2-METHYLENE-3-PHENACYLBENZOTHIAZOLINE: DIMERIZATION AND REACTIONS WITH ELECTRON-DEFICIENT ACETYLENES AND OLEFINS

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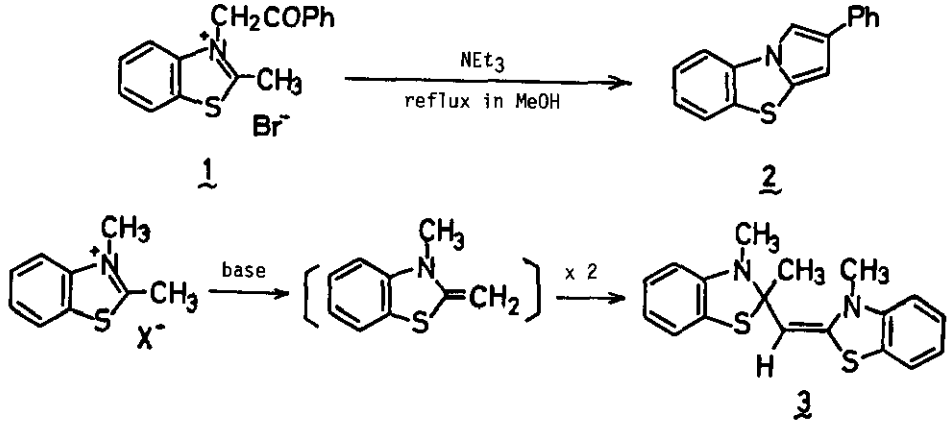
Abstract ——— On treatment with triethylamine in acetonitrile at 0°C, 2-methy-3-phenacylbenzothiazolium bromide gave a dimer of 2-methylene-3-phenacylbenzothiazoline in a quantitative yield. The methylene base, generated in situ, reacted with electron-deficient acetylenes and olefins to give 3-substituted 2-phenylpyrrolo[2,1-b]benzothiazole via a Michael type adduct; in some cases Michael type adducts were isolated. On the other hand, the methylene base reacted with tetracyanoethylene to give 2-butadienylidenebenzothiazoline derivative, which on heating in acetic anhydride afforded 1-benzoyl-2-cyano-pyrrolo[2,1-b]benzothiazole with the elimination of malononitrile.

On treatment with aqueous sodium carbonate 2,4-dimethyl-3-phenacylthiazolium bromide undergoes an intramolecular condensation to yield 3-methyl-6-phenylpyrrolo[2,1-b]thiazole[1]. It has later been proved, however, that aqueous base was unsuitable for cyclization of such quaternary thiazolium salts[2], and an alternate cyclization method of the thiazolium salts to the pyrrolo[2,1-b]thiazole

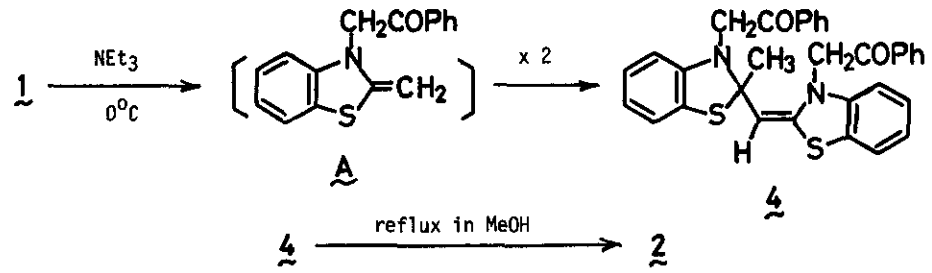


Scheme 1

systems has been developed by Molloy et al.[3] It has also been reported that on treatment with triethylamine in methanol under reflux 2-methyl-3-phenacylbenzothiazolium bromide (1) afforded a 35% yield of 2-phenylpyrrolo[2,1-b]benzothiazole (2) together with a significant amount of unidentified compound[4]. On the other hand, it is known that the methylene base derived from 1,3-dimethylbenzothiazolium salts exists as a dimer[5], whose structure was confirmed as 3[6] (Scheme 1). Although Kröhnke and Friedrich[4] have described that pyrrolobenzothiazole 2 could be formed from either N-phenacylide or methylene base, the corroborating evidence for species generated from 2-methyl-3-acylmethylthiazolium salts and base has not so far been reported in the literature.

