2,3-POLYMETHYLENEQUINOLINES

XIX. PREPARATION AND BIOLOGICAL ACTIVITY OF 4-AMINO-2,3-POLYMETHYLENEQUINOLINES

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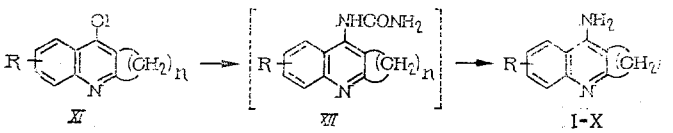
The 4-amino-2,3-polymethylenequinolines are of interest because of their physiological activity [1, 2,3], but their preparation from the corresponding 4-chloro-2,3-polymethylenequinolines and ammonia presents some difficulty owing to the low mobility of the halogen atom. Attempts to carry out this reaction in a phenol medium at 180°C have led not to the desired 4-amino- but the 4-phenoxy derivatives [4]. On replacing the phenol by p-cresol, 4-amino derivatives have indeed been formed but have been accompanied by significant amounts of the 4-p-cresoxy analogs [5]. The reaction can be effected in an alcohol medium by heating at 230-240°C under pressure for 20-24 h [4].

The present communication is concerned with the successful preparation of ten aminopolymethylenequinolines of this type (I-X) (see Table 1). The procedure was to condense the chloro derivatives (XI) with urea, using molten phenol as reaction medium, followed by hydrolysis of the putative, proximate products of the reaction, viz. the 4-carbamido-2,3-polymethylenequinolines (XII):



Preliminary experiments had shown that good yields of the products could be obtained by this means. In no single case was formation of phenoxy derivatives observed, and the amount of resinification was insignificant. It should be observed that the phenol plays an essential part in the reaction, as attempts to condense (XI) with urea in its absence were abortive. Evidently therefore the phenol subserves not only the function of a solvent but acts also as an active promoter of the reaction. This catalytic effect can be accounted for by the formation of hydrogen bonding between the phenolic hydroxyl group and the nitrogen atom of (XI), resulting in an increase in the electron-acceptor properties of the latter grouping; the consequent reduction in electron density at C(4) then promotes and S_N2-type reaction at this point in the molecule.

The properties of the compounds listed in Table 1 reveal their complete identity with corresponding compounds obtained earlier by other methods, and their structure was further confirmed by examination of the IR spectra which show oscillation ranges at 3520-3524 and 3396-3430 cm^{-1} (ν_{NH_2}), and at 2937-2949 and 2880-2897 cm^{-1} (ν_{CH_2}).

The toxicity and general pharmacological properties of the products have been determined in mice and in rats. In addition, we have taken this opportunity further to develop our previous studies [6, 7] of the anti-curare activity of certain 2,3-polymethylenequinolines. With this end in view we have examined the influence of these ten compounds on the effects of muscle relaxants of antagonistic, and depolarizing type, respectively. The two primary drugs selected for this purpose were diplacin [4,4'-{m-phenylenebis-(oxyethylene)}-bis{hexahydro-1-hydroxy-7-(hydroxymethyl)-1H-pyrrolizinium chloride}] (antagonistic), and ditilin (dicholine diiodide succinate) (depolarizing), respectively. The test materials were introduced in the

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TABLE 1. 4-Amino-2,3-polymethylenequinolines

Compound	R	n	Yield, (%)	Mp (°C)[1]	
				our values	literature
I	H	3	82	183—5	181 [4]
II[2]	6-Br	3	89	239—240	—
III[3]	8-Cl	3	92	264—5	—
IV	6-CH_3	3	81	224—5	223 [9]
V	8-CH_3	3	89	206—7	204,5 [9]
VI	6-CH_3O	3	83	214—5	215 [4]
VII	H	4	70	183—4	183—4 [4]
VIII[4]	6-Br	4	72	258	—
IX	6-Cl	4	85	260	260 [5]
X	6-CH_3	5	90	209	209 [5]

