Phosphorus Pentoxide in Organic Synthesis; XVII[1]. A New Synthesis of 4-Arylamino-2,3-polymethylenequinolines

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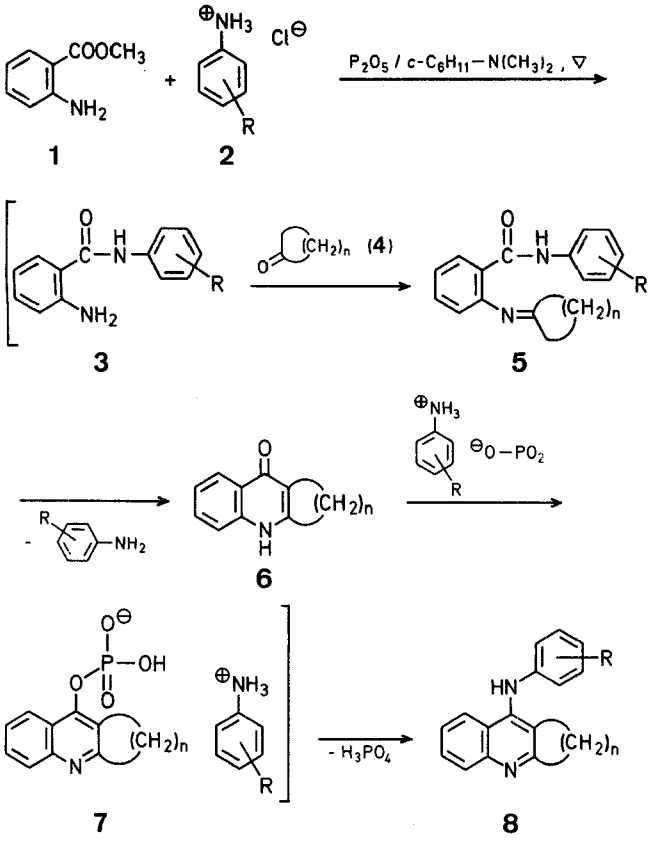
Many 4-substituted 2,3-polymethylenequinolines possess a wide spectrum of pharmacological activities. 9-Amino-1,2,3,4-tetrahydroacridine (Tacrine) is known to be a potent anticholinesterase inhibitor[3,4]. Accordingly, Tacrine as well as structurally related compounds have been intensively investigated, and some 4-*N*-substituted 4-amino-2,3-polymethylenequinolines were shown to be analeptics, respiratory stimulants, and analgetics[5,6,7].

These compounds are usually attainable via the corresponding hydroxy compounds which are prepared through different routes[8,9]. On treatment with phosphoryl chloride, the hydroxy compounds are converted into the corresponding chloro derivatives. The latter are condensed with appropriate amines in the presence of phenol to give the required 4-amino-2,3-polymethylenequinolines[5,9,10,11]. We have previously reported[12] a new, one-step procedure for the synthesis of 4-amino- and 4-dimethylamino-2,3-polymethylenequinolines using hexamethylphosphoric triamide or phosphorus pentoxide/amine mixtures. The present investigation deals with the application of this new, one-step procedure for the synthesis of a series of 4-arylamino-2,3-polymethylenequinolines from simple starting materials.

It is found that methyl anthranilate (**1**) reacts with cycloalkanones **4** in a mixture of phosphorus pentoxide, *N,N*-dimethylcyclohexylamine, and a suitable aromatic amine hydrochloride **2** to give directly the corresponding 4-arylamino-2,3-polymethylenequinolines **8a–k**. In all cases investigated, the reaction proceeded at 220 °C for 20 h to give the products **8a–k** in 43–64% yield (Scheme **A** and Table).



Scheme **A**

Table. 4-Arylamino-2,3-polymethylenequinolines (**8a-k**) prepared

Product No.	R	n	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]
8a	H	4	63	234–236° (toluene)	235–236°[15]
8b	3-CH_3	4	45	131–133° (petrol ether)	132–134°[15]
8c	4-CH_3	4	64	180–182° (ligroin, b.p. 100–140°)	181–182°[15]
8d	4-C_2H_5	4	56	120–121° (petrol ether)	$C_{21}H_{22}N_2$ (302.4)
8e	4-F	4	51	176–177° (ligroin, b.p. 100–140°)	$C_{19}H_{17}FN_2$ (292.4)
8f	H	5	56	194–196° (ligroin, b.p. 100–140°)	195–196°[16]
8g	3-CH_3	5	55	140–141° (ligroin, b.p. 100–140°)	140–141°[16]
8h	4-CH_3	5	43	163–165° (ligroin, b.p. 80–100°)	164–165°[16]
8i	H	6	57	212–213° (ligroin, b.p. 100–140°)	$C_{21}H_{22}N_2$ (302.4)
8j	4-CH_3	6	64	155–156° (petrol ether)	$C_{22}H_{24}N_2$ (316.4)
8k	H	10	49	152–153° (benzene)	$C_{25}H_{30}N_2$ (358.5)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.17, N ±0.11.

