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THE USE OF POLYPHOSPHORIC ACID IN THE POMERANZ–FRITSCH SYNTHESIS OF ISOQUINOLINES

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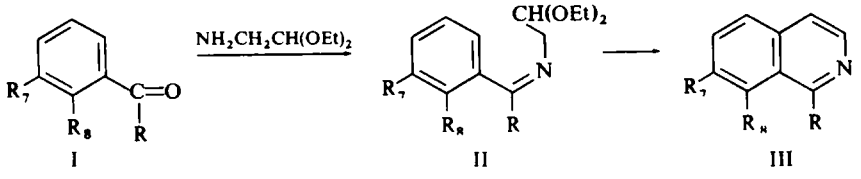
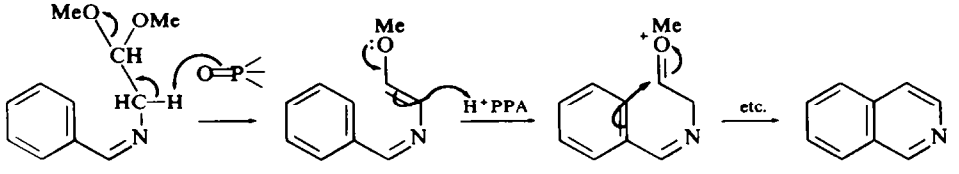
Abstract—A number of 7,8 and 1-substituted isoquinolines have been synthesized by the Pomeranz–Fritsch procedure using polyphosphoric acid as cyclizing agent. Though giving only moderate yields the method was successful in all cases, particularly for the preparation of 8-substituted isoquinolines, which in most cases are unobtainable from cyclization using sulphuric acid. In addition, the 12*H*-[1]-benzoxepino[2.3.4-*ij*]isoquinoline system, present in the culanine alkaloids, has been elaborated.

THE Pomeranz–Fritsch method[1] for the synthesis of isoquinolines (I → III) has primarily been used when the orientation problems associated with the other procedures[2] would have yielded isomeric mixtures. In general, yields given by the Pomeranz–Fritsch method are lower than those obtained by other routes[2] and the reactions give much tarry material. Using 70% sulphuric acid yields frequently fall in the range 0% (for isoquinoline itself) to 30%, although a few 6 and 7 oxygenated isoquinolines have been produced in yields up to 80%. However, most reactions which would have led to 8-oxygenated bases have failed.[2] More recently polyphosphoric acid[3a] and orthophosphoric acid[3b] have been used as cyclizing agents.[3] We had occasion to prepare some 8-oxygenated isoquinolines and have investigated the use of polyphosphoric acid in this connection.



I II III

Application of polyphosphoric acid (PPA) arises from the fact that it is a mild reagent, even though a strongly dehydrating agent. It does not usually bring about charring or polymerization, most probably because it is a poor proton source. A likely mechanism for the cyclization is as shown, the polyphosphoric acid acting as a dehydrating agent, rather than a proton donor or Lewis acid.



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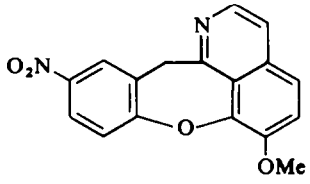
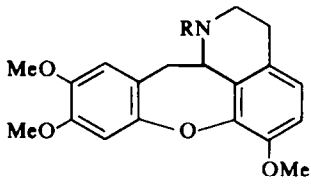
Although polyphosphoric acid is available commercially we preferred to prepare the reagent as required so minimising any possibility of its prior hydration. Best yields were obtained when the theoretical P_2O_5 content was 80·9%, an amount which has usually afforded optimal yields in other reactions.[4]

Using this procedure we have prepared several 7,8 and 1-substituted isoquinolines including the tetracyclic compound IV which contains the skeleton present in the alkaloid cularine (V, R = Me)



IV



V

The results are summarized in Table 1.

