Synthetic Uses of Polyphosphoric Acid and its Ethyl Ester. Part II.[1] Syntheses of Indolin-2(3*H*)-ones and Imidazoquinolines

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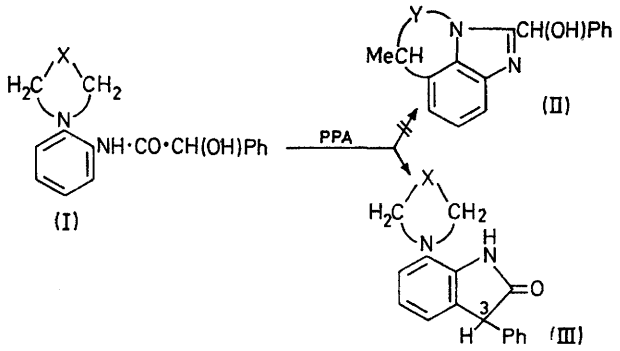
Dialkylamino-substituted indolin-2(3*H*)-ones were prepared by cyclisation of the required mandelanilides with hot polyphosphoric acid. A new reagent (PPEt) obtained from polyphosphoric acid and ethanol produced imidazoquinolines from aminobenzimidazoles and β-keto-esters and a 1,8-naphthyridine from 2-aminopyridine and ethyl α-methylacetoacetate, reactions which could not be brought about by PPA. The scope of the new reagent is discussed.

It was also shown that PPA offers no advantage over sulphuric acid in various Skraup reactions.

THE action of hot polyphosphoric acid (PPA) on the dialkylamino-substituted mandelanilides (I; X = $[CH_2]_{2-4}$ and $CH_2{\cdot}O{\cdot}CH_2$) could feasibly lead to formation of the appropriate benzimidazoles (II) by analogy with our previous work on the effect of this reagent on amides.[2] However, the main products of such a reaction were the indolones (III; X as before) in *ca.* 50% yield apart from an insoluble, tarry residue. Since the tar contained phosphorus and its hydrolysis with sulphuric acid gave starting material (I) it was assumed to be mainly a polyphosphate ester of (I). The highest yield of indolone occurred with the morpholine derivative (I; X = $CH_2{\cdot}O{\cdot}CH_2$) possibly because its hydroxy-group is hydrogen bonded intra- or inter-molecularly to the morpholine oxygen thereby preventing polyphosphate formation. Some evidence for such bonding was obtained from its n.m.r. spectrum in which the hydroxylic and benzylic protons [*cf.* (I)] appeared by contrast to other mandelanilides (I) as a pair of doublets at τ 5·82 and 4·81 respectively. The former doublet was removed and the latter collapsed to a singlet on addition of deuterium oxide. The piperazino-mandelanilide (I; X = $CH_2{\cdot}NMe{\cdot}CH_2$) failed to cyclise and gave only tar. Our attempts to induce benzimidazole formation (II) by methylating the hydroxy-group in (I) acid thereby



preventing cyclodehydration to the indoles (III) were unsuccessful. Invariably the corresponding indolones were produced in yields similar to those given by the unmethylated compounds (I).

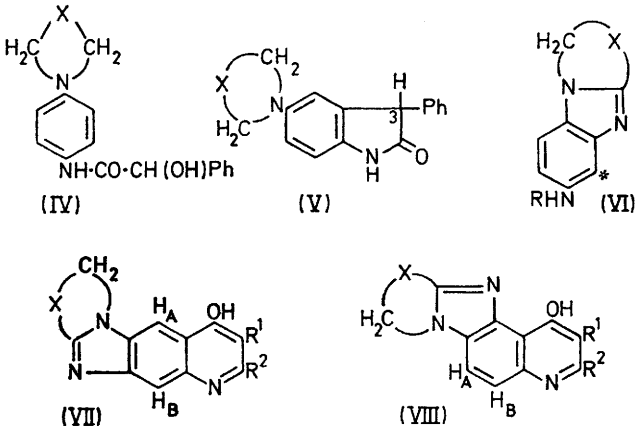
[1] Part I, D. A. Denton and H. Suschitzky, *J. Chem. Soc.*, 1963, 4741.

