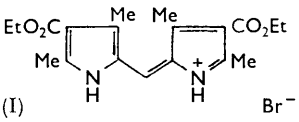
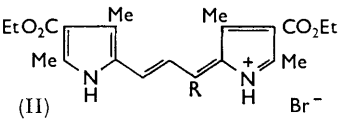
1292. *The Reaction of Dipyrromethene Salts with Methyl Ketones and with Dicyanomethane*

By P. Bamfield, A. W. Johnson, and J. Leng

Reaction of the hydrobromides of dipyrromethenes containing at least one ester group with acetone or butan-2-one yields trimethine salts. The reaction involves preliminary nucleophilic addition of the ketone to the methene salt and similar additions of dicyanomethane are also described, although the first-formed adducts do not undergo further rearrangement in this series.

We have observed that when the dipyrromethene hydrobromide (I) is heated under reflux with acetone it is converted in almost quantitative yield into the trimethine (II; R = Me) after about 8 hours. A similar reaction of compound (I) with butan-2-one gave compound (II; R = Et).


(I)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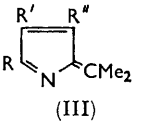
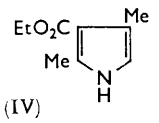

(III)

Trimethines of type (II) have been prepared previously from 2,3,4-trisubstituted pyrroles by reaction with ethyl orthoformate and acetone in presence of hydrogen bromide. The earlier authors [1] regarded the reaction as an initial condensation of acetone with the pyrrole, to give an intermediate, compound (III), which then reacted with ethyl orthoformate and another mole of the pyrrole. Repetition of this work using ethyl 2,4-dimethylpyrrole-3-carboxylate (IV) showed that the initial reaction was in fact a rapid formation of the dipyrromethene salt (I; $\lambda_{max.}$ 475 mμ), which was converted completely into the trimethine salt (II; R = Me, $\lambda_{max.}$ 599 mμ) after being kept overnight in presence of acetone. The same trimethine has also been obtained from the pyrrole (IV) by reaction with methyl vinyl ketone, or crotonaldehyde,[2] and other preparations of trimethines have been described, particularly by Treibs and his co-workers.[3] The formation of trimethines by the present method, *i.e.*, by reaction of dipyrromethenes with acetone, was not observed with alkyldipyrromethenes containing no ester substituents, but on the other hand the isomer (V) of compound (I), containing an α-ester group, reacted much more rapidly with acetone and gave the analogous trimethine in good yield. No evidence was obtained in this case for the formation of the isomeric trimethines containing two α- or two β-ester groups.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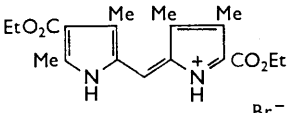
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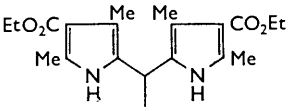
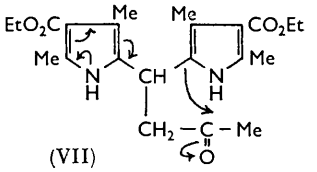

(VI)

The reaction is therefore regarded as an initial addition of acetone to the dipyrromethene to form the *meso*-acetonyldipyrromethane [*e.g.*, compound (VI)], an addition which will be facilitated by the conjugated ester group in the 5-position of the ring, *e.g.*, in compound (V), to a greater extent than ester groups in the 4-position [as in compound (I)]. The rearrangement of the acetonyldipyrromethanes to the trimethines may be regarded as intramolecular, involving a mechanism such as (VII), or intermolecular if the acetonyl

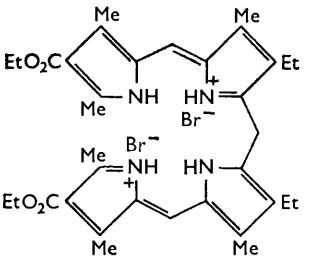
[1] A. H. Cook and J. R. Majer, *J.*, 1944, 482.
[2] A. Treibs and E. Herrmann, *Annalen*, 1955, **592**, 1.
[3] A. Treibs *et al.*, *Annalen*, 1954, **589**, 207; 1955, **592**, 11; 1958, **612**, 242; 1959, **627**, 166; M. Strell and F. Kreis, *Chem. Ber.*, 1954, **87**, 1011.

derivative undergoes fission to a pyrrole and a methyl β-pyrrolylvinyl ketone which recombine subsequently to the trimethine.

