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PHOSPHOROUS PENTOXIDE-PYRIDINE: A NEW COMBINATION FOR BISCHLER-NAPIERALSKI REACTION

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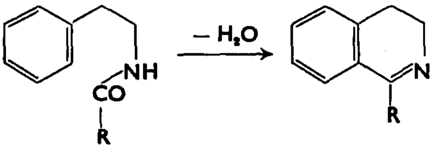
Abstract—The Bischler-Napieralski type of cyclisation can be effected by treating appropriately substituted acyl β-phenethylamides with phosphorous pentoxide in boiling pyridine. Isoquinolines can be recovered as the free base from the resultant pyridine layer; this reaction gives a good yield.

THE usefulness of the Bischler-Napieralski reaction and its modifications[1] for the preparation of 3,4-dihydroisoquinoline derivatives by dehydrating acyl β-phenethylamides is well established. The methods of Pictet[2] and Mannich[3] for the synthesis of isoquinolines may also be regarded as the modified forms of this reaction.



Phosphoryl chloride, usually in combination with benzene hydrocarbons, is now most extensively used as the cyclisation agent in these reactions. For more drastic conditions, phosphorous pentoxide is recommended, usually with boiling xylene, while the same agent in boiling tetralin is considered the most powerful dehydrating combination[4] in this type of reaction. A combination of phosphoryl chloride-phosphorous pentoxide[5] is also used in some cases, but since phosphoryl chloride is more easily handled this would seem to be the main reason of its popularity.

In minor cases, thionyl chloride,[6] and phosphorous pentachloride in cold chloroform[7] are also used, the latter of which appears to have a special feature to effect the cyclisation when phosphoryl chloride and phosphorous pentoxide are ineffective.[8] Polyphosphoric acid[9] will also be mentioned as a new reagent to be used for the same cyclisation purpose.

With all these reagents or reagent combinations the ring closure proceeds in acidic condition from the beginning to the end of the reaction, and thus the cyclisation of amide possessing any acid-sensitive group might suffer from some change either during the reaction or during the working up of the product. Thus, according to the

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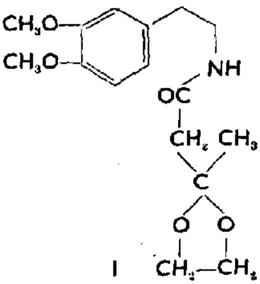
[1] W. M. Whaley and T. R. Govindachari *Organic Reactions* VI. 74 (1951).
[2] A. Pictet and A. Gams *Ber.* **43**, 2384 (1910).
[3] C. Mannich and O. Walter *Arch. Pharm.* **265**, 1 (1927).
[4] *Organic Reactions* VI, 99.
[5] *Ibid.* 95.
[6] H. Avenarius and R. Pschorr *Ber.* **62**, 321 (1929); J. M. Gulland and C. J. Virden *J. Chem. Soc.* 1791 (1929); *Asta Akt. Ges.* D.R.P. 614703 (Friedl. 21, 688 (1934)).
[7] J. M. Gulland and R. D. Haworth *J. Chem. Soc.* 581, 1132, 1834, 2083, (1928); 658, (1929); 2872, 2881, 2885, 2893 (1931).
[8] H. Kondo and S. Ishiwata *Ber.* **64**, 1533 (1931); R. Robinson and S. Sugasawa *J. Chem. Soc.* 280 (1933).
[9] H. R. Snyder and F. X. Werber *J. Amer. Chem. Soc.* **72**, 2962 (1950).

writers' experiments, the cyclisation of β-3,4-dimethoxyphenethyl-β-ethylenedioxybutyramide (I) by means of phosphoryl chloride in boiling benzene gave always an isoxazoline derivative (III) rather than the expected (IV). The former was probably produced by a prototropic change of 1-acetonylisoquinoline derivative (II) in its enolic form (II'), the hydrolysis product of (IV) by the agency of acid formed during the cyclisation reaction.*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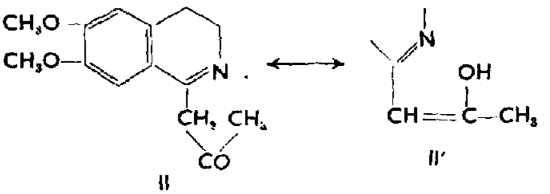
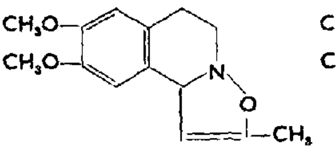

