QUININDINES.

XVI. SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF SOME ALKYL, ARALKYL, AND AMINO ALKYL KETONES OF THE SERIES 1, 2-DIHYDRO-4H-β-QUININDINE

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Only one 3-acyl-1,2-dihydro-4H-β-quinindine with a nonaryl substituent (R) on the RCO group has been previously described: That is the 3-acetyl derivative. It was obtained by reacting 1,2-dihydro-4H-β-quinindine with acetic anhydride [1]. Other examples of alkyl, aralkyl, haloalkyl, and dialkylaminoalkyl ketones of the 4H-β-quinindine series were synthesized to obtain substances with potential pharmacological activity. Substances with various pharmacological activities have previously been discovered in the class of amino ketones [2].

The starting 4-dimethyl-1,2-dihydro-4H-β-quinindine (I) was obtained by the action of an aqueous alkali on the iodomethylate (IIa) or on the methylmethosulfate (IIb) of β-quinindane. Without isolating it, I was reacted with aliphatic (propionic, butyric) acid chlorides, aliphatic-aromatic (phenyl and diphenyl acetic) acid chlorides, and halogen-substituted (chloroacetic, β-chloro-, and β-bromopropionic) acid chlorides.

The reaction was accomplished in two ways: either with excess acid chloride in the presence of an aqueous alkali (a Schotten–Baumann type of reaction) or through a reaction with an acylating agent in an anhydrous medium (ether) using triethylamine as the basic reagent. The C-acylation goes so easily that the hydrolysis of the acid chlorides does not prevent the principal reaction from taking place even in an aqueous alkali. As a result the 3-propionyl (III), 3-butyroyl (IV), 3-phenylacetyl (V), 3-diphenylacetyl (VI), and 3-chloroacetyl (VII) derivatives of 4-methyl-1,2-dihydro-4H-β-quinindine were obtained with good yields. When I is reacted with β-chloro- or β-bromopropionyl chloride in the presence of an aqueous alkali, two compounds are obtained according to thin layer chromatographic (TLC) data; they could not be separated after several recrystallizations. One of these substances, as judged by its R_f values in various solvent systems, is formed in the reaction with both the chloro and bromo derivatives. The spots of both compounds disappeared in the chromatogram with time after reacting the mixture of these products with an alcoholic solution of potassium hydroxide, and one spot of a new compound appeared: the same one for both the halide-substituted ones. Based on the elemental analysis and the IR and UV spectra, the structure of 3-β-ethoxypropionyl-4-methyl-4H-1,2-dihydro-β-quinindine (VIII) was assigned to this compound. Similarly, the β-dialkylaminopropionyl derivatives are obtained with a satisfactory yield by reacting secondary amines with the mixture of products; here both spots of the starting substances also disappear in this reaction. Proceeding from what has been stated above, it can be assumed that not only does acylation take place but also dehydrohalogenation as a result of the reaction of I with the β-halopropionyl chlorides in an alkaline medium; as a result of this a mixture of the 3-β-halopropionyl (IX) and 3-acryloyl (X) derivatives is obtained. One and the same substance is obtained by the reaction of electron-excess reagents with this mixture as a result of the nucleophilic substitution of the halogen and nucleophilic addition to the double bond. Therefore in order to obtain β-aminoethyl ketones (XIa-c), we introduced a mixture of substances IX and X without separating them into the reaction with the secondary amines (dimethylamine, N-methylpiperazine, and morpholine). Aminomethyl ketones (XIIa-b) were obtained by reacting these same amines with VII. It is interesting to note that the β-piperazinylethyl ketone (XIb) is obtained in the reaction with N-methylpiperazine twice as rapidly as the piperazinylmethyl ketone (XIIb) judging from the TLC data. Evidently the

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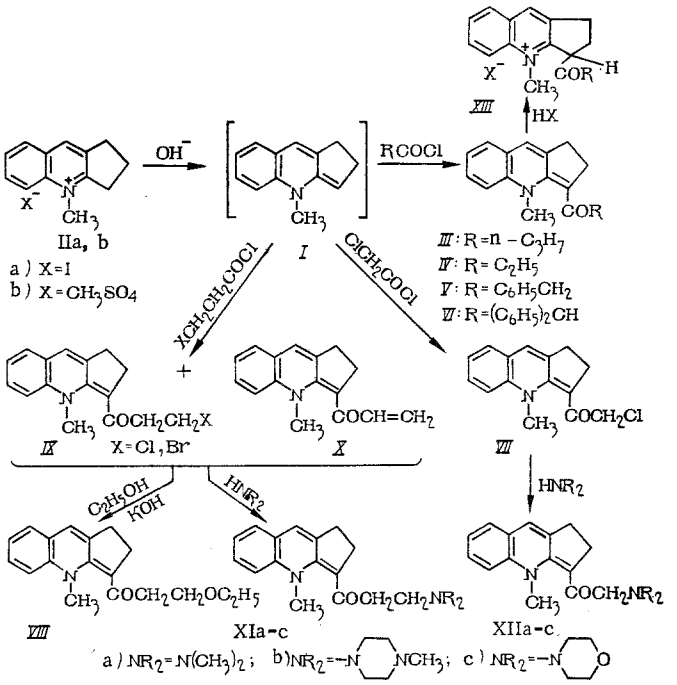
reaction in the first case proceeds through the intermediate formation of vinylketone X which, as was said above, is formed very easily.



