## QUININDENES

## X. ELECTROPHILIC SUBSTITUTION AT POSITION 3 OF 4-METHYL-1,2-DIHYDRO-4H- $\beta$ -QUININDENE

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Substances exerting an effect on the central nervous system are found among the derivatives of  $\beta$ -quinindene [1, 2]. It appeared of interest to prepare 3-substituted  $\beta$ -quinindenes and the corresponding quaternary salts in order to study the chemical and biological properties.

We have established that the unstable 4-methyl-1,2-dihydro-4H- $\beta$ -quinindene (I), which is prepared [3] by the action of alkali on  $\beta$ -quinindene methiodide (II), is readily acylated at position 3 and the formed 3-acyl-4-methyl-1,2-dihydro-4H- $\beta$ -quinindenes (III) are completely stable crystalline compounds. Stabilization occurs owing to the introduction of electron-accepting substituents at position 3 where a significant negative charge is centered, which is evidently the cause of the instability of I.

In order to study further the properties of derivatives of the  $\beta$ -quinindene system we carried out several other electrophilic substitution reactions of I at position 3.

On mixing an ether solution in the cold with phenyl isocyanate, m-chlorophenyl isocyanate, and phenyl isothiocyanate, the reaction products, 3-phenylcarbamoyl-, 3-m-chlorophenyl-carbamoyl-, and 3-phenyl-thiocarbamoyl-4-methyl-1,2-dihydro-4H- $\beta$ -quinindene (IVa, IVb, and V respectively; Table 1) separated almost immediately. Compound IVa was converted by the action of hydriodic acid into 3-phenylcarbamoyl- $\beta$ -quinindane methiodide (VI) and the corresponding bisulfate (VII) was formed by the reaction of IVa with sulfuric acid in acetone; the bisulfates (IXa and IXb; Table 2) were prepared analogously from the ketones (IIIa and IIIb). Methyl 4-methyl-1,2-dihydro-4H- $\beta$ -quinindene-3-carboxylate (X) was obtained by the action of methyl chloroformate in benzene on I in the presence of aqueous alkali.

On reacting I with toluenesulfonyl chloride under analogous conditions an almost black precipitate was obtained which we were unable to purify.

3-nitroso-4-methyl-1,2-dihydro-4H- $\beta$ -quininedene (XI) was formed by the nitrosation of I with amyl nitrite in ether; the black blue crystalline substance was soluble in water and organic solvents and the color of the solution was highly dependent on the polarity of the solvents: in strongly polar solvents (water, alcohol, and dimethylformamide) the color of the solution was blue, in weakly polar solvents (hexane and ether) the color was red, and in solvents of medium polarity (acetone and chloroform) the color was green. Aqueous solutions of XI were decolorized on acidification and 3-isonitroso- $\beta$ -quinindane methiodide (XII) was formed by the action of hydriodic acid on XI; compound XII is easily hydrolyzed to XI. This hydrolysis was successfully suppressed during the crystallization of XII from water by the addition of a small quantity of hydrochloric acid.

The derivatives of 4-methyl-1,2-dihydro-4H- $\beta$ -quinindene-3-carboxylic acid IVa, IVb, V, and X, which are prepared for the first time, are colored crystalline, completely stable substances.

The structure of the obtained compounds was confirmed by the UV and IR spectra. The UV spectrum of VI  $[\lambda_{max} 243 \text{ m}\mu \text{ (lgc } 4.60), 328 \text{ m}\mu \text{ (lgc } 4.03), in alcohol]}$  is very similar to the spectrum of II  $[\lambda_{max} 245 \text{ m}\mu \text{ (lgc } 4.60), 328 \text{ m}\mu \text{ (lgc } 4.03), in alcohol]}$ 

S. Ordzhonikidze All-Union Scientific-Research Chemicopharmaceutical Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 3, pp. 16-20, March, 1971. Original article submitted January 16, 1970.

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m $\mu$  (lge 4.41), 328 m $\mu$  (lge 4.09)] on account of the absence of conjugation of the substituent in position 3 of the  $\beta$ -quinindane system with the main chromophore, the quinoline ring.

