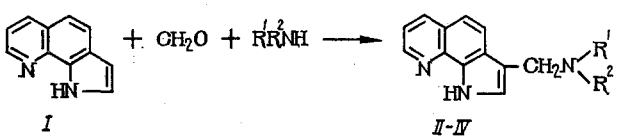
SYNTHESIS OF SOME DERIVATIVES OF 1H-PYRROLO[3,2-h]QUINOLINE

V. P. Shabunova, Zh. F. Sergeeva,
R. N. Akhvlediani, A. M. Vasil'ev,
N. V. Gorelova, and N. N. Suvorov

UDC 615.31:547.831].012.1

Among condensed idole derivatives the attention of biologists and chemists has been attracted in recent years by pyrroloquinolines with various ring linkages. It has been shown that many of them (both synthetic and of natural origin) possess well-defined antitumoral, antimalarial, tuberculostatic, antiinflammatory, hypotensive, analgesic, and other activities [1-4]. In the search for new biologically active substances among the pyrroloquinolines we have performed some typical electrophilic substitution reactions (the Mannich, the Vilsmeier, and the azo-coupling reactions) not known for 1H-pyrrolo[3,2-h]quinoline (I), have obtained the corresponding pyrroloquinolinylmagnesium iodide, and have performed syntheses from it. Some pharmacological properties of the compounds obtained have been studied.

The Mannich reaction has been described only for 2-methyl-1H-pyrrolo[3,2-h]quinoline [5]. We have performed this reaction with the unsubstituted heterocycle, an improved method of synthesizing which has been proposed previously [6]. Aminoalkylation was carried out by the method that has become traditional in the indole series – with dimethylamine, piperidine, and morpholine.



I *II-IV*

II $R^1 = R^2 = CH^3$; III $NR^1R^2 =$ piperidinyl
IV $NR^1R^2 =$ mopholinyl

The azo-coupling reaction of (I) was performed in dimethylformamide–water (1 : 1) in weakly acidic or neutral media with the diazonium salts obtained from aniline, p-nitroaniline, and p-chloroaniline. The azo derivatives (V, VI, and VII) were isolated with yields of 66-94%.

We have established that (I) readily takes part in the Vilsmeier reaction with N,N-dimethylformamide (DMFA) forming 3-formyl-1H-pyrrolo[3,2-h]quinoline (VIII) in good yield (93%). However, the reaction of (I) with N,N-dimethylacetamide or N,N-dimethylchloroacetamide under the same or even more severe conditions did not lead to the corresponding 3-acetyl and 3-chloroacetyl derivatives. 3-Acetyl-1H-pyrrolo[3,2-h]quinoline (IX) was synthesized with a yield of 89.5% by the Grignard method from 1H-pyrrolo[3,2-h]quinolin-1-ylmagnesium iodide. This Grignard reagent was also used for the synthesis of 3-allyl-1H-pyrrolo[3,2-h]quinoline (X) and the pyridine analog of tryptamine – 3-β-(aminoethyl)-1H-pyrrolo[3,2-h]quinoline (XI). (See scheme on the following page.) In addition, an attempt was made to synthesize carboxylic acid derivatives of the heterocycle under study. From the products of the reaction of compound (I) with monochloroacetic acid in an alkaline medium under increased pressure we isolated 1H-pyrrolo[3,2-h]quinolin-3-ylacetic acid (XIII). When (I) was treated with sodium ethyl carbonate [7], 1H-pyrrolo[3,2-h]quinoline-3-carboxylic acid (XII) was obtained.

From the absence of the signal of a proton in position 3 of the ring at 6.57 ppm in the PMR spectra of the compounds described above (II-XIII) it was established that in all cases substitution took place in position 3 of the pyrroloquinoline nucleus.

Compound (I) was methylated by the action of sodium amide and methyl iodide in liquid ammonia, giving 1-methylpyrrolo[3,4-h]quinoline (XIV) with a yield of 95%. The methiodide of 1H-pyrrolo[3,2-h]quinoline (XV) was formed in high yield by boiling (I) with methyl iodide for 3 h. The structures of the newly synthesized compounds were confirmed by their UV, IR, and PME spectra.

