

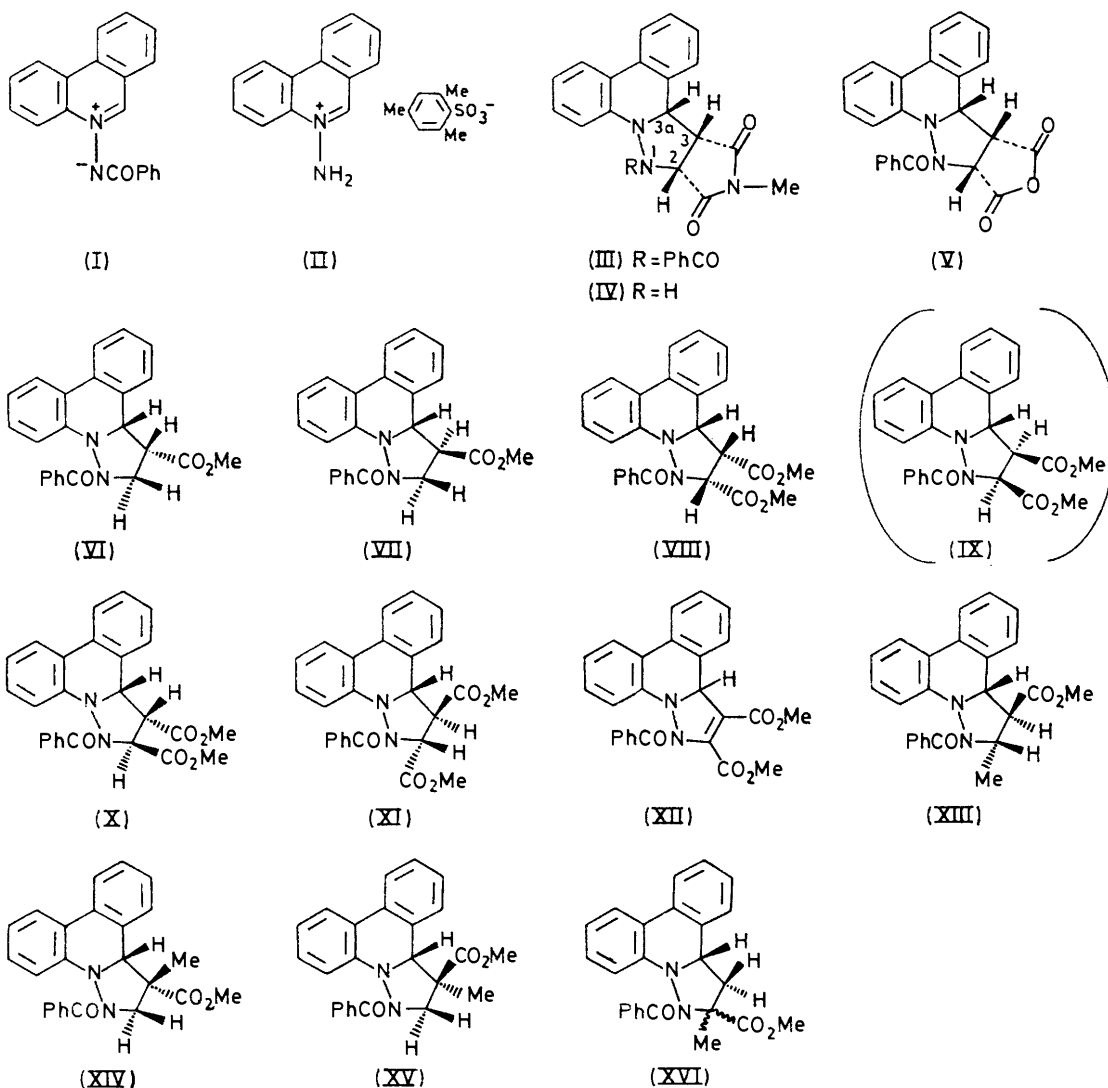
## Stereochemistry of the 1,3-Dipolar Cycloaddition Reaction between *N*-(Phenanthridin-5-io)benzamidate and Olefins

