INVESTIGATION OF 2,3-POLYMETHYLENEQUINOLINES

XVI.* SYNTHESIS OF SUBSTITUTED β-QUININDAN-9-CARBONAMIDES

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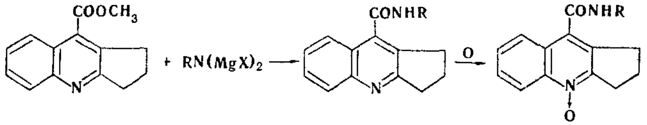
A method for obtaining substituted β-quinindan-9-carbonamides from the corresponding methyl esters and dimagnesylamines has been developed. The UV and IR spectra, the toxicity, and the anticurare activity of these compounds have been studied, and it has been shown that they are oxidized by hydrogen peroxide to the corresponding N-oxides.

β-Quinindan-9-carbonamides have not been studied previously. In selecting methods for the synthesis of these compounds, we attempted unsuccessfully to synthesize the corresponding acid chloride by the action of phosphorus pentachloride in phosphorus oxychloride or an excess of thionyl chloride.

The dimagnesylamine method [2] proved to be more successful.



I–VIII

Methyl-β-quinindan-9-carboxylate (obtained by the ordinary esterification of the acid) on reaction with dimagnesylamines forms substituted β-quinindan-9-carbonamides (I-VIII, Table 1) with good yields.

In reactions with monomagnesylamines (from piperidine, morpholine, diethylamine, and N-methylpiperazine), satisfactory results were observed only for N-bromomagnesiopiperidine, which gave the piperidide (IX) with a yield of 53%.

This difference in the reactions of the mono- and dimagnesylamines must be due to the lower nucleophilicity of the former, and also to steric hindrance in them caused by the second alkyl radical on the nitrogen.

Compounds (I-IX) are colorless crystalline substances possessing basic properties and forming water-soluble hydrochlorides.

With compounds (I) and (III) as examples it was shown that (I-IX) can readily be oxidized by hydrogen peroxide in glacial acetic acid to the corresponding N-oxides.

With benzaldehyde in boiling acetic anhydride, the piperidide (IX) gives a good yield of the piperidide of 3-benzylidene-β-quinindan-9-carboxylic acid.

In experiments on white mice, the hydrochlorides of (I, III-V, VII, and IX) (aqueous solutions injected intraperitoneally)† had low toxicities [LD_{50} about 1500 mg/kg, except for (I), for which it is 417 mg/kg]. These substances greatly enhance the muscle-relaxing effect of ditiline. Compound (IX) possesses anticurare activity.

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* For Communication XV, see [1].

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TABLE 1. Substituted β-Quinindan-9-carbonamides (I-VIII)

Compound	R	bp, °C*	Empirical formula	N, %		UV spectrum, λ max nm (log ε)	Hydrochloride mp, °C (dec.)	Yield, %
				exp.	calc.			
I	iso-C_3H_7	154—155	$C_{16}H_{18}N_2O$	11,1	11,0	238(4,69), 295(4,00), 308(4,06), 322(4,1)	275	49
II	$CH_2{=}CH{-}CH_2$	124—125	$C_{16}H_{16}N_2O$	10,9	11,1	238(4,72), 295(4,03), 308(4,07), 322(4,11)	224—226	40
III	n-C_4H_9	108—109	$C_{17}H_{20}N_2O$	10,3	10,4	238(4,73), 295(4,05), 308(4,09), 322(4,13)	243	50
IV	cyclo-C_6H_{11}	197—198	$C_{19}H_{22}N_2O$	9,3	9,5	238(4,69), 295(4,04), 308(4,07), 322(4,09)	268	45
V	$C_6H_5CH_2$	121—122	$C_{20}H_{18}N_2O$	9,4	9,3	238(4,63), 295(3,91), 308(3,97), 322(4,01)	235	42
VI	$C_6H_5CH_2(CH_3)CH$	126—127	$C_{22}H_{22}N_2O$	8,4	8,5	238(4,72), 295(4,00), 308(4,06), 322(4,11)	229—231	32
VII	C_6H_5	255—256	$C_{19}H_{16}N_2O$	9,4	9,7	239(4,75), 292(4,19), 308(4,11), 322(4,10)	298	61
VIII	p-$CH_3C_6H_4$	253—254	$C_{20}H_{18}N_2O$	9,0	9,3	238(4,76), 282(4,15), 308(4,12), 322(4,09)	285—287	64

*Compounds (I-V) were crystallized from aqueous methanol and the others from ethanol.