D. I. Mendeleev Moscow Institute of Chemical Technology. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 6, pp. 53-58, June, 1978. Original article submitted January 5, 1978.

0091-150X/78/1206-0734$07.50

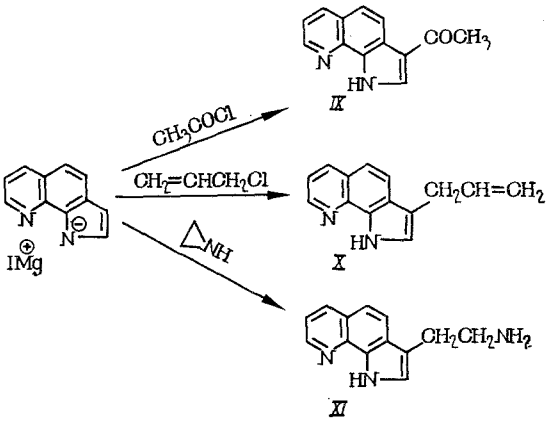
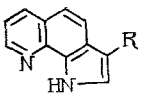
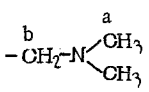
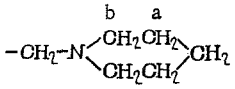
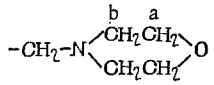
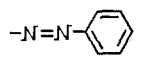
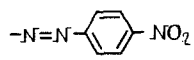
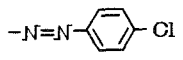


TABLE 1. Characteristics of the Substituted Pyrroloquinolines (II-XIII)



	R	Found, %			Molecular formula	Calculated, %			IR spectra† cm⁻¹		Chemical shifts,‡ ppm
		C	H	N		C	H	N	NH	characteristic absorption bands	
II		74,98	6,75	18,68	$C_{14}H_{15}N_3$	74,63	6,71	18,74	3200	—	δ_a=2,20; δ_b=3,75
III		77,04	7,33	15,64	$C_{17}H_{19}N_3$	76,97	7,16	15,87	3100	—	δ_a=1,55; δ_b=2,50; δ_c=3,75
IV		72,50	6,80	15,72	$C_{16}H_{17}N_3O$	71,93	6,44	15,72	3170	—	δ_a=3,65; δ_b=2,50; δ_c=3,75
V		75,30	4,62	20,05	$C_{17}H_{12}N_4$	74,99	4,44	20,56	3215	—	—
VI		64,08	3,53	21,95	$C_{17}H_{11}N_5O_2$	64,39	3,51	22,08	3140	1530 s (C—NO_2) 1340 s (C—NO_2)	— —
VII		66,46	3,71	17,92	$C_{17}H_{11}N_4Cl$	66,51	3,62	18,26	3220	—	—
VIII	—CHO	73,48	4,30	14,36	$C_{12}H_8N_2O$	73,20	4,08	14,27	3220	1660 (C=O)	δ_{CHO}=10,03
IX	—COC_3H	74,57	4,57	13,30	$C_{13}H_8N_2O$	74,30	4,67	13,33	3280	1650 (C=O)	δ_{CH_2}=2,51
X	—CH_2CH_2=CH_2 (a b c)	80,99	6,09	13,68	$C_{14}H_{12}N_2$	80,76	5,76	13,43	3490	1000 m (CH_2=CH—)	δ_a=3,48; δ_b=6,04; δ_c=5,08
XI	—$CH_2CH_2NH_2$	—	—	—	$C_{13}H_{13}N_3$*	—	—	—	3180	1640 (NH_2)	δ_{NH_2}=3,80 δ_{CH_2}~2,89
XII	—COOH	68,25	4,23	12,77	$C_{12}H_8N_2O_2$	67,92	3,77	13,20	3180	1665 (C=O)	—
XIII	—CH_2COOH	68,91	4,30	12,58	$C_{13}H_{10}N_2O_2$	68,99	4,41	12,38	3250	1690 (C=O)	δ_{CH_2}=3,76

*The tryptamine analog was analyzed in the form of its salt with adipic acid (see Experimental part).

