Tetrahedron Vol. 35, pp. 2463 to 2470
Pergamon Press Ltd., 1979. Printed in Great Britain

QUINOXALINES AND RELATED COMPOUNDS—XI[1]

THE FORMATION OF FUSED PYRROLES BY THE CONDENSATION OF HALOAZINES WITH METHYLAZINES

R. K. ANDERSON,[a] S. D. CARTER and G. W. H. CHEESEMAN*
Department of Chemistry, Queen Elizabeth College, Campden Hill, London W8 7AH, England

(*Received in UK 27 April* 1979)

Abstract—2-Chloroquinoxaline reacts with a series of 2-methyl-3-substituted quinoxalines (**1a–j**) giving, in moderate yields, 6-substituted-pyrrolo[1,2-a: 4,5-b']-diquinoxalines (**2a–j**). Similar polycyclic compounds (**9a–c**; **11b,c**; and **13b**) are formed from 4-methylquinazolines (**8a–c**), 1-methylphthalazines (**10b,c**) and 2-hydroxy-4-methylpyrimidine (**12b**); the reaction failing with 2-methylquinazolines and 3-methylcinnolines. Polycyclic materials (**17a–c**) are also obtained by using chloropyrazines (**15a,b**) as the haloazine component. Four novel ring systems have thus been obtained; the mechanism is discussed.

The high m.p. orange solid (methylquinoxaline orange) obtained, in low yield, by heating 2-methylquinoxaline either alone at 200°[2] or with dilute hydrochloric acid[3] has been shown to be 6-methylpyrrolo[1,2-a: 4,5-b']diquinoxaline (**2b**).[4] The same material may be obtained, in much better yield, by the acid catalysed reaction of 2-chloroquinoxaline with 2,3-dimethylquinoxaline.[4]

A number of apparently similar reactions are known. Pratt *et al.* have prepared, *inter alia*, the indolizinoquinoxaline (**4**) by heating 2-chloro-3-(carbomethoxycyanomethyl)quinoxaline (**3**) with pyridine.[5] 3-Chloro-6-methylpyridazine in refluxing phosphoryl chloride forms the tricyclic compound (**5**);[6] similar treatment of the isomeric amides (**6**) gives, apart from the desired nitriles, two highly coloured compounds, one of which was shown to be **7**.[7]

Wishing to investigate the scope of this type of condensed pyrrole forming reaction, and at the same time to shed some light on the mechanism, we have examined the reactions of a variety of methylazines with several chloroazines.

RESULTS

(See Table 1). Ten different 2-methylquinoxalines (**1a–j**) have been reacted with 2-chloroquinoxaline. With the exception of 2-methylquinoxaline (**1a**) itself, all react smoothly in acetone at room temperature under acid catalysis affording the pyrrolodiquinoxalines (**2b–j**) in moderate yields, there being no evident correlation between the nature of the substituent and either the yield or rate of reaction. While (**1a**) reacts fairly rapidly with 2-chloroquinoxaline the complexity of the crude product is such that only a very poor yield of the parent heterocycle (**2a**) can be obtained. To date, the best method of forming (**2a**) is by the decarboxylation of **2j**.

4-Methylquinazolines (**8a–c**) also react with 2-chloroquinoxaline giving the corresponding polycyclic compounds (**9a–c**); in these cases, however, it is necessary to use acetic acid as the solvent, the reaction being extremely slow in acetone. Even more forcing conditions (acetic acid; 50–60°) are needed for the methylphthalazines (**10b,c**). While 1-methylphthalazine itself (**10a**) appeared to react extensively giving a highly coloured product (λ_{max} 490 nm) the multiplicity of products prohibited the isolation of the parent heterocycle (**11a**). At first sight the lower reactivity of 4-methylquinazolines and 1-methylphthalazines is somewhat surprising as the Me groups in these compounds are normally noticeably more reactive than those in 2-methylquinoxalines;[8] we shall return to this point.

Other methyl diazines such as, *inter alia*, 3-methyl-4-phenyl-6-chlorocinnoline, 2-methyl-4-phenyl-6-chloroquinazoline and 2-methyl-4-hydroxyquinazoline did not give the hoped for polycycles. Cinnolines were recovered intact even from fairly drastic conditions and the 2-methylquinazolines gave only minor amounts of coloured materials which showed the expected long wavelength triplet centred at, e.g. 416 nm (for the product from 2-methyl-4-hydroxy-quinazoline) with considerable amounts of starting material being recovered. Mass spectra and tlc showed that these coloured materials were complex mixtures of, *inter alia*, the desired pentacycle, hydrolysis products, and 2:1 adducts and these reactions were not pursued. The low reactivity of cinnolines is not unexpected but in general a Me group at the 2-quinazoline position is of comparable reactivity to one at the 2-quinoxaline position.[8]

Some preliminary experiments revealed, unsurprisingly that non benzo fused methyl diazines were considerably less reactive than the benzodiazines with which we have so far been dealing. Methyl-pyrazines do not react with 2-chloroquinoxaline under those conditions efficacious for 2-methylquinoxalines. 4-Methylpyrimidine (**12a**) reacts extensively (acetic acid; 50°) the mixture going deep red and depositing a solid; dilution with water gave an encouraging transient deep blue-green colour (see Experimental on quinazolines). Work-up, however, gave a deep brown solid, tlc of which showed it to be a complex mixture and attempts to isolate the desired heterocycle (**13a**) were not successful. 2-Hydroxy-4-methylpyrimidine (**12b**) is far more satisfactory, giving a reasonable yield of the polycycle (**13b**) albeit contaminated with a compound thought to be **14**.

That the chloroazine could be varied was shown by the

*Present address: Beecham Pharmaceuticals, Chemotherapeutic Research Centre, Brockham Park, Betchworth, Surrey RH3 7AJ, England.

Table 1.

