SYNTHESIS OF N-SUBSTITUTED 4-AMINO-2,3-PENTAMETHYLENEQUINOLINES

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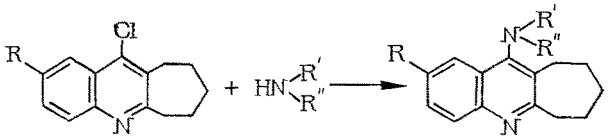
4-Amino-2,3-pentamethylenequinolines are of interest as physiologically active compounds [1,2]. The present work is devoted to the synthesis of the N-substituted 4-amino-2,3-pentamethylenequinolines (V - XXIX) with the aim of testing their biological activity and of establishing a possible relationship between the activity and the structure. The synthesis was carried out by the interaction of 4-chloro-2,3-pentamethylenequinolines I-IV with primary or secondary amines in phenol medium:



I: R = H; II: R = CH_3; III: R = Cl; IV: R = Br

V-XXIX

The reaction was carried out with difficulty, requiring prolonged heating and involving, in the majority of cases, the formation of significant quantities of the corresponding 4-phenoxy-2,3-pentamethylenequinolines. To obtain analytically pure compounds it was necessary to resort to multiple crystallizations, which led to reduced yields. Compound I reacted more smoothly and at a lower temperature (140°C), whereas compounds II-IV only reacted at 170-175°C.

N-substituted 4-amino-2,3-pentamethylenequinolines (see Table 1) are colorless crystalline compounds having a basic character which react with mineral acids to form salts dissolved in water.

The UV spectra of V-XXII have three maxima: 232-236, 306-312, and 320-326 nm.* On introduction of halogen or methyl groups at position 6 of 2,3-pentamethylenequinolines, there is observed a clearly defined bathochromic shift of the absorption band to longer wavelengths The nature of the amine entering position 4 has no effect on the position of the maxima.

Compounds V-XI, XIII, XIV, XVI-XXIX were subjected to biological tests.† The toxicity (LD_{50}), the analgesic activity (by the heat method of MacDonald and Wolf), and the anticurare activity (the ability to elimiate or reduce the myorelaxant effect of diplacinum) were investigated. The greatest toxicity (68-148 mg/kg) is possessed by XXIII and XXIX. Morpholino and arylpiperazino derivatives showed significantly lower toxicity (205-1050 mg/kg), decreasing in the following order: XVI > V, VI > XIII, XIV > XI > IX > X > VIII. Compounds VII, IX, XIII, XIV, and XVI raise the threshold of pain perceptibility 2-2 1/2 times; the analgesia is retained for 60-90 min. Weak anticurare activity was found in VI, VII, and XXIV.

EXPERIMENTAL

4-Chloro-6-bromo-2,3-pentamethylenequinoline (IV). To 0.2 mole of phosphorus oxychloride was gradually added 0.05 mole of 4-hydroxy-6-bromo-2,3-pentamethylenequinoline. The mixture was heated on a water bath for 30 min and then poured into ice water; the solution formed after decomposition of the

*UV spectra were run in alcohol on an SF-4 spectrophotometer.

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TABLE 1. N-Substituted 4-Amino-2,3-pentamethylenequinolines