II

II'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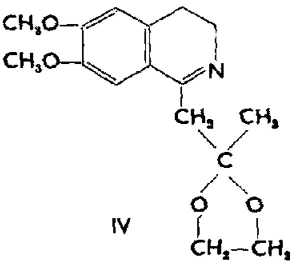
IV

In connection with a synthesis now being carried out in our laboratory, we hoped to find a new combination for the Bischler-Napieralski reaction, which allows the cyclisation to take place in a basic medium as a whole. For that purpose, two types of combination (i) phosphoryl chloride-pyridine and (ii) phosphorous pentoxide-pyridine were examined, of which the latter seemed preferable. Since phosphorous pentoxide itself is rather inconvenient to handle, it was mixed with inert material such as purified sea-sand, coarsely powdered limestone, or alumina.

Some preliminary experiments carried out with this new combination, in which sea-sand only was used as the diluent for phosphorous pentoxide with satisfactory results, are described in this paper.

When β-(3,4-dimethoxyphenethyl)-acetamide (V) was treated with a mixture of phosphorous pentoxide and sand in boiling pyridine, 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (VI) was recovered in a good yield from the supernatant pyridine layer, which also contained some of the starting amide. From the pyridine washing of the caked residue practically none of the product was recovered, showing that all the product existed in the pyridine layer as the free base. The corresponding benzamide (VII) also gave a comparable result. Both isoquinolines (VI) and (VIII) were identified with the authentic specimens.

The cyclisation of β-(3,4-dimethoxyphenethyl)-benzyl-acetamide (IX) by this means is probably worth noting. From the resultant pyridine layer a yellowish oil was recovered, which was fairly unstable, turning reddish on exposure to air. The presence of 6,7-dimethoxy-1-methylene-2-benzyl-1,2,3,4-tetrahydroisoquinoline (X)

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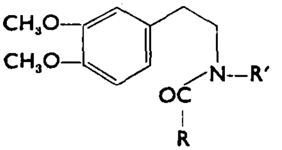
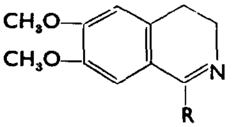
* The details of this experiment will be published in the forthcoming paper.

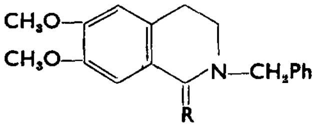
in this oil was established (i) by treating the oil with hydrochloric acid in the presence of potassium iodide, giving the stable quaternary benzyl iodide (XI), and (ii) by oxidising the oil with potassium permanganate in pyridine solution, furnishing *N*-benzylcorydaldin (XII). Direct oxidation of the pyridine layer of the reaction mixture also gave the same product.



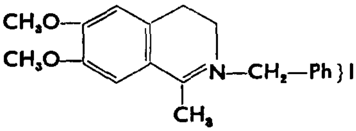
V: $R = CH_3$, $R' = H$
VII: $R = Ph$, $R' = H$
IX: $R = CH_3$, $R' = CH_2Ph$



VI: $R = CH_3$
VIII: $R = Ph$



X: $R = CH_2$
XII: $R = O$



XI

The feature of this new combination exists in that, though the isoquinoline formation takes place on the surface of phosphorous pentoxide under acidic condition, the acid formed—probably metaphosphoric acid—will soon become neutralised with pyridine, liberating isoquinoline from the surface of the dehydrating agent, which then moves into the pyridine layer as a free base, and this will certainly be favourable for the synthesis of isoquinolines which contain any group sensitive to acid.

Application of this new combination to various other types of phenethylamides is now under progress, and the results will be the subject of further communications.

