10) and subsequent 1,3-hydrogen shift, although (10) was not detected (Schemes 1 and 3).

When an electron-donating methyl group is introduced at the 3-position, cyclization at the 2-position would be favoured;[7] this, in turn, would cause more steric compression in the intermediate 9a*H*-quinolizine (9) than that in the indolizine formation, *i.e.* the release of the steric compression would be more favourable in the indolizine formation. This effect is more remarkable in the reaction of the 3,5-dimethylpyridinium ylide (1h) and isoquinolinium (1i) ylides in which the position adjacent to the reaction centre is substituted. The predominant formation of (6) over (5) in the cases of (1e), (1f), and (1g) suggests that (5) has a larger steric compression than (6) does when $R^3$ = Me or $R^2$ = bulky

But. Otherwise, (6) could be formed *via* a sterically more favoured path, *i.e.* (7) → (10) → (6) (Scheme 3).

This type of [4 + 2]π cycloaddition reaction can be extended to such diazabenzenium dicyanomethylides as pyridinium (16), pyridazinium (17), and phthalazinium (18) dicyanomethylides. The ylide (16) with TPP readily gave the indolizine (19), whereas the ylides (17) and (18) produced the primary 1 : 1 adducts (20) and (21), respectively, in excellent yields; however, their attempted conversions into the indolizines were unsuccessful. Examination of the $^1$H n.m.r. spectrum (Table



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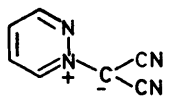

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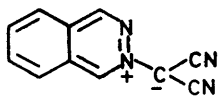

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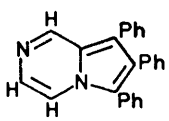

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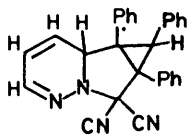

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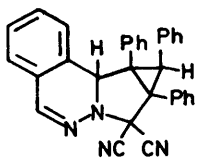


(21)

3 of SUP 22893) of (20) suggests that the adduct consists of two configurational isomers, which could not be separated by t.l.c. However, no differences between the chemical shifts of these possible isomers were observed in the $^{13}$C n.m.r. spectrum (Table 3 of SUP 22893).

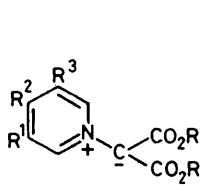
In order to explore the generality of this reaction, the further reaction of pyridinium bis(alkoxycarbonyl)-methylides (22a—g) was examined. As summarized in Table 2, these reactions gave, generally, poor or no

TABLE 2

Products from reaction of bis(alkoxycarbonyl)methylides (22) with TPP (2)

| | Bis(alkoxycarbonyl)-methylide | | | | Reaction time (h) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| | R | R$^1$ | R$^2$ | R$^3$ | | | |
| (22a) | Me | H | H | H | 10—23 | (3a) | 20—51 |
| (22b) | Et | H | H | H | 10—30 | | |
| (22c) | Me | H | H | Me | 26 | (3f) + (4f) | 4 (8 : 1) |
| (22d) | Me | H | Me | H | 29 | (3b) | 0.7 |
| (22e) | Me | Me | H | Me | 7—36 | | |
| (22f) | Me | H | –[CH=CH]$_2$– | | 4 | (3i) + (24) | 21 + 62 |
| (22g) | Me | H | COPh | H | 13 | (3m) | 20 |

yield of the indolizines. Formation of the TPP dimer (23) predominated and the ylides were recovered unchanged, except in the reactions of the pyridinium (22a), isoquinolinium (22f), and 4-benzoylpyridinium (22g) ylides, among which the isoquinolinium ylide (22f) is so reactive as to give a 21% yield of the indolizine (3i) and a 62% yield of the 1 : 1 adduct (24). Thermolysis of (24) in refluxing xylene or DMF produced the indolizine (3i) in good yield. Finally, it is noted that the attempted preparation of benzylpyridinium bis(methoxycarbonyl)-methylide resulted in the formation of the 4-benzoyl-pyridinium ylide (22g). The methylene group, whose



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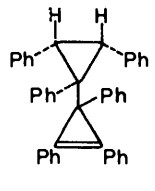

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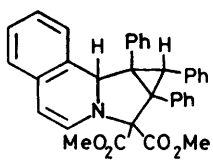

(24)

a; R = Me, R$^1$ = R$^2$ = R$^3$ = H
b; R = Et, R$^1$ = R$^2$ = R$^3$ = H
c; R = Me, R$^1$ = R$^2$ = H, R$^3$ = Me
d; R = Me, R$^1$ = R$^3$ = H, R$^2$ = Me
e; R = Me, R$^1$ = R$^3$ = Me, R$^2$ = H
f; R = Me, R$^1$ = H, R$^2$ = R$^3$ = [CH = CH]
g; R = Me, R$^1$ = R$^3$ = H, R$^2$ = COPh

hydrogens are highly active owing to the electron-withdrawing capacity of the phenyl and pyridinium groups, is likely to be susceptible to oxidation under the basic conditions employed ($K_2CO_3$, $Al_2O_3$).