Cpd	R	m.p. (°C)	Yield (%)[a]	Found % C	Found % H	Found % N	Required % C	Required % H	Required % N	$(M^+$found $- M^+$ required$)\times 10^5$
2a	H[4]	244-5	7		-			-		-
2b	Me[4]	257-8	74[b]		-			-		-
2c	Cl	241-2	46	67.0	3.2	18.0	67.0	3.0	18.4	5
2d	OMe	286-7	44	72.1	4.5	18.3	72.0	4.0	18.7	11
2e	OEt	211	63	72.6	4.7	17.5	72.6	4.5	17.8	3
2f	OPh	253-4	55	76.1	3.9	15.3	76.2	3.9	15.5	7
2g	Ph	224	57	79.9	4.1	16.2	79.8	4.1	16.2	4
2h	CO_2Et	203-4	30	69.2	4.1	16.6	70.2	4.1	16.3	10
2i	Ac	204-5	74	73.4	4.1	17.5	73.1	3.9	17.9	7
2j	CO_2H	170 dec	$\geqslant 27$[c]		-			-		-
9a	H	312-4	30	75.1	3.8	21.0	75.5	3.7	20.7	4
9b	Me	305	46	75.9	4.1	19.8	76.0	4.3	19.7	5
9c	Ph	315	65[d]	79.4	4.5	16.3	79.8	4.1	16.2	5
11a	H	-	-		-			-		-
11b	Me	257-8	34	76.2	4.5	19.9	76.0	4.3	19.7	1
11c	Ph	>350	31 (77)[e]	79.4	4.3	16.3	79.8	4.1	16.2	1
17a	Me R'=H	201-2	10[e]	72.1	4.7	23.8	71.8	4.3	23.9	-
17b	Ph R'=H	224-5	3	76.9	3.9	18.7	77.0	4.1	18.9	-
17c	Ph R'=Ph	263	30	83.0	4.5	12.5	83.0	4.5	12.5	5

a) The yields here quoted are those after the first purification step (i.e. - one recrystallisation or sublimation) and are based on the chloroazine.
b) Crude; m.p. 254-5°.
c) Based on the amount of (2 a) obtained after vacuum sublimation. See experimental.
d) Crude; m.p. 284°.
e) Based on unrecovered methyl azine.

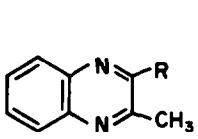
use of chloropyrazines. 2-Chloropyrazine (**15a**) and 2-chloro-5,6-diphenylpyrazine (**15b**) gave the expected polycycles (**17a–c**) with 2,3-dimethylquinoxaline (**1b**) and 2-methyl-3-phenylquinoxaline (**1g**). The conditions needed are forcing (acetic acid; reflux) and in the case of **17a,b** the yields are very poor.

DISCUSSION

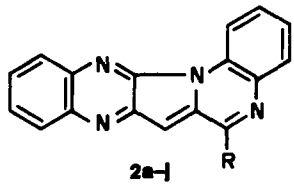
Several possible mechanisms exist for these cyclisation reactions. The initial step could be quaternisation in a similar mechanism to that proposed by Pratt and Keresztesy[5] (Scheme 1) but we felt this to be inherently unlikely because of the low nucleophilicity of quinoxalines (for which our reaction works best). The alternative first step is the formation of a C–C bond, either by chloride displacement[4] (Scheme 2) or by addition to the unsubstituted C–N double bond (Scheme 3).

Were the formation of a diquinoxalinylmethane (**18** cf the formation of diquinolylmethanes[9]) the initial step, then a "blocked" 2-chloroquinoxaline (e.g. **2c**) should afford this type of intermediate (**19**) upon reaction with 2,3-dimethylquinoxaline (**2b**) as the normal cyclisation could no longer occur. However, even under forcing conditions (acetic acid; reflux) no such material was observed, starting materials (or hydrolysis products) being recovered; similar negative results were obtained using several other combinations of reaction partners, Scheme 2 may therefore be eliminated.

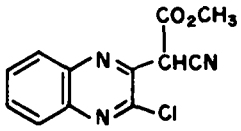
Any proposed mechanism must account for the less facile reaction of 1-methylphthalazines and 4-methylquinazolines despite indications that these Me groups are more reactive than those in 2-methylquinoxalines.[8] This can be simply explained on the basis of Scheme 3 if one examines the role of the acid catalyst more closely. Addition of carbon acids to azines is by now a well established phenomenon (see particularly the