EXPERIMENTAL

6,7-*Dimethoxy*-1-*methyl*-3,4-*dihydroisoquinoline* (VI). This is described in detail as a general procedure. 3,4-(β-Dimethoxyphenethyl)-acetamide (V: 0·5 g) in pure pyridine (30 c.c.) was kept under gentle boiling, and to this solution was added an intimate mixture of phosphorous pentoxide (5 g) and dry sand (50 g) in four portions with stirring. Some time later, stirring became impossible due to caking of the dehydrating agent. After being refluxed for 6 hours, the dark-coloured pyridine layer was decanted and the residue extracted with 3 × 10-c.c. portions of hot pyridine. From the combined pyridine solution the solvent was removed *in vacuo*, leaving yellowish syrup (0·5 g), which was dissolved in benzene. The benzene solution was repeatedly extracted with dilute hydrochloric acid, and the combined acid solution was basified and salted out. The liberated base was collected in benzene, dried and evaporated, giving a faint yellow syrup (0·45 g) which solidified on standing. When purified from *n*-hexane, it formed colourless prisms of m.p. 108–109°, which was not depressed on admixture with an authentic specimen. The yield was 0·38 g, or *c.* 85% of the pure product.

From the original benzene solution a small amount of the starting amide was recovered.

The melting-points of the hydrochloride (199–200°) and of the picrate (210–212°) were also the same as recorded by previous workers.

6,7-*Dimethoxy-*1-*phenyl*-3,4-*dihydroisoquinoline* (VIII) forms colourless prisms from ethyl acetate; its melting-point of 120° was not depressed when admixed with an authentic sample. It gave a yield of 0·3 g, or *c.* 83% from 0·35 g of the starting amide.

6,7-*Dimethoxy*-1-*methylene*-2-*benzyl*-1,2,3,4-*tetrahydroisoquinoline* (X). The cyclisation of the amide (IX) was carried out as above. When pyridine was removed *in vacuo*, there remained a yellowish brown viscous oil, which could not be purified because of its unstable nature in air and was directly converted into the quaternary salt.

6,7-*Dimethoxy*-1-*methyl*-2-*benzyl*-3,4-*dihydroisoquinolinium iodide* (XI). The above-mentioned oil was treated with hydrochloric acid added with sufficient amount of potassium iodide; the yellowish solid which was separated was purified from alcohol, and formed stable yellow needles of m.p. 183–184°, being identified by mixture melting-point test with an authentic sample prepared from the compound (VI), benzyl chloride and potassium iodide. Thus, 0·41 g of the pure iodide (XI) was obtained from 0·5 g of the amide (IX), yield *c.* 76%.

Oxidation of 6,7-*Dimethoxy*-1-*methylene*-2-*benzyl*-3,4-*dihydroisoquinoline* (X). (i) The crude base (X: 0·2 g), obtained as above, in pure pyridine (30 c.c.), was oxidised by adding an aqueous potassium permanganate solution (made from 0·2 g of the oxidising agent and 30 c.c. of water) with stirring and cooling in the running water. After about 2 hours stirring, the unreacted permanganate was decomposed by adding enough methanol, filtered from manganese dioxide, and the filtrate was evaporated *in vacuo*, yielding a colourless glass, which solidified on standing. Purified from *n*-hexane, the benzylcorydaldin thus obtained formed colourless prisms of m.p. 84°, which was not depressed on admixture with an authentic specimen prepared as shown below. The yield was 0·2 g, which is nearly the theoretical value (Found: C, 72·8; H, 6·1; N, 4·9. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7).

(ii) The direct oxidation of the pyridine solution gave the same compound. Thus, the amide (IX: 0·3 g) was cyclised in boiling pyridine as already stated. The pyridine layer was decanted from the caked residue and was directly treated with an aqueous solution of potassium permanganate (0·3 g in 30 c.c. of water) and treated as previously described. The residue was dissolved in a mixfure of benzene and *n*-hexane (100 c.c. each), purified through an alumina column, and the solvent was removed by distillation. The residue was purified from *n*-hexane, giving 0·18 g of pure benzylcorydaldin of m.p. 84°, which remained unchanged when admixed with an authentic sample.

An authentic N-*benzylcorydaldin*. 6,7-Dimethoxy-3,4-dihydro-*N*-benzylisoquinolinium chloride (1 g) in *c.* 10 c.c. of water was oxidised by adding an alkaline potassium ferricyanide solution (8 g of ferricyanide in 60 c.c. of 10% sodium hydroxide solution) with stirring and water-cooling for a period of half an hour; stirring was continued for an additional half-hour. The filtrate was repeatedly extracted with ether, dried, and evaporated, leaving a yellowish solid, which was purified from *n*-hexane, forming colourless prisms of m.p. 84°, giving a yield of 0·8 g, or *c.* 86% of the pure product (Found: C, 72·9; H, 6·3. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4).