# 2,3-POLYMETHYLENEQUINOLINES

## XIV.* 9-ALKYLAMINO-β-QUININDANES

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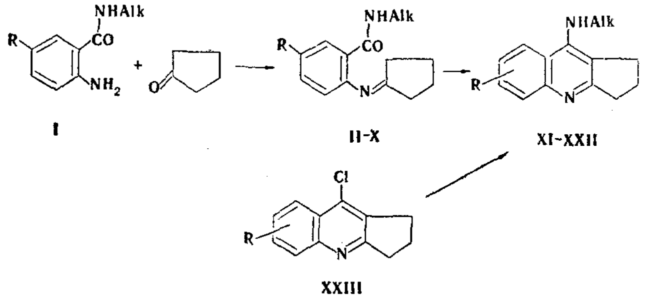
UDC 547.836

9-Alkylamino-β-quinindanes were obtained by cyclization of alkylamides of N-cyclopentylideneanthranilic acids. Their properties and biological activity were studied, the $pK_a$ values of the 9-butylamino-β-quinindanes were determined, and a correlation of the $pK_a$ values with the $\sigma_{epi}$ substituent constants for quinoline was found.

Little study has been devoted to 9-alkylamino-β-quinindanes. In the present study we accomplished the synthesis of 9-alkylamino-β-quinindanes by intramolecular cyclization of alkylamides of N-cyclopentylideneanthranilic acids (II-X) (method A).



The alkylamides of N-cyclopentylideneanthranilic acids (II-X, Table 1) were obtained by refluxing the alkylamides of anthranilic acids (I) [2] with cyclopentanone in benzene. Cyclopentanone condenses better with the methylamides, ethylamides, and n-butylamides of anthranilic acids and less well with the isobutylamides of anthranilic acids. We were unable to accomplish the reaction between the isopropylamide of anthranilic acid and cyclopentanone; this may be explained by steric hindrance.

TABLE 1. Alkylamides of N-Cyclopentylideneanthranilic Acids

| Compound | R | Alk | mp, °C | Empirical formula | N, % |  | $\lambda_{max}$, nm | lg ε | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | found | calc. |  |  |  |
| II | H | $CH_3$ | 182 | $C_{13}H_{16}N_2O$ | 12,8 | 13,0 | 225,340 | 4,67; 3,68 | 60 |
| III | H | $C_2H_5$ | 184—186 | $C_{14}H_{18}N_2O$ | 12,2 | 12,2 | 225,340 | 4,69; 3,44 | 62 |
| IV | H | $n\text{-}C_4H_9$ | 167 | $C_{16}H_{22}N_2O$ | 10,8 | 10,9 | 225,340 | 4,56; 3,62 | 45 |
| V | H | $i\text{-}C_4H_9$ | 166—169 | $C_{16}H_{22}N_2O$ | 10,8 | 10,9 | 225,340 | 4,50; 3,20 | 27 |
| VI | $CH_3$ | $n\text{-}C_4H_9$ | 164—166 | $C_{17}H_{24}N_2O$ | 10,1 | 10,3 | 225,346 | 5,16; 3,23 | 38 |
| VII | Cl | $n\text{-}C_4H_9$ | 171—174 | $C_{16}H_{21}ClN_2O$ | 9,4 | 9,6 | 226,351 | 4,59; 3,62 | 37 |
| VIII | Cl | $i\text{-}C_4H_9$ | 199—200 | $C_{16}H_{21}ClN_2O$ | 9,5 | 9,6 | 226,351 | 4,64; 3,73 | 28 |
| IX | Br | $n\text{-}C_4H_9$ | 169—170 | $C_{16}H_{21}BrN_2O$ | 8,4 | 8,3 | 226,351 | 4,63; 3,66 | 60 |
| X | Br | $i\text{-}C_4H_9$ | 201—202 | $C_{16}H_{21}BrN_2O$ | 8,2 | 8,3 | 225,353 | 4,78; 3,85 | 42 |

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*See [1] for communication XIII.

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 531-534, April, 1973. Original article submitted March 6, 1972.

TABLE 2. 9-Alkylamino-β-quinindanes (XI-XXII)