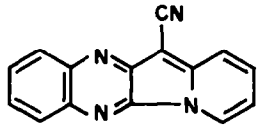
1a–l



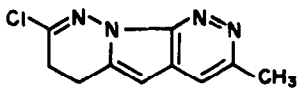
2a–l



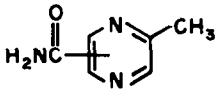
3



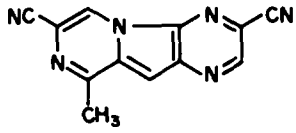
4



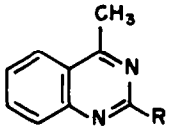
5



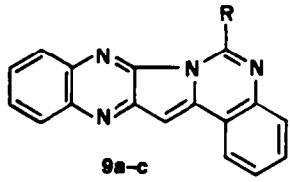
6



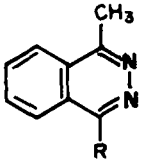
7



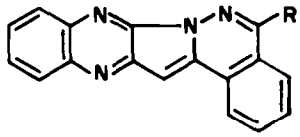
8a–c



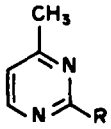
9a–c



10a–c

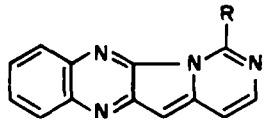


11b, c

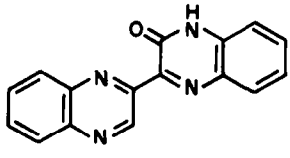


12a, b

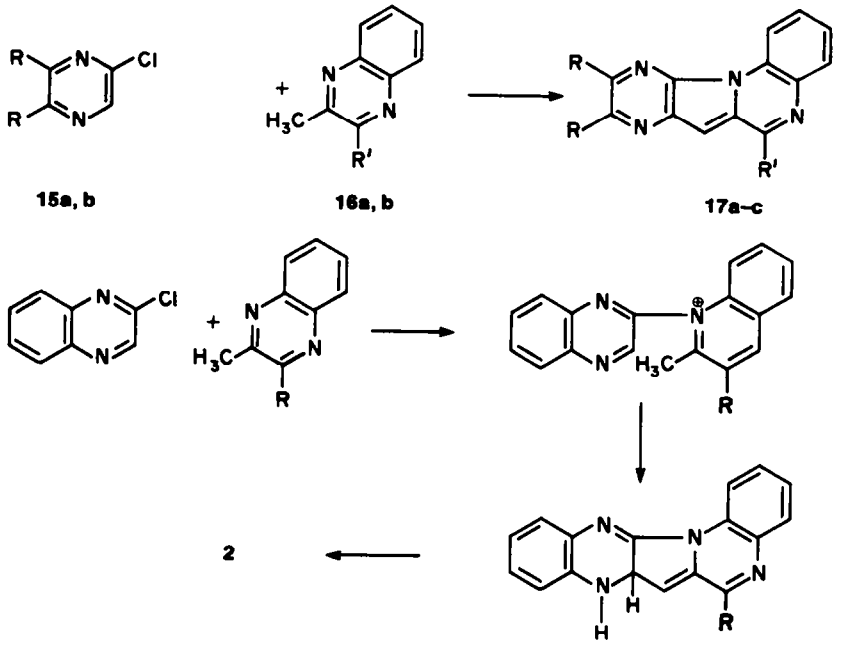
7



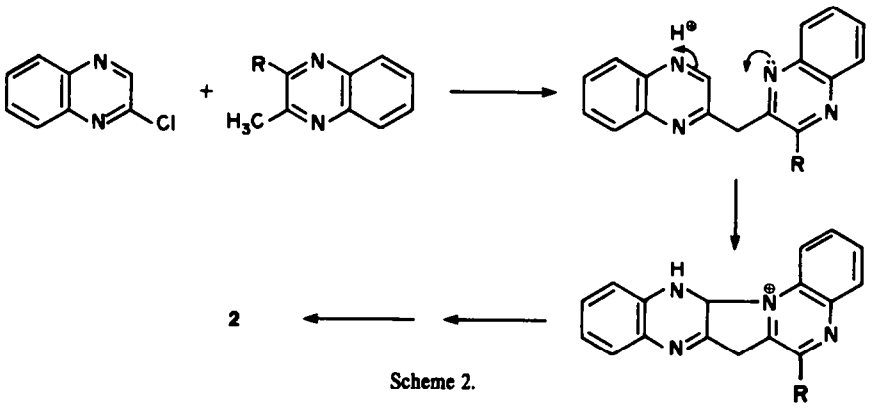
13a, b



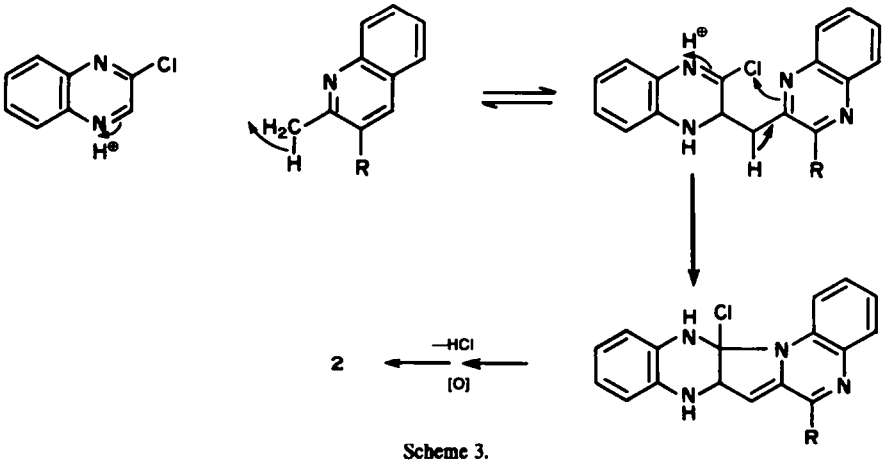
14



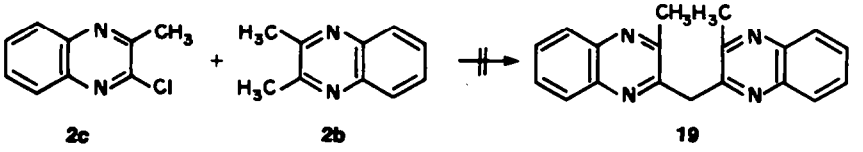
Scheme 1.



Scheme 2.



Scheme 3.



work of Albert *et al.*)[8] and in certain cases is known to be reversible.[10] If the first (and rate determining) step of the reaction is the addition of the methyl azine to a protonated molecule of 2-chloroquinoxaline, then the ease of reaction will depend upon the relative basicities of the two azines; quinazolines are far stronger bases than quinoxalines and phthalazines are yet stronger, thus, other things being equal, one could expect the observed order of reactivity. Similar arguments would apply were the cyclisation step acid catalysed and rate determining.

As may have been noticed this type of reaction is not normally useful for the preparation of the parent heterocycles; as an alternative approach we therefore examined the reactions of 2-chloro-3-methylquinoxaline (**1c**) with quinoxaline, quinazoline, and phthalazine; this approach (**1c** → **2a**) corresponds to that type of reaction observed by Pratt and Keresztesy.[5] Under our conditions (acid catalysis; acetone or acetic acid at room temperature) all these three reactions gave mixtures of highly coloured compounds and were not preparatively useful; that the parent heterocycles (**2a**,**9a**) had been formed in the first two reactions was easily established (accurate mass measurements; R_f values). The reaction complexity is not altogether unexpected (*vide infra*) but a point of interest which emerges is the relative speeds of reaction of the three diazines. Quinoxaline reacts in acetone at room temperature giving a moderate yield (albeit a mixture) of cyclic products (accurate mass measurements); the other two diazines react not at all under these conditions and even in acetic acid, reaction is slow at room temperature. This implies that, at least in these three cases, acid catalysed addition of the methyl group to the azine cannot be the rate determining step of the reaction.

Certain of these ring forming reactions give unexpectedly low yields (when a product can even be isolated). All these cases have a feature in common—the intermediates (and the final products) possess an unsubstituted C–N double bond and are thus susceptible to secondary reactions such as addition of another molecule of methyl azine; this may explain the product complexity which usually pertains in these cases. Out of the six examples where the intermediate (leading to **2a**, **9a**, **11a**, **13a**, **17a**, **17b**) could be envisaged as reacting further in only one case (**9a**) was a reasonable yield of polycyclic product isolated (from the quinazoline **8a**) and the 1,2-bond of quinazolines is not noted for its propensity to add nucleophiles. The complexity of the reaction of 2-chloro-3-methylquinoxaline with the three diazines may also be explicable on this basis.