A related observation was the formation of the trimethine (II; R = Me) from the 1,19-dideoxybiladiene-ac, compound (VIII), by reaction with acetone, and a somewhat similar mechanism can be envisaged in this case.

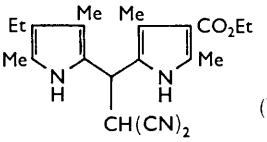


(VII)

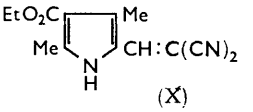


(VIII)

Several examples are known of the addition of acetone to unsaturated systems, particularly iminium salts, as for example berberine,[4] and various quinonoid systems, *e.g.*, pristimerin.[5] The 1,6-addition of nucleophiles to dipyrromethene salts to yield *meso*-substituted dipyrromethanes is also well established and examples of such nucleophiles include hydroxide and methoxide,[6] cyanoacetic ester,[7] methylmagnesium iodide,[8] and bisulphite.[9] The addition of dicyanomethane to a number of dipyrromethenes which contain at least one ester group has been observed in the present work. The same products, *i.e.*, *meso*-dicyanomethyldipyrromethanes [*e.g.*, compound (IX)] have also been prepared



(IX)



(X)

by Michael addition of trialkylpyrroles to the condensation products [10] [*e.g.*, compound (X)] of dicyanomethane and 2-formylpyrrole esters, although the presence of an ester group in the alkylpyrrole prevented the addition reaction, which accords with the accepted view of the Michael reaction. The *meso*-dicyanomethyldipyrromethanes were quite stable and self-condensation or fission products were not observed as in the case of the cyanoacetic ester adducts.[7]

Experimental

Ultraviolet and visible spectra were determined for ethanol solutions and infrared spectra for chloroform solutions except where otherwise stated. Nuclear magnetic resonance spectra were determined for trifluoroacetic acid solutions with a Perkin-Elmer R10 instrument operating at 60 Mc./sec. and using tetramethylsilane as internal reference. Light petroleum refers to the fraction b. p. 60—80°.

Ethyl 5-[4-(4-*Ethoxycarbonyl*-3,5-*dimethyl*-2-*pyrrolyl*)-*but*-3-*en*-2-*ylidene*]-2,4-*dimethyl*-5H-*pyrrole*-3-*carboxylate Hydrobromide* (II; R = Me).—(*a*) A 50% solution of hydrobromic acid in acetic acid (1 ml.) was added to a solution of ethyl 2,4-dimethylpyrrole-3-carboxylate [11] (1·10 g.) and ethyl orthoformate (1·65 ml.) in acetone (7 ml.). An immediate yellow precipitate ($\lambda_{max.}$ 475 mμ) separated but when the reaction mixture was kept overnight it had $\lambda_{max.}$ 600 mμ with only a weak absorption at 475 mμ. The volatile compounds were removed by evaporation

[4] J. Gadamer, *Arch. Pharm.*, 1905, **243**, 31.
[5] P. K. Grant and A. W. Johnson, *J.*, 1957, 4669.
[6] K. J. Brunings and A. H. Corwin, *J. Amer. Chem. Soc.*, 1942, **64**, 593.
[7] A. C. Jain and G. W. Kenner, *J.*, 1959, 185.
[8] H. Booth, A. W. Johnson, F. Johnson, and R. Langdale-Smith, *J.*, 1963, 650.
[9] A. Treibs and R. Zimmer-Galler, *Annalen*, 1963, **664**, 140.
[10] H. Fischer and M. Neber, *Annalen*, 1932, **496**, 1.
[11] H. Fischer and B. Walach, *Ber.*, 1925, **58**, 2818.