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*N*-(Phenanthridin-5-io)benzamidate reacts with activated olefins such as *N*-methylmaleimide, maleic anhydride, dimethyl maleate, dimethyl fumarate, methyl acrylate, methyl methacrylate, and methyl *trans*-crotonate to give 1 : 1 cycloadducts, whose stereochemistry has been deduced from n.m.r. spectroscopic data. The adducts from *N*-methylmaleimide, maleic anhydride, and dimethyl maleate have the all-*cis*(2*H*,3*H*,3*aH*)-stereochemistry. These results are rationalised in terms of secondary molecular orbital interactions. With acrylates such stereospecificity is lost, suggesting that this effect is of lesser importance.

WHEN 1,3-dipoles such as azomethine ylides, azomethine imides, and nitrones undergo cycloaddition to conjugated olefins, the possibilities of 'endo' and 'exo' stereo-

1,3-dipolar cycloaddition reactions is scarce and its interpretation is controversial,<sup>1</sup> in contrast with the extensive data available on Diels–Alder reactions.<sup>2</sup>



chemistry arise just as in the case of Diels–Alder reactions. However, information on the stereochemistry of

<sup>1</sup> (a) R. Huisgen, H. Hauck, R. Grashey, and H. Seidel, *Chem. Ber.*, 1969, **102**, 736; (b) B. E. Landberg and J. W. Lown, *J.C.S. Perkin I*, 1975, 1326; (c) A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc. (C)*, 1971, 874; N. Dennis, A. R. Katritzky, T. Matuo, S. K. Parton, and Y. Takeuchi, *J.C.S. Perkin I*, 1974, 746; (d) J. W. Lown and K. Matsumoto, *J. Org. Chem.*, 1971, **36**, 1405.

We now report on some stereochemical aspects of the 1,3-dipolar cycloadditions between *N*-(phenanthridin-5-

<sup>2</sup> For example (a) Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, 1970, **92**, 6543; Y. Kobuke, T. Sugimoto, and J. Furukawa, *ibid.*, 1972, **94**, 3633, and references cited therein; (b) J. M. Mellor and C. F. Webb, *J.C.S. Perkin II*, 1974, 17, 26; B. C. C. Cantello, J. M. Mellor, and C. F. Webb, *ibid.*, p. 22, and references cited therein.

io)benzamidate (I) and several activated olefins. In general, the cycloaddition was carried out by stirring at room temperature or refluxing a solution of equimolar amounts of (I)<sup>3</sup> and the olefin in benzene. After evaporation the crude material was purified either by recrystallisation or by preparative t.l.c.

When the benzamidate (I) was treated with *N*-methylmaleimide at room temperature, a single 1:1 adduct (III) was obtained in 70% yield. The stereochemical relationship of H-2, -3, and -3a was readily ascertained from the n.m.r. spectrum. The *N*-methyl signal appears at 0.65 p.p.m. to higher field than that of *N*-methylsuccinimide ( $\delta$  2.81). A molecular model indicates that the *N*-methyl group can be oriented in the shielding cone of the benzene ring only when H-2, -3, and -3a are in the all-*cis*(2H,3H,3aH)-configuration (Figure 1).

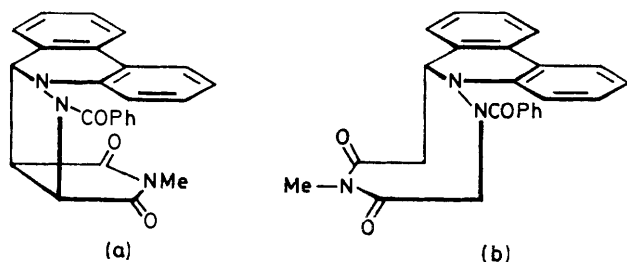


FIGURE 1

That the benzoyl group has no effect on the stereochemical result was demonstrated by the fact that the cycloadduct (IV) obtained in 69% yield from the reaction of the *N*-aminophenanthridinium salt (II)<sup>\*,3</sup> with *N*-methylmaleimide in the presence of base also showed the high field *N*-methyl signal ( $\Delta\delta$  0.68 p.p.m.); the adduct thus has the same stereochemistry as (III).