[1]Compounds (I), (III), and (VI) crystallized from dioxane; (II) from toluene; (IV) and (VII) from benzene; (V) and (VIII) from xylene; and (IX) and (X) from ethanol.
[2]Found %: Br 30.0; N 10.8. $C_{12}H_{11}BrN_2$. Calculated %: Br 30.5; N 10.7
[3]Found %: Cl 15.9; N 12.7. $C_{12}H_{11}ClN_2$. Calculated %: Cl 16.2; N 12.8.
[4]Found %: Br 28.4; N 10.0. $C_{13}H_{13}BrN_2$. Calculated %: Br 28.8; N 10.1.

form of suspensions in starch mucilage. All ten compounds had typical CNS-stimulant properties as evidenced by induction of tremors and clonic-tonic convulsions, culminating in cessation of respiration and death of the animal. The LD_{50} ranged from 17 to 100 mg/kg, and this high toxicity was especially marked in the cases of (I), (VII), and (IX), the LD_{50} of which was 17.5, 31.3, and 30.9 mg/kg, respectively. The same three compounds (I, VII, and IX) were able to abolish the effect of a 5 mg/kg dose of diplacin and so protect 75% mice (compound I) and 42% mice (compound VII) against this drug. All 10 compounds, especially (I) and (VII), showed a capacity to reinforced the effects of a 10 mg/kg dose of ditilin.

These experiments demonstrate that an anti-curare effect is brought into play only against antagonist-type muscle relaxants, a conclusion consonant with the results obtained by us previously [6, 7] with other 2,3-polymethylenequinolines.

The occurrence, among polymethylenequinolines of this type of active antidepressor and sedative agents [5], as also the fact of the tricyclic structure of such compounds, induced us to undertake an examination of the psychotropic activity of one of them (compound I), the particular pharmacological effects selected for the study being those commonly used in investigations of this kind [8].

In mice, (I), at dose levels 1.5 and 15.0% of the LD_{50} (0.3 and 3.0 mg/kg, respectively), deepened the hypothermic effect of a 5 mg/kg dose of reserpine, but, on the contrary, inhibited the action of this alkaloid when its dose was lowered to 2 mg/kg. A 3 mg/kg dose of (I) delayed the development of ptosis induced in its absence by 2 and 5 mg/kg doses of reserpine (the effect was more clearly pronounced at the lower dose level of the primary drug), intensified the generic toxicity of the amphetamines, foreshortened hexobarbital induced sleep, and, while the said dose of (I) (3 mg/kg) increased the intensity and duration of nicotiniform tremors and convulsions, it was without effect on similar convulsions induced by corazole (pentamethylenetetrazole), and was unable to prevent the extensor phase in electric shock.

It is evident that the pharmacological results we have described testify to the presence in (I) of molecular features conducive to the status of the compound as a CNS stimulant.

EXPERIMENTAL

4-Amino-2,3-polymethylenequinolines (I-X). Solutions of (XI) (0.03 mole) in molten phenol (15 g) were treated with urea (0.05 mole) and heated at 180-190° for 8 h. The resulting reaction mixtures were cooled and freed from phenol by treatment with a 10% solution of caustic alkali. The insoluble residues so obtained were, in each case, dissolved in 10% hydrochloric acid (30 ml) and boiled for 2 h. The resulting solutions were filtered and the filtrates made alkaline. The precipitates obtained were recrystallized.

LITERATURE CITED

1. F. H. Shaw, S. Gershon, and G. A. Bentley, J. Pharm. Pharmacol., 9, 666 (1957).
2. S. Gershon, and F. H. Shaw, J. Pharm. Pharmacol., 10, 638 (1958).
3. S. Gershon, Nature, 186, 1072 (1960).
4. V. Petrov, J. Chem., Soc., 634 (1947).
5. M. V. Sigal, Jr., B. J. Brent, and P. Marchini, US Patent No. 3,232,945 [Chem. Abstr., 64, 14174g (1968)].
6. É. S. Abramochkin and M. E. Konshin, Khim.-Farm. Zh., No. 7, 10 (1970).
7. D. I. Uvarov, A. S. Zaks, L. G. Zil'bermints, M. E. Konshin, and T. A. Kapitonenko, Khim.-Farm. Zh., No. 2, 17 (1973).
8. I. P. Lapin, Tr. Leningrad. Nauch-Issled. Psikhonevrol. Inst., 34, 31 (1966). [Chem. Abstr., 68, 1740g (1968)].
9. M. Lamant, Ann. Chim., [13], 4, 87 (1959).