†Solvent mineral oil or, in the case of (X), carbon tetrachloride.

‡Solvent for (II) CD_3OD, for (III) carbon tetrachloride, and for (VIII-XIII) dimethyl sulfoxide).

The properties of the compounds (II-XIII) are given in Table 1.

EXPERIMENTAL

Biological

The biological activities of compounds (II, III, V, VI, VIII, IX, XI, and XV) were investigated in the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry (Laboratory of Corresponding Member of the Academy of Medical Sciences of the USSR G. N. Pershin), and also in the Oncological Center of the Academy of Medical Sciences of the USSR. These compounds possess a low tuberculostatic activity in relation to strain H-37R. A high tuberculostatic activity was shown only by the thiosemicarbazone of 3-formal-1H-pyrrolo[3,2-h]quinoline. This compound retarded the growth of the tubercle bacilli in a concentration of 0.03 μg/ml in the absence of serum. However, in the presence of serum the activity fell. Compound (XV) possessed no antispasmodic, analgesic, or local anesthetic activity. In urethane-narcotized cats the intravenous administration of 5-10 mg/kg of this compound caused a brief hypotensive reaction. Larger doses proved to be lethal. The substance possessed cytotoxic action on C-37 and L5178 cultures and Ehrlich's tumor.

We also studied the radioprotective properties of compound (I) and (XI). The experiment was performed with random-bred female white mice with an average weight of 23-25 g. The substances investigated were dissolved in distilled water ex tempore and were administered 5-10 min before γ irradiation on a volume of 0.1 ml per 10 g weight of the animal. The dose of γ radiation was 900 R at a power of the source of 34 R/min. The radioprotective activities of the compounds were estimated from the percentage survival rate of the mice and from the mean lifetimes of the animals that died. The radioprotective effect of compound (XI) was 20% and of compound (I) 10% at mean lifetimes of 8.8 ±0.5 and 7.3 ±1.5 days, respectively.

Chemical

The IR spectra were recorded on a UR-10 instrument in mineral oil or in carbon tetrachloride. The electronic spectra were obtained on a Specord instrument at a layer thickness of 1 cm in ethanol. The PMR spectra were recorded on a Varian HA-100D spectrometer using as solvents bistrideuteromethyl sulfoxide and carbon tetrachloride, and as internal standard hexamethyldisiloxane. The accuracy of the measurement of the chemical shift $\delta = 0.01$ ppm. The results of elementary analysis and of IR and PMR spectroscopy are given in Table 1.

3-Dimethylaminomethyl-1H-pyrrolo[3,2-h]quinoline (II). The Mannich reaction was performed by Dewar's method [5]. From 3.4 g (0.02 mole) of (I) was obtained 3.9 g (84.5%) of substance (II) with mp 165.5-166.5°C (from aqueous ethanol). UV spectrum, λ_{max} nm, log ε: 217 (3.13), 244 (3.87), 272 (4.61), 333 (3.52).

3-Piperidinomethyl-1H-pyrrolo[3,2-h]quinoline (III). Similarly, 3.46 g (0.02 mole) of (I) and piperidine gave (III) with a yield of 4.7 g (88.6%), mp 149.5-151.5°C (from aqueous ethanol). UV spectrum, λ_{max}, nm (log ε): 206 (4.32), 232 (4.22), 259 (4.80), 322 (4.02), 340 (3.90).

3-Morpholinomethyl-1H-pyrrolo[3,2-h]quinoline (IV). This was obtained similarly by the Mannich reaction with a yield of 67.4%; mp 143°C (from ethanol); UV spectrum, λ_{max}, nm (log ε): 217 (4.50), 224 (3.85), 333 (3.60).