A cycloadduct (V) of the same stereochemistry was obtained when the benzamidate (I) reacted with maleic anhydride; the coupling constants ( $J_{2,3} = J_{3,3a} = 8$  Hz) are in good agreement with the values observed for (III).

Heating the benzamidate (I) with methyl acrylate in refluxing benzene for 10 min gave a quantitative yield of two isomeric adducts (VI) and (VII) in the ratio 1.1:1.0 (by n.m.r. spectroscopy). In the n.m.r. spectra, the methoxycarbonyl signal of (VI) ( $\delta$  2.91) occurs 0.79 p.p.m. to higher field than that of (VII) ( $\delta$  3.70), a consequence of the former group being situated almost directly over the benzene ring.

The benzamidate (I) gave a single adduct (VIII), in 63% yield, when treated with dimethyl maleate in refluxing benzene for 21 h. On the other hand, compound (I), on refluxing with dimethyl fumarate in benzene for 5 h, afforded two further adducts, (X) and (XI), in 14 and 42% yields, respectively, which were isomeric with (VIII). The stereochemistry of these adducts was again defined by the chemical shifts of the methoxycarbonyl groups. Models of the four possible stereoisomers (VIII)—(XI)

\* Cycloaddition of (II), for example, with methyl acrylate gave directly the aromatised product, methyl pyrazolo[1,5-*f*]phenanthridine-3-carboxylate.

indicate that at least one of the methoxycarbonyl groups in (VIII) and (X) lies over the benzene ring and should be diamagnetically shielded, whereas the methoxycarbonyl proton signals in (IX) and (XI) should appear at the normal positions. Indeed, the C-3 methoxycarbonyl protons in (VIII) and (X) are shielded by 0.7 and 0.9 p.p.m. relative to the other methyl ester group ( $\delta$  3.67 and 3.86, respectively), but the signals due to the C-2 and C-3 methoxycarbonyl groups of (XI) appear at an essentially the same position ( $\delta$  3.77 and 3.71). This, together with the facts that the isomer (VIII) was obtained by catalytic hydrogenation of the unsaturated ester (XII), prepared by the reaction of (I) with dimethyl acetylenedicarboxylate,<sup>3</sup> and that the geometry of the olefins is retained in the adducts (the maleate and fumarate giving isomeric adducts) suggests that the adduct (VII) has the all-*cis*(2H,3H,3aH)-stereochemistry, and the other two isomers, (X) and (XI), have the *trans*, (2H,3H)-*cis*(3H,3aH)- and *trans*-(2H,3H)-*trans*-(3H,3aH)-configuration, respectively.

The reaction of the benzamidate (I) with methyl *trans*-crotonate in refluxing benzene for 8 h gave a single adduct (XIII) in 80% yield, whose methoxycarbonyl signal appears at the normal position ( $\delta$  3.72), in agreement with the assignment. The configuration of the 2-methyl group was assigned on the assumption that the addition proceeded with the retention of the geometry of the olefin.

Methyl methacrylate also reacted with the benzamidate (I) in refluxing benzene, to produce three isomeric adducts (XIV)—(XVI) in 40, 31, and 17% yields, respectively. The stereochemistry of (XIV) and (XV) was readily assigned by comparison of the chemical shifts of the methoxycarbonyl groups [ $\delta$  2.90 for (XIV) and 3.80 for (XV)] with those of (VI) ( $\delta$  2.91) and (VII) ( $\delta$  3.70). The high-field shift of the 3-methyl group of (XV) ( $\delta$  0.91) relative to that of (XIV) ( $\delta$  1.61) also supported this stereochemical assignment. The third isomer was assigned the gross structure (XVI). The n.m.r. spectrum shows a methyl singlet at  $\delta$  2.00, a methoxycarbonyl singlet at  $\delta$  3.62, and an ABX multiplet for the 3- and 3a-protons.