In the present paper we wish to report the evidence for generation of 2-methylene-3-phenacylbenzothiazoline (methylene base) from bromide 1.

Dimer of Methylene Base. A solution of triethylamine (3.0mmol) in dry acetonitrile (5 ml) was added, drop by drop, to a suspension of bromide 1 (3.0 mmol) in dry acetonitrile (50 ml) with stirring, under nitrogen, at 0°C: the reaction mixture turned to a clear solution, and then yellow crystals were separated out during 30 min. Filtration gave crystals, which were washed with acetone (100 ml) and dried to afford pure yellow crystals 4, mp 105-109°C (dec), in a quantitative yield. From the filtrate triethylammonium bromide was obtained quantitatively. On the basis of spectral data the structure of 4 was assigned as a dimer like 3. It is thus evident that the species generated from bromide 1 is 2-methylene-3-phenacylbenzothiazoline A, but not N-phenacylide.



Scheme 2

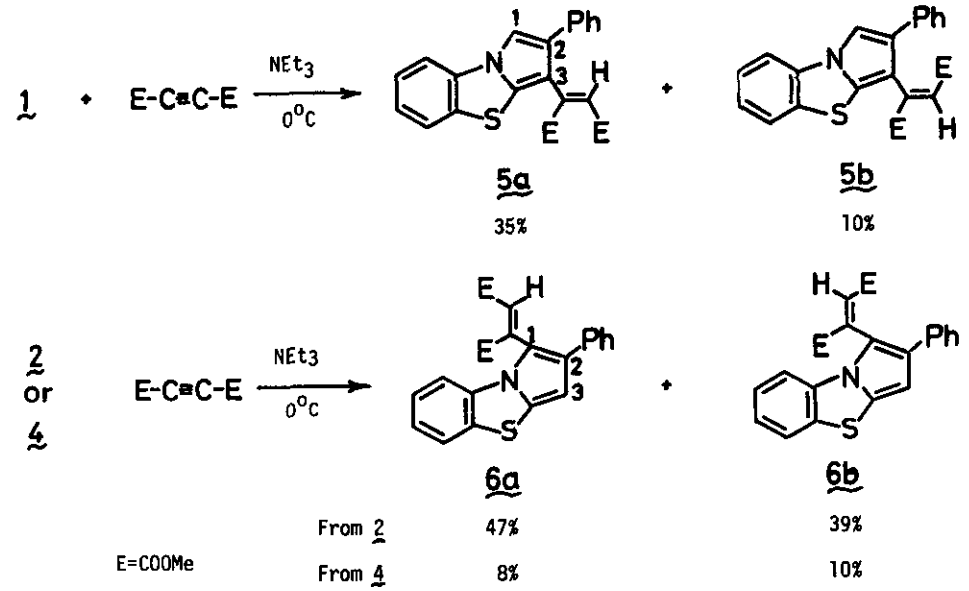
4: IR (KBr) 1705, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (3H, s, CH_3), 4.31 (1H, s, =CH), 4.58, 4.77 (each 1H, d, CH_2, J=18.5 Hz), 5.10, 5.14 (each 1H, d, CH_2, J=19.5 Hz), 5.93-7.08 (18H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 33.8 (q, CH_3), 48.5, 51.0 (each t, CH_2), 79.1 (s, quat. C), 88.1 (d, =CH), 191.8, 195.5 (C=O); MS m/e 267 $(M^+/2)$[7].

