HETEROCYCLIC COMPOUNDS

VIII. SUBSTITUTED AMIDES OF 2,3-PENTAMETHYLENEQUINOLINE-4-CARBOXYLIC ACID*

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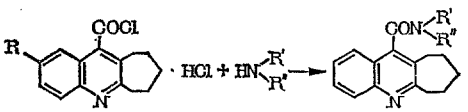
Among 2,3-polymethylenequinoline derivatives we have found substances which possess analgesic and analeptic activity, plus some that reduce the curarizing effect of diplacin [1,3-di(β-platyneciniomethoxy) benzene hydrochloride] [1, 2]. Some substituted amides of 2,3-polymethylene-4-carboxylic acids have shown analgesic and anesthetic activity [3, 4]. In the present work, to study the effect of substituents in the quinoline ring and in the amide part of the molecule on physiological activity, we have synthesized a number of substituted amides of 2,3-pentamethylenequinoline-4-carboxylic acid and of its 6-methyl derivative:



I: R=H; II: R=CH$_3$ III-XXI

The synthesis was performed by heating the starting materials – 2,3-pentamethylenequinoline-4-carbonyl chloride hydrochloride (I) or 6-methyl-2,3-pentamethylenequinoline-4-carbonyl chloride hydrochloride (II) and the appropriate primary or secondary amine – in benzene medium in the presence of triethylamine as acid-binding agent. The substituted amides of 2,3-pentamethylenequinoline-4-carboxylic acids (III-XXI; see Table 1), which were obtained in 55-80% yield, are colorless, crystalline substances which have basic properties; they form well-crystallized, water-soluble hydrochlorides. The UV spectra† have four maxima: at 232-240, 280-286, 306-312, and 320-326 nm. When there is a methyl group in the 6-position, a bathochromic shift of the spectrum is observed.

Compounds IV-VI, VIII-XI, and XVII-XIX were subjected to testing for biological activity. The experiments were carried out on white mice, to which the preparations were introduced intraperitoneally. Acute toxicity was studied by calculation of the LD_{50} by the Pershin method, recording deaths of animals over a 24-h period. The effect of the preparations was studied on the curarizing effect of a competing (diplacin – 10 mg/kg) and of a depolarizing (ditilin[succinylcholine] – 4.5 mg/kg) myorelaxant, in doses equal to 0.1 –0.2 LD_{50}.

The toxic action of most of the substances is displayed 1 to 2 min after introduction. It is characterized by an initial tremor and rapidly developing motor excitation susperseded by tonic-clonic spasms at the height of which a part of the animals perish. Compounds VI, X, XI, and XVII cause spasms after 10-45 min, which is probably connected with peculiarities in absorption and transport through the hemato-encephalic barrier. The toxicity (LD_{50}) of the compounds studied varies within the range 84-375 mg/kg, and decreases in the series: V>III>VI>XVIII>IX>XIV>XI>XVII>X. Ability to cause a decurarizing effect is displayed only with respect to diplacin and is inherent to compounds VI and XVIII. The myorelaxant action of ditilin, on the contrary, is intensified by compounds IX, XV, XVI, and XVII. A parallelism between expression of pro- and anticurare effect was not detected.

* For communication VII, see [1].

† The UV spectra were taken for alcoholic solutions on an SF-4 spectrophotometer.

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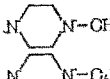
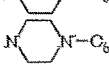
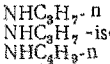
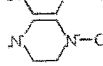
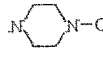
TABLE 1. Substituted Amides of 2,3-Pentamethylenequinoline-4-carboxylic Acid (III-XXI)