and then methanol (20 ml.) was added to the residue. The solid was separated and washed with more methanol (10 ml.) and dried in air giving a violet powder (224 mg.) which was crystallised from chloroform (Soxhlet) when it formed violet needles, m. p. 226—229° (lit.,[2] 226°) (Found: C, 56·9; H, 6·15; N, 6·15. Calc. for $C_{22}H_{29}BrN_2O_4$: C, 56·8; H, 6·25; N, 6·0%), $\lambda_{max.}$ ($CHCl_3$) 289, 356, and 600 mμ ($\varepsilon_{max.}$ 11,300, 5520, and 192,000); $\lambda_{infl.}$ 562 mμ ($\varepsilon_{infl.}$ 31,000); $\nu_{max.}$ (KBr disc) 1706 cm.$^{-1}$ (ester carbonyl). The n.m.r. spectrum showed signals at 1·92 (s; 2 methene protons), 5·46 (q; methylenes of ethyl groups), 7·13, 7·18, 7·32 (all s; 5 :C·CH_3 groups), and 8·46 τ (t; methyls of ethyl groups).

(*b*) Diethyl 3,3′,5,5′-tetramethyl-2,2′-dipyrromethene-4,4′-dicarboxylate hydrobromide [12] (110 mg.) and acetone (50 ml.) were heated under reflux for 8 hr., when a violet precipitate and solution formed. The solvent was evaporated and methanol (10 ml.) was added to the residue. The solid was separated, washed with ethanol (10 ml.), and dried in air to give a violet powder (71 mg.), m. p. 225—228°, the spectral properties of which were identical with those of the previous preparation.

(*c*) 2,18-Diethoxycarbonyl-8,12-diethyl-1,3,7,13,17,19-hexamethyl-1,19-dideoxybiladiene-ac dihydrobromide (VIII; 250 mg.) in acetone (60 ml.) was heated under reflux for 72 hr. when dark blue crystals had separated from the solution. The product was cooled and the violet-blue needles (54 mg.), m. p. 226—228°, were removed and proved to be identical with the product from the previous preparation.

Ethyl 5-[4-(5-*Ethoxycarbonyl*-3,4-*dimethyl*-2-*pyrrolyl*)-*but*-3-*en*-2-*ylidene*]-2,4-*dimethyl*-5H-*pyrrole*-3-*carboxylate Hydrobromide*.—(*a*) Diethyl 3,3′-4′,5-tetramethyl-2,2′-dipyrromethene-4,5′-dicarboxylate hydrobromide [(V), see below, 200 mg.] and acetone (50 ml.) were heated under reflux for 30 min. when a blue crystalline *product* had separated. The reaction mixture was cooled and the solid separated, washed with acetone (10 ml.), and then dried in air when it was obtained as violet needles with a green lustre (125 mg.). After crystallisation from chloroform–light petroleum it had m. p. 191—192° (Found: C, 56·3; H, 5·9; N, 6·2. $C_{22}H_{29}BrN_2O_4$ requires C, 56·8; H, 6·25; N, 6·0%), $\lambda_{max.}$ ($CHCl_3$) 291, 299, 366, and 604 mμ ($\varepsilon_{max.}$ 13,700, 13,700, 3220, and 113,000), $\lambda_{infl.}$ 568 mμ ($\varepsilon_{infl.}$ 38,000); $\nu_{max.}$ (KBr disc) 1701 cm.$^{-1}$ (ester carbonyl). The n.m.r. spectrum showed signals at 1·90 (s; 2 methene protons), 5·44, 5·49 (both q; methylenes of ethyl groups), 6·98, 7·09 (s; methene protons), 5·44, 5·49 (both q; methylenes of ethyl groups), 6·98, 7·09 (2), 7·57, and 7·59 (all s; 5 = C·CH_3 groups), and 8·42 τ (t; methyls of ethyl groups).