On heating in methanol under reflux for 1.5 h, dimer 4 was converted to pyrrolobenzothiazole 2, mp 127-129°C (lit.[4] mp 127-129°C), in 43% yield: it seems to suggest that pyrrolobenzothiazole 2 might be formed via dimer 4 in the Kröhnke method[4].

Reaction of Methylene Base with Acetylenes. In order to capture methylene base A, the dehydrobromination of bromide 1 was performed in the presence of acetylenes. A general procedure is illus-

trated as follows. A solution of triethylamine (3.0 mmol) in dry acetonitrile (5 ml) was added, drop by drop, to a suspension of bromide 1 (3.0 mmol) and an acetylene (3.0 mmol) in dry acetonitrile (50 ml) with stirring, under nitrogen, at 0°C. After the reaction mixture was stirred at the same temperature for 2 h, it was concentrated in vacuo to leave a residue. Benzene (100 ml) was added to the residue, and insoluble triethylammonium bromide was removed by filtration. The filtrate was again concentrated in vacuo, and the residue was chromatographed on silica gel using benzene-hexane (1:1) as the eluent.

In the reaction in the presence of dimethyl acetylenedicarboxylate (DMAD), two isomeric compounds, 5a and 5b, whose molecular formulas agreed with that of a compound derived from 1:1 adduct of DMAD to methylene base A with dehydration, were obtained. In other words, 5a and 5b corresponded to a 1:1 adduct of DMAD to pyrrolobenzothiazole 2. On the other hand, pyrrolobenzothiazole 2 reacted with DMAD to give two isomeric 1:1 adducts, 6a and 6b, which are different from both 5a and 5b (Scheme 3).



Scheme 3

On the basis of spectral evidence, 5a and 5b were assigned as cis- and trans-3-bis(methoxycarbonyl)-vinyl-2-phenylpyrrolo[2,1-b]benzothiazole, and 6a and 6b as cis- and trans-1-bis(methoxycarbonyl)-vinyl-2-phenylpyrrolo[2,1-b]benzothiazole, respectively.

5a: yellow needles; mp 151-152.5°C; IR (KBr) 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63, 3.70 (each 3H, s, OCH_3), 5.65 (1H, s, =CH), 7.02-7.64 (10H, m, 1-H + ArH); UV λ_{max}^{EtOH} nm (log ε) 203 (4.60), 251 (4.45), 356 (4.21); MS m/e 391 (M^+).

5b: yellow needles; mp 127-128°C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41, 3.60 (each 3H, s,

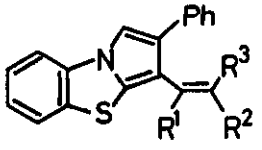
OCH_3), 6.80 (1H, s, =CH), 7.12-7.62 (10H, m, 1-H + ArH); UV λ_{max}^{EtOH} nm (log ε) 203 (4.66), 230 (4.52), 253 (4.38), 372 (3.33); MS m/e 391 (M^+).

6a: yellow needles; mp 144-145°C; IR (KBr) 1720, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61, 3.77 (each 3H, s, OCH_3), 6.24 (1H, s, =CH), 6.38 (1H, s, 3-H), 7.13-7.80 (9H, m, ArH); UV λ_{max}^{EtOH} nm (log ε) 206 (4.56), 253 (4.37), 382 (3.60); MS m/e 391 (M^+).

6b: red needles; mp 132-133°C; IR (KBr) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30, 3.60 (each 3H, s, OCH_3), 6.43 (1H, s, 3-H), 7.13 (1H, s, =CH), 7.09-7.65 (9H, m, ArH); UV λ_{max}^{EtOH} nm (log ε) 206 (4.56), 256 (4.39), 420 (3.24); MS m/e 391 (M^+).