The reaction is believed to proceed through the initial formation of an *o*-aminobenzanilide **3**, followed by condensation with the ketone to **5** and subsequent ring closure to the quinolinone **6**. The latter is then aminated in the reaction mixture to give **8** (Scheme **A**). In support of this view is the similar mechanism we have previously adopted[12] in connection with the production of 4-dimethylamino-2,3-polymethylenequinolines by the reaction of methyl anthranilate with cycloalkanones in hexamethylphosphoric triamide. Actually, in the latter case, intermediates of the types **3** and **6** could be isolated and characterized. In the present case, although such intermediates could not be isolated, the proposed mechanism seems quite plausible, since it has been reported[13] that a type of phosphoric amide analogous to hexamethylphosphoric triamide is formed in phosphorus pentoxide/amine hydrochloride mixtures.

In the present investigation, the use of the ester derivative seems to be essential for the production of **8**. It has been found that reaction of anthranilamide (**9**) with cyclohexanone in phosphorus pentoxide/amine hydrochloride mixtures leads to the unsubstituted amino derivative **13** (Tacrine). In this case, it is assumed that anthranilonitrile (**10**) is first formed through dehydration of the amide under the experimental conditions. Further condensation of the amino group with cyclohexanone and subsequent cyclization by attack on the electrophilic nitrile carbon leads to the imine **12**

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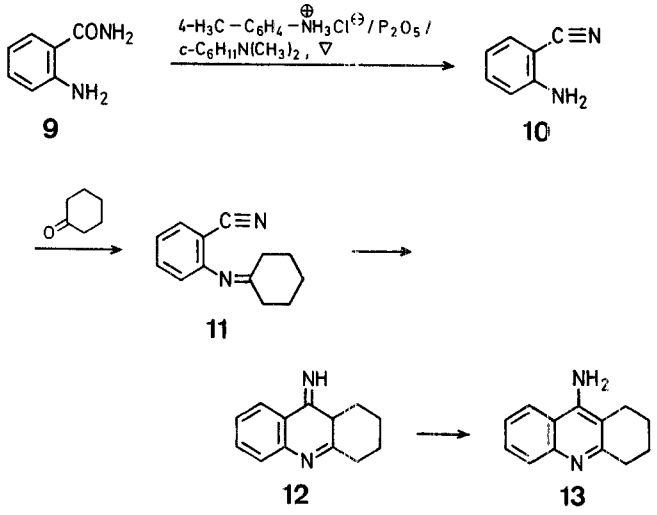
which tautomerizes to **13** (Scheme **B**). It has been previously reported[14] that anthranilonitrile reacted with cyclohexanone in presence of zinc chloride to give **13**.



Scheme **B**

Compounds **8a–c**, **8f–h**, and **13**, have been previously reported[15,16]. The structures of the new derivatives **8d, e, i–k** are based on analogy, microanalytical I.R., N.M.R., and mass spectral data.

In pesticide screening[17], protective fungicide activity was found for **8a** at 10 ppm against *Erysiphe graminis* (mildew) on barley; insecticide activity for **8c–e, g, h** at 12.5 ppm against Aedes larvae in water; anthelmintic activity in sheep for **8c, e, j**.

4-Arylamino-2,3-polymethylenequinolines (8a–k); General Procedure:

Phosphorus pentoxide (28.4 g, 0.2 mol), *N,N*-dimethylcyclohexylamine (25.4 g, 0.2 mol), and the aromatic amine hydrochloride (**2**; 0.2 mol) are mixed at room temperature and then heated on an oil bath at 220 °C until a clear homogeneous mixture is obtained. The mixture is allowed to cool to below 150 °C, and methyl anthranilate (**1**; 7.58 g, 0.05 mol) is added dropwise followed by the cycloalkanone (**4**; 0.06 mol). The mixture is again heated at 220 °C with stirring for 20 h. After cooling to 100 °C, 2 molar sodium hydroxide solution (450 ml) is added and stirring is continued for further 30 min at room temperature. In some cases, a precipitate is formed, which is filtered off, otherwise the alkaline solution is extracted with ether (3 × 250 ml) and the extract evaporated to dryness under reduced pressure. The products **8a–k** are then crystallized from the suitable solvents (Table).

9-Amino-1,2,3,4-tetrahydroacridine (13):

The reagent mixture is prepared as described above from 4-toluidine hydrochloride (28.7 g, 0.2 mol), phosphorus pentoxide (28.4 g, 0.2 mol), and *N,N*-dimethylcyclohexylamine (25.4 g, 0.2 mol). Anthranilamide (**9**; 6.8 g, 0.05 mol) is added followed by cyclohexanone (5.95, 0.06 mol) and the mixture is heated at 220 °C for 20 h. After cooling to 100 °C, 2 molar sodium hydroxide (450 ml) is added and stirring is continued for further 30 min. The alkaline solution is then extracted with ether (3 × 250 ml), the ether washed with water, dried, and evaporated to dryness under reduced pressure. The residue is washed with ligroin (b.p. 100–140 °C) and the solid separated is recrystallized from the same solvent to give **13**; yield: 3.0 g (30%); m.p. 182–184 °C (Lit.[12], m.p. 182–183 °C).

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