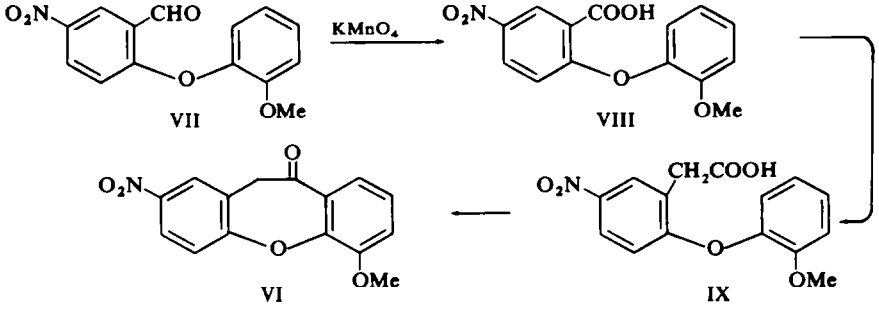
TABLE 1. POMERANZ–FRITSCH CYCLIZATION USING POLYPHOSPHORIC ACID

Isoquinoline	% Yield*
8-Hydroxy-7-methoxy	12
7,8-Dimethoxy	6
1-Methyl	6–12
7-Methoxy-1-methyl	6–16
7,8-Dimethoxy-1-methyl	36
Compound IV	26

* Based on amount of I

For the preparation of 1-methylisoquinolines the starting ketones were formed from the lithium salt of the appropriate benzoic acid and lithium methyl, a procedure similar to that used by Baddiley *et al.*[5] for the preparation of benzylidene acetone from cinnamic acid. The method gave good yields in each case and provides a convenient and efficient route to formation of unsymmetrical ketones.

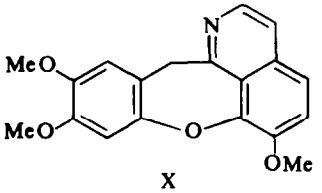
The dibenz(*b,f*)oxepin derivative VI, the precursor of IV, was obtained by the scheme shown (VII → VI).



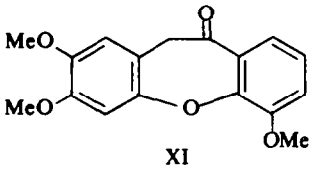
VII VIII VI IX

Condensation of sodium guaiacolate with 2-chloro-5-nitrobenzaldehyde in aqueous dioxan afforded the diphenyl ether (VII).[6] Oxidation of the aldehyde (VII) followed by Arndt-Eistert chain extension to IX proceeded in 30% overall yield. Cyclization of the phenylacetic acid (IX) with polyphosphoric acid[6] gave the dibenz(*b.f*)oxepinone (VI) in 26% yield.

Isoquinoline formation from VI is analogous to the route employed by Kametani *et al.*[7,8] in the synthesis of the precursor (X) of cularine (V, R = Me) and cularimine (V, R = H), form 2,3,6-trimethoxydibenz-(*b.f*)-oxepin-10(11 *H*)one (XI). This latter cyclization, however, proceeded in a lower yield (14%).[8]



X



XI

As can be seen from Table 1 all ring closures attempted were successful, although with somewhat disappointing yields (6–36%). Thus use of polyphosphoric acid shows some improvement over that of 70% sulphuric acid, and notably in formation of 8-oxygenated isoquinolines, which in most cases are unobtainable from cyclizations using sulphuric acid. It is also relevant to mention that although a number of new syntheses of *reduced* isoquinolines have appeared[9] the yields of dehydrogenated product tend to be so variable that the Pomeranz–Fritsch procedure is still the method of choice in many cases for the isoquinolines themselves.

EXPERIMENTAL

Pomeranz–Fritsch reaction

General procedure. Aminoacetal (0·03 mole) and the aldehyde or ketone (0·03 mole) were boiled under reflux with xylene (100 ml) under a Dean–Stark trap until no further water was removed by the trap (6–44 hr). The solvent was removed and the oily Schiff base (II) added to polyphosphoric acid (prepared from orthophosphoric acid [75 ml, *d* 1·75] and P_2O_5 [114 g]) at 100°. The resultant cherry-red mixture was maintained at 100° with occasional swirling for 90 min, under anhydrous conditions, allowed to cool, left overnight and then poured into ice-water. After acidification with HCl non-basic material was removed with ether. The aqueous soln was basified with aqueous ammonia and extracted 3 times with benzene. The combined extracts were dried (K_2CO_3) and solvent removed to give the required III.

1-*Methylisoquinoline* was prepared from acetophenone in yields varying between 6–12%, and was characterized as its methiodide, m.p. 207–207·5° (lit.[10] 207·5°).

7-*Methoxy*-1-*methylisoquinoline. m*-Methoxybenzoic acid (10 g) was dissolved in an aqueous solution of lithium hydroxide monohydrate (2·71 g) and the mixture evaporated to dryness to leave the Li salt which was thoroughly dried over P_2O_5 *in vacuo*.