| Compound | R | Alk | mp of the base, °C* | mp (dec.) of hydrochloride, °C | Empirical formula | N, % |  | $\lambda_{max}$, nm | lg ε | Yield, % |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | found | calc. |  |  | A | B |
| XI | H | $CH_3$ | 193 | 279 | $C_{13}H_{14}N_2$ | 14,3 | 14,2 | 222, 248, 332 | 4,27; 4,30; 3,98 | 42 | — |
| XII | H | $C_2H_5$ | 164—165 | 268 | $C_{14}H_{16}N_2$ | 13,3 | 13,2 | 222, 248, 328 | 4,44; 4,46; 4,12 | 55 | — |
| XIII | H | $n$-$C_4H_9$ | $114^3$ | 240 | $C_{16}H_{20}N_2$ | 11,5 | 11,5 | 222, 248, 330 | 4,29; 4,26; 3,94 | 54 | 38 |
| XIV | H | $i$-$C_4H_9$ | 102—104 | 236 | $C_{16}H_{20}N_2$ | 11,4 | 11,5 | — | — | 54 | — |
| XV | 7-$CH_3$ | $n$-$C_4H_9$ | 132—133 | 260 | $C_{17}H_{22}N_2$ | 11,2 | 11,0 | 224, 248, 332, 348 | 4,13; 4,24; 4,06; 4,07 | 47 | 62 |
| XVI | 5-$CH_3$ | $n$-$C_4H_9$ | 89—91 | 270 | $C_{17}H_{22}N_2$ | 11,0 | 11,0 | 238, 247, 333, 346 | 4,7; 4,69; 4,45; 4,49 | — | 54 |
| XVII | 5-Cl | $n$-$C_4H_9$ | 124—125 | 252 | $C_{16}H_{19}ClN_2$ | 10,3 | 10,2 | 229, 247, 338 | 4,7; 4,53; 4,32 | — | 39 |
| XVIII | 7-Cl | $n$-$C_4H_9$ | 121—123 | 237 | $C_{16}H_{19}ClN_2$ | 10,1 | 10,2 | 223, 252, 339, 353 | 4,74; 4,57; 4,2; 4,21 | 41 | — |
| XIX | 7-Cl | $i$-$C_4H_9$ | 112 | 230 | $C_{16}H_{19}ClN_2$ | 10,0 | 10,2 | 222, 254, 334 | 4,26; 4,19; 3,79 | 37 | — |
| XX | 7-$CH_3O$ | $n$-$C_4H_9$ | 154—156 | 250 | $C_{17}H_{22}N_2O$ | 10,4 | 10,4 | 228, 253, 312, 341, 356 | 4,48; 4,66; 4,05; 4,27; 4,28 | — | 56 |
| XXI | 7-Br | $n$-$C_4H_9$ | 138 | 254 | $C_{16}H_{19}BrN_2$ | 9,0 | 8,8 | 224, 252, 340, 352 | 4,26; 4,28; 4,02; 4,0 | 25 | 38 |
| XXII | 7-Br | $i$-$C_4H_9$ | 109—110 | — | $C_{16}H_{19}BrN_2$ | 8,9 | 8,8 | 226, 256, 336 | 4,22; 4,11; 3,68 | 32 | — |

*Compounds XIII, XV, and XVI were crystallized from petroleum ether, while the rest were crystallized from petroleum ether—benzene.

The alkylamides of cyclopentylideneanthranilic acids (II-X) were obtained as colorless crystalline substances that are soluble in organic solvents. Two maxima at 225-226 and 340-353 nm are observed in the UV spectra of these compounds. The IR spectra contain $\nu_{NH}$ bands at 3392-3396 and 3277-3293 cm$^{-1}$, $\nu_{=CH}$ bands at 3032-3046 cm$^{-1}$, and $\nu_{CH_2}$ bands at 2923-2946 and 2857-2866 cm$^{-1}$.

Intramolecular cyclization accompanied by the formation of 9-alkylamino-β-quinindanes (XI-XXII) (Table 2) occurs when II-X are heated with excess phosphorus oxychloride.

In connection with the low accessibility of the alkylamides of some substituted anthranilic acids, 9-alkylamino-β-quinindanes were also obtained by condensation of substituted 9-chloro-β-quinindanes (XXIII) with amines (method B). Compound XXIII reacts with butylamine in phenol solution on heating to 160-165° for 20 h to give XI-XXII.

Compounds XI-XXII were obtained as colorless crystalline substances that display basic character and form water-soluble hydrochlorides. The IR spectra of XI-XXII contain $\nu_{NH}$ bands at 3413-3423 cm$^{-1}$, $\nu_{=CH}$ bands at 3040-3043 cm$^{-1}$ and $\nu_{CH_2}$ bands at 2940-2946, 2909-2916, and 2860-2863 cm$^{-1}$. The UV spectra of ethanol solutions of 9-alkylamino-β-quinindanes contain two short-wave absorption bands with maxima at 222-238 and 247-256 nm and a long-wave band with a maximum at 328-338 nm for XI-XIII, XVII, XIX, and XXII and two maxima at 332-341 and 346-356 nm for XV, XVI, XVIII, XX, and XXI.

The $pK_a$ of the 9-butylamino-β-quinindanes (Table 3, Fig. 1) were determined by a spectrophotometric method. It is apparent from the data in Table 3 and Fig. 1 that the $pK_a^M$ and $pK_a^T$ values differ only little from one another, depend to a considerable extent on the character of the substituents in the quinoline ring, and correlate well with the $\sigma_{epi}$ substituent constants for quinoline [4].