[2] O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1964, 2609.

Also we prepared the isomeric *para*-substituted mandelanilides (IV; X = $[CH_2]_{2-4}$ and $CH_2{\cdot}O{\cdot}CH_2$) which were made to cyclise with PPA to give the corresponding indolones (V; X as before).

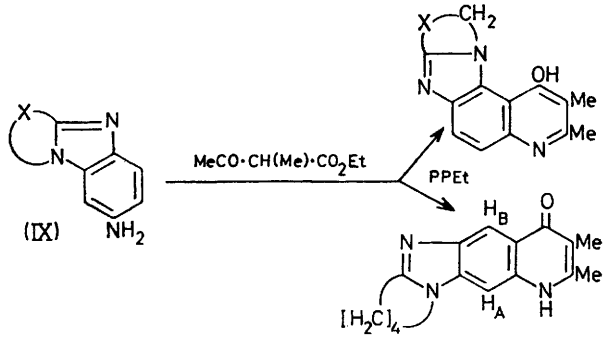
The use of concentrated sulphuric acid as a cyclisation agent for the preparation of 3-phenylindolones from mandelanilides with no substituents in the aniline ring has been reported.[3] Since the completion of our work polyphosphoric acid has been employed[4] for making 3-phenyl-5-methoxyindol-2(3*H*)-one from *N*-*p*-methoxyphenylmandelamide a reaction for which sulphuric acid was unsuitable.

The reaction between β-keto-esters and arylamines in hot PPA has recently been utilised by us for preparing various dialkylamino-substituted 4-hydroxyquinaldines.[5] We attempted to apply this method to the synthesis of a fused four-ring system containing the imidazo-quinoline moiety, by the reaction of for instance the 5-aminobenzimidazole (VI; R = H, X = $[CH_2]_2$) with ethyl methylacetoacetate. This should produce the linear imidazoquinoline (VII; $R^1 = R^2$ = Me, X = $[CH_2]_2$), or its



angular isomer since cyclisation could feasibly occur in two ways with both *ortho*-positions in (VI) being vacant. However, neither the established conditions of heating the reactants in PPA at *ca.* 140° for 0·75 hr. nor forcing conditions at a temperature of *ca.* 180° for up to 6 hr. produced anything but starting materials. The failure of PPA to cause ring-closure was attributed to extensive protonation of the amino- and hetero-nitrogen atom in the starting amine (VI) which would deactivate the benzene ring towards the Friedel–Crafts-type cyclisation of the intermediate amide (VI; R = $CMe{\cdot}CO_2Et$). In order to lessen the acidity of the reagent we allowed it to react with ethanol (*cf.* Experimental section). We suggest that this modified PPA is called, for the sake of convenience, the ethyl ester of polyphosphoric acid (PPEt.). Preliminary investigations of our reagent (PPEt) showed the existence of P–OH (τ −1·93, acidic OH) and P–O–Et groups (τ 5·86 quintet and τ 8·70 triplet) in the ratio of *ca.* 1 : 1. The i.r. spectrum appears to be typical of alkyl phosphates and shows the presence of P–OH, P=O, P–O–C (alkyl), and P–O–P moieties. Paper chromatography indicates 11 components, five of which make up the bulk of the reagent. From the i.r. spectrum and paper chromatography it is not likely that chains above 3 or 4 phosphate units are present.