EXPERIMENTAL

M.ps are uncorrected and were determined using a Gallenkamp apparatus or a Koffler microscope hostage. IR spectra were taken on a Unicam SP-200 spectrometer in Nujol mulls. UV spectra were measured in 96% EtOH using a Unicam SP-800A apparatus. NMR spectra were measured on a Perkin–Elmer R10 or R12B machine using TMS as internal standard with $CDCl_3$ as solvent unless otherwise stated. Mass spectra were obtained using an AEI MS9 or MS30 at 70 eV and peak abundances are quoted as a percentage of the base peak.

2-Methyl-3-phenoxyquinoxaline (**1f**). 2-Chloro-3-methylquinoxaline[11] (3.6 g, 20 mmol) was added to a melt of sodium phenoxide in phenol [from Na (2 g, 87 mmol) and phenol (100 g)] at 90° and the whole heated at 110–120° for 24 hr. After cooling, the mixture was triturated with 2N NaOH (800 ml) and the buff coloured product filtered off. Purification by passage through alumina (C_6H_6 as eluant) gave **1f** as a white solid (4.65 g, 98%); m.p. 101–102°; δ 2.8 (3H, s, Me) and 7.0–8.2 (9H, m, ArH). (Found: C, 76.3; H, 4.9; N, 11.8. $C_{15}H_{12}N_2O$ requires: C, 76.3; H, 5.1; N, 11.9%).

2-Carbethoxy-3-methylquinoxaline (**1e**). A soln of ethyl α-oximinoacetoacetate[12] (32 g, 0.2 mol) in water (150 ml) was added to *o*-phenylenediamine (21.6 g, 0.2 mol) in aqueous AcOH (50% by volume; 48 ml) and the whole heated under reflux for 1.5 hr. After cooling, the mixture was thoroughly extracted with petrol (40–60°) and evaporation of the extracts gave the crude product (4.5 g); recrystallisation from EtOH-water (1:3) gave **1e** as fluffy white needles (3.5 g, 8%); m.p. 73–75°, lit.[13] 74°; ν_{max} 1718 cm^{-1}; δ 1.64 (3H, t, CH_2CH_3), 2.98 (3H, s, 3-Me), 4.61 (2H, q, CH_2) and 7.6–8.3 (4H, m, ArH).

3-Methylquinoxaline-2-carboxylic acid (**1j**). A slurry of **1e** (1.1 g) in 5N NaOH (25 ml) was refluxed for 4 hr. After cooling, the mixture was made acid to congo red with 2N H_2SO_4 and the crude acid filtered off (0.6 g, 64%; m.p. 152° dec.); m.p. (water[b]) 155° dec., lit.[14] 154.5°; ν_{max} 3450 and 1705 cm^{-1}; δ 3.2 (3H, s, Me); 7.7–8.6 (4H, m, ArH) and 8.8 br (1H, s, OH). (Found: C, 63.9; H, 4.4; N, 15.0. Calc. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9%).

o-Aminoacetophenone. o-Nitroacetophenone (10 g, 60 mmol) in AcOH (80 ml) and water (20 ml) was heated at 100° while slowly adding Fe powder (14 g, 250 mmol) over 2.5 hr and stirring vigorously; after 1.5 hr a further 20 ml of water was added. The mixture, after dilution with water (200 ml) was cooled and extracted with ether. After washing with Na_2CO_3 aq (until neutral) and water, the ethereal extract was dried ($MgSO_4$) and evaporated down giving the amine as a light brown liquid (7.6 g, 93%) which did not require further purification.

The acyl derivatives required for quinazoline synthesis were prepared in standard fashion.

2-Acetylamino-5-chlorobenzophenone. 2-Amino-5-chlorobenzophenone (23 g) and a little Zn dust were heated in Ac_2O (12 ml) and AcOH (10 ml) at 100° for 1 hr. Addition of the resultant soln to water (250 ml) gave a white solid which was filtered off and recrystallised from EtOH giving fine white needles (23.4 g, 86%); m.p. 117–118°, lit.[15] 117°; ν_{max} 3200, 1665 and 1640 cm^{-1}; λ_{max} 238 and 324 nm; δ 2.2 (3H, s, Me), 7.4–7.9 (7H, m, Ph and 4,6-H), 8.63 (1H, d, $J_{3,4}$ 9Hz, 3-H) and 10.6 br (1H, s, NH).

6-Chloro-2-methyl-4-phenylquinazoline. Ammonia was passed through a suspension of 2-acetylamino-5-chlorobenzophenone (7g) in molten ammonium acetate (45 g) at 165° for 3 hr. After cooling and adding water, the product was extracted into ether, washed with 2N NaOH, dried ($MgSO_4$) and evaporated down giving the quinazoline in a high degree of purity (6.4 g, 98%); m.p. 107°, lit.[16] 105–107°. Recrystallisation from petrol 60–80° (35 ml) gave a pale yellow solid (5.5 g, 85%); m.p. 107–109°; ν_{max} (HCBD mull) 1555 and 1490 cm^{-1};[17] δ 2.9 (3H, s, Me) and 7.5–8.1 (8H, m, ArH).

Prepared using the same method[18] were the following quinazolines:

4-Methylquinazoline.[18] *2,4-Dimethylquinazoline* (**8b**)—49% after vacuum distillation, *4-Methyl-2-phenylquinazoline* (**8c**)—80% "crude"; m.p. 89–90°, lit.[19] 90°; λ_{max} 261, 286, 320 and 330 (i) nm; δ 2.97 (3H, s, Me), 7.2–8.1 (7H, m) and 8.65 (2H, q).

1-Phenylphthalazine. Phthalazine[20] (4 g, 31 mmol) in THF (50 ml) was added to PhMgBr [from Mg (1 g, 41 mmol) in THF (20 ml) and bromobenzene (6 g, 38 mmol) in THF (30 ml)] and refluxed under N_2 for 6 hr. After stirring overnight at room temp., excess Grignard reagent was destroyed by the addition of sat NH_4Cl aq and the crude product extracted into ether. The extracts were washed with 10N NaOH, dried ($MgSO_4$) and evaporated down giving 1,2-dihydro-1-phenylphthalazine[21] as a dark, viscous oil. The crude dihydro compound was heated in refluxing benzene (150 ml) with MnO_2[c] (20 g; 8 hr) and filtered, while hot, through Hiflo, washing the solids thoroughly with benzene. Evaporation of the solvent gave a fairly pure sample of the product (5.65 g, 89%). Recrystallisation from toluene gave

[b] Care must be taken to avoid prolonged heating as this acid decarboxylates fairly readily.