Compounds XI a-c and XII a-c, which were synthesized, were characterized by their IR and UV spectra. The starting compounds VII-IX and compounds XIa-c and XIIa-c have the same bands in their IR spectra which the previously synthesized [1, 3] 3-acyl-1,2-dihydro-β-quinindines have: 1640-1650 cm^{-1} (w.), 1590-1608 cm^{-1} (s.), 1561-1572 cm^{-1} (s.), 1510-1522 cm^{-1} (s.) and 1492-1508 cm^{-1} (w.).† The last two bands merge completely or partially in some cases. The band at 1510-1522 cm^{-1} can be assigned to the C=O group by analogy with the 3-aroyl derivatives [1, 3]; the others characterize the aromatic (condensed) system. The sharp decrease in the frequency of the carbonyl band in these compounds is connected with the considerable contribution of the bipolar structure with the $>\overset{+}{N}=C-C=C-O^-$ fragment [1, 3]. The UV spectra of these compounds are similar to each other; the four intense bands at 221-226 nm (lg ε 4.2-4.6); 268-270 nm (lg ε 3.7-3.8); 315-320 nm (lg ε 3.8-3.9); and 426-445 nm (lg ε 4.2-4.3) are the most characteristic. The last band is caused by the intense yellow color of the substances we investigated. Analogous bands but somewhat shifted to the longwave region had been noted for the 3-aroyl derivatives previously synthesized [1, 3]. The basicity of a number of the 3-acyl-1,2-dihydro-4H-β-quinindines obtained was measured potentiometrically. The pK_a values in 80% ethyl alcohol are given in Table 1. It is evident from Table 1 that the compounds investigated are quite strong bases. It was previously shown [1, 3] that a proton is added at the $C_{(3)}$ atom of the 3-acyl-1,2-dihydro-4H-β-quinindines during salt formation forming structure XIII; decolorization of the solution takes place at the same time. The pK_a values of the alkyl, aralkyl, and haloalkyl ketones correlate satisfactorily with the Taft induction constants (see Fig. 1):

$$pK_a = 6{,}5 - 2{,}1\ \sigma^* \qquad (1)$$

Assuming that $\sigma^* = \sigma^\circ + 0.60$, which was previously obtained [3] for the 3-aroyl-substituted compounds, for the aryl substituents, the equation ($pK_a = 5.5 - 1.4\ \sigma^\circ$) can be rewritten in the form

$$pK_a = 6{,}6 - 1{,}4\ \sigma^*. \qquad (2)$$

It is evident after comparing Eqs. (1) and (2) that the sensitivity of the nonaryl-substituted ketones to the influence of the electronic effects (ρ^*) is considerably greater. Judging from Eq. (1) compound (XIIa) should have an equilibrium constant for the protonation reaction at $C_{(3)}$ $pK_a = 5.7$ ($\sigma\, CH_2N(CH_3)_2 \sim 0.4$). The value determined experimentally is several orders of magnitude greater: $pK_a = 8.4$. Upon taking this fact

†s. is a strong band; w. is a weak band.