Li wire (2 g) was pressed into dry ether (100 ml) under dry O_2-free N_2 and MeI (15·9 g, 7·0 ml) in dry ether (20 ml) added over 20 min and then maintained under reflux for 2 hr, with stirring. The ethereal Li–Me thus obtained was filtered by N_2 pressure through a glass-wool plug on to a suspension of lithium-*m*-methoxybenzoate (9·3 g) in dry ether (100 ml). The mixture was stirred vigorously under N_2 and maintained under reflux for 7 hr. The white suspension was then poured into ice-water (200 ml) to give two layers. The aqueous layer was extracted with ether (twice) and the extracts added to the organic layer and dried ($CaCl_2$). Removal of the solvent and distillation of the residue gave *m*-methoxyacetophenone (4·75 g, 53·8%), η_D^{22} 1·5405, b.p. 123–124 /9·3 mm (lit.[11] b.p. 125 /14 mm).

m-Methoxyacetophenone was converted to 7-*methoxy*-1-*methylisoquinoline* in yields of 6–16% characterized as its *methiodide*, yellow needles from EtOH, m.p. 279° (dec). (Found: C, 45·5; H, 4·5; N, 4·7.

$C_{12}H_{14}NOI$ requires: C, 45·7; H, 4·5; N, 4·4%). Schlittler and Müller[12] cite m.p. 283–284° (dec), no analytical figures given.

7,8-*Dimethoxy*-1-*methylisoquinoline*. *o*-Vanillin (22·8 g) was treated with Me_2SO_4 and KOH aq in a manner similar to that described by Barger and Silberschmidt[13] for vanillin, to give *o*-veratraldehyde (19·9 g, 80%) m.p. 50–52° (lit.[14] m.p. 51°). A small amount of by-product (ca. 5%) thought to be 2,3-dimethoxybenzaldehyde dimethylacetal, $(MeO)_2C_6H_3CH(OMe)_2$ was isolated as a yellow oil. This was also found when *o*-vanillin was methylated with Me_2SO_4 in methanolic KOH.[15] *o*-Veratraldehyde (19·5 g) in water (500 ml) was oxidized with $KMnO_4$ (30 g) in water (600 ml) at 80° for 2 hr to give *o*-veratric acid (15·4 g, 72%) m.p. 121·5–123·5° (lit.[16] m.p. 120–122°). *o*-Veratric acid (14·0 g) was converted to 2,3-dimethoxyacetophenone (4·2 g, 30%) in the manner described above for *m*-methoxyacetophenone. The product had b.p. 141–145°/12 mm. (lit.[17] b.p. 143–144°/14 mm) and was characterized as its 2,4-*dinitrophenylhydrazone* as orange needles, m.p. 181°. (Found: C, 53·0; H, 4·7; N, 15·4. $C_{16}H_{16}N_6O_4$ requires: C, 53·3; H, 4·5; N, 15·6%).

2,3-Dimethoxyacetophenone (6 g) was converted to 7,8-*dimethoxy*-1-*methylisoquinoline* (2·4 g, 36%) as a pale oil b.p. 175–182°/10 mm. This was characterized as its *picrate* which crystallized from aqueous EtOH as bright yellow needles, m.p. 223–224° (dec). (Found: C, 50·0; H, 3·7; N, 13·0. $C_{18}H_{16}N_4O_9$ requires: C, 50·0; H, 3·6; N, 12·7%).

The *methoidide* of 1-methyl-7,8-dimethoxy-isoquinoline crystallized from a mixture of ether–EtOH as stout yellow needles m.p. 185–186° (dec). (Found: C, 45·2; H, 4·7; N, 4·1. $C_{13}H_{16}O_2NI$ requires: C, 44·7; H, 5·0; N, 3·9%).

8-*Hydroxy*-7-*methoxyisoquinoline* was obtained from *o*-vanillin in 12% yield and converted to its *methiodide* which crystallized as yellow needles from ether–$CHCl_3$, m.p. 196–197°. (Found: C, 42·6; H, 4·0. $C_{11}H_{12}O_2NI$ requires: C, 41·7; H, 3·8%).

7,8-*Dimethoxyisoquinoline*. *o*-Veratraldehyde (16 g) was converted to 7,8-*dimethoxyisoquinoline* as a colourless oil (0·27 g, 6%) b.p. 140°/1 mm, which was characterized as its *methiodide*, yellow needles from EtOH, m.p. 178°. (Found: C, 43·4; H, 4·3; N, 4·1. $C_{12}H_{14}O_2NI$ requires: C, 43·5; H, 4·3; N, 4·2%).