3-Phenylazo-1H-pyrrolo[3,2-h]quinoline (V). A few drops of a 0.1 N solution of caustic soda was added to a solution of 0.84 g (0.005 mole) of (I) in 20 ml of DFMA and 20 ml of water to bring the pH to 6.0-7.0 and, at 5°C, a solution of 0.005 mole of benzenediazonium chloride prepared by the usual method was slowly run in. During the whole of the process the pH was kept at about 5.0 by the addition of 0.1 N caustic soda. Coupling was carried out at 5-10°C for 3 h. The yellow-orange precipitate formed was filtered off and washed with water. Yield of 0.91 g (66.4%), mp 224-225°C (from acetone). UV spectrum, λ_{max}, nm (log ε): 203 (4.78), 243 (4.79), 274 (4.63), 370 (4.88).

3-(4-Nitrophenylazo)-1H-pyrrolo[3,2-h]quinoline (VI). This was obtained by the method described above from 0.84 g (0.005 mole) of (I) and an equimolar amount of p-nitrobenzenediazonium chloride. Red-orange crystals with mp 321-322°C (decomp., from DMFA). Yield 1.10 g (68%). UV spectrum, λ_{max}, nm (log ε): 203 (4.13), 242 (4.09), 274 (4.23), 408 (4.45).

3-(4-Chlorophenylazo)-1H-pyrrolo[3,2-h]quinoline (VII). The coupling of 0.84 g (0.005 mole) of (I) and an equimolar amount of p-chlorobenzenediazonium chloride was carried out by the method described for compound (V). The brown precipitate of the azo compound (VII) obtained was filtered off. Yield 1.45 g (94%), mp

277-279°C (from ethanol). UV spectrum, λ_{max}, nm (log ε): 205 (4.23), 217 (4.22), 243 (4.25), 272 (4.09), 374 (4.26).

3-Formyl-1H-pyrrolo[3,4-h]quinoline (VIII). To 2.9 g (0.04 mole) of freshly-distilled dimethylformamide cooled to 0°C was slowly added 1.6 g (0.011 mole) of phosphorus oxychloride. The reaction mixture was stirred at room temperature for 1 h and then 1.68 g (0.01 mole) of (I) in 4 ml of DMFA was added. The resulting mixture was heated at 80°C for 3 h and left overnight, after which it was poured into water, 0.1 N caustic soda solution was added to give an alkaline reaction, and the precipitate that deposited was filtered off. Yield 1.85 g (94%), mp 237-238°C (from ethanol). UV spectrum (ethanol), λ_{max} nm (log ε): 217 (4.31), 255 (4.47), 339 (2.27). Thiosemicarbazone of (VIII), mp 335-336°C (from DMFA). Found, %: C 57.9, H 4.1, N 26.2, S 11.8%. $C_{13}H_{11}N_5S$. Calculated, %: C 57.9, H 4.1, N 25.9, S 11.9.

3-Acetyl-1H-pyrrolo[3,2-h]quinoline (IX). A solution containing 16.8 g (0.1 mole) of (I) in 50 ml of absolute ether was added to an ethereal solution of 0.15 mole of methylmagnesium iodide. The mixture was kept at a boil for 2 h and was cooled to 5°C, after which a solution of 8.8 g (0.11 mole) of acetyl chloride in 50 ml of absolute ether was added and the resulting mixture was boiled for another 10 h. Then it was cooled and was poured into 50 ml of 2% acetic acid, and the light brown precipitate that deposited was filtered off. Yield 22.6 g (89.5%), mp 231-232°C (from ethanol). UV spectrum (ethanol), λ_{max}, nm (log ε): 205 (3.08), 229 (4.1), 257 (3.62), 322 (3.83), 392 (3.70).

3-Allyl-1H-pyrrolo[3,4-h]quinoline (X). A solution of 1.15 g (0.009 mole) of allyl bromide in 50 ml of absolute benzene was added to a solution of 0.13 mole of 1H-pyrrolo[3,2-h]quinolinylmagnesium iodide in absolute ether. The ether was distilled off and the reaction mixture was boiled for 4 h and was then poured into water, and the white precipitate that deposited was filtered off. Yield 0.61 g (60%), mp 113-114°C (from ethanol). UV spectrum (ethanol), λ_{max}, nm (log ε): 218 (4.48), 242 (3.87), 269 (4.59), 332 (3.57).