The quinoline (VII; $R^1 = R^2$ = Me, X = $[CH_2]_2$) was prepared in 85% yield by heating a mixture of the above mentioned starting materials [(VI; R = H, X = $[CH_2]_2$) and $MeCO{\cdot}CH(Me){\cdot}CO_2Et$] and PPEt to 165° for 0·75 hr. The product (VII) was assigned the linear imidazoquinoline structure on the basis of its n.m.r. spectrum which showed *para*-splitting of the H_A and H_B protons ($J_{HA/HB}$ 1 Hz). This is opposed to *ortho*-splitting (*ca.* 9 Hz *cf.* Table 2) which would have been expected if cyclisation of the intermediate (VI; R = $CMe = CMe{\cdot}CO_2{\cdot}Et$) had occurred onto the starred position of the benzene ring [*cf.* (VI)]. A number of similar cyclisations which had also failed in PPA were carried out in PPEt with the amines (VI; R = H, X = $[CH_2]_3$, $[CH_2]_4$, and $CH_2{\cdot}O{\cdot}CH_2$) and ethyl α-methyl acetoacetate and in one case (VI; R = H, X = $[CH_2]_3$) with α-benzylacetate which gave exclusively the corresponding angular imidazoquinolines (VIII; $R^1 = R^2$ = Me or in the last case R^1 = H, R^2 = Ph, X as before) (*cf.* Table 1). The structure was again deduced mainly from n.m.r. spectra which showed *ortho*-splitting of the aromatic protons (*cf.* Table 2). The 6-aminobenzimidazole (IX; X = $[CH_2]_4$) when treated similarly in PPEt with ethyl α-methylacetoacetate gave a mixture of the isomers (X; X = $[CH_2]_3$) and (XI) in 80% and 10% yield respectively. Separation was achieved by fractional crystallisation from chloroform and identification was possible because of the different splitting patterns of their aromatic protons (*cf.* Table 2). On the basis of their i.r. spectra the angular isomer (X) exists predominantly in the hydroxy-form (band at 2700 $cm.^{-1}$) while the linear isomer (XI) was assigned the



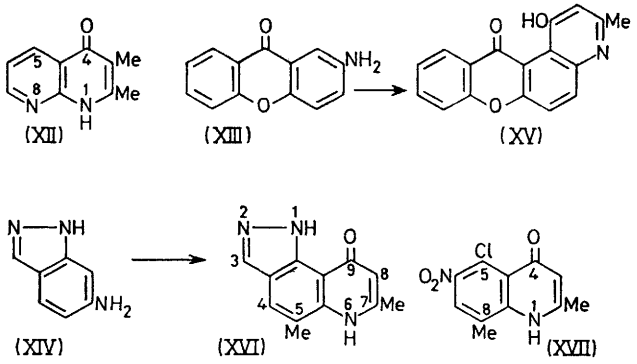
quinolone structure (band at 1650 $cm.^{-1}$). Also we used the new reagent to synthesise the napthyridine (XII) from 2-aminopyridine and ethyl α-methylacetoacetate in good yield while PPA gave only small quantities of

[3] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 1957, 4789.
[4] P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, 1968, **33**, 1640.
[5] R. Garner and H. Suschitzky, *J. Chem. Soc.* (*C*), 1966, 186.

product probably because of deactivation of the pyridine ring by protonation.

A few cyclocondensations of complex amines with methyl acetoacetate were, however, equally successful with PPA. Thus, 2-aminoxanthone (XIII) and 6-aminoindazole (XIV) gave the corresponding quinaldines (XV) and (XVI) respectively while 5-chloro-2-methyl-4-nitroaniline yielded the quinoline (XVII) when made to react with ethyl α-methylacetoacetate in PPA without recourse to PPEt.

Also we used the known polyphosphate ester (PPE)



for the above reactions which did not respond to PPA treatment but without success. In fact, we found that it offered no advantage over PPA in our reactions.

[6] Y. Kanaoka, E. Sato, and O. Yanemitsu, *Tetrahedron*, 1968, **24**, 259 Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, *Chem. and Ind.*, 1965, 473; Y. Kanaoka, E. Sato, and Y. Ban, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 101, and papers quoted therein.

This reagent which has been widely investigated by a group of Japanese workers [6] is prepared [7] from phosphorus pentoxide and anhydrous diethyl ether in chloroform.