[c] The dihydro compound was resistant to alkaline ferricyanide oxidation. Mustafa *et al.* claim to have isolated the oxidised compound directly from the mixture.[22]

3.35 g (53%) of a pale brown solid; m.p. 141–142°, lit.[23] 139–141°; λ_{max} 279 nm; δ 7.4–8.3 (9H, m, carbocyclic ArH) and 9.65 (1H, s, pyridazinyl H).

The same method[24] was used for the preparation of **10a** δ (CCl_4) 2.95 (3H, s, Me), 8.0 br (4H, s, 5, 6, 7, 8-H) and 9.42 (1H, s, 4H) except that diisopropyl ether was used as the solvent.

1-Methyl-4-phenylphthalazine (**10c**). MeMgI [from Mg (0.67 g, 28 mmol) in ether (14 ml) and MeI (3.6 g, 25 mmol) in ether (22 ml)] was added under N_2 to a suspension of 1-phenylphthalazine (3 g, 14.6 mmol) in diisopropyl ether (60 ml) and the whole refluxed, under N_2 with stirring, for 16.5 hr. After leaving overnight at room temp., the mixture was worked up as above giving a quantitative yield of *1,2-dihydro-1-methyl-4-phenylphthalazine* as a viscous brown oil; δ 1.48 (3H, d, J 7 Hz, Me), 4.35 (1H, q, J 7 Hz, 1-H), 6.0 br (1H, s, NH) and 7.2–7.8 (9H, m, ArH). Oxidation by heating with MnO_2 (15 g; 6 hr) in refluxing benzene (150 ml) gave the desired product (**10c**; 3.2 g, 100%). Recrystallisation from benzene–petrol, 60–80° gave a pale brown solid (1.6 g, 50%); m.p. 123–125°, lit.[25] 125–126°; λ_{max} 274.5 nm; δ 3.06 (3H, s, Me) and 7.6–8.4 (9H, m, ArH).

1,4-Dimethylphthalazine (**10b**). This was prepared (42% crude; m.p. 104–108°, lit.[25] 108°; 21% after recrystallisation from water; m.p. 104–106°) by the action of MeMgI upon 1-hydroxyphthalazine[4] using the procedure reported by Marxer *et al.*[24] for the preparation of 1,4-bis[dimethylaminopropyl]-phthalazine with the exception that diisopropyl ether was used as solvent instead of THF.

6-Chloro-3-methyl-4-phenylcinnoline. A soln of 2-amino-5-chlorobenzophenone (50 g, 216 mmol) in ether (850 ml) was slowly added to ethereal EtMgBr [from Mg (25 g, 0.97 mol) in ether (120 ml) and EtBr (64 ml, 0.87 mol) in ether (200 ml)] with stirring; after addition of all the ketone the mixture was gently heated for 30 min. After cooling, excess Grignard reagent was decomposed with sat NH_4Cl aq and the product extracted into ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness giving a quantitative yield of 1-(2'-amino-5'-chlorophenyl)-1-phenylpropan-1-ol; δ (CCl_4) 1.82 (3H, t, Me), 2.1 (3H, m, CH_2 and OH), 3.6 br (2H, s, NH_2), 6.33 (1H, d, 3'-H) and 6.85–7.35 (7H, m, 4', 6' H and Ph). The crude carbinol was dehydrated by heating in refluxing sulphuric acid (30%, 70 ml; 1 hr); after cooling and neutralisation with 0.880 ammonia the product was extracted with CCl_4 giving a *ca.* 1:1 mixture (NMR spectroscopy) of (Z)- and (E)-1-(*2'-amino-5'-chlorophenyl*)-1-*phenylpropene.* The crude propene was suspended in 2N HCl 1.1 l) and diazotised at −3 to 3° by the slow addition of 10% $NaNO_2$ aq (210 ml) with stirring. The resultant thick yellow suspension was stirred at 4° for 64 hr, taken to pH 8 with 0.880 ammonia, and filtered, giving the crude product as an orange-brown solid. Recrystallisation from 90% EtOH gave *6-chloro-3-methyl-4-phenylcinnoline* (25.5 g, 47% from the starting ketone) as dull yellow needles; m.p. 165–166°; λ_{max} 234.5 (ϵ 52,100), 304 (ϵ 6000), and 331 (ϵ 5000); δ (CCl_4) 2.65 (3H, s, Me), 7.2–7.7 (7H, m) and 8.37 (1H, d); *m/e* 256 (35%), 255 (20%), 254 (100%, M^+), 239 (5%), 226 (4%), 225 (10%), 192 (9%), 191 (62%, M–N_2–Cl), 190 (16%), 189 (50%), 165 (10%), m* 225 (254→239), 201 (254→226) and 142.5 (191→165). (Found: C, 70.6; H, 4.15; N, 10.9. $C_{15}H_{11}N_2Cl$ requires: C, 70.7; H, 4.35; N, 10.9%).

6-Chloropyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2c**). Chloroquinoxaline[26] (3 g, 18 mmol) and 2-chloro-3-methylquinoxaline[11] (4.2 g, 24 mmol) were stirred at room temp. in acetone (50 ml) together with conc HCl (5 drops) until tlc indicated the absence of 2-chloroquinoxaline (3 days). After evaporation of the solvent, the residue was thoroughly triturated with $NaHCO_3$ aq and the crude product filtered off and dried. Recrystallisation from EtOAc gave **2c** (2.5 g, 46%; m.p. 239–40°) as fine orange-red needles. An analytical sample was obtained by a further recrystallisation; λ_{max} 274 (ϵ 86,000), 304 i (ϵ 9600), 358 i (ϵ 7100), 370 (ϵ 10,600), 387 (ϵ 11,500), 447 i (ϵ 3200), 467 (ϵ 4100), and 493 nm i (ϵ 3000); δ (TFA d) 7.5–9.3 (8H, m), and 9.9 (1H, dd, 1-H); *m/e* 306 (36%), 304 (100%, M^+), 269 (18%), 141 (7%), 114 (8%), and 102 (10%). Similarly prepared were the following:

[4]Kindly donated by Aspro Nicholas Ltd.

Pyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2a**). The crude solid was sublimed under vacuum (190°; 0.5 mm) giving **2a** (7%) as a yellow–orange solid; m.p. 244–245°.[4]

6-Methylpyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2b**). The crude product (74%; m.p. 254–5°, lit.[4] 257–8°) was conveniently purified either by crystallisation from dimethyl sulphoxide or by vacuum sublimation (200°; 0.2 mm).

6-Methoxypyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2d**). The crude solid was crystallised from toluene giving **2d** (44%) as yellow-orange needles (m.p. 285–6°); two further recrytallisations afforded an analytical sample: λ_{max} 267.5 i (ϵ 34,900), 273.5 (ϵ 39,800), 294.5 (ϵ 17,400), 304 i (ϵ 13,700), 342 i (ϵ 5700), 360 (ϵ 10,900), 376 (ϵ 12,200), 437 i (ϵ 4200), 452 (ϵ 4700) and 490 nm i (ϵ 2900); *m/e* 300 (100%, M^+), 271 (20%), 257 (23%), 167 (7%), 142 (5%), 129 (9%), 114 (5%), 102 (22%), 90 (18%), 76 (11%) and 75 (10%).

6-Ethoxypyrrolo[1,2-a:4,5-b'] diquinoxaline (**2e**). The crude solid was recrystallised from EtOAc giving **2e** (63%) as fine yellow-orange needles, m.p. 210–211°. Further recrystallisation gave an analytical sample; λ_{max} 267.5 i (ϵ 33,700), 274.5 (ϵ 39,600), 296 (ϵ 16,500), 305 i (ϵ 13,200), 345 i (ϵ 5700), 362 (ϵ 10,200), 378 (ϵ 11,600), 433 i (ϵ 3400), 455 (ϵ 4400) and 490 nm i (ϵ 3000); *m/e* 314 (100%, M^+), 299 (15%), 286 (100%, M-C_2H_4); 270 (6%), 257 (18%, 286-HCO), 167 (6%), 156 (18%), 143 (9%), 129 (12%), 114 (6%), 102 (24%), 90 (15%) and 76 (9%); m* 261 (314→286).

6-Phenoxypyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2f**). The crude solid was recrystallised from toluene giving **2f** as fine orange needles (53%; m.p. 252–3°). Further recrystallisation gave an analytical sample, m.p. 253–4°; λ_{max} 275 (ϵ 50,100), 364 (ϵ 15,100), 380 (ϵ 16,000) and 466 nm (ϵ 5400); *m/e* 363 (28%), 362 (100%, M^+), 361 (36%), 181 (15%), 113 (11%).

6-Phenylpyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2g**). The crude solid was recrystallised from benzene giving **2g** (57%; m.p. 222–4°) as fine orange-red needles; further recrystallisation gave an analytical sample; λ_{max} 243 i (ϵ 22,700), 277 i (ϵ 38,000), 284 (ϵ 42,400), 290 i (ϵ 38,800), 318 i (ϵ 12,200), 362 i (ϵ 9400), 375 (ϵ 13,400), 391 (ϵ 15,400), 470 i (ϵ 5200), 483 (ϵ 5600) and 506 nm i (ϵ 4800); *m/e* 346 (100% M^+), 269 (7%) 218 (21%) and 77 (6%); m* 137.5 (346→218).

6-Carbethoxypyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2h**). The crude solid was vacuum sublimed (200°; 0.5 mm) giving **2h** (30%) as purple needles; m.p. 203–204°; ν_{max} 1720 cm^{-1}; λ_{max} 279 i (ϵ 28,700), 284 (ϵ 32,400), 290 i (ϵ 27,700), 317 i (ϵ 6000), 364 i (ϵ 5400), 378 (ϵ 8600), 397 (ϵ 10,500), 491 i (ϵ 3000), 507 (ϵ 3200) and 555 nm i (ϵ 1500); *m/e* 342 (62%, M^+), 270 (100%, M-$CO_2C_2H_4$), 243 (6%), 168 (6%), 167 (5%), 142 (18%), 115 (9%), 114 (18%), 102 (27%), 90 (24%), 76 (18%) and 75 (12%); m* 213 (342→270).

6-Acetylpyrrolo[1,2-a:4,5-b']*diquinoxaline* (**2i**). The crude solid was recrystallised from EtOAc giving **2i** as fine purple needles (74%); ν_{max} 1695 cm^{-1}; λ_{max} 274 i (ϵ 35,500), 284 (ϵ 47,600), 294 (ϵ 41,600); 320.5 (ϵ 8200), 360 i (ϵ 8000), 378 (ϵ 11,900), 397 (ϵ 13,100), 498 i (ϵ 3900), 516 (ϵ 4000) and 548 i (ϵ 2600); *m/e* 313 (23%), 312 (100%, M^+), 284 (31%, M-CO), 270 (36%, M-CH_2CO), 269 (27%, M-CH_3CO), 163 (17%), 113 (25%), 101 (17%).

Pyrrolo[1,2-a:4,5-b']*diquinoxaline-6-carboxylic acid* (**2j**). 2-Chloroquinoxaline (315 mg, 1.9 mmol) and 3-methylquinoxaline-2-carboxylic acid (450 mg, 2.4 mmol) were stirred at room temp in acetone (20 ml) together with conc HCl (2 drops) until tlc indicated the absence of 2-chloroquinoxaline (3 days). The red-black solid was filtered off, washed with water, and dried (0.3 g); λ_{max} 281, 370, 390 and 476 nm. Vacuum sublimation (190°; 0.5 mm) resulted in decarboxylation giving the parent heterocycle **2a** (0.14 g, 27%).