TABLE 1. 3-Acyl-4-methyl-1,2-dihydro-4H-β-quinindines

Compound	Method of synthesis	Yield (in %)	Melting point (in deg)*	pK_a in 80% alcohol (± 0.05)	Found (in %)			Empirical formula	Calculated (in %)		
					C	H	N		C	H	N
III	1B	62	179—80	6,35	79,90	7,09	5,70	$C_{16}H_{17}NO$	80,30	7,20	5,85
IV	1B	84	183—4	6,96	80,54	7,69	—	$C_{17}H_{19}NO$	80,60	7,55	—
V	1A	49	119—20	—	83,66	6,09	—	$C_{21}H_{19}NO$	83,31	6,29	—
VI	1A	93	150—1	5,87	86,17	6,18	3,94	$C_{27}H_{23}NO$	85,85	6,21	3,77
VII	1A	56	138—9	4,53	—	—	Cl 13,41	$C_{15}H_{14}ClNO$	—	—	Cl 13,65
VIII	—	—	71—2	—	75,99	7,42	5,06	$C_{18}H_{21}NO_2$	76,29	7,45	4,94
XIa	2A	44†	118—9	—	76,41	7,65	10,13	$C_{18}H_{22}N_2O$	76,48	7,94	9,91
XIb	2B	33†	108—9	—	74,45	7,99	12,19	$C_{21}H_{27}N_3O$	74,74	8,06	12,15
XIc	2B	12†	121—2	—	74,21	7,39	—	$C_{20}H_{24}N_2O_2$	74,05	7,46	—
XIIa	2A	69	92—3	8,40	76,07	7,55	10,59	$C_{17}H_{20}N_2O$	76,08	7,50	10,44
XIIb	2B	48	138—2	7,47; 5,36	74,52	8,03	12,87	$C_{20}H_{25}N_3O$	74,30	8,04	12,99
XIIc	2B	59	111—3	—	73,20	7,07	—	$C_{19}H_{22}N_2O_2$	73,50	7,14	—
XIV [1]	—	—	101—103	6,37	—	—	—	—	—	—	—

* All of the compounds except VIII melt with decomposition. Compounds III, IV, VIII, XIb, XIIa, and XIIb were crystallized from hexane; V, VI, and 3-acetyl-4-methyl-1,2-dihydro-4H-β-quinindine (XIV) from ether; VII from an alcohol–ether mixture; XIa from an alcohol–petroleum ether mixture; and XIc and XIIc from petroleum ether.

† Calculation based on IIb.

into consideration and also the fact that after adding 1 mole of acid a solution of XIIa remains intensely yellow, it can be assumed that the first proton is added to this compound at the dimethylamino group. According to Eq. (1) the second constant should lie in the range $pK_a = 3.1\text{-}3.2$ ($\sigma\, CH_2N\langle^{CH_3}_{CH_3}_{H} \cong 1.1$) [4] and will not be determinable in 80% alcohol potentiometrically. Similarly the first constant for XIIb (pK_a = 7.47) should be related to the protonation of one of the nitrogens of the piperazine ring, most probably to which a methyl group has been added. As concerns the second constant (pK_a = 5.36) it is evident that it corresponds to the addition of a proton to another nitrogen in the piperazine since only after adding 3 mole of acid does a solution of XIIb begins to decolorize. Employing the above basicity of the compounds synthesized, we obtained salts with sulfuric (for VI and XIb) and maleic (for XIa, b, XIIa, b) acids from some of the 3-acyl derivatives. Salts with different ratios of the base and acid were obtained depending on the structure of the original ketone, for example XIIa yields the monomaleate, XIIb the dimaleate, and XIb the trimaleate.

The antiarrhythmic activity of compounds VI, XIa, XIb, XIIa, and XIIb (Table 2) was investigated. Arrhythmia in rats brought on by an intravenous injection of aconitine (30 μg/kg) was used as the experimental model. The investigation was carried out in parallel with quinidine. Male rats weighing 100-160 g were used for the experiment. Narcosis was brought on by a 10% solution of urethan (1 ml per 100 g of weight intraperitoneally). Electrocardiograms in shunt II were recorded. An intravenous injection of aconitine into the control rats disrupted cardiac rhythm in all cases. Reestablishment of the sinus rhythm was as a rule not observed within the first 30 min after the injection of aconitine. The compounds investigated were injected in various doses into a vein within 1 min of the onset of arrhythmia The doses amounted to approximately one fifth to one third of the LD_{50}.

It was established that compounds XIb, XIIa, and VI exert a weak diluting effect on arrhythmia caused by aconitine (see Table 2). Compounds XIIb and XIa possess no antiarrhythmic activity. Certain other aspects of the pharmacological activity of the quinindine derivatives were investigated along with their antiarrhythmic effect. Compounds XIa, XIb, and XIIa possess a weak histamine-like effect; they cause a contraction of a segment of a guinea pig's intestines in concentrations of 10^{-5} to $1 \cdot 10^{-4}$ g/ml; this effect is relieved by Dimedrol at a concentration of $1 \cdot 10^{-6}$ g/ml. The preparations investigated have no effect on the peripheral cholinoreactive systems and on smooth muscles.