We have recently shown [1] that PPA can replace sulphuric acid in the preparation of quinoline (70% yield)

TABLE 1

Substituted imidazo[4,5-*f*]quinolines of type (VIII) and (X) and imidazo[4,5-*g*]quinolines of type (VII) and (XI)

Type of quinoline	X	R¹	R²	M.p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(VII) [a]	$[CH_2]_2$	Me	Me	260°	85	55·4	5·5	12·9	$C_{15}H_{15}N_3O,2HCl$	55·7	5·3	12·9
(VIIIa) [b]	$[CH_2]_3$	Me	Me	>300	57	71·7	6·4	16·0	$C_{16}H_{17}N_3O$	71·9	6·4	15·7
(VIIIb) [b]	$[CH_2]_3$	H	Ph	260	55	76·1	5·4	13·3	$C_{20}H_{17}N_3O$	76·1	5·4	13·3
(VIIIc)	$[CH_2]_4$	Me	Me	290	84	57·4	6·4	11·5	$C_{17}H_{19}N_3O,2HCl$	57·7	6·0	11·9
(VIIId) [b]	$CH_2{\cdot}O{\cdot}CH_2$	Me	Me	>300	47	66·9	5·6	15·6	$C_{15}H_{15}N_3O_2$	66·9	5·6	15·6
(Xa) [c]	$[CH_2]_2$	Me	Me	>300	52	71·1	6·1	16·6	$C_{15}H_{15}N_3O$	71·1	6·0	16·6
(Xb) [d]	$[CH_2]_3$	Me	Me	>300	80	71·6	6·5	15·3	$C_{16}H_{17}N_3O$	71·9	6·4	15·7
(XI) [d]		Me	Me	>300	10	71·7	6·5	15·5	$C_{16}H_{17}N_3O$	71·9	6·4	15·7

[a] Its infrared spectrum shows it to be a quinolone. [b] Recrystallised from anisole. [c] Recrystallised from DMF. [d] Formed in admixture (*cf.* text).

TABLE 2

The chemical shifts (τ-values) of protons in the imidazoquinolines of type (VII), (VIII), (X), and (XI) in CF_3CO_2D

Number of compound in Table 1	2-Me	3-Me	H_A	H_B	Methylenes * α	Methylenes * β	Methylenes * γ	Methylenes * δ	ε	$J_{HA/HB}$
(VII)	6·99s	7·37s	1·74	1·74	5·25t	6·0	7·0m			1Hz
(VIIIa)	6·97s	7·38s	1·75d	1·58d	5·33t	7·5	7·7m	6·45t		9Hz
(VIIIb) †	—	—	1·58d	1·42d	5·31t	7·3	7·8m	6·42t		9Hz
(VIIIc)	7·72s	8·19s	2·83d	2·23d	5·55t	7·9		8·5b	6·7t	9Hz
(VIIId)	7·4s	7·77s	2·05t		4·9s	5·5	6·1b			9Hz
(Xa)	7·43s	7·8s	2·23d	2·08d	5·21t	6·9—7·5b	6·77t			9Hz
(Xb)	6·99s	7·35s	1·8d	1·6d	4·87t	7·5	8·0m	6·47t		9Hz
(XI)	6·99s	7·39s	1·6d	1·03d	5·43t	7·4	8·0m	6·03t		1Hz

* Labelled α, β, γ, *etc.* from the 2-position of the imidazole ring. † The R^2 = Ph showed its protons at 1·8—2·3 as a complex and R^1 = H was buried under it.

and 6-nitroquinoline (36% yield) by the Skraup synthesis. As an extension to this work we used PPA for making quinolines with methoxy- and trifluoromethyl-groups *i.e.* substituents that are usually hydrolysed by

TABLE 3

Yields of quinolines by Skraup synthesis in polyphosphoric and sulphuric acid

Quinoline	Yield (%) P.P.A.	Yield (%) H_2SO_4 [a]
6-MeO	27	66
8-MeO	10	27
6-NO_2	40	70
5-NO_2	39	59
7-NO_2	10	14
5-CF_3	0	6
7-CF_3	0	32

[a] The figures in this column are taken from the literature.

sulphuric acid under Skraup conditions. Also we studied the use of PPA in Skraup syntheses with nitroanilines and 2-aminopyridines. The results which are listed in Table 3 show that the conventional method with sulphuric acid is superior. PPEt gave results similar to PPA.

[7] G. Schramm, H. Grotsch, and W. Pollmann, *Angew. Chem. Internat. Edn.*, 1962, **1**, 1; W. Pollmann and G. Schramm, *Biochim. Biophys. Acta*, 1964, **80**, 1.

EXPERIMENTAL

Polyphosphoric acid was commercial tetraphosphoric acid (Albright and Wilson) containing *ca.* 85% of phosphorus pentoxide.