Vicinal coupling constants for H-2, -3, and -3a varied with substitution over a wide range (Table 1), making it hazardous to assign *cis*- or *trans*-stereochemistry from these values only.

All the aforementioned cycloadducts are stable under the reaction conditions used; thus the product mixtures are assumed to be kinetically determined. The results are summarised in Table 2. The 1,3-dipolar cycloadditions of the benzamidate (I) with *N*-methylmaleimide, maleic anhydride, and dimethyl maleate are stereospecific and the adducts have the all-*cis*-configuration. Similar results have been reported for the reactions of 3,4-dihydroisoquinoline *N*-oxide,<sup>4a</sup> 1-(benzodiazinio)-

<sup>3</sup> Y. Tamura, Y. Miki, Y. Nishikawa, and M. Ikeda, *J. Heterocyclic Chem.*, 1976, **13**, 317.

<sup>4</sup> Y. Tamura, Y. Miki, K. Nakamura, and M. Ikeda, *J. Heterocyclic Chem.*, 1976, **13**, 23.

TABLE 1

Compd.	Chemical shifts ( $\delta$ ) and coupling constants (Hz) of cycloadducts (in CDCl <sub>3</sub> )						
	H-2	H-3	H-3a	C <sub>2</sub> -CO <sub>2</sub> Me	C <sub>3</sub> -CO <sub>2</sub> Me	J <sub>2,3</sub>	J <sub>3,3a</sub>
(III) <sup>a</sup>	5.82 (d)	3.87 (t)	4.85 (d)		2.16 (NMe)	7.5	7.5
(IV) <sup>a</sup>	4.33 (t) <sup>b</sup>	3.60 (t)	4.69 (d)		2.13 (NMe)	7.5	7.5
(V) <sup>a</sup>	6.07 (d)	4.27 (t)	5.04 (d)			8	8
(VI)	3.2—4.0 4.5—4.9	3.2—4.0	4.5—4.9		2.91	<i>c</i>	<i>c</i>
(VII)	3.2—3.9 4.5—4.9	3.2—3.9	4.54 (d)		3.70	<i>c</i>	9.5
(VIII)	5.64 (d)	3.95 (dd)	4.89 (d)	3.67	2.93	10	8
(X)	5.32 (d)	3.51 (dd)	5.13 (d)	3.86	2.96	7.5	3
(XI)	5.78 (d)	ca. 3.7 <sup>d</sup>	4.55 (d)	3.77	3.71	8	10
(XIII)	4.95 (m)	3.07 (dd)	4.65 (d)	(or 3.71) 1.48 (2-Me) (d, 7 Hz)	(or 3.77) 3.72	8	10.5
(XIV)	4.27 (ABq)		4.28 (s)		1.61 (3-Me) 2.90	J <sub>2,2'</sub> 12	
(XV)	3.15 (d), 5.17(d)		4.96 (s)		0.91 (3-Me) 3.80	J <sub>2,2'</sub> 12	
(XVI)		2.1—3.0	4.86 (q)	3.62	2.00 (3-Me)	J <sub>3,3'</sub> 12, J <sub>3,3a</sub> 5.5, J <sub>3',3a</sub> 11.5	

<sup>a</sup> In (CD<sub>3</sub>)<sub>2</sub>SO. <sup>b</sup> Became a doublet after treatment with deuterium oxide. <sup>c</sup> Coupling constants not determined owing to the complexity of the signals. <sup>d</sup> Masked by two CO<sub>2</sub>Me signals.