6-Methylquinoxalino[2',3':2,3]*pyrrolo*[1,5-c]*quinazoline* (**9b**). 2-Chloroquinoxaline (1.2 g, 7.3 mmol) and 2,4-dimethylquinazoline (1.4 g, 8.9 mmol) were stirred at room temp. in AcOH (20 ml) together with conc HCl (1 drop) until tlc indicated the absence of 2-chloroquinoxaline (6 days). The yellow-brown mixture was poured into water (80 ml), giving a deep blue-green suspension, and basified with 0.880 ammonia. The crude product was filtered off and washed with water giving a green solid (2 g) which rapidly turned orange (aerial oxidation of intermediate dihydro compound?). Soxhlet extraction of this solid with EtOAc gave, upon

filtration of the EtOAc, an orange solid (0.95 g, 46%; m.p. 300–6°). Vacuum sublimation followed by recrystallisation from EtOAc gave the pure material as a fluffy yellow solid; λ_{max} 256 (ε 31,000), 289 (ε 35,900), 318 (ε 31,000), 356 (ε 11,100), 368 (ε 10,800) and 434 nm (ε 10,100); *m/e* 285 (18%), 284 (100%, M^+), 283 (17%) and 142 (8%, M^{2+}). Similarly prepared were the following compounds:

Quinoxalino[2',3':2,3]*pyrrolo*[1,5-c]*quinazoline* (**9a**). After Soxhlet extraction of the crude product as above, an orange solid (30%, m.p. 312–4°) was obtained. Vacuum sublimation (250°; 0.1 mm) and recrystallisation from EtOAc gave **9a** as orange needles (20%); λ_{max} 255 (ε 28,400), 290 (ε 36,300), 323 (ε 29,300), 360 (ε 12,000), 372 (ε 10,700), 420 i (ε 8400), 438 (ε 9800) and 460 nm i (ε 7400); *m/e* 271 (18%), 270 (100%, M^+), 269 (8%), 244 (3%) and 135 (9%, M^{2+}).

6-*Phenylquinoxalino*[2',3':2,3]*pyrrolo*[1,5-c]*quinazoline* (**9c**). The crude red solid was extracted with petrol 60–80° to remove unreacted starting materials and the residual crude product (65%; m.p. 284°) was purified by vacuum sublimation (250°; 0.2 mm), recrystallisation from EtOAc and a further vacuum sublimation, giving **9c** as a yellow solid; λ_{max} 256 (ε 28,800), 293 (ε 31,000), 325 (ε 31,800), 361 (ε 10,600) and 440 nm (ε 8100); *m/e* 347 (27%), 346 (100%, M^+), 345 (60%), 344 (7%) and 173 (6%, M^{2+}).

5-*Methylquinoxalino*[2',3':2,3]*pyrrolo*[1,5-c]*phthalazine* (**11b**). 2-Chloroquinoxaline (1.645 g; 10 mmol) and 1,4-dimethylphthalazine (1.99 g, 12.6 mmol) were stirred at 50–58° in AcOH (30 ml) together with conc HCl (3 drops) until tlc indicated the absence of the chloroazine (4 days). The deep red-black suspension was then poured into water and neutralised with Na_2CO_3 aq; filtration of the crude product gave an almost black solid which gradually turned brown (1.5 g). Vacuum sublimation of this material gave **11b** (992 mg, 35%) as an orange solid; λ_{max} 253 (ε 33,700), 275 (ε 26,500), 288 (ε 32,400), 341 (ε 25,600), 374 (ε 12,800), 438 i (ε 4700), 456 (ε 6000), and 480 nm i (ε 4300); *m/e* 285 (18%), 284 (100%, M^+), 283 (9%), 256 (4%) and 142 (9%, M^{2+}). Similarly prepared was:

5-*Phenylquinoxalino*[2',3':2,3]*pyrrolo*[1,5-c]*phthalazine* (**11c**). Fractional vacuum sublimation (0.1 mm) of the crude red solid afforded 1-methyl-4-phenylphthalazine, the polycyclic material **11c**, and an involatile residue. The yield of **11c** from the chloroazine was 31%; recrystallisation from EtOAc gave the pure compound, λ_{max} 256 (ε 32,100), 288 (ε 27,500), 346 (ε 32,700), 375 i (ε 12,000), 433 (ε 4600), 458 (ε 5700) and 487 nm i (ε 4300); *m/e* 347 (26%), 346 (100%, M^+), 345 (39%) and 173 (10%, M^{2+}). Extraction of the initial aqueous filtrate gave a further batch of unreacted phthalazine (no 2-chloroquinoxaline); the yield of **11c** based upon the amount of unrecovered phthalazine was 77%.

6-*Methylpyrazino*[2',3':4,5]*pyrrolo*[1,2-a]*quinoxaline* (**17a**). 2-Chloropyrazine (3.44 g, 30 mmol) and 2,3-dimethylquinoxaline (6.32 g, 40 mmol) were heated with conc HCl (5 drops) at 100° for 14 hr. Treatment of the resultant dark solid with $NaHCO_3$ aq followed by steam distillation afforded unreacted dimethylquinoxaline (5 g, 79%). Extraction of the residual aqueous suspension with CH_2Cl_2 followed by recrystallisation (CH_2Cl_2/petrol 60–80°) of the brown solid obtained upon evaporation of the solvent gave **17a** as a yellow solid (0.2 g, 10%; m.p. 197–198°). Analytical material was obtained by vacuum sublimation (twice; 180°, 0.1 mm) followed by recrystallisation from EtOH giving 0.1 g (5%); λ_{max} 254 i (ε 9600), 264 (ε 13,000), 271.5 i (ε 11,800), 277.5 i (ε 10,400), 327 i (ε 3400), 339 (ε 5000), 353 (ε 5600), 396 i (ε 3200), 408 (ε 3400); and 430 nm i (ε 2400); δ 2.82 (3H, s, Me), 7.15 (1H, s, H-7), 7.1–8.4 (4H, m, 2, 3, 4, and 7-H), 8.5–8.9 (2H, ABq, 9 and 10-H) and 9.51 (1H, dd, 1-H).