Compound	R	$N\langle^{R'}_{R''}$	Yield (in %)	mp, deg	N found (%)	Empirical formula	N calculated (%)	Hydrochloride mp, deg
III	H	NHC_3H_7-n	79,8	149—50	9,79	$C_{18}H_{22}N_2O$	9,95	237—9
IV	H	NHC_3H_7-iso	76,7	210—11	9,84	$C_{18}H_{22}N_2O$	9,95	>300
V	H	NHC_5H_9-n	81,3	137—9	9,63	$C_{19}H_{24}N_2O$	9,44	222—3
VI	H	NHC_5H_9-iso	80,8	162—3	9,58	$C_{19}H_{24}N_2O$	9,44	250—2
VII	H	$NHCH_2C_6H_5$	64,5	163—4	8,24	$C_{22}H_{22}N_2O$	8,47	241—3
VIII	H		59,4	152—3	9,11	$C_{20}H_{24}N_2O$	9,08	238—40
IX	H		71,8	146—8	12,90	$C_{20}H_{25}N_3O$	12,98	248—9
X	H		77,5	130—2	10,67	$C_{25}H_{27}N_3O$	10,90	241—3
XI	H		70,4	148—50	10,46	$C_{26}H_{29}N_3O$	10,52	247—8
XII	HC_3	NHC_3H_7-n	76,4	160—1	9,42	$C_{19}H_{24}N_2O$	9,54	243—5
XIII	HC_3	NHC_3H_7-iso	77,3	229—30	9,42	$C_{19}H_{24}N_2O$	9,71	>300
XIV	HC_3	NHC_5H_9-n	78,9	150—1	9,01	$C_{20}H_{26}N_2O$	8,96	235—7
XV	HC_3	NHC_5H_9-iso	75,2	153—4	9,01	$C_{20}H_{26}N_2O$	6,18	248—9
XVI	HC_3	$NHCH_2C_6H_5$	60,3	155—6	8,13	$C_{23}H_{24}N_2O$	7,95	221—4
XVII	HC_3		60,1	165—7	8,68	$C_{21}H_{26}N_2O$	8,45	217—8
XVIII	HC_3		54,0	140—2	9,07	$C_{30}H_{24}N_2O$	9,25	254—6
XIX	HC_3		70,3	173—5	12,44	$C_{31}H_{27}N_3O$	12,62	253—4
XX	HC_3		75,7	166—8	10,51	$C_{26}H_{29}N_3O$	10,35	250—2
XXI	HC_3		69,4	164—5	10,13	$C_{27}H_{31}N_3O$	9,95	257—9

EXPERIMENTAL

6-Methyl-2,3-pentamethylenequinoline-4-carboxylic Acid. A solution of 0.1 mole of 5-methylisatin in 50 ml of 30% potassium hydroxide solution was added to a solution of 0.15 mole of cyclopentanol in 100 ml of ethyl alcohol. The reaction mixture was heated on a water bath for 10 h, the ethanol was distilled off under vacuum, the residue was poured into 200 ml of water, and the excess cyclopentanol was extracted with ether. The aqueous extract was acidified with acetic acid, the precipitate which was formed was filtered off, and it was crystallized from alcohol. Yield, 60%; mp, 307°. Found, %: N 5.56. $C_{16}H_{17}NO_2$. Calculated, %: N 5.49.

2,3-Pentamethylenequinoline-4-carbonyl Chloride Hydrochloride (I). 2,3-Pentamethylenequinoline-4-carboxylic acid (dry, 40 g) was added portion-wise to 40 ml of phosphorus oxychloride, and the mixture was heated at 110-115° for an hour. During the heating period, 40 g of phosphorus pentachloride was added in small portions. At the end of the heating period, the excess phosphorus oxychloride was distilled off under vacuum, 50 ml of toluene was added to the residue, and the precipitate of I which fell was filtered off and crystallized from dichloroethane. The yield was 38 g (88%); mp 170°.

6-Methyl-2,3-pentamethylenequinoline-4-carbonyl chloride hydrochloride (II) was prepared similarly. The yield of it was 39 g (92%); mp 190°.

Substituted Amides of 2,3-Pentamethylenequinoline-4-carboxylic Acid (III-XXI). To 0.01 mole of I in 15 ml of benzene was added 0.01 mole of the amine and 0.03 mole of triethylamine. The reaction mixture was heated on a water bath for an hour. After cooling the reaction mixture, the precipitate of triethylamine hydrochloride was filtered off, the benzene was distilled off from the filtrate, and the residue was recrystallized.

The hydrochlorides of the substituted amides of 2,3-pentamethylene-4-carboxylic acids were prepared by passing hydrogen chloride into alcoholic solutions of the bases.

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