TABLE 2

## Product distribution in cycloaddition reactions

1,3-Dipole	Olefin	<i>cis</i> (3H,3aH)-Adduct	<i>trans</i> (3H,3aH)-Adduct
(I)	<i>N</i> -Methylmaleimide	(III) 100 (70) <sup>b</sup>	0 (0)
(II)	<i>N</i> -Methylmaleimide	(IV) 100 (69)	0 (0)
(I)	Maleic anhydride	(V) 100 (70)	0 (0)
(I)	Dimethyl maleate	(VIII) 100 (63)	0 (0)
(I)	Methyl acrylate	(VI) 52.4 <sup>a</sup> (60)	(VII) 47.6 (30)
(I)	Methyl methacrylate	(XIV) 55.9 <sup>a</sup> (40)	(XV) 44.1 (31)
(I)	Methyl <i>trans</i> -crotonate	ca. 0 (0)	(XIII) ca. 100 (80)

<sup>a</sup> Product ratio determined by n.m.r. spectroscopy. <sup>b</sup> Isolated yield (%) in parentheses.

benzamides,<sup>4</sup> and 1-(isoquinolin-2-yl)acetylide<sup>1b,5</sup> with either maleimides or dimethyl maleate. These stereochemical results may be rationalised in terms of secondary molecular orbital interactions. The transition state depicted in Figure 2(a) closely resembles

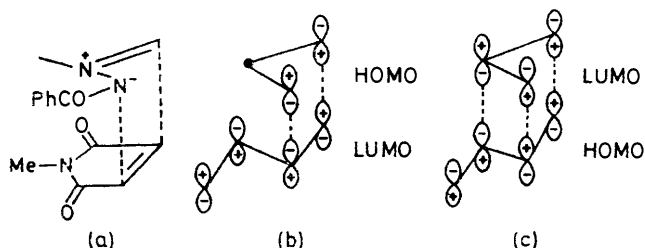


FIGURE 2

that proposed for the interpretation of *endo*-selectivity in Diels-Alder reaction, in which there is a favourable secondary orbital interaction between occupied diene (HOMO) and unoccupied olefin molecular orbitals (LUMO) or between unoccupied diene (LUMO) and occupied olefin molecular orbitals (HOMO).<sup>6</sup> In the 1,3-dipolar cycloaddition, however, the secondary interaction shown in Figure 2(b) must be negligible, but that in Figure 2c is bonding in character: consequently the transition state shown in Figure 2(a) is expected to be favoured.

<sup>5</sup> N. S. Basketter and A. O. Plunkett, *J.C.S. Chem. Comm.*, 1975, 594.

The situation with acrylates is complicated. The ratios of products from methyl acrylate and methyl methacrylate are close to 1:1. Apparently, the secondary effect is of smaller importance in these cases. Of particular interest is the case of methyl *trans*-crotonate, in which only the *exo*-CO<sub>2</sub>Me addition product (XIII) was obtained. In this and the methacrylate cases another factor, such as an attractive interaction<sup>2a</sup> between the methyl group and the 1,3-dipole, must be involved.

TABLE 3

Effect of solvent in the reaction of the benzamidine (I) with methyl acrylate

Solvent	Reaction		Product ratio (VI) : (VII) <sup>a</sup>
	time (min)	temp. (°C)	
PhH	10	80	1.08 : 1
CH <sub>3</sub> CN	10	82	1.18 : 1
MeOH	30	65	1.53 : 1

<sup>a</sup> Determined by n.m.r. analysis of the crude reaction mixture after evaporation of the solvent.

Finally, the product ratio is affected by the solvent used. Thus, the ratio of the isomers (VI) and (VII) from the reaction of the benzamidine (I) and methyl acrylate increased with increasing polarity of the solvent (Table 3). The observed effects are similar to those

<sup>6</sup> R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie and Academic Press, 1970, p. 145.

reported for the Diels–Alder reaction between methyl acrylate and cyclopentadiene.<sup>7</sup>

#### EXPERIMENTAL

N.m.r. spectra were determined with a Hitachi R-20A spectrometer (tetramethylsilane as internal standard). I.r. spectra were recorded with a Hitachi EPI-G2 spectrophotometer. Preparative layer chromatography (p.l.c.) was carried out on Merck alumina PF254.