(*b*) Ethyl 2,4-dimethylpyrrole-3-carboxylate (668 mg.) and ethyl 2-formyl-3,4-dimethylpyrrole-5-carboxylate [14] (780 mg.) were dissolved in acetone (30 ml.) at 40° and then hydrobromic acid in acetic acid (1 ml. of 50%) was added. A solid was precipitated immediately from the yellow-green solution and after the mixture had been heated for 30 min. it was cooled, and the solid separated. It was washed with acetone (30 ml.) and dried at 80° when it formed feathery green needles (1·56 g., 84%), m. p. 189—191°. The ultraviolet, visible, and infrared spectra were identical with those of the previous product.

Ethyl 5-[5-(4-*Ethoxycarbonyl*-3,5-*dimethyl*-2-*pyrrolyl*)-*pent*-4-*en*-3-*ylidine*]-2,4-*dimethyl*-5H-*pyrrole*-3-*carboxylate Hydrobromide* (II; R = Et).—(*a*) Hydrobromic acid in acetic acid (1 ml. of 50%) was added to a solution of ethyl 2,4-dimethylpyrrole-3-carboxylate (1·1 g.) and ethyl orthoformate (1·65 ml.) in butan-2-one (10 ml.). An immediate orange precipitate of the dipyrromethene hydrobromide separated. The mixture was heated under reflux for 4 hr. when the spectrum of the product showed that only a trace of the dipyrromethene salt ($\lambda_{max.}$ 475 mμ) was present. After cooling, the precipitated blue needles were separated and washed with methanol (15 ml.). After drying *in vacuo*, the product (70 mg.) was crystallised from chloroform–light petroleum and had m. p. 183—185° (Found: C, 57·8; H, 6·3; N, 5·5. $C_{23}H_{31}BrN_2O_4$ requires C, 57·7; H, 6·45; N, 5·85%), $\lambda_{max.}$ ($CHCl_3$) 291, 357, and 603 mμ ($\varepsilon_{max.}$ 11,000, 5510, and 191,000), and $\lambda_{infl.}$ 568 mμ ($\varepsilon_{infl.}$ 30,000); $\nu_{max.}$ (KBr disc) 1705 cm.$^{-1}$ (ester carbonyl). The n.m.r. spectrum showed signals at 2·00 (s; 2 methene protons), 5·47 (q; 2 methylenes of ester ethyl groups), 6·70 (q; methylene of *meso*-ethyl group), 7·14 (3), 7·32 (1) (both s; 4 :C·CH_3 groups), 8·47 and 8·53 τ (t; methyls of ester ethyls also superimposable on methyl of *meso*-ethyl group).

(*b*) Diethyl 3,3′,5,5′-tetramethyldipyrromethene-4,4′-dicarboxylate hydrobromide (250 mg.) and butan-2-one (50 ml.) were heated under reflux for 8 hr. After cooling, the crystalline product

[12] H. Fischer and W. Zerweck, *Ber.*, 1922, **55**, 1942.

was separated and washed with methanol (10 ml.) when it formed blue needles (20 mg.), m. p. 184—186° with spectral properties identical with those of the previous preparation.

Ethyl 2-(2,2-*Dicyanovinyl*)-3-*ethyl*-5-*methylpyrrole*-4-*carboxylate*.—Ethyl 3-ethyl-2-formyl-5-methylpyrrole-4-carboxylate [13] (300 mg.) and dicyanomethane (120 mg.) were dissolved in warm ethanol (5 ml.). Diethylamine (0·25 ml.) was added, and the mixture kept at room temperature for 30 min. The crude *product* was separated and crystallised from ethanol as long, yellow needles (244 mg., 66%), m. p. 171—173° (Found: C, 65·3; H, 5·8; N, 16·5. $C_{14}H_{15}N_3O_2$ requires C, 65·4; H, 5·9; N, 16·3%), $\nu_{max.}$ 1585 (C=C bond of dicyanovinyl), 1700 (ester carbonyl), 2210 (CN), and 3410 (NH) cm.$^{-1}$.