EXPERIMENTAL

The UV spectra were taken on an SF-4 instrument using ethanolic solutions, and the IR spectra on an IKS-14 instrument with an LiF prism using 0.003 M solutions in carbon tetrachloride.

Methyl β-Quinindan-9-carboxylate. A mixture of 0.5 mole of β-quinindan-9-carboxylic acid, 200 ml of absolute methanol, and 100 ml of concentrated sulfuric acid was heated on the water bath for 12 h. The excess of methanol was distilled off and the residue was diluted with water and neutralized with 10% sodium carbonate solution. The resulting precipitate of methyl β-quinindan-9-carboxylate was filtered off and crystallized from aqueous methanol. Yield 59 g (52%), mp 82-83°C [3].

Alkylamides and Arylamides of β-Quinindan-9-carboxylic Acid (I-VIII). To 0.05 mole of a dimagnesylamine obtained in the usual way from 0.05 mole of an amine and 0.1 mole of ethylmagnesium bromide was added 0.05 mole of methyl β-quinindan-9-carboxylate in diethyl ether. The mixture was heated for 3 h and was then decomposed with a saturated solution of ammonium chloride. The precipitate of a substituted β-quinindan-9-carbonamide that deposited was filtered off and crystallized from a suitable solvent. The IR spectra of (I-VIII) contained the following bands, cm^{-1}: ν_{NH} 3392-3426; $\nu_{=CH}$ 3046-3053; ν_{CH_2} 2946-2957; 2916-2929, and 2820-2869.

Piperidide of β-Quinindan-9-carboxylic Acid (IX). An ethereal solution of 0.05 mole of methyl β-quinindan-9-carboxylate was added to 0.1 mole of N-bromomagnesiopiperidine, and the mixture was heated for 3 h. The precipitate that deposited after the decomposition of the reaction mixture was filtered off and crystallized from ethanol. Yield 7.5 g (54%), mp 197-199°C. Found, %: N 10.2. $C_{18}H_{20}N_2O$. Calculated, %: N 10.0.

N-Oxide of the Isopropylamide of β-Quinindan-9-carboxylic Acid. A solution of 2 g of the amide (I) in 10 ml of glacial acetic acid was treated with 5 ml of 26% hydrogen peroxide, and the mixture was heated at 80°C for 5 h. Then it was diluted with water and neutralized with 10% sodium carbonate solution. The precipitate that deposited was filtered off and crystallized from ethanol. Yield 1.2 g (56%), mp 222-223°C. Found, %: N 10.2; $C_{16}H_{18}N_2O_2$. Calculated, %: N 10.4.

The N-oxide of the butylamide of β-quinindan-9-carboxylic acid was obtained similarly. Yield 54%, mp 161-163°C (ethanol). Found, %: N 9.9. $C_{17}H_{20}N_2O_2$. Calculated, %: N 9.8.

Piperidide of 3-Benzylidene-β-quinindan-9-carboxylic Acid. A solution of 1 g of the piperidide (IX) and 0.5 g of benzaldehyde in 10 ml of acetic anhydride was heated for 2 h. This gave 0.68 g (52%) of a substance with mp 207-208°C (ethanol). Found, %: N 7.8. $C_{25}H_{24}N_2O$. Calculated, %: N 7.6.

LITERATURE CITED

1. D. I. Uvarov, M. E. Konshin, A. S. Zaks, L. G. Zil'bermints, and T. A. Kapitonenko, Zh. Fiz. Khim. (1973) (in press).
2. P. A. Petyunin, Yu. V. Kozhevnikov, and L. A. Tetyueva, Zh. Obshch. Khim., 33, 1261 (1963).
3. M. Los and W. H. Stafford, J. Chem. Soc., 1680 (1959).