*all-cis*(2H,3H,3aH)-1-Benzoyl-1,2,3,3a-tetrahydro-N-methylpyrazolo[1,5-f]phenanthridine-2,3-dicarboximide (III).—A solution of the benzamidate (I) (74.5 mg) and N-methylmaleimide (26 mg) in benzene (5 ml) was stirred for 7 h at room temperature. The precipitated crystals were collected and recrystallised from ethyl acetate to give white crystals (71 mg, 70%) of (III); m.p. 267–269° (Found: C, 73.15; H, 4.6; N, 10.3.  $C_{25}H_{16}N_3O_3$  requires C, 73.3; H, 4.7; N, 10.3%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 710 and 1 660 cm<sup>-1</sup>.

*all-cis*(2H,3H,3aH)-1,2,3,3a-Tetrahydro-N-methylpyrazolo[1,5-f]phenanthridine-2,3-dicarboximide (IV).—Potassium carbonate (207 mg) was added to a stirred solution of the salt (II) (394 mg) and N-methylmaleimide (111 mg) in dimethylformamide (10 ml). The mixture was stirred for 5 h at room temperature and evaporated. The residue was extracted with chloroform. The extract was washed with water, dried (MgSO<sub>4</sub>), and concentrated to give white crystals (210 mg, 69%) of (IV); m.p. 225–227° (from ethanol) (Found: C, 70.5; H, 5.0; N, 13.6.  $C_{18}H_{16}N_3O_2$  requires C, 70.8; H, 4.95; N, 13.8%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 705 cm<sup>-1</sup>.

*all-cis*(2H,3H,3aH)-1-Benzoyl-1,2,3,3a-tetrahydropyrazolo[1,5-f]phenanthridine-2,3-dicarboxylic Anhydride (V).—By a procedure similar to that described for the adduct (III), the benzamidate (I) (74.5 mg) and maleic anhydride (25 mg) gave white crystals (70 mg, 70%) of (V); m.p. 180–182° [from acetone–light petroleum (b.p. 60–80°)] (Found: C, 70.9; H, 5.2; N, 6.5.  $C_{24}H_{16}N_2O_4$  requires C, 70.6; H, 5.0; N, 6.3%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 790 cm<sup>-1</sup>.

Methyl *cis*- and *trans*-1-Benzoyl-1,2,3,3a-tetrahydropyrazolo[1,5-f]phenanthridine-3-carboxylates [(VI) and (VII)].—A solution of the benzamidate (I) (74.5 mg) and methyl acrylate (2 ml) in benzene (3 ml) was heated under reflux for 10 min, then concentrated and the residue was subjected to p.l.c. with ether–light petroleum (b.p. 30–60°) (1:1) to give two products; the adduct (VI) (60%) had m.p. 140–141° [from benzene–light petroleum (b.p. 60–80°)] (Found: C, 74.8; H, 5.3; N, 7.3.  $C_{24}H_{20}N_2O_3$  requires C, 75.0; H, 5.2; N, 7.3%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 630 cm<sup>-1</sup>; the adduct (VII) (30%) had m.p. 69–71° [from light petroleum (b.p. 60–80°)] (Found: C, 75.0; H, 5.4; N, 7.1%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 630 cm<sup>-1</sup>.

Dimethyl *all-cis*(2H,3H,3aH)-1-Benzoyl-1,2,3,3a-tetrahydropyrazolo[1,5-f]phenanthridine-2,3-dicarboxylate (VIII).—(A) From the benzamidate (I). A solution of compound (I) (74.5 mg) and dimethyl maleate (38 mg) in benzene (5 ml) was heated under reflux for 21 h, then evaporated *in*

*vacuo*, and the residue was purified by p.l.c. with chloroform–benzene (1:1) to give white crystals (70 mg, 63%) of (VIII); m.p. 209–210° [from acetone–light petroleum (b.p. 60–80°)] (Found: C, 70.4; H, 5.1; N, 6.2.  $C_{26}H_{22}N_2O_5$  requires C, 70.6; H, 5.0; N, 6.3%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 765, 1 735, and 1 640 cm<sup>-1</sup>.