It is reasonable to conclude that the vinyl groups are located at the 3-position in 5a, 5b, and at the 1-position in 6a, 6b, respectively, because in the ^1H NMR spectra the proton on the pyrrolo ring in the former isomers appears at lower field than that in the latter isomers. It has been reported that 2,6-dimethylpyrrolo[2,1-b]thiazole reacted with DMAD to give a mixture of two isomeric 5-bis(methoxycarbonyl)vinyl derivatives[8]: the formation of 6a and 6b is compatible with the above reported result. The geometry of the vinyl groups in each isomer could be assigned on the basis of ^1H NMR and electronic spectral data. The inspection of molecular models indicates that the olefinic proton in the Z isomer and terminal methoxycarbonyl group in the E isomer are orientated in the shielding cone of the 3-phenyl group, respectively. As is shown above, the olefinic proton in 5a or 6a appears at higher field than that in 5b or 6b, whereas the terminal methoxycarbonyl group shows the opposite relation. It is thus concluded that 5a and 6a are Z isomers, while 5b and 6b are E isomers. This conclusion is strongly supported by comparison of their electronic spectral data with those of geometrical isomers of analogous compounds[8].

Similarly, the reaction in the presence of dicyanoacetylene gave a mixture of two isomeric pyrrolobenzothiazoles 7a and 7b. From the reaction in the presence of benzoylacetylene, however, the sole pyrrolobenzothiazole 8 was formed in low yield together with dimer 4 (59%). Structural elu-



7a: R^1=R^2=CN, R^3=H 21%
7b: R^1=R^3=CN, R^2=H 10%
8: R^1=R^3=H, R^2=COPh 9%

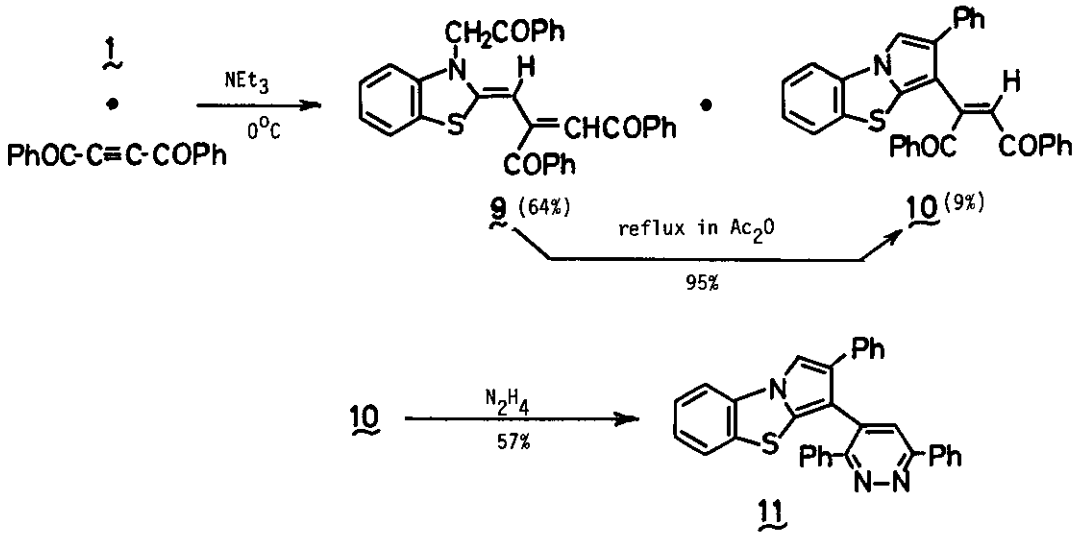
cidation of 7a, 7b, and 8 was accomplished on the basis of spectral data.

7a: yellow needles; mp 247-248°C; IR (KBr) 2200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.40 (1H, s, =CH), 7.43-7.86 (10H, m, 1-H + ArH); UV λ_{max}^{EtOH} nm (log ε) 203 (4.37), 250 (4.28), 305 (3.48), 396 (4.07); MS m/e 325 (M^+).

7b: yellow needles; mp 205-206°C; IR (KBr) 2220, 2200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1H, s, =CH), 7.20-7.76 (10H, m, 1-H + ArH); UV λ_{max}^{EtOH} nm (log ε) 203 (4.78), 248 (4.69), 303 (3.90), 400 (4.11); MS m/e 325 (M^+).