Diethyl 3,3′,4′,5-*Tetramethyldipyrromethene*-4,5′-*dicarboxylate Hydrobromide*.—Ethyl 2-formyl-3,4-dimethylpyrrole-5-carboxylate [14] (1 g.) and ethyl 2,4-dimethylpyrrole-3-carboxylate (0·85 g.) were dissolved in warm ethanol (20 ml.), and, after cooling, the solution was treated with aqueous hydrogen bromide (5 ml. of 48%). After 3 hr., the crude product was separated, and washed successively with ethanol and ether. The *product* (1·5 g., 69%) crystallised from chloroform–light petroleum as red needles, m. p. 177—178° (Found: C, 53·3; H, 5·8; N, 6·5. $C_{19}H_{25}BrN_2O_4$ requires C, 53·7; H, 5·9; N, 6·6%), $\lambda_{max.}$ 487 mμ ($\varepsilon_{max.}$ 100,200).

Ethyl meso-*Dicyanomethyl*-3,3′,4′,5,5′-*pentamentyldipyrromethane*-4-*carboxylate*.—(*a*) Ethyl 2-(2,2-dicyanovinyl)-3,5-dimethylpyrrole-4-carboxylate [10] (500 mg.) and 2,3,4-trimethylpyrrole (500 mg.) in ethanol (50 ml.) were heated under reflux for 3 hr. After removal of the solvent under reduced pressure, the residue was extracted with hot light petroleum (3 × 4 ml.) in order to remove excess of 2,3,4-trimethylpyrrole. The *product* crystallised from ethanol as colourless prisms (300 mg., 41%), m. p. 202—204° (Found: C, 68·5; H, 7·1; N, 15·7. $C_{20}H_{24}N_4O_2$ requires C, 68·15; H, 6·8; N, 15·9%), $\lambda_{max.}$ 224 and 305 mμ ($\varepsilon_{max.}$ 20,180 and 14,070), $\nu_{max.}$ 3500, 3460, 3405 (NH), 2195 (CN), 1695 (ester carbonyl), and 1660 cm.$^{-1}$ (bonded carbonyl), probably indicating intermolecular hydrogen bonding.

(*b*) Ethyl 3,3′,4′,5,5′-pentamethyldipyrromethene-4-carboxylate [15] (195 mg.) and dicyanomethane (72 mg.) were dissolved in ethanol (10 ml.) containing diethylamine (0·2 ml.), and the mixture heated under reflux for 4 hr. After removal of the solvent under reduced pressure, the dark coloured, tarry residue was extracted with boiling light petroleum (4 × 10 ml.) and then crystallised from ethanol as colourless prisms (23 mg., 10%), m. p. 201—203°, alone and mixed with the previous product. The spectral properties were also similar to those of the previous preparation.

Ethyl meso-*Dicyanomethyl*-3-*ethyl*-3′,4′,5,5′-*tetramethyldipyrromethane*-4-*carboxylate*.—This was prepared similarly from ethyl 2-(2,2-dicyanovinyl)-3-ethyl-5-methylpyrrole-4-carboxylate (100 mg.) and 2,3,4-trimethylpyrrole (100 mg.). The *product* was crystallised from ethanol as colourless prisms (52 mg., 35%), m. p. 213—215° (Found: C, 68·5; H, 7·0; N, 15·7. $C_{21}H_{26}N_4O_2$ requires C, 68·8; H, 7·1; N, 15·3%), $\lambda_{max.}$ 228 and 306 mμ ($\varepsilon_{max.}$ 15,800 and 13,020), $\nu_{max.}$ 3500, 3460, 3405 (NH), 2195 (CN), 1690 (ester carbonyl), and 1655 cm.$^{-1}$ (bonded carbonyl).