Dialkylamino-substituted Mandelanilides.—A solution of the appropriate *N*-2- or *N*-4-aminophenyl heterocycle [8] and mandelic acid (1 mol.) in dry xylene was held at reflux for 8 hr. The water formed was collected in a Dean and Stark apparatus. Removal of the solvent under reduced pressure left the crude mandelanilide which was recrystallised from benzene. I.r. spectra in Nujol invariably showed bands at *ca.* 3250 cm.$^{-1}$ (NH) and at *ca.* 1650 and 1525 cm.$^{-1}$ (amide I and II bands). Results are listed in Table 4. When α-methoxyphenylacetic acid and *o*-aminophenylpiperidine were made to react as above o-(*α-methoxyphenylacetamido*)-*phenylpiperidine* (60%) m.p. 66° was obtained (Found: C, 74·0; H, 7·6. $C_{20}H_{24}N_2O_2$ requires C, 74·0; H, 7·45%); τ ($CDCl_3$) 8·30 (β and γ-methylenes of piperidine), 7·20 (α-methylenes), 6·53 (OMe), 5·27 (CH), and 1·67 (2-H in aniline ring).

Indolin-2(3H)-ones.—A solution of the appropriate mandelanilide (2 g.) in PPA (20 g.) was stirred at 147° for 2 hr. The reaction mixture was cooled and diluted with water (100 ml.) and the intractable gum was filtered off. The filtrate was adjusted to pH 8 by addition of aqueous ammonia (*d* 0·880) and the precipitated 5-*N*-heterocyclic substituted indoles (V) were filtered off. The 7-substituted isomers (III) were extracted from the alkaline solution with chloroform, and recrystallised from benzene or ethanol. Their i.r. spectra showed (in Nujol) bands at *ca.* 3150 (NH) and 1700 cm.$^{-1}$ (cyclic amide C=O). Details of the i.r. spectra are given in Table 5 and of the n.m.r. spectra in Table 6.

[8] O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1963, 4666; O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, 1963, 1666.

[9] Y. Kanaoka, M. Machida, D. Yonemitsu, and Y. Ban, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1065.

Hydrolysis of the intractable gum with hot aqueous sulphuric acid (50%) for 12 hr. gave the corresponding mandelanilide. Preparation of indolin-2(3*H*)-ones by heating, for instance, a mixture of mandelic acid (2·3 g.), *o*-aminophenylpiperidine (2·65 g.), and polyphosphoric acid (40 g.) at 147° for 2 hr. gave starting materials only.

Ethyl Ester of Polyphosphoric Acid (*PPEt*).—Ethanol (40·5 ml.) was slowly added to stirred, fresh polyphosphoric acid (100 g.). The rate of addition was controlled so that the temperature of the reaction mixture did not rise above 60°. When cool, the reagent was stored in an air-tight container and was ready for use without further purification.

Polyphosphate Ester (*PPE*).—This was prepared as previously described.[9]

TABLE 4

2- and 4-*N*-Heterocyclic substituted mandelanilides [(I) and (III)]

X	Type	Yield (%)	M.p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
$[CH_2]_2$	(I)	80	68°	73·0	6·8	$C_{18}H_{20}N_2O_2$	73·0	6·8
,,	(IV)	65	173	72·8	6·6	,,		
$[CH_2]_3$	(I)	90	111	73·5	7·2	$C_{19}H_{22}N_2O_2$	73·5	7·15
,,	(IV)	75	172	73·7	6·7	,,		
$[CH_2]_4$	(I)	Quant.	128	74·1	7·3	$C_{20}H_{24}N_2O_2$	74·1	7·45
,,	(IV)	60	130	73·6	7·0	,,		
$[CH_2{\cdot}O{\cdot}CH_2]$	(I)	Quant.	123	68·9	6·7	$C_{18}H_{20}N_2O_3$	69·2	6·45
,,	(IV)	85	210	69·1	6·1	,,		
$[CH_2{\cdot}NMe{\cdot}CH_2]$	(I)	Quant.	167	70·1	6·9	$C_{19}H_{23}N_3O_2$	70·1	6·95

