SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PYRROLO-, PYRIDO- AND AZEPINO[2,3-b]QUINOLINE DERIVATIVES

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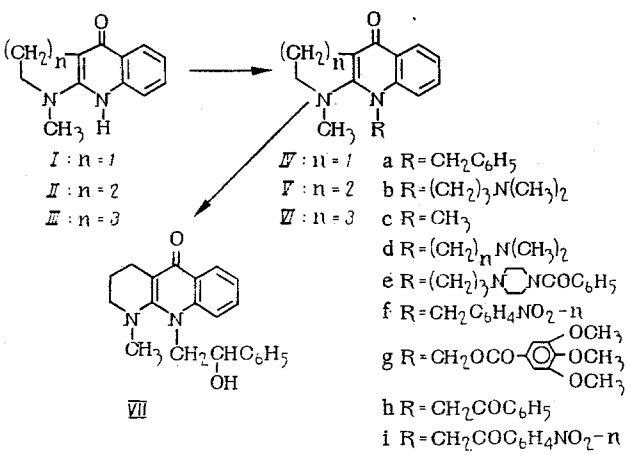
Tricyclic compounds containing a quinoline nucleus fused with aromatic or saturated azaheterocycles are currently attracting the attention of researchers in connection with the fact that some of their derivatives have diverse biological activities. For example, benzo[b]-1,8-naphthyridin-5-one derivatives in which the nitrogen of the quinoline ring is substituted by a γ-dimethylaminopropyl grouping have pronounced antidepressant activity [1], while 2,3-dihydropyrrolo[2,3-b]quinoline derivatives possess antiinflammatory properties [2].

In view of this, it would be of interest to investigate the reaction of pyrrolo- (I), pyrido- (II) and azepinoquinolone (III) derivatives previously synthesized by us [3] with various alkylating agents, and to study the pharmacological activity of the compounds obtained.

In studying the alkylation of I-III, we found that the best conditions for this reaction comprise the use of sodium hydride as proton acceptor and dimethylformamide as solvent. Under these conditions, the process proceeds quite smoothly and gives satisfactory yields of the N-alkylation products (IVa, IVb, Va, Vb, Vh, and VIa-VIg) (see Table 1 and Experimental Section).

It should be noted that some of these substances form stable crystal hydrates and solvates with water and solvents. Their structure was demonstrated by mass-spectrometric analysis, IR spectroscopy, and nonaqueous titration.



In the IR spectra of compounds Ia, Ib, IIa, IIb, and IIIa-h, an intense absorption band belonging to the amide CO group is observed in the 1630 cm^{-1} region, a band (C=C bond) is observed at 1580 cm^{-1}, and the broad band in the 2500-2700 cm^{-1} region (associated NH) disappears. Reaction of compound II with α-bromoacetophenone gives the N-phenacyl derivative (Vh), the IR spectrum of which has an intense band in the 1705 cm^{-1} region (benzoyl CO).

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TABLE 1. Pyrrolo-, Pyrido-, and Azepino[2,3-b]quinoline Derivatives