3-(β-Aminoethyl)-1H-pyrrolo[3,2-h]quinoline (XI). A solution of 5.6 g (0.13 mole) of ethyleneimine in 50 ml of absolute tetrahydrofuran was added to a solution of 0.13 mole of 1H-pyrrolo[3,2-h]quinolinylmagnesium iodide in absolute ether, and then the ether was distilled off and the reaction mixture was boiled under reflux for 6 h, after which it was cooled and was poured into 50 ml of 10% ammonium chloride solution. The light brown precipitate that deposited was filtered off. Yield 1.7 g (80.5%), mp 158-159°C (from ethanol). The base obtained was unstable and it was therefore converted into the adipate, mp 204-205°C. Found, %: C 66.6, H 6.2, N 14.5.

1H-Pyrrolo[3,2-h]quinoline-3-carboxylic Acid (XII). In small portions, 18 g (0.4 mole) of dry ice was added to a solution obtained by dissolving 4.6 g (0.2 mole) of metallic sodium in 100 ml of absolute ethanol, and the reaction mixture was kept for 1 h. The white precipitate of sodium ethyl carbonate that deposited was filtered off, washed with absolute ether, and dried, Yield 17.55 g.

A mixture of 3.4 g (0.02 mole) of (I) and 17.5 g (0.16 mole) of sodium ethyl carbonate was slowly heated over 1 h to 250°C and was kept at this temperature for 4 h, after which it was cooled and poured into 200 ml of cold water; 10% hydrochloric acid was added to pH 3.0 and the brown precipitate that deposited was filtered off. Yield 3.36 g (86.3%), mp 305-306°C (from ethanol).

1H-Pyrrolo[3,2-h]quinolin-3-ylacetic Acid (XIII). A mixture of 1.68 g (0.01 mole) of compound (I), 1.4 g (0.015 mole) of monochloroacetic acid, and 5.61 g (0.1 mole) of caustic potash in 30 ml of water was heated in an autoclave at 250°C in an atmosphere of nitrogen for 12 h. The resulting solution of the potassium salt of the acid was poured into 100 ml of water and the unchanged initial (I) was extracted with ether. The acid (XIII) was precipitated from the aqueous solution by acidification with 10% acid to pH 5.0. The yellowish precipitate that deposited was filtered off. Yield 0.77 g (35%), mp 241-242°C (from ethanol).

1-Methylpyrrolo[3,2-h]quinoline (XIV). Liquid ammonia (20 ml) was treated with powdered ferric chloride (0.3 g), and then 1 g of metallic sodium was added. After the blue dye becomes grey (about 20 min), 3.4 g (0.02 mole) of I is added. The reaction mixture was stirred for 20 min and then 3.5 g (0.025 mole) of methyl iodide was added and after the mixture had been allowed to stand for 10 min, the ammonia was evaporated off, 150 ml of cold water was added, and the white precipitate that deposited was filtered off. Yield 3.5 g (95%), mp 52.5-53.5°C (from ethanol). Found, %: N 15. $C_{12}H_{10}N_2$. Calculated, %: N 15.3. The IR spectrum (paraffin oil, CCl_4) lacked the characteristic NH band at 3200-3100 cm^{-1}. UV spectrum (ethanol), λ_{max}, nm (log ε): 217 (3.49), 266 (3.67).

1H-Pyrrolo[3,2-h]quinoline Methiodide (XV). A mixture of 1.68 g (0.01 mole) of compound (I) and 1.70 g (0.012 mole) of methyl iodide was boiled on a water bath for 3 h. Then 20 ml of benzene was added and the resulting yellow precipitate was filtered off. Yield 2.9 g (92%), mp 203-204°C (from ethanol). Found, %: N 9.1.