(B) From the unsaturated adduct (XII). Compound (XII)<sup>8</sup> (65 mg) was hydrogenated in methanol (40 ml) over platinum oxide (70 mg) at atmospheric pressure and room temperature for 12 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by p.l.c. with benzene–chloroform (2:1) to give white crystals (39 mg, 60%) of (VIII); m.p. 209–210°.

Dimethyl *trans*(2H,3H)-*cis*-(3H,3aH)- and *trans*-(2H,3H)-*trans*-(3H,3aH)-1-Benzoyl-1,2,3,3a-tetrahydropyrazolo[1,5-f]phenanthridine-2,3-dicarboxylate [(X) and (XI)].—A solution of the benzamidate (I) (74.5 mg) and dimethyl fumarate (38 mg) in benzene (5 ml) was refluxed for 5 h to give two products, which were separated by p.l.c. with benzene–ethyl acetate (10:1); the adduct (X) (14%) had m.p. 176–177° [from benzene–light petroleum (b.p. 60–80°)] (Found: C, 70.9; H, 5.2; N, 6.5.  $C_{26}H_{22}N_2O_5$  requires C, 70.6; H, 5.0; N, 6.3%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 735 and 1 630 cm<sup>-1</sup>; the adduct (XI) (42%) had m.p. 156–157° [from benzene–light petroleum (b.p. 60–80°)] (Found: C, 71.0; H, 5.1; N, 6.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 735 and 1 650 cm<sup>-1</sup>.

Methyl *trans*(2H,3H)-*trans*(3H,3aH)-1-Benzoyl-1,2,3,3a-tetrahydro-2-methylpyrazolo[1,5-f]phenanthridine-3-carboxylate (XIII).—A solution of the benzamidate (I) (317 mg) and methyl *trans*-crotonate (2 ml) in benzene (20 ml) was refluxed for 8 h and concentrated. The residue was purified by p.l.c. with ether–light petroleum (b.p. 30–60°) (5:3) to give white crystals (339 mg, 80%) of (XIII); m.p. 149–150° (from methanol) (Found: C, 75.35; H, 5.6; N, 6.9.  $C_{25}H_{22}N_2O_3$  requires C, 75.4; H, 5.6; N, 7.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 635 cm<sup>-1</sup>.

Methyl *cis*(3Me,3aH)- and *trans*(3Me,3aH)-1-Benzoyl-1,2,3,3a-tetrahydro-3-methylpyrazolo[1,5-f]phenanthridine-3-carboxylate and Methyl 1-Benzoyl-1,2,3,3a-tetrahydro-2-methylpyrazolo[1,5-f]phenanthridine-2-carboxylate [(XIV), (XV), and (XVI)].—A solution of the benzamidate (I) (208 mg) and methyl methacrylate (2 ml) in benzene (20 ml) was refluxed for 1.5 h to give three isomeric products which were separated by p.l.c. with ether–light petroleum (b.p. 30–60°) (1:1); the adduct (XIV) (40%) had m.p. 158–159° (from methanol) (Found: C, 75.3; H, 5.6; N, 6.9.  $C_{25}H_{22}N_2O_3$  requires C, 75.4; H, 5.6; N, 7.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 630 cm<sup>-1</sup>; the adduct (XV) (31%) had m.p. 124–125° (from n-hexane) (Found: C, 75.4; H, 5.6; N, 7.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 730 and 1 640 cm<sup>-1</sup>; the adduct (XVI) (17%) had m.p. 170–171° (from n-hexane) (Found: C, 75.2; H, 5.6; N, 7.0%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 740 and 1 630 cm<sup>-1</sup>.

[6/148 Received, 23rd January, 1976]

<sup>7</sup> J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, 1962, **84**, 292.