Compound	Yield (%)	Melting point (deg)	Found (%)				Empirical formula	Calculated (%)				Mass spectrum M^+
			C	H	N	Cl		C	H	N	Cl	
IVb	58	236—7	54,20	7,07	10,74	18,77	$C_{17}H_{23}N_3O \cdot 2HCl \cdot H_2O$	54,25	7,18	10,17	18,78	285
Va	85	172—3	69,26	6,45	7,95	10,17	$C_{20}H_{20}N_2O \cdot HCl \cdot 0,5H_2O$	68,57	6,29	8,02	10,15	304
Vb	56	187—8	57,72	7,26	11,16	—	$C_{18}H_2{}^*N_3O \cdot 2HCl$	58,06	7,26	11,29	—	299
VIa	60	152—3	70,74	6,57	8,02	9,78	$C_{21}H_{22}N_2O \cdot HCl$	71,09	6,49	7,89	10,02	—
VIb*	87	187—8	—	—	—	16,21	$C_{19}H_{27}N_3O \cdot 2HCl \cdot C_3H_7OH$	—	—	—	16,19	313
VIc†	51	155—6	—	—	9,77	12,07	$C_{15}H_{18}N_2O \cdot HCl$	—	—	10,05	12,75	242
VId	60	174—6	54,58	7,45	10,75	17,55	$C_{18}H_{25}N_3O \cdot 2HCl \cdot 1,5H_2O$	54,14	7,52	10,53	17,79	299
VIe‡	35	163—5	60,93	6,92	10,86	12,49	$C_{28}H_{34}N_4O_2 \cdot 2HCl \cdot H_2O$	61,20	6,92	10,20	12,93	—
VIf	13	164—5	62,91	5,71	10,44	8,81	$C_{21}H_{21}N_3O_2 \cdot HCl$	63,08	5,51	10,51	8,87	—
VIg	45	156—7	62,47	6,30	5,53	6,61	$C_{27}H_{32}N_2O_6 \cdot HCl$	62,73	6,39	5,42	6,87	—

Note. Compounds IVb, Va, and VIf were crystallized from alcohol, and Vb, VIa-VIe, and VIg were crystallized from isopropanol.

*Nonaqueous titration with hydrochloric acid in acetic anhydride gives a molecular weight of 443.

†IR spectrum: ν_{CO}(amide) 1610 cm^{-1}

‡IR spectrum: ν_{CO}(amide), CO(ketone) 1630 cm^{-1} (broad); UV spectrum: λ_{max} 258 nm (log ε = 4.39), 344 nm (log ε = 3.96).

Reduction of the product Vh with sodium borohydride gives a compound VII containing a N-(β-phenyl-β-hydroxyethyl) fragment. The appearance of an OH absorption band at 3250 cm^{-1} and the absence of a CO absorption band at 1705 cm^{-1} in the IR spectrum of compound VII indicates the reduction of the phenacyl carbonyl group.

In studying the pharmacological properties of the compounds synthesized, we are primarily interested in their psychotropic, especially antidepressant, activity. In addition, we also studied their effect on the vegetative nervous system, arterial pressure, and respiration.

We did not discover any compounds with pronounced psychotropic activity among the tetrahydropyrroloquinoline derivatives (IVa and IVb). In experiments on urethane-narcotized cats, compound IVa displayed weak adrenomimetic activity (causing increased arterial pressure and contraction of third eyelid) at doses of 1-5 mg/kg (intravenous). Compound IVb had a weak ganglion-blocking action; at doses of 3-5 mg/kg it decreased the response of the arterial pressure, respiration, and third eyelid to the administration of cytisine. The action of the pyridoquinolines (Va and Vb) was analogous. Compound Va, like IVa, possessed weak adrenomimetic activity. In experiments on urethane-narcotized cats, Va gave rise to a short-lived increase in arterial pressure and a contraction of the third eyelid at doses of 1-5 mg/kg. As in the case of IVa, a hypotensive phase was observed before the hypertensive phase in a number of experiments. These effects were relieved by adrenolytics (tropaphene or phentolamine), confirming the adrenomimetic nature of these effects.

The adrenomimetic properties of Vh were retained when the benzyl radical was replaced by β-phenylhydroxyethyl. Thus, Vh caused an increase in arterial pressure and contraction of the third eyelid at doses of 1-3 mg/kg, and reduced the number of drops bleeding from the vessels of an isolated rabbit ear by 30% at a concentration of 10^{-5}. Compound Vb, like IVb, possessed a weak ganglion-blocking activity. The N-substituted pyrido[2,3-b]quinolines had little effect on the central nervous system.