A shift of the long-wave absorption band in the direction of greater wavelength (to 360 m $\mu$ ) is observed in the UV spectrum of XII; this occurs on account of the conjugation of the exocyclic C = N bond with the quinoline ring.

The UV spectra of the substituted 4-methyl-1,2-dihydro-4H- $\beta$ -quinindenes (IVa, IVb, X, and XI) differ from the UV spectra of the quaternary salts. The latter are characterized by the presence of very intense absorption in the visible region (410-420 m $\mu$ ) due to the increase in chain conjugation.

In the IR spectrum of XII the band  $\nu_{C=N}$  1588 cm<sup>-1</sup> is present but the hydroxyl band is concealed under the broad band from the hydroxyl of the crystallization water  $\nu_{OH}$  3370 cm<sup>-1</sup> (very broad). The reduction in the absorption frequency  $\nu_{C=N}$  in XII as compared to the frequencies of normal oximes arises on account of the specific contribution of the limiting structure XIII in which the multiplicity of the C=N bond is reduced.



 $\stackrel{1}{CH_{3}}$   $\stackrel{-}{N} = \stackrel{-}{OH}$ 

ХM



~100 189-94 (reprecipitated 0,83 Darkred from dimethylformamide with water)

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5,96 5,06

79,47 71,43

C<sub>20</sub>H<sub>1</sub>,N,O 20H<sub>17</sub>CIN20

22205

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79,2571,93

Y ellow

 $0,53 \\ 0,67$ 

--80 (from alcohol) --178,5 (from acetc

8-80 7-178

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C20H18N2S

z

H

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Empirical formula

z

Η

С

Color of compound

å

Melting point (in degrees) \*

Yield (in %)

Com -

Found (in %)

Calculated (in %)

"The substances melted with decomposition.

TABLE 2. 3-Aroyl- and 3-Arylcarbamoyl- $\beta$ -quinindene Bisulfates

Com - pound	Melting point(in degrees)*	Found (in %)				Empirical	Calculated (in %)			
		С	Н	N	s	Iormuta	С	Н	N	S
IXa IXb VII	200—201 136—7 179—80	$62,46 \\ 57,23 \\ -$	5,03 4,16 	3,42 $\overline{7,31}$	$\frac{8,62}{8,21}$	$\begin{array}{c} C_{20}H_{19}NO_5S\\ C_{20}H_{18}CINO_5S\\ C_{20}H_{20}N_2O_5S\end{array}$	62,32 57,21	4,97 4,32 —	$3,63$ $\overline{7,00}$	$\frac{8,32}{8,01}$

\*The substances melted with decomposition.

TABLE 3. Shift of C = O Group Absorption Band in IR Spectra

Com - pound	v(in cm <sup>-1</sup> )	Compound	v(in cm <sup>-1</sup> )
VI	1 689	IVa	1 620
VIIIa	1 690	IIIa	1 500
	—	X	1 670

In the IR spectrum of IVa there is a strong sharp band at 3300  $\rm cm^{-1}$  which is attributed to the NH absorption in the amide group.

A shift of the carbonyl band in the direction of the lower frequencies (see Table 3) is observed for the 4-methyl-1,2dihydro-4H- $\beta$ -quinindene-3-carboxylic acid derivatives IVa and X as also in the case of 3-benzoyl-4-methyl-1,2-dihydro-4H- $\beta$ -quinindene (IIIa). The corresponding quaternary salts

VI and VIIIa have in the spectra carbonyl bands with the usual frequencies for such groups (see Table 1). This shift can be explained by the presence of conjugation of the C = O bond with the electron pair on the nitrogen atom through the C = C double bond in the five membered ring, i.e., by a significant contribution from the limiting structure of the type XIVa-XIVc



The greatest shift of the carbonyl band to the long-wave region is observed for IIIa; in the case of IVa and X the shift is less on account of the competitive conjugation of the C = O group with the free electron pair on the amide nitrogen atom (in IVa) or on the methoxyl oxygen atom (in X). Therefore, in IVa the electron density on atom  $C_3$  must be greater and on the oxygen correspondingly less than the electron density on the same atoms in IIIa. This is confirmed by the data from dipole moment measurements and  $pK_a$  values. The dipole moment of IIIa is 3.32 D and for IVa is 2.87 D (in benzene). This is in agreement with the suggestion that the charge is greater on the negative end of the dipole (the oxygen atom) in IIIa than in IVa; the data on the basicity of these compounds agrees with this (if it is taken into consideration that a proton is added at the  $C_3$  atom); IVa ( $pK_a$  8.68, in 80% alcohol solution) is more than two orders more basic than IIIa ( $pK_a$  6.15, in 80% alcohol solution).