2-(2′-*Methoxyphenoxy*)5-*nitrobenzoic acid*. 2-(2′-Methoxyphenoxy)5-nitrobenzaldehyde (2 g) was dissolved in acetone (25 ml) and water (25 ml) was added. The mixture was stirred and maintained under reflux as a soln of $KMnO_4$ (1·62 g) in water (35 ml) was allowed to flow slowly in over a period of 1 hr. Stirring and heating was continued for a further hr by which time all the permanganate had been decolourized.

The mixture was made alkaline with 10% KOH aq and filtered while hot. The residue (MnO_2) was washed with hot water. As the combined filtrate and washings cooled a little unreacted aldehyde precipitated and was removed. The soln was then acidified with 4N-HCl to yield a colourless ppt. 2-(2′-*Methoxyphenoxy*)-5-*nitrobenzoic acid* was filtered off and dried (1·9 g, 90%). This was recrystallized from aqueous EtOH to give colourless needles, m.p. 184°. (Found: C, 58·4; H, 3·8. $C_{14}H_{11}O_6N$ requires: C, 58·1; H, 3·8%).

2-(2′-*Methoxyphenoxy*)5-*nitrophenylacetic acid*. Thionyl chloride (1·64 g, 1 ml) was added to 2-(2′-methoxyphenoxy)-5-nitrobenzoic acid (2 g) and the mixture boiled under reflux for 90 min under anhydrous conditions.

Excess thionyl chloride was then distilled off, final traces being removed by distillation with dry benzene to leave the pure acid chloride as a solid.

Diazomethane (0·6 g), prepared from N-nitrosomethylurea (2·2 g)[18] in dry ether, was added to a suspension of the acid chloride in dry ether, during 90 min, with swirling of the mixture. After standing overnight at 0° the brown crystalline diazoketone was filtered off. Concentration of mother liquors gave a further quantity (total 1·3 g).

The diazoketone, dissolved in dioxan (10 ml), was added with stirring to a mixture of freshly prepared Ag_2O (1·1 g),[19] anhyd Na_2CO_3 (2·5 g) and sodium thiosulphate (1·5 g) in water (100 ml) at 60°.

The mixture was stirred for a further hr and a half with the temp being increased to 90° for the final 30 min. The soln was cooled and freed from colloidal Ag impurities by passing the alkaline soln down an alumina column (4 in × 1 in). The eluate was then acidified and the product precipitated as a yellow sticky solid, which was washed and dried *in vacuo* to give as a yellow-brown solid 2-(2′-methoxyphenoxy)-5-nitrophenylacetic acid (0·7 g). This represents an overall yield of 33·4% from the benzoic acid, and 30·0% from 2-(2′-methoxyphenoxy)-5-nitrobenzaldehyde. It crystallized from petroleum ether (b.p. 60–80°) as colourless needles, m.p. 137°, (lit.[6] m.p. 141°).

10,11-*Dihydro-2-nitro-6-methoxy-10-oxo-dibenz-(bf)-oxepine* (VI). Polyphosphoric acid was prepared from phosphoric acid (35 ml, *d* 1·75) and P_2O_5 (52·5 g) by heating on a steam bath for 18 hr.

The foregoing phenylacetic acid (4·65 g) was added to the polyphosphoric acid at 160° to give a cherry red soln. After then heating at 100° for 2½ hr, the soln, on cooling, was poured into ice-water. The solid material given was taken up in benzene and the soln extracted. The combined benzene solns were washed with 10% $NaHCO_3$aq (twice), water (twice), dried ($MgSO_4$) and concentrated. The 10,11-dihydro-2-nitro-6-methoxy-10-oxo-dibenz(*bf*)oxepine (VI; 2·38 g, 51%) crystallized as yellow needles, m.p. 197–198°, (lit.[6] m.p. 195°), ν_{max} 1704 cm^{-1} (C=O).

6-*Methoxy-10-nitro-12H-[1]-benzoxepino[2.3.4-ij]isoquinoline* (IV). The oxepinone (VI, 1·5 g) was converted into the isoquinoline (IV, 0·42 g, 26%), which was purified by sublimation at 185–195°/0·2 mm. The sublimed isoquinoline (IV) crystallized from benzene as pale yellow needles m.p. 256–258° (dec). (Found: C, 66·2; H, 3·9; N, 9·1; Me, 10·1. $C_{17}H_{12}O_4N_2$ requires: C, 66·4; H, 4·0; N, 9·3; MeO, 10·3%). No absorption attributable to N—H stretch was present in the IR spectrum.

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