TABLE 5

5- and 7-*N*-Heterocyclic substituted 3-phenyl oxindoles [(V) and (III)]

X	Type	Yield (%)	M.p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
$[CH_2]_2$	(III)	50	208°	77·3	6·75	$C_{18}H_{18}N_2O$	77·7	6·5
,,	(V)	28	235	78·1	6·8	,,		
$[CH_2]_3$	(III)	50	159	77·8	6·9	$C_{19}H_{20}N_2O$	78·1	6·9
,,	(V)	35	227	78·1	6·5	,,		
$[CH_2]_4$	(III)	45	179	78·3	7·0	$C_{20}H_{22}N_2O$	78·4	7·2
,,	(V)	58	218	78·0	6·9	,,		
$CH_2{\cdot}O{\cdot}CH_2$	(III)	60	205	73·6	6·4	$C_{18}H_{18}N_2O_2$	73·5	6·2
,,	(V)	77	226	73·2	6·6	,,		

TABLE 6

The chemical shifts (τ-values) of protons in the 5- and 7-*N*-heterocyclic substituted3-phenyl oxindoles (V) and (III) in deuteriopyridine

X	Type	Methylenes in X	$CH_2{\cdot}N{\cdot}CH_2$	3-H
$[CH_2]_2$	(III)	8·05 [c]	6·70 [c]	5·4 [a]
$[CH_2]_2$	(V)	8·29 [c]	6·98 [b]	5·06 [a]
$[CH_2]_3$	(III)	8·42 [c]	7·16 [c]	5·48 [a]
$[CH_2]_3$	(V)	8·55 [c]	7·10 [c]	5·09 [a]
$[CH_2]_4$	(III)	8·28 [c]	6·80 [b]	5·32 [a]
$[CH_2]_4$	(V)	8·55 [c]	6·71 [b]	5·07 [a]
$[CH_2{\cdot}O{\cdot}CH_2]$	(III)	6·20 [b]	7·08 [b]	5·07 [a]
$[CH_2{\cdot}O{\cdot}CH_2]$	(V)	6·20 [b]	7·03 [c]	5·06 [a]

[a] Singlet. [b] Triplet. [c] Broad.

Cyclocondensations in PPEt.—(a) *Imidazo*[4,5-f]*quinolines* [(VIII) and (X)] *and imidazo*-[4,5-*g*]*quinolines* [(VII) and (XI)]. The required 5-(VI) or 6-aminobenzimidazole [10] (IX) was obtained by hydrolysis of the corresponding *N*-acetyl derivative [11] with hydrochloric acid. The unknown

[10] K. H. Saunders, *J. Chem. Soc.*, 1955, 3275; A. R. Freedman, O. S. Payne, and A. R. Day, *J. Hetero. Chem.*, 1966, **3**, 257.

[11] R. Garner and H. Suschitzky, *J. Chem. Soc.* (*C*), 1967, 74.

morpholino-compound (VI; R = H, X = CH_2·O·CH_2) had m.p. 202° (ethanol) (Found: C, 63·5; H, 6·0. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·9%). A mixture of the aminobenzimidazole (2·0 g.), ethyl α-methylacetoacetate (2·5 ml.) and PPEt (20 g.) was kept at 165° for 0·75 hr. The cooled reaction mixture was diluted with ice–water (100 ml.) and the solution was adjusted to pH 8 by addition of ammonia (*d* 0·880). The precipitated product was filtered off and recrystallised from anisole or DMF. The filtrate yielded some unchanged aminobenzimidazole when extracted with chloroform. Details of the new compounds are given in Tables 1 and 2.

(b) 2,3-*Dimethyl*-1,8-*naphthyrid*-4(1H)-*one* (XII).—A mixture of PPEt (20 g.), ethyl α-methylacetoacetate (2·5 ml.), and 2-aminopyridine (2·0 g.) was treated as above. The reaction mixture, finally adjusted to pH 8, was extracted repeatedly with chloroform. Removal of the solvent gave the crude product which was chromatographed over alumina with benzene–chloroform (1 : 1) as eluant to give 2,3-*dimethyl*-1,8-*naphthyrid*-4(1H)-*one* (1·0 g.), m.p. 120° (Found: C, 68·9; H, 5·7; N, 16·0. $C_{10}H_{10}N_2O$ requires C, 69·0; H, 5·8; N, 16·1%); $\nu_{max.}$ 3200 (NH), 1660 (C=O), 1630 (C=N), and at 1570 cm.$^{-1}$ (C=C).