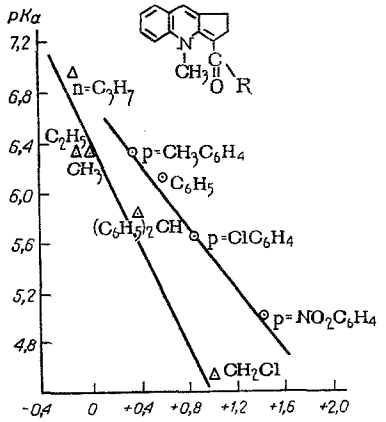


Fig. 1. Correlation of the pK_a value of the 3-acyl-4-methyl-1,2-dihydro-4H-β-quinindines with the Taft induction constants.

TABLE 2. Pharmacological Activity of 3-Acyl-4-methyl-1,2-dihydro-4H-β-quinindines

Compound	LD_{50} (in mg/kg, intravenously; mice)	Antiarrhythmic activity (in mg/kg, aconitine intravenously)	Spasm of isolated guinea pig intestine (in g/ml)
VI	122	25—50 (±)	No effect
XIa	18,5	1—5 (—)	10^{-4}
XIb	17,5	5 (±)	10^{-4}
XIIa	43	10—20 (+)	10^{-4}—10^{-5}
XIIb	97	10—25 (—)	No effect
Quinidine	80	5 (++)	—

Designations: (-) no effect; (±) variable effect, sets in within 15-20 min after injection; (+) restoration of rhythm of duration varying from 15 sec to 20 min; (++) restoration of sinus rhythm.

EXPERIMENTAL METHOD

β-Quinindane Methylmethosulfate (IIb). Into a solution of 37 g of β-quinindane [5] in 130 ml of benzene was poured 27 ml of dimethylsulfate. The precipitate IIb (49 g) was filtered off within 45 min, the mother liquor was boiled for 30 min. After cooling an additional amount of IIb was filtered off. The overall yield was 54 g (83% of theoretical), mp 128-129°C (from an acetone–alcohol mixture, 10:1). Found, %: C 56.86; H 5.60; S 10.55. $C_{14}H_{17}NOS$. Calculated, %: C 57.00; H 5.76; S 10.80.

Alkyl and Aralkyl Ketones of the 4-Methyl-1,2-dihydro-4H-β-quinindine Series (III-VII). Method 1A. To a solution of 0.005 mole of IIb * in 20 ml of water was added 15 ml of ether, and 7 ml of a 10% sodium hydroxide solution (0.019 mole) was run in. The mixture was agitated in a stream of nitrogen or argon for 10 min, 0.01 mole of the appropriate acid chloride was added, and the mixture was agitated for 15-20 min. The precipitate was filtered off. When necessary an additional amount of the substance (see Table 1) was obtained from the ether layer and from the chloroform extracts of the aqueous layer after evaporating the solvent.

Method 1B. To a solution of 0.005 mole of IIb in 20 ml of water in a separatory funnel was added 15 ml of ether. In a stream of nitrogen was run in 5 ml of 10% sodium hydroxide (0.015 mole), and the

* A suspension of IIa was used in the synthesis of VI [4].

mixture was shaken for 15 min. The water layer was run off, the ether layer was quickly transferred into a flask, and 25 ml of triethylamine was added. While cooling with ice, 0.01 mole of the carboxylic acid chloride was added dropwise. After discontinuing the cooling the mixture was agitated for 30 min. The residue was filtered off and washed with water. When the ketone was highly soluble, water was added to the mother liquor and an additional amount of product was extracted out with ether (see Table 1).

Reaction of 4-Methyl-1,2-dihydro-4H-β-quinindine (I) with β-Halopropionyl Chlorides. To a solution of 2.95 g of IIb in 40 ml of water was added 30 ml of ether and in a stream of nitrogen 21 ml of 10% sodium hydroxide; the mixture was agitated for 10 min. Then was added 2.52 g of β-bromopropionyl chloride and the mixture was agitated for 30 min. The precipitated reaction product was filtered off. To the mother liquor was added chloroform, the organic layer was separated, dried with roasted magnesium sulfate, and the solvent was driven off in vacuo. The overall product yield was 1.75 g, mp 175°C (from hexane). In the chromatogram (on a thin layer of aluminum oxide with degree of activity II in ether) were two spots: an orange one with R_f = 0.68 (IX, X = Br) and a yellow one with R_f = 0.75 (X).

The reaction with β-chloropropionyl chloride was carried out analogously. The product yield was 3.11 g from 5 g of IIb; it was recrystallized from hexane. Two spots were present on the chromatogram run under the same conditions: an orange one with R_f = 0.58 (IX, X = Cl) and a yellow one with R_f = 0.75 (X).