Compound	R	$N\begin{smallmatrix}R'\\R''\end{smallmatrix}$	Yield, %	Mp, °C		Found N, %	Empirical formula	Calculated N, %
				base	hydrochloride			
V	H	C_6H_5N	60,5	178—80	222—4	11,81	$C_{24}H_{27}N_3$	11,72
VI	H	$p-CH_3C_6H_4N$	49,7	146—7	221—2	11,61	$C_{25}H_{29}N_3$	11,32
VII	H	$o-CH_3C_6H_4N$	47,4	139—40	215—7	11,59	$C_{25}H_{29}N_3$	11,32
VIII	CH_3	C_6H_5N	58,6	187—9	227—9	11,22	$C_{25}H_{29}N_3$	11,32
IX	CH_3	$p-CH_3C_6H_4N$	48,3	149—50	262—4	11,08	$C_{26}H_{31}N_3$	10,92
X	CH_3	$o-CH_3C_6H_4N$	46,7	161—2	207—9	10,71	$C_{26}H_{31}N_3$	10,92
XI	CH_3	ON	44,5	193—4	252—4	9,49	$C_{19}H_{24}N_2O$	9,44
XII	CH_3	CH_3N	43,8	115—6	232—4	13,73	$C_{20}H_{27}N_3$	13,59
XIII	Cl	C_6H_5N	61,2	188—9	242—4	10,95	$C_{24}H_{26}ClN_3$	10,71
XIV	Cl	$p-CH_3C_6H_4N$	60,8	163—4	261—3	10,62	$C_{25}H_{28}ClN_3$	10,34
XV	Cl	$o-CH_3C_6H_4N$	59,1	153—4	230—3	10,11	$C_{25}H_{28}ClN_3$	10,34
XVI	Cl	ON	50,8	160—1	230—2	9,04	$C_{18}H_{21}ClN_2O$	8,83
XVII	Cl	CH_3N	50,1	130—1	265—7	12,65	$C_{19}H_{24}ClN_3$	12,72
XVIII	Br	C_6H_5N	53,4	195—6	245—7	9,73	$C_{24}H_{26}BrN_3$	9,63
XIX	Br	$p-CH_3C_6H_4N$	53,2	146—8	265—7	9,59	$C_{25}H_{28}BrN_3$	9,33
XX	Br	$o-CH_3C_6H_4N$	50,8	136—7	223—5	9,18	$C_{25}H_{28}BrN_3$	9,33
XXI	Br	ON	47,4	166—8	246—8	7,92	$C_{18}H_{21}BrN_2O$	7,75
XXII	Br	CH_3N	51,4	131—2	267—9	11,37	$C_{19}H_{24}BrN_3$	11,23
XXIII·HCl	H	$C_6H_5CH_2NH$	57,7	—	249—25	7,95	$C_{21}H_{22}N_2HCl$	8,27
XXIV·HCl	H	$n-C_4H_9NH$	43,2	—	231—4	9,0	$C_{18}H_{24}N_2HCl$	9,19
XXV·HCl	H	$cyclo-C_6H_{11}NH$	36,1	—	260—1	8,10	$C_{20}H_{26}N_2HCl$	8,48
XXVI·HCl	H	$(C_2H_5)_2N$	31,8	—	229—30	9,43	$C_{18}H_{24}N_2HCl$	9,20
XXVII·HCl	CH_3	$C_6H_5CH_2NH$	39,7	—	255—6	8,27	$C_{22}H_{24}N_2HCl$	7,95
XVIII·HCl	CH_3	$n-C_4H_9NH$	45,8	—	167—9	9,13	$C_{19}H_{26}N_2HCl$	8,81
XXIX·HCl	Cl	$C_6H_5CH_2NH$	44,1	—	253—4	7,63	$C_{21}H_{21}ClN_2HCl$	7,50

reaction mixture was filtered. The filtrate was neutralized with ammonia and the precipitate which separated was filtered. Yield was 79%, mp 110-111°C (from acetone). Found %: N 4.59. $C_{14}H_{13}BRClN$. Calculated %: N 4.50.

4,6-Dichloro-2,3-pentamethylenequinoline (III) was prepared in the same way as IV; mp 104-105°C (from acetone). Found %: N 5.45. $C_{14}H_{13}Cl_2N$. Calculated %: N 5.26.

4-Chloro-6-methyl-2,3-pentamethylenequinoline (II) was prepared in the same way as IV; mp 90°C (from acetone). Found %: N 6.00. $C_{15}H_{16}ClN$. Calculated %: N 5.71.

N-Substituted 4-Amino-2,3-pentamethylenequinolines (V - XXIX). To 0.01 mole of I-IV in 0.04 mole of molten phenol was added 0.02 mole of amine, and the mixture was heated at 140-175°C for 20-24 h. The reaction mixture was cooled, then ether and 10% caustic were added. The ether layer was separated and evaporated. The volatile components were removed from the residue by steam distillation, the residue was acidified with dilute hydrochloric acid and filtered, the filtrate was made alkaline. The precipitated base was crystallized from a suitable solvent.

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