Of the azepinoquinoline derivatives, two compounds (VIa and VIe) possessed some properties characteristic of antidepressants. Like other tricyclic antidepressants (imizine, etc.), both compounds reinforce the stimulating effect of amphetamine. When white mice are injected subcutaneously with VIa in doses of 10-25 mg/kg or with VIe in doses of 25-50 mg/kg, their body temperature is 1-2.5° higher than when amphetamine is administered alone. Compound VIe increases the group toxicity of amphetamine. When administered to white mice alone in doses of 5 and 10 mg/kg, amphetamine causes the death of 10 and 60% of the mice, respectively. If VIe is administered simultaneously (in a dose of 50 mg/kg), amphetamine causes the death of 30% of the mice at a dose of 5 mg/kg and 90% of the mice at a dose of 10 mg/kg.

Both compounds (at doses of 25-50 mg/kg) have the ability to diminish the depressant action of reserpine (hypothermia and ptosis in white mice), but this effect is much less marked than in the case of the known tricyclic antidepressant imizine.

The ability of the other hexahydro- and tetrahydroazepino[2,3-b]quinoline derivatives (VIb and VId) to increase the effect of amphetamine and decrease the effect of reserpine was less marked than in the case of VIa and VIe, or was not observed at all (VIc, VIg, and VIf).

The azepinoquinoline derivatives had little effect on the vegetative nervous system. Like compounds IVa and Va, compound VIa, containing a benzyl radical in the 11 position of the tricyclic system, possessed adrenomimetic activity, but this was less pronounced than in the case of IVa and Va. Like compounds IVb and Vb, compound VIb possessed weak ganglion-blocking activity.

The toxicity of the compounds was tested on white mice by subcutaneous injection: The LD_{50} (mg/kg) was 490 for IVa, 205 for IVb, 755 (inside) for IVi, 390 for Va, 205 for Vb, 95 for Vh, 320 for Vi, 382 for VIa, 300 for VIb, 350 for VIc, 380 for VId, 270 for VIe, 500 for VIf, and 500 for VIg.

Thus, this study has shown some connection between chemical structure and action.

The pyrroloquinoline derivatives (IVa and IVb) containing a benzyl radical possessed adrenomimetic activity, which was retained when the pyrroline ring was replaced by a tetrahydropyridine ring. When a hydrogenated azepine ring was introduced, the adrenomimetic activity was retained but was less pronounced than in the case of the corresponding pyrrolo- and pyridoquinoline derivatives.

When the benzyl radical was replaced by β-phenyl-β-hydroxyethyl, the adrenomimetic activity increased in the case of the tetrahydropyridoquinoline derivatives.

The pyrrolo-, pyrido-, and azepinoquinoline derivatives containing a dimethylaminopropyl chain possess weak ganglion-blocking activity.

EXPERIMENTAL

The IR spectra of the substances were recorded on an IK-10 or Perkin-Elmer 457 instrument in the form of pastes in mineral oil, and the UV spectra were recorded on an ESPS-3 recording spectrophotometer in alcohol. The mass spectra were recorded on an MKh-1303 instrument fitted with a direct inlet into the source, with an ionizing voltage of 50 eV.

1-Methyl-4-oxo-9-benzyl-1H-2,3,4,9-tetrahydropyrrolo[2,3-b]quinoline Hydrochloride (IVa). Sodium hydride (0.92 g) was added over 1 h to 4.0 g of oxo compound (I) in 40 ml of dry dimethylformamide (DMF) at 70°. The mixture was kept at 90° for 4 h, treated over 50 min with 3.15 g of benzyl chloride in 10 ml of dry DMF, and kept at 100° for 3 h. The reaction mixture was evaporated, the residue treated with chloroform, the solution filtered, and the filtrate washed with water. The chloroform layer was dried with sodium sulfate, filtered, and the chloroform evaporated off. The residue was dissolved in acetone and alcoholic HCl added to give 3.7 g (55%) of IVa, mp 190-191° (from alcohol). Mass spectrum: M^+ 290. Found, %: C 68.50; H 5.84; N 8.41; Cl 10.63. $C_{19}H_{19}ClN_2O \cdot 0.5H_2O$. Calculated, %: C 67.90; H 5.98; N 8.37; Cl 10.58.