Ethyl meso-*Dicyanomethyl*-4′-*ethyl*-3,3′,5,5′-*tetramethyldipyrromethane*-4-*carboxylate*.—(*a*) This was prepared similarly from ethyl 2-(2,2-dicyanovinyl(-3,5-dimethylpyrrole-4-carboxylate (200 mg.), and 3-ethyl-2,4-dimethylpyrrole (0·2 ml.) in ethanol (20 ml.) by heating under reflux for 12 hr. The *product* crystallised from ethanol as colourless prisms (171 mg., 57%), m. p. 185—187° (Found: C, 68·7; H, 7·05; N, 15·4%; *M*, 340. $C_{21}H_{26}N_4O_2$ requires C, 68·8; H, 7·1; N, 15·3%); *M*, 366), $\lambda_{max.}$ 229 and 304 mμ ($\varepsilon_{max.}$ 16,680 and 13,320); $\nu_{max.}$ 3500, 3460, 3405 (NH), 2195 (CN), 1690 (ester carbonyl), 1660 (bonded carbonyl) cm.$^{-1}$.

(*b*) Ethyl 4′-ethyl-3,3′,5,5′-tetramethyldipyrromethene-4′-carboxylate hydrobromide [16] (200 mg.) in chloroform (5 ml.) was washed successively with dilute aqueous ammonia and water, and dried (Na_2SO_4). After removal of the chloroform by evaporation under reduced pressure, the orange-red crystalline residue was dissolved in ethanol (200 ml.) containing diethylamine (0·2 ml.). Warm dicyanomethane (0·1 ml.) was added, and the mixture heated under reflux for 1 hr. After removal of the solvent by evaporation under reduced pressure, the semi-solid residue was triturated with light petroleum (10 ml.), separated, and crystallised from ethanol as colourless prisms (34 mg., 18%), m. p. 184—187°, raised to 185—187° after a further crystallisation from ethanol. The ultraviolet and infrared spectra were identical with those of the previous product.

[13] D. Dolphin, R. Grigg, A. W. Johnson, and J. Leng, *J.*, 1965, 1460.
[14] H. Fischer and J. Hierneis, *Annalen*, 1931, **492**, 21.
[15] H. Fischer and B. Walach, *Annalen*, 1926, **450**, 109.
[16] H. Fischer, P. Halbig, and B. Walach, *Annalen*, 1927, **452**, 268.

Diethyl meso-*Dicyanomethyl*-3,3′,5,5′-*tetramethyldipyrromethane*-4,4′-*dicarboxylate*.—Diethyl 3,3′,5,5′-tetramethyldipyrromethene-4,4′-dicarboxylate hydrobromide (200 mg.) and dicyanomethane (50 mg.) were dissolved in chloroform (25 m.) containing diethylamine (1 ml.), and the mixture heated under reflux for 15 hr. After removal of the solvents by evaporation under reduced pressure, the *residue* crystallised from ethanol as colourless prisms (113 mg., 59%), m. p. 210—212° (Found: C, 64·4; H, 6·1; N, 13·5. $C_{22}H_{26}N_4O_4$ requires C, 64·4; H, 6·4; N, 13·7%), $\lambda_{max.}$ 230 and 306 mμ ($\varepsilon_{max.}$ 22,500 and 17, 270); $\lambda_{infl.}$ 280 mμ (ε 13,500).

Diethyl meso-*Dicyanomethyl*-3,3′,4′,5-*tetramethyldipyrromethane*-4,5′-*dicarboxylate*.—This was prepared similarly from diethyl 3,3′,4′,5-tetramethyldipyrromethene-4,5′-dicarboxylate hydrobromide (100 mg.) and dicyanomethane (25 mg.), which were heated under reflux in chloroform (12 ml.) containing diethylamine (0·5 ml.) for 20 min. The product crystallised from ethanol as colourless prisms (27 mg., 28%), m. p. 180—182° (decomp.) (Found: C, 64·2; H, 6·4. $C_{22}H_{26}N_4O_4$ requires C, 64·4; H, 6·4%), $\lambda_{max.}$ 248 and 305 mμ (ε, 18,700 and 14,200); $\lambda_{infl.}$ 261 mμ (ε, 16,700).

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