3-(β-Ethoxypropionyl)-4-methyl-1,2-dihydro-4H-β-quinindine (VIII). A solution of 1 g of the reaction product from I and β-bromopropionyl chloride (IX, X = Br + X) in 30 ml of 5% alcoholic potassium hydroxide was kept at room temperature for a day and 600 ml of water was poured in. The mixture was extracted with chloroform and dried over roasted magnesium sulfate. The solvent was evaporated in vacuo and VIII was obtained after recrystallization from petroleum ether.

Aminoketones of the 4-Methyl-1,2-dihydro-4H-β-quinindine Series (XIa-c, XIIa-c). Method 2A. To a solution of 0.5 g of VII or the reaction product from I and β-chloropropionyl chloride (IX, X = Cl + X) in 1 ml of chloroform was added 5 ml of dimethylamine. The solution was maintained at about 20°C for a day and 20 ml of chloroform and 15 ml of water were added. The chloroform layer was washed several times with water and passed through a column packed with aluminum oxide with a degree of activity of II; XIa and XIIa were eluted with chloroform (see Table 1).

Method 2B. Compound VII or the reaction product of I and β-chloropropionyl chloride (IX, X = Cl + X), 0.3 to 1 g, was heated with a 6- to 10-fold (by weight) quantity of N-methylpiperazine (at 50°C) or morpholine (at 60°C) until the spot of the starting substance disappeared completely from the TLC (dichloroethane–acetone, 10:1). The mixture was diluted threefold with ether, and the hydrochloride of the starting amine was filtered off. The solution was passed through a column packed with aluminum oxide with a degree of activity of II, and XIb, c and XII b, c were eluted with ether (see Table 1). The reaction in which XIb is obtained proceeds for one-half h, XIIb 1 h, XIc* 1 h, and XIIc 2 h.

Salts of the 3-Acyl Derivatives of 4-Methyl-1,2-dihydro-4H-β-quinindine. The Sulfates. To a saturated solution of 0.1 g of the 3-acyl derivative in acetone with cooling was added a freshly prepared 4-5% solution of sulfuric acid in acetone until decolorization was obtained. The precipitate was filtered off, washed with acetone, and recrystallized. Sulfate from VI, yield 95%, mp 218-219°C (decomp., from alcohol). Found %: S 6.78. $C_{27}H_{23}NO \cdot H_2SO_4$. Calculated %: S 6.74. Sulfate from XIb, yield 75%, mp 196-197°C (decomp., from methanol). Found %: S 14.91. $C_{21}H_{27}N_3O \cdot 3H_2SO_4$. Calculated %: S 15.22.

The Maleates. To a saturated solution of 0.1 g of the ketone in absolute ether was added a saturated solution of maleic acid in absolute ether until precipitation ceased. The precipitate was filtered off, washed with ether, and recrystallized. Maleate from XIa, yield 93%, mp 98-99°C (decomp., from acetone). Found %: C 65.94; H 6.88. $C_{18}H_{22}N_2O \cdot C_4H_4O_4$. Calculated %: C 66.26; H 6.64. Maleate from XIb, yield 74%, mp 122-122.5°C (decomp., from absolute alcohol). Found %: C 56.31; H 5.73; N 6.02. $C_{21}H_{27}N_3O \cdot 3C_4H_4O_4 \cdot H_2O$. Calculated %: C 56.30; H 5.87; N 5.98. Maleate from XIIa, yield 84%, mp 137-138°C (decomp., from acetone). Found %: C 65.34; H 5.97; N 7.03. $C_{17}H_{20}N_2O \cdot C_4H_4O_4$. Calculated %: C 65.34; H 6.29; N 7.29. Maleate from XIIb, yield 95%, mp 136-137°C (decomp., from alcohol). Found %: C 58.65; H 5.85; N 7.68. $C_{20}H_{25}N_3O \cdot 2C_4H_4O_4 \cdot H_2O$. Calculated %: C 58.65; H 6.11; N 7.33.

The determination of the pK values (see Table 1) of compounds III, IV, VI, VII, XIIa, and XIIb was carried out potentiometrically on their 0.001 M solutions in 80% alcohol (by volume) at 25°C with 0.1 N hydrochloric acid employing glass and aqueous calomel electrodes. The pK_a values were calculated by

* When synthesizing XIc, the product from the reaction of I and β-bromopropionyl chloride (IX, X = Br + X) was introduced with the morpholine into the reaction.

the well known method [5] from eight points corresponding to 10-80% neutralization; a PHM-26 (Radiometr, Denmark) potentiometer was used.

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