## EXPERIMENTAL

<u>3-Arylcarbamoyl- and 3-Phenylthiocarbamoyl-4-methyl-1,2-4H- $\beta$ -quinindenes (IVa, IVb, and V).</u> To a suspension of 0.002 g-mole of II [4] in 5 ml of water was added 5 ml of ether and 2.5 ml of 10% sodium hydroxide solution. The mixture was stirred in a stream of argon for 10 min, the aqueous layer was separated, and 0.004 g-mole of substituted isocyanate or isothiocyanate was added to the ether solution. After 10 min, the precipitate was filtered off. Chromatography was carried out on a thin layer of alumina of activity grade II in a mixture of acetone and chloroform (3:20).  $\beta$ -Quinindane (R~0.9) was marker.

<u>3-Phenylcarbamoyl- $\beta$ -quinindane Methiodide (IV)</u>. A solution of 0.66 g of potassium iodide in 0.5 ml of 20% acetic acid solution was added to a suspension of 0.3 g of IVa in 2 ml of 20% acetic acid solution. The precipitate which separated was filtered off. The yield was 0.31 g (72%) of a substance with mp 221-222°C (decomp., from alcohol). Found, %: C 55.34; H 4.20.  $C_{20}H_{19}IN_2O$ . Calculated, %: C 55.81; H 4.19.

<u>3-Carbomethoxy-4-methyl-1,2-dihydro-4H- $\beta$ -quinindene (X)</u>. To a suspension of 1.24 g of II in 10 ml of water was added 8 ml of benzene and 5 ml of 10% sodium hydroxide solution with stirring under a stream of argon. After 15 min, 0.76 ml of chloroformic ester was added. After 1 h, compound II (0.3 g) was fil-

tered off, the benzene layer was evaporated, and 0.3 g (42% on converted II) of X was obtained with mp 108-108.5° (decomp., from alcohol),  $R_5$  1.01 (acetone-chloroform, 3:20),  $\beta$ -quinindane as marker. Found, %: C 74.49; H 6.40; N 5.70. C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>. Calculated, %: C 74.69; H 6.22; N 5.81.

<u>Nitrosation of 4-Methyl-1,2-dihydro-4H- $\beta$ -quinindene (I)</u>. To a suspension of 4.96 g of II in 40 ml of water was added with stirring under a stream of argon 40 ml of ether and 20 ml of 10% sodium hydroxide solution. After 10 min, freshly distilled amyl nitrite (4.8 ml) was added to the ether layer. Compound XI (2.8 g) was filtered off after 7 h. An ethereal solution of hydrogen chloride was added to a concentrated alcoholic solution of XI, the solvent was decanted from the precipitate which separated, the precipitate was dissolved in water, and a saturated aqueous solution of potassium iodide was added. The precipitate of XII was filtered off and had mp ~260° (decomp., from 0.3 N hydrochloric acid solution). Found, %: I 35.44; H<sub>2</sub>O 4.50. C<sub>13</sub>H<sub>13</sub>IN<sub>2</sub>O·H<sub>2</sub>O<sup>\*</sup>. Calculated, %: I 35.50; H<sub>2</sub>O 5.03.

Bisulfates of 3-Benzoyl-, 3-p-Chlorobenzoyl-, and 3-Phenylcarbamoyl- $\beta$ -quinindane (IXa, IXb, and <u>VII)</u>. To a suspension of IIIa, IIIb, or IVa in acetone was added an equimolar quantity of a 10% solution of sulfuric acid in acetone. The precipitate which separated after the addition of ether was filtered off and recrystallized from alcohol.

\*The water of crystallization was lost on drying in vacuum (15 mm) at 75° over phosphorus pentoxide.

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