The mono- and dihydrochlorides of 1-methyl-4-oxo-9-(β,β-dimethylaminoethyl)-1H-2,3,4,9-tetrahydropyrrolo[2,3-b]quinoline (IVb), 1-methyl-5-oxo-10-substituted-1,2,3,4,5,10-hexahydropyrido[2,3-b]quinolines (Va and Vb), and 1-methyl-6-oxo-11-substituted-1H-2,3,4,5,6,11-hexahydroazepino[2,3-b]quinolines (VIa-VIg) were prepared analogously under the same temperature–time conditions (see Table 1).

1-Methyl-5-oxo-10-(α-benzoylmethyl)-1,2,3,4,5,10-hexahydropyrido[2,3-b]quinoline (Vh). Sodium hydride (0.9 g) was added over 1 h to 4.3 g of compound II in 40 ml of dry DMF at 70°. The mixture was kept at 90° for 4 h, treated over 50 min with 4.4 g of α-bromoacetophenone in 30 ml of dry DMF at 20°, and kept at 80° for 2.5 h. The solvent was evaporated off, the residue treated with chloroform, the solution filtered, and the filtrate washed with water. The chloroform layer was dried with sodium sulfate, filtered, and the chloroform evaporated off. The residue was triturated with petroleum ether to give 3.7 g (43%) of Vh, mp 137-138° (from alcohol). IR spectrum: νCO(benzoyl) 1705 cm^{-1}, νCO(amide) 1625 cm^{-1}. UV spectrum: λ_{max} 245 nm (log ε = 4.70), 349 nm (log ε = 3.83), 364 nm (log ε = 3.78). Found, %: C 76.20; H 6.09; N 8.24. $C_{22}H_{22}N_2O_2$. Calculated, %: C 76.30; H 6.36; H 8.09.

1-Methyl-4-oxo-9-(p-nitrophenacyl)-1H-2,3,4,9-tetrahydropyrrolo[2,3-b]quinoline (IVi). Sodium hydride (1.2 g) was added over 1 h to 9.0 g of compound I in 80 ml of dry DMF at 50°. The mixture was kept at 65° for 1.5 h, treated over 1.5 h with 11 g of α-bromo-p-nitroacetophenone in 50 ml of DMF at 3-5°, and kept at 20° for 10 h. The solvent was evaporated off, the residue treated with chloroform, the solution filtered, and the filtrate washed with water. The chloroform layer was dried with sodium sulfate, filtered, and the chloroform evaporated off. The residue was kept in heptane for 3-4 days, the solvent decanted off, and the residue triturated with 200 ml of methanol to give 8.0 (48.7%) of IVi, mp 167-168° (from isopropanol). IR spectrum: νCO(benzoyl) 1700 cm^{-1}, νCO(amide) 1625 cm^{-1}. Found, %: C 66.01; H 4.68; N 11.41. $C_{20}H_{17}N_3O_4$. Calculated, %: C 66.12; H 4.68; N 11.57.

Hydrochloride of IVi: mp 243-244° (from alcohol). Found, %: Cl 8.55. $C_{20}H_{17}N_3O_4 \cdot HCl$. Calculated, %: Cl 8.87.