8: yellow needles; mp 186-187°C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02, 8.02 (each 1H, d, =CH, J=16.0 Hz), 7.20-8.05 (15H, m, 1-H + ArH); MS m/e 379 (M^+).

On the other hand, the reaction of bromide 1 with dibenzoylacetylene in the presence of triethylamine afforded Michael type adduct 9 of the acetylene to methylene base A as a major product, together with pyrrolobenzothiazole 10. The compound 9 was converted to 10 on heating in acetic anhydride. The reaction of 10 with hydrazine hydrate gave pyridazine derivative 11, suggesting that the vinyl group in 10 is in Z form (Scheme 4).



Scheme 4

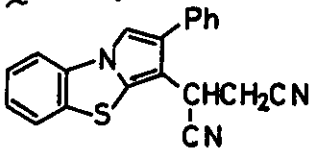
9: red needles; mp 210-212°C (dec); IR (KBr) 1680, 1660, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.72 (1H, s, =CH), 5.95 (2H, s, CH_2), 6.96 (1H, s, =CH), 7.21-8.17 (19H, m, ArH); ^{13}C NMR (DMSO-d_6) δ 51.6 (CH_2), 90.5 (=CH), 185.2, 191.7, 197.9 (C=O); UV λ_{max}^{EtOH} nm (log ε) 202 (4.50), 243 (4.24), 269 (4.06), 487 (4.36); MS m/e 501 (M^+).

10: yellow needles; mp 219-220°C; IR (KBr) 1665, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.00 (1H, s, =CH), 7.40-8.17 (19H, m, ArH), 8.23 (1H, s, 1-H); UV λ_{max}^{EtOH} nm (log ε) 202 (4.49), 255 (4.35), 423 (3.66); MS m/e 483 (M^+).

11: colorless prisms; mp 279-280°C; IR (KBr) 1580, 1560, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10-7.97 (20H, m, ArH), 7.70 (1H, s, 1-H); MS m/e 479 (M^+).

It is thus evident that the reaction of bromide 1 with an acetylene in the presence of triethylamine proceeds via an initial formation of methylene base A, followed by the reaction of A with the acetylene to form a Michael type adduct like 9, which gives a pyrrolobenzothiazole with loss of water.

Reaction of Methylene Base with Olefins. Next we have investigated the reaction of methylene base A with olefins. In the reaction with maleonitrile or fumaronitrile in chloroform under similar conditions, the same pyrrolobenzothiazole 12 was obtained in 31 or 28% yield respectively, together with dimer 4. Similarly, methylene base A reacted with N-(p-methoxyphenyl)maleimide to give pyrrolobenzothiazole 13 in 40% yield[9].



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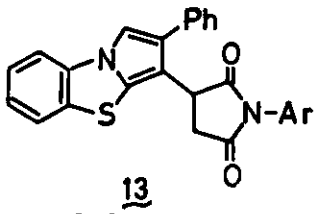
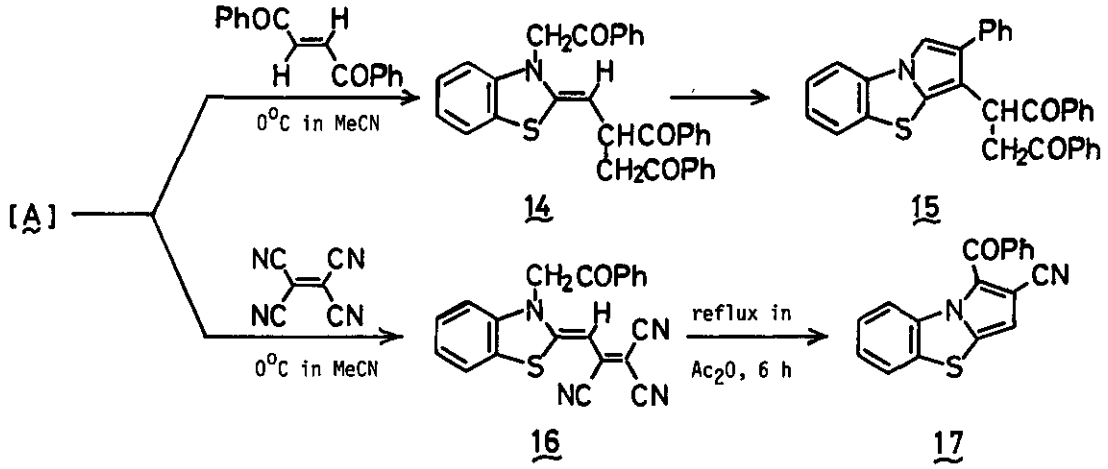