Cyclocondensations in PPA.—(a) 7-*Methyl*-1H-*pyrazolo*-[5,4-f]*quinolin*-8(6H)-*one* (XVI). A mixture of 6-aminoindazole (2·0 g.), PPA (20 g.), and methyl acetoacetate (2·5 ml.) was heated at 147° for 0·75 hr. Water (100 ml.) was added to the cool reaction mixture which yielded a buff precipitate. This was filtered off and heated in sulphuric acid [50 ml.; 50% (v/v)] for 1 hr. Dilution of the reaction mixture with water (300 ml.) and addition of ammonia (*d* 0·880) (to pH 8) gave the ketone (XVI) (1·2 g., 40%), m.p. 300° (anisole) (Found: C, 66·0; H, 4·6; N, 21·2. $C_{11}H_9N_3O$ requires C, 66·3; H, 4·6; N, 21·1%); $\nu_{max.}$ at 3250 (pyrazolo-NH), 3150 (quinolone-NH), 1650 (C:O) 1610 (C=N), and 1570 cm.$^{-1}$ (C=C); τ (CF_3CO_2D) 7·42 (7 Me-group, singlet), 2·87 (s, 8-H), 2·40 (d, 4-H), 1·88 (d, 5-H, $J_{4,5}$ 9 Hz), and 1·49 (3-H) [*cf.* (XVI)].

(b) 1-*Hydroxy*-3-*methyl*-12H-[1]*benzopyrano*[4,3-b]*quinolin*-12-*one* (XV). A mixture of 2-aminoxanthone (2 g.), PPA (20 g.) and methyl acetoacetate (2·5 ml.) was kept at 147° for 0·75 hr. It was then treated with water (100 ml.) to give a precipitate which was filtered off and extracted with hot pyridine (10 ml.). The pyridine solution was chromatographed on alumina with chloroform as eluant to give, as the first fraction, the *ketone* (XV) (0·6 g., 29%), m.p. 225° (anisole) (Found: C, 73·6; H, 4·0; N, 5·2. $C_{17}H_{11}N_3O$ requires C, 73·6; H, 4·4; N, 5·1%); τ ($CDCl_3$) 7·39 (3-Me), 3·04 (H-pyridine), and a complex system between 1·5—2·9 (benzopyrano H). Later fractions from the column gave 2-aminoxanthone (0·4 g.).

(c) 5-*Chloro*-2,3,8-*trimethyl*-6-*nitro*-4-*quinolone* (XVII). A mixture of 5-chloro-2-methyl-4-nitroaniline (2 g.), PPA (20 g.), and ethyl α-methylacetoacetate (2·5 ml.) were treated as in (b). The aqueous reaction mixture was adjusted to pH 8 with ammonia (*d* 0·880) which precipitated the quinoline (XVII) (10%) as red prisms, m.p. 186° (anisole) (Found: C, 53·9; H, 4·1; N, 10·9. $C_{12}H_{11}ClN_2O_3$ requires C, 54·1; H, 4·2; N, 10·5%); $\nu_{max.}$ 3250 (NH), 1650 (C:O), and 1560 cm.$^{-1}$ (NO_2); τ ($CDCl_3$) 7·91 (8-Me), 7·55 (3-Me), 1·59 (7-H), and −1·5 (NH). The mother liquors gave starting nitroaniline (0·5 g.) on extraction ($CHCl_3$).

(d) Attempts to prepare any of the products mentioned under PPEt gave only starting material even at 165° for 6 hr.

Reactions in PPE.—Reactions effected with PPA (*cf.* above) were also successful in PPE but none of the PPEt syntheses could be carried out.

Skraup Syntheses in PPA.—Conditions were as previously described [1] and results are compared with those reported for sulphuric acid in the Skraup synthesis (*cf.* Table 3).

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