1-Methyl-5-oxo-10-(p-nitrophenacyl)-1,2,3,4,5,10-hexahydropyrido[2,3-b]quinoline Hydrochloride (Vi). Sodium hydride (1.1 g) was added over 1 h to 8.6 g of compound II in 80 ml of dry DMF at 50°. The mixture was kept at 80° for 2 h, treated over 1.5 h with 10.0 g of α-bromo-p-nitroacetophenone in 50 ml of dry DMF at 3-5°, and kept at 20° for 10 h. The solvent was evaporated off, the residue treated with chloroform, the solution filtered, and the filtrate washed with water. The chloroform layer was dried with sodium sulfate, filtered, and the chloroform evaporated off. The residue was dissolved in ether and treated with alcoholic HCl to give 7.2 g (43%) of the hydrochloride (VIi), mp 253-254° (from alcohol). IR spectrum: νCO(benzoyl) 1690 cm^{-1}, νCO(amide) 1650 cm^{-1}. Found, %: C 60.87; H 4.90; N 10.32; Cl 8.61. $C_{21}H_{19}N_3O_4 \cdot HCl$. Calculated, %: C 60.94; H 4.90; N 10.15; Cl 8.58.

1-Methyl-5-oxo-10(β-hydroxy-β-phenylethyl)-1,2,3,4,5,10-hexahydropyrido[2,3-b]quinoline (VII). Sodium borohydride (2.3 g) was added over 1 h to a solution of 3.5 g of compound Vh in 60 ml of methanol at 10°, and the reaction mixture kept at 10° for 30 min and at 70° for 1 h. The mixture was adjusted to pH 5.5 with glacial acetic acid at room temperature, evaporated, treated with 5 ml of water and 2 N sodium hydroxide solution, and the aqueous phase adjusted to pH 9.0. The aqueous layer was extracted with chloroform (3 × 20 ml). The combined chloroform extracts were dried with sodium sulfate, filtered, evaporated, and the residue triturated with a 1:2 mixture of ether and petroleum ether, to give 3.3 g (95%) of VII, mp 133-134° (from isopropanol). IR spectrum: $\nu_{CO(amide)}$ 1610 cm^{-1}, ν_{OH} 3250 cm^{-1}. UV spectrum: λ_{max} 255 nm (log ε = 4.62), 346 nm (log ε = 3.82), 361 nm (log ε = 3.78). H^1NMR spectrum: δ_{nm} = 1.53 (3-CH_2), 2.73 (4-CH_2), 3.03 (2-CH_2), 3.16 (N—CH_3), 4.20 (N_{10}—CH_2), 5.45 (α-CH), 7.09-8.16 (C—H_{arom}). Found, %: C 75.42; H 6.75; N 8.24. $C_{22}H_{24}N_2O_2$. Calculated, %: C 75.86; H 6.89; N 8.04.

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SYNTHESIS AND ANTITUMOR ACTIVITY OF N-ACYL SARCOLYSINE DERIVATIVES

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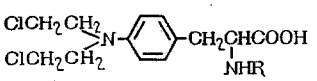
The antitumor activity of alkylating compounds depends to a considerable extent on properties such as the reactivity of the alkylating di(2-chloroethyl)amino group, the solubility or hydrophilic-lipophilic balance of the compound, and its ability to engage in metabolic changes. With the object of seeking antitumor substances which are distinguished from known substances in having a more favorable combination of the above characteristics, we have synthesized sarcolysine analogs containing acyl residues of three types, viz., amide, urethane, and sulfamide compounds I-IX (Table 1).



I-IX

We prepared these compounds on the basis of data indicating that the presence of hydrophobic acyl groups in compounds leads to a significant change in their partition coefficient, i.e., the ratio of their solubilities in lipid and aqueous phases [1]. According to the data in [2-6], the introduction of phenacetyl or palmityl residues or benzoxycarbonyl groups into amino acids leads to the appearance of antitumor activity. In [7-9] it was reported that the N-formyl, N-acetyl and N-palmitoyl derivatives of sarcolysine have an antitumor action, and that the last of these possesses pronounced hydrophobic properties.

All the compounds were synthesized by reacting sarcolysine with the corresponding acid chlorides under modified Schotten—Baumann conditions. In some cases, the required compound had to be additionally purified to remove sarcolysine impurities; this was carried out via the cyclohexylammonium salts. Compounds I and VIII are already known [7, 10], but were needed for comparison. The antitumor activity of VIII has not been investigated before.

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