13

12: colorless prisms; mp 138-140°C; IR (KBr) 2270, 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (2H, d, CH_2, J=7.5 Hz), 4.44 (1H, t, >CH, J=7.5 Hz), 7.28-7.76 (10H, m, ArH); MS m/e 327 (M^+).

13: colorless needles; mp 130-131°C; IR (KBr) 1780, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (1H, dd, J= 5.6, 18.5 Hz), 3.12 (1H, dd, CH_2, J=9.2, 18.5 Hz), 3.73 (3H, s, OCH_3), 4.33 (1H, dd, >CH, J=5.6, 9.2 Hz), 6.80-7.60 (14H, m, ArH); MS m/e 452 (M^+).

The reaction of methylene base A with trans-dibenzoylethylene gave a mixture of Michael type adduct 14 and pyrrolobenzothiazole 15. The relative yields of 14 and 15 changed with reaction time: the yields of 14 and 15 were 71 and 3% or 65 and 10% in the reaction for 2 or 3 h, respectively. When 14 in chloroform was allowed to stand overnight at room temperature, 14 was completely converted to 15. In contrast to 9 having a dienamine structure, the olefinic and methylene hydrogens in 14 were readily deuterated on treatment with deuterium oxide.



Scheme 5

On the other hand, the reaction with tetracyanoethylene showed a different pattern. In this case,

tricyanobutadienylidenebenzothiazoline derivative 16 was obtained in 37% yield. The compound 16 was resistant to dehydration, but instead 1-benzoyl-2-cyanopyrrolobenzothiazole 17 was formed in 81% yield on heating 16 in acetic anhydride.

Structural elucidation of 14, 15, 16 and 17 was accomplished on the basis of spectral data.

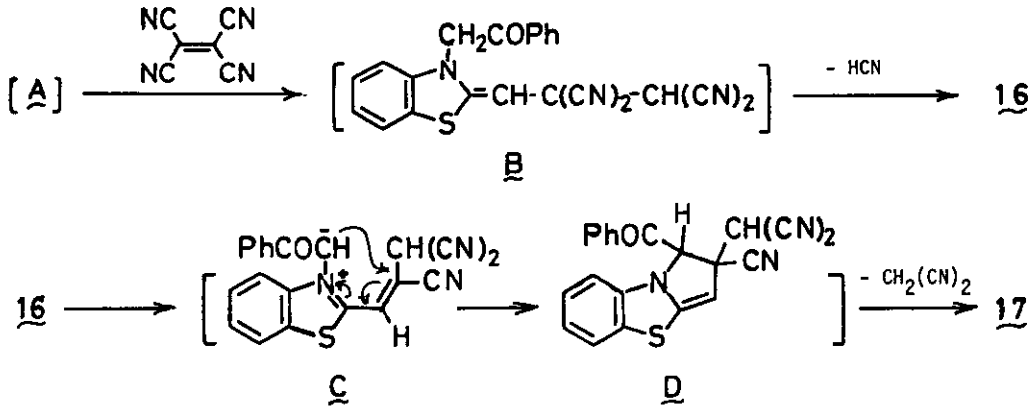
14: dark yellow needles; mp 109-110°C; IR (KBr) 1710, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (1H, dd, CH_2, J=4.2, 18.3 Hz), 3.85 (1H, dd, CH_2, J=10.5, 18.3 Hz), 4.13 (1H, d, =CH, J=10.5 Hz), 4.55 (1H, td, ⇒CH, J=4.2, 10.5 Hz), 4.86 (2H, s, CH_2), 6.30-8.03 (19H, m, ArH).