## EXPERIMENTAL

M.p.s were taken on a Yanagimoto micro-melting-point apparatus. I.r. spectra were obtained on a Jasco IR-G or a Hitachi EPI-G3 spectrometer. $^1$H N.m.r. spectra were measured on a JEOL C-60HL or a JEOL 4H-100 instrument. $^{13}$C N.m.r. spectra were recorded on a JEOL FX-60 pulsed Fourier-transform spectrometer operating at 15.040 MHz, using 10-mm o.d. tubes, in 0.1—0.2M-solutions in $CDCl_3$ at 22 °C; chemical shifts are in p.p.m. downfield from internal $SiMe_4$. Partial proton decoupling was used to distinguish between individual carbon atoms. Mass spectra were obtained on a JEOL 01SG-2 spectrometer. T.l.c. was performed on Kieselgel $PF_{254}$ (0.25 mm) and on the preparative scale using the same substrate (1.00 mm).

The dicyanomethylides (1a—l), (16), (17), and (18) and the bis(alkoxycarbonyl)methylides (22a—g) were prepared according to the method of Linn *et al.*[10] and of Kobayashi *et al.*,[11] respectively.

The general reaction conditions and purification procedures are illustrated by the following examples.

$^1$H and $^{13}$C N.m.r., i.r., and mass spectra as well as m.p.s and analytical data for new compounds are available as Supplementary Publication No. SUP 22893 (5 pp.).

*Reaction of* (1a) *with TPP.*—A mixture of (1a) (0.43 g, 3 mmol) and (2) (0.81 g, 3 mmol) in dry DMF (20 ml) was heated under reflux with stirring for 4 h. The solvent was removed *in vacuo*. The dark brown oil was dissolved in benzene (15 ml) and chromatographed on silica gel (Wako C-100). Elution with hexane gave 1,2,3-triphenylindolizine (3a) as pale yellow crystals (0.26 g) which were recrystallized from hexane, while elution with hexane–benzene (1 : 1 v/v) gave the quinolizine (5a) as pink crystals (0.35 g), recrystallized from hexane–benzene.

*Reaction of* (1h) *with TPP.*—A mixture of (1h) (0.51 g, 3 mmol) and TPP (0.81 g, 3 mmol) in DMF (15 ml) was refluxed with stirring for 10 h. The solvent was removed

*in vacuo*. The residue was dissolved in benzene (20 ml) and the unchanged ylide was removed by filtration. The filtrate was subjected to chromatography on silica gel (120 g). Elution with hexane (200 ml) then hexane–benzene (1 : 1 v/v, 300 ml) gave the indolizine (3h) (0.62 g) as pale yellow crystals which were recrystallized from hexane.

*Reaction of* (1k) *with TPP*.—A mixture of (1k) (0.51 g, 3 mmol) and TPP (0.81 g, 3 mmol) was heated under reflux with stirring for 5 h. After evaporation of the solvent, the residual oil was chromatographed on silica gel, using hexane (200 ml), hexane–benzene (1 : 1 v/v; 300 ml), and hexane–benzene (2 : 3 v/v; 200 ml) as eluant. Evaporation gave as the main product a pale yellow powder (0.75 g), m.p. 160—180 °C, consisting of a mixture of (7k) and (8k), which were separated by preparative t.l.c. in hexane–benzene (5 : 1 v/v).

*Reaction of* (16) *with TPP*.—A mixture of (16) (0.43 g, 3 mmol) and TPP (0.81 g, 3 mmol) in DMF (15 ml) was refluxed with stirring for 5 h and was worked up as described above, giving the indolizine (19) (47%).

*Reaction of* (17) *and* (18) *with TPP*.—A mixture of (17) (0.43 g, 3 mmol) and TPP (0.81 g, 3 mmol) in DMF (15 ml) was heated under reflux for 4 h. Usual work-up afforded the 1 : 1 adduct (20) (90%).

In the same manner (8 h reflux), the 1 : 1 adduct (21) was obtained in 89% yield from (18).

*Reaction of* (22c) *with TPP*.—A solution of (22c) (1.0 g) and TPP (1.0 g) was heated under reflux in DMF (10 ml) for 26 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel with hexane, hexane–benzene, and benzene as eluant. From the first fraction was obtained the dimer of TPP (23), m.p. 182—186 °C (lit.,[9] 179.5—180.5 °C); *m/e* 536 ($M^+$); δ($CDCl_3$) 3.18 (s, 2 H) and 6.7—7.8 (m, 30 H). From the second fraction was isolated pale green crystals of (3f) + (4f), which were recrystallized from ethanol (55 mg, 4%), m.p. 164—167 °C. From the third fraction was recovered the ylide (22c) (0.18 g, 18%).

4-*Benzoylpyridinium Bis(methoxycarbonyl)methylide* (22g).—A solution of 4-benzylpyridine (3.72 g) and dimethyl bromomalonate (4.22 g) in acetone (30 ml) was allowed to stand at room temperature for 24 h. The mixture was concentrated, and diluted with 10% aqueous potassium carbonate (30 ml). The crude product was extracted with chloroform, dried, and chromatographed on an alumina column with benzene–chloroform as eluant. Evaporation gave red *crystals* (0.75 g, 10%), m.p. 222—225 °C (from benzene) (Found: C, 65.45; H, 5.0; N, 4.4. $C_{17}H_{15}NO_5$ requires C, 65.15; H, 4.8; N, 4.45%); *m/e* 313 ($M^+$); $\nu_{max.}$ (KBr) 1 735 $cm^{-1}$; δ($CDCl_3$) 3.79 (s, 6 H), and 7.2—8.85 (m, 9 H).

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