$C_{12}H_{10}N_2I$. Calculated, %: N 9.1. UV spectrum (ethanol): λ_{max}, nm ($\log \varepsilon$): 203 (4.52), 219 (4.55), 247 (4.15), 282 (4.52), 384 (3.86).

LITERATURE CITED

1. L. H. Zalkow, J. B. Nabor, K. Freuch, et al., J. Chem. Soc. (C), No. 21,3551 (1971).
2. US Patent No. 2,691,823, Chem. Abstr., 49, 14813e (1955).
3. H. Erlenmeyer, Helv. Chem. Acta, 36, 941 (1953).
4. Japanese Patent No. 73 28,439; Chem. Abstr., 80, 3485 (1974).
5. M. Dewar, J. Chem. Soc., 615 (1944).
6. Zh. F. Sergeeva, R. N. Akhvlediani, V. P. Shabunova, et al., Khim. Geterotsikl. Soedin., 12, 1656 (1975).
7. J. Jones and B. A. Hems, Manuf. Chem., 46, 395 (1975).

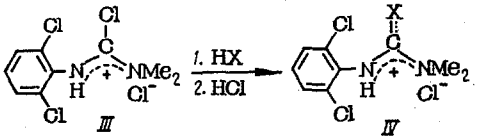
SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF NEW N,N',N''-SUBSTITUTED GUANIDINES

R. G. Glushkov, L. N. Dronova, L. A. Nikolaeva, B. A. Medvedev, M. D. Mashkovskii, N. P. Solov'eva, K. F. Turchin, and I. V. Persianova

UDC 615.217.22:547.495.9]012.1

The new synthesis of 2-(2,6-dichlorophenylamino)-2-imidazoline (klofelin; clonidine) (I) that we have developed [1, 2], based on the use as the starting materials of N-dichloromethylene-N,N-dimethylammonium chloride (II) [3, 4] and α-chloro-N'-(2,6-dichlorophenyl)-N,N-dimethylformamidine hydrochloride (III), has created the prerequisites for obtaining from (II) and (III) various N,N',N''-substituted guanidines which are of interest in connection with the search for new hypotensive agents. In this connection, in the present work we have synthesized and subjected to pharmacological study previously unknown hydrochlorides of N-substituted N'-(2,6-dichlorophenyl)-N'',N''-dimethylguanidines of the general formula (IV), which may be considered as "open" analogs of klofelin.

Compounds (IV) were synthesized from (III) [1, 2] by treating it with ammonia, primary aliphatic and aromatic amines, and secondary heterocyclic amines in isopropanol or acetonitrile.



III

IVa) X = NH_2
b) X = $NHCH_2CH_2NEt_2$
c) X = 4-$MeOC_6H_4NH$
d) X = 4-ClC_6H_4NH
e) X = piperidino
f) X = mopholino
g) X = 4-methylpiperazino

The yields and properties of compounds (IV) are given in Table 1.

The compounds obtained are fairly strong bases (pK_a 7.42-10.37); their structure was confirmed by IR and UV spectroscopy. The IR spectra of compound (IV) show absorption bands of C = N groups in the 1620-1665 cm^{-1} region and the UV spectra of them are characterized by the presence of absorption maxima in the 237-272 nm region.

By a method analogous to that used for the production of (IV), from sydnophen (V) [5] and the "immonium chloride" (II) we also synthesized new structural analogs (VI) of the psychostimulator sydnocarb (VIIa) [6], differing from the latter by the fact that in position 5 of the sydnone ring in place of a urea residue they include a fragment of a substituted guanidine ring.

Compounds (VI) were synthesized by the reaction of sydnophen with an equimolar amount of (II) in acetonitrile followed by treatment of the substituted "chloroformamidinium" chloride (VIII) with ammonia, benzylamine, and phenylhydrazine in the same solvent.

S. Ordzhanikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 6, pp. 59-64, June, 1978. Original article submitted December 16, 1977.

0091-150X/78/1206-0738$07.50