The biological activity of XIII, XV, XX, and XVI, and XXI* was investigated. The experiments were performed on white mice; the systemic toxicity ($LD_{50}$) and the character of the interrelationships with the muscle relaxants diplatsin and ditilin were studied. All of the compounds are toxic: $LD_{50}$ ranges from 16.6 to 45.5 mg/kg. Compounds XIII, XIV, and XXI have weak anticurare activity, while XV, XX, and XXI sharply intensify the muscle-weakening effect of ditilin.

## EXPERIMENTAL

The UV spectra were recorded with an SF-4a spectrophotometer. The IR spectra at 2600-3500 cm$^{-1}$ (carbon tetrachloride solutions) and at 600-1700 cm$^{-1}$ (mineral oil pastes) were recorded with an IKS-14 spectrophotometer.

The ionization constants of the 9-butylamino-β-quinindanes were determined by a spectrophotometric method (with an SF-4a spectrophotometer) with $6 \cdot 10^{-6}$-$4 \cdot 10^{-5}$ M aqueous

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* The tests were carried out by Professor A. S. Zaks and L. G. Zil'bermints (Master of Medical Sciences), to whom the author extends his thanks.

TABLE 3. Ionization Constants* of 9-Butylamino-$\beta$-quinindanes

| Compound | $pK_a^M$ | $pK_a^T$ | r, ρ, s |
|---|---|---|---|
| XIII | 9,15±0,03 | 9,11 | r 0,999<br>ρ 4,949<br>s 0,005 |
| XV | 9,36±0,02 | 9,32 | |
| XX | 9,33±0,05 | 9,29 | |
| XVIII | 8,37±0,05 | 8,31 | |
| XXI | 8,39±0,04 | 8,33 | |
| XVI | 9,37±0,03 | 9,33 | |
| XVII | 7,95±0,04 | 7,92 | |

*$K_a^M$ is the mixed ionization constant, and $K_a^T$ is the thermodynamic ionization constant.

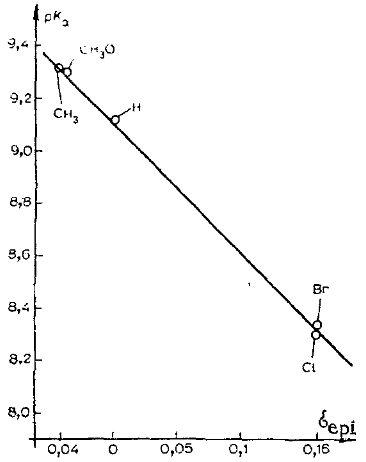

Fig. 1. Dependence of the $pK_a^T$ values of 9-butylamino-$\beta$-quinindanes on the $\sigma_{epi}$ constants of substituents for quinoline.

solutions at 25 ± 1°. A weighed sample of the investigated compound was dissolved in 0.002 M hydrochloric acid; the necessary pH of the solutions was created by means of 0.01 M buffer mixtures. The pH values were determined with a pH-340 device. The $pK_a^M$ and $pK_a^T$ values were calculated by the method in [5]. The reaction constants (ρ), the correlation coefficient (r), and the standard deviation (s) were calculated by the method of least squares [6].

Alkylamides of N-Cyclopentylideneanthranilic acids (II-X). A mixture of 0.01 mole of the alkylamide of anthranilic acid and 0.01 mole of cyclopentanone in 5 ml of benzene was refluxed for 5-6 h, after which it was cooled and the precipitate was removed by filtration and crystallized from alcohol (Table 1).

9-Alkylamino-$\beta$-quinindanes (XI-XXII). A. A 3-ml sample of phosphorus oxychloride was added to 0.01 mole of II-X, and the mixture was heated on a water bath for 1 h. It was then poured into cold water, and the aqueous mixture, after decomposition of the phosphorus oxychloride, was heated to dissolve the salts of XI-XXII. The solution was filtered off from the small amount of insoluble material, and the filtrate was made alkaline with sodium hydroxide solution. The precipitated bases (XI-XXII) were removed by filtration and crystallized (Table 2).

B. A 0.03-mole sample of substituted 9-chloro-$\beta$-quinindane (XXIII) [7] was dissolved in 10 g of fused phenol, 0.06 mole of the appropriate amine was added, and the mixture was heated on a metal bath at 160-165° for 20 h. It was then cooled, and 40-50 ml of benzene was added. The resulting solution was washed three times with 25-ml portions of 10% alkali solution. The benzene and volatile impurities were removed by steam distillation, and the residue was dissolved by heating in 10% hydrochloric acid. The resulting solution was filtered, the filtrate was made alkaline, and the precipitated base was purified by the usual method (Table 2). The hydrochlorides of XI-XXII were obtained by passing dry hydrogen chloride into an ether solution of the bases.

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