This compound can also be prepared, albeit in even lower yield, by the same procedure as the following compounds:

6-*Phenylpyrazino*[2',3':4,5]*pyrrolo*[1,2-a]*quinoxaline* (**17b**). 2-Chloropyrazine (1.72 g, 15 mmol) and 2-methyl-3-phenylquinoxaline (4.4 g, 20 mmol) were heated in refluxing AcOH (20 ml) for 8 hr with conc HCl (5 drops). After removal of starting materials by steam distillation, the residual soln was extracted with $CHCl_3$ and the organic layer evaporated to dryness. Addition of ether afforded the crude product (0.5 g) and repeated vacuum sublimation (180°; 0.1 mm) afforded a small yield (0.13 g, 3%) of the polycyclic material (**17b**) as a yellow solid; m.p. 224–5°; λ_{max} 257 i (ε 10,500), 271.5 i (ε 12,800), 282 (ε 14,400), 296 i (9700), 330 (ε 4000), 344.5 (ε 5100), 355 (ε 5400), 408 i (ε 3300), 421 (ε 3600) and 441 nm i (2,600); δ 7.35 (1H, s, 7-H), 7.41–8.25 (8H, m), 8.75 (2H, ABq, 9, 10-H), and 9.71 (1H, dd, 1-H). Similarly prepared from 2-chloro-5,6-diphenylpyrazine[27]:

6,9,10-*Triphenylpyrazino*[2',3':4,5]*pyrrolo*[1,2-a]*quinoxaline* (**17c**). The crude ether-insoluble, material (30%; m.p. 253–4°) was recrystallised from EtOAc giving the pure material as fine yellow needles (21%); λ_{max} 252 i (ε 15,400), 280 (ε 18,800), 302 i (ε 14,700), 365 i (ε 7100), 385 (ε 9400), 412 i (ε 5800), 430 (ε 5000), and 454 nm i (ε 3100); δ 7.2–7.95 (16H, m), 7.95–8.20 (3H, m, 2,3,4-H) and 9.72 (1H, dd, J_o 7.2 Hz, J_m 1.8 Hz, 1-H); *m/e* 449 (47%), 448 (100%, M^+), 447 (53%) and 224 (24%, M^{2+}).

1-*Hydroxypyrimido*[1',5':1,2]*pyrrolo*[3,4-b]*quinoxaline* (**13b**). 2-Chloroquinoxaline (1.6 g, 9.7 mmol) and 2-hydroxy-4-methylpyrimidine hydrochloride (1.5 g, 10.2 mmol) were stirred in AcOH (25 ml) at 40° until tlc indicated the absence of chloroquinoxaline (6 days). The mixture was poured into water (100 ml) giving a transient deep green colour, and neutralised with $NaHCO_3$. Filtration of the resultant suspension gave a dull green–yellow solid (1.65 g) which rapidly turned yellow. The product was a fairly clean mixture of the desired **13b** (M^+ 236.0698, $C_{13}H_8N_4O$ requires: 236.0698) and another product (M^+ 274.0868, $C_{16}H_{10}N_4O$ requires: 274.0855). Preparative tlc (EtOAc) of a small amount of the crude material gave the byproduct, tentatively identified as **14**; λ_{max} 273.5, 292, 325 and 382 nm; δ(DMSOd_6) 7.3–7.8 (3H, m), 7.85–8.5 (5H, m) and 9.6 (1H, s, 3'-H) (the high field multiplet is about superimposable with the corresponding three proton multiplet of 2-hydroxy-3-methylquinoxaline) followed by the polycycle **13b**; λ_{max} 252, 278, 342–350, 359 and 417 nm; δ(DMSOd_6) 6.7 (1H, d, J 8 Hz, 4-H), 6.8 (1H, s, 5-H), 7.38 (1H, d, J 8 Hz, 3-H) and 7.8–8.5 (4H, m, 7, 8, 9, 10-H).

Acknowledgements—The authors wish to thank Ward, Blenkinsop and Co. Ltd., for financial support (for R.K.A.) and the S.R.C. for a research studentship (to S.D.C.).

REFERENCES

[1]Part X. S. D. Carter and G. W. H. Cheeseman, *Tetrahedron* **34**, 981 (1978).
[2]H. Smith-Broadbent and R. C. Anderson, *J. Org. Chem.* **27**, 2679 (1962).
[3]C. L. Leese and H. N. Rydon, *J. Chem. Soc.* 303 (1955).
[4]G. W. H. Cheeseman and B. Tuck, *Tetrahedron Letters* 4851 (1968).
[5]E. F. Pratt and J. C. Keresztesy, *J. Org. Chem.* **32**, 49 (1967).
[6]H. Lund and S. Gruhn, *Acta. Chem. Scand.* **20**, 2637 (1966).
[7]W. Schwaiger and J. P. Ward, *Rec. Trav. Chim. Pays Bas.* **91**, 1175 (1972).
[8]For a brief survey see S. D. Carter, Ph.D. Thesis, University of London (1975).
[9]G. Scheibe and E. Daltrozzo, *Adv. Heterocyclic Chem.* **7**, 153 (1966).
[10]A. Albert and H. Mizuno, *J. Chem. Soc.* Perkin I, 1615 (1973).
[11]G. T. Newbold and F. S. Spring, *Ibid.* 519 (1948).
[12]M. Wolff, *Liebigs Ann.* **325**, 134 (1902).
[13]H. Dahn and H. Hauth, *Helv. Chim. Acta* **42**, 1214 (1959).
[14]A. S. Elina and L. G. Tsyul'nikova, *J. Gen. Chem., U.S.S.R.* **34**, 2089 (1964).
[15]F. D. Chattaway, *J. Chem. Soc.* **85**, 340 (1904).
[16]S. C. Bell and P. H. L. Weis, *J. Org. Chem.* **30**, 3576 (1965).
[17]L. H. Sternbach, S. Kaiser and E. Reeder, *J. Am. Chem. Soc.* **82**, 475 (1960).
[18]K. Schofield, T. Swain and R. S. Theobald, *J. Chem. Soc.* 1924 (1952).
[19]A. Bischler and F. J. Howell, *Ber. Dtsch Chem. Ges.* **26**, 1384 (1893).
[20]S. D. Carter and G. W. H. Cheeseman, *Org. Preparations and Procedures Int.* **6**, 67 (1974).
[21]A. Hirsch and D. Orphanos, *J. Heterocyclic Chem.* **3**, 38 (1966).
[22]A. Mustafa, A. H. Harhash and A. A. S. Saleh, *J. Am. Chem. Soc.* **82**, 2735 (1960).

[23]E. Hayashi and E. Oishi, *Yakugaku Zasshi* **86**, 576 (1966); *Chem. Abstr.* **65**, 15373 (1966).
[24]A. Marxer, V. Salzmann and F. Hofer, *Helv. Chim. Acta* **52**, 1376 (1969).
[25]M. A. Shah and G. A. Taylor, *J. Chem. Soc.* (C). 1651 (1970).
[26]G. W. H. Cheeseman, *Ibid.* 1804 (1955).
[27]G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.* **74**, 1580 (1952).