15: colorless prisms; mp 173.5-175°C; IR (KBr) 1690, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.37 (1H, dd, CH_2, J=4.2, 18.3 Hz), 4.40 (1H, dd, CH_2, J=10.5, 18.3 Hz), 5.47 (1H, dd, ⇒CH, J=4.2, 10.5 Hz), 7.02-8.05 (20H, m, 1-H + ArH); MS m/e 485 (M^+).

16: red needles; mp 158-160°C (dec); IR (KBr) 2200, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.23 (1H, s, =CH), 6.44 (2H, s, CH_2), 7.53-8.34 (9H, m, ArH); UV λ_{max}^{EtOH} nm (log ε) 201 (4.19), 246 (3.97), 382 (3.80), 395 (3.75), 480 (3.82), 506 (3.99); MS m/e 368 (M^+).

17: colorless needles; mp 215°C; IR (KBr) 2230, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (1H, s, 3-H), 7.20-8.40 (9H, m, ArH); MS m/e 302 (M^+).

It has been reported that tetracyanoethylene reacted with aromatic or heterocyclic nuclei to introduce a tricyanovinyl group into the ring system via initial addition across the double bond in the ethylene, followed by the base-induced elimination of hydrogen cyanide[10]. Thus the pathway for the formation of 16 can be illustrated as shown in Scheme 6. Tetracyanoethylene adds to methylene base A to yield B, followed by the base-induced elimination of hydrogen cyanide to give 16. On the other



Scheme 6

hand, the formation of 17 from 16 may be explained as follows. The compound 16 isomerizes to N-ylide C, followed by an intramolecular cyclization to yield D. Subsequent elimination of malononitrile from D gives 17. The elimination of malononitrile has been observed in the reaction of

2H,3H-thieno[3,2-b]pyrrol-3-one with tetracyanoethylene leading to the formation of the corresponding 2-dicyanomethylene derivative[11].

References and Notes

1. H. Kondo and F. Nagasawa, J. Pharm. Soc. Jpn. (Yakugaku Zasshi), 1937, 57, 1050.
2. It has been reported that treatment of 2-methyl-3-phenacylthiazolium bromide with aqueous base afforded 4-acetyl-2,3-dihydro-2-hydroxy-2-phenyl-4H-1,4-thiazine (D. J. Adam and M. Wharmby, Tetrahedron Lett., 1969, 3063).
3. B. B. Molloy, D. H. Reid, and F. S. Skelton, J. Chem. Soc., 1965, 65.
4. F. Kröhnke and W. Friedrich, Chem. Ber., 1963, 96, 1195.
5. O. Mumm, H. Hinz, and J. Diederichsen, ibid., 1939, 72, 2107.
6. J. Metzger, H. Larive, E. Vincent, and R. Dennilauler, J. Chem. Phys., 1963, 60, 944.
7. All new compounds in this paper gave satisfactory elemental analyses.
8. O. Ceder and B. Beijer, Tetrahedron, 1972, 28, 4341.
9. The yields of 12 and 13 from the reaction in acetonitrile were lower than those in chloroform.
10. B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, J. Am. Chem. Soc., 1958, 80, 2806; G. N. Sausen, V. A. Engelhardt, and W. J. Middleton, ibid., 1958, 80, 2815; W. E. Noland, W. C. Kuryla, and R. F. Lange, ibid., 1959, 81, 6010.
11. J. W. Van Dyke, Jr., and H. R. Snyder, J. Org. Chem., 1962, 27, 3888.

Received, 4th July, 1981