SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF CYCLOALKYL[b]PYRROLIDINE ALCOHOLS

T. G. Nikolaeva, L. K. Kulikova, and A. P. Kriven'ko

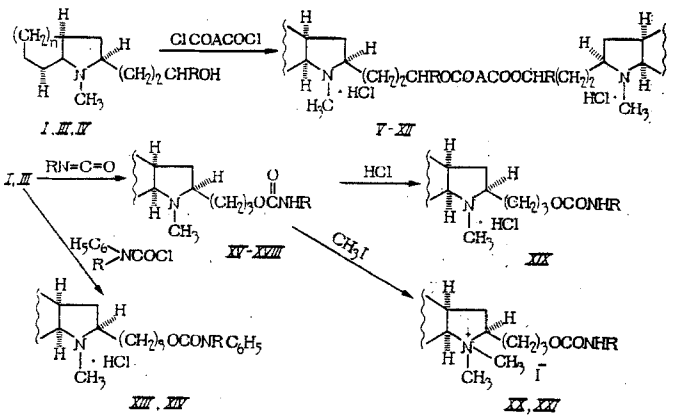
UDC 615.214.22:547.743].012.1.07

The physiological activity of alcohols in the cycloalkyl[b]pyrrolidine series and compounds based upon them is known only as a single patent in the literature [4, 5]. The development of new preparative methods for the stereo-directed synthesis of alcohols of the cyclopenta[b]-pyrrolidines series, and for octahydroindoles and related materials [6, 7] allowed the formulation of an investigation to obtain and study the biological activity of their various derivatives.

The starting materials were 3-[1-methyl-2-cyclopenta[b]pyrrolidinyl]propan-1-ol (I), 3-(2-octahydroindolyl)propan-1-ol (II) and its N-methyl homolog (III), and 4-(1-methyl-2-octahydroindolyl)butan-2-ol (IV), isolated in the form of its separate isomers. The latter, as was established earlier by ^{13}C NMR and x-ray structural analysis, had cis-linked carbo- and heterocycles, and cis oriented hydrogen atoms on the chiral centers of the bicycle [2, 3].

Interaction of aminoalcohols I, III, and IV with the acid chlorides of isomeric phthalic acids gave in high yields a series of esters in the form of the dihydrochlorides V-XII, easily soluble in water.

Acylation of the cycloalkyl[b]pyrrolidinylpropanols I and III with butyl and benzylisocyanates and N-alkyl-N-phenylcarbamoyl chloride gave the esters of mono- and di-substituted carbamic acids XV-XVIII and their salts XII, XIV, XIX-XXI.



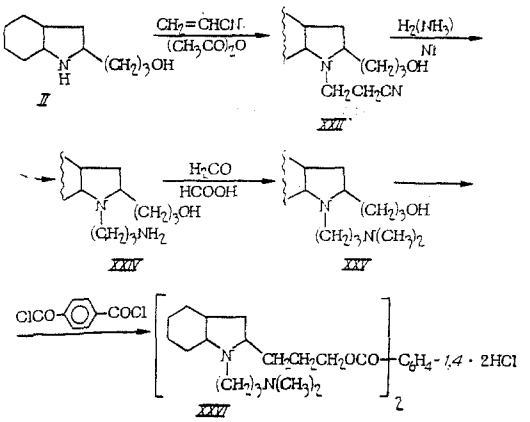
R = H (I, III, V—X), CH_3 (IV, XI, XII); C_2H_5 (XIV), C_4H_9 (XV, XVII, XX, XXI), $CH_2C_6H_5$ (XVI, XVIII, XIX); A = 1,4-C_6H_4 (V, VIII, XI), 1,3-C_6H_4 (VI), 1,2-C_6H_4 (VII, IX, X, XII); n = 1 (I, V—VII, XIII—XVI, XIX, XX), 2 (III, IV, VIII—XII, XVII, XVIII, XXI)

Conversion to the diaminoesters XXVI was brought about by the synthesis of 3-[1-(γ-dimethylaminopropyl)-2-octahydroindolyl]propan-1-ol (XXV) by means of successive reactions of cyanoethylation of the aminoalcohol II, reduction of the obtained aminonitrile XXII, and N-methylation of the reduction product XXIV.

To selectively cyanoethylate the amino function in compound II, the reaction was carried out in the presence of a catalytic amount of acetic anhydride. The hydroxyaminonitrile XXII showed a high boiling point and upon distillation in vacuum decomposed into the starting materials which were identified as the hydrochloride XXIII; it was subsequently reduced without preliminary purification. The reduction of compound XXII was brought about catalytically

N. G. Chernishev University, Saratov. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 7, pp. 836-840, July, 1989. Original article submitted June 17, 1988.

 0091-150X/89/2307-0588$12.50



in alcohol saturated with excess ammonia, which was necessary to suppress by-products arising from the secondary amine. Since acylation of the diaminoalcohol XXIV with terephthaloyl chloride can proceed both on the hydroxyl and on the primary amino group, the latter was derivatized by N-methylation to a tertiary amino group (compound XXV). The above transformations allowed the preparation of compounds with different distances between the nitrogen atoms, which is known to determine the character and the strength of physiological activity to a significant degree.

The composition and structure of the new materials obtained was estabished on the basis of their elemental analyses (Table 1) and IR spectra. In the spectra of the isomeric phthalates V-XII and XXVI, the presence of intense absorption bands in the 1715-1730 cm^{-1} region characterized the presence of the ester group. IR spectra of the cabamates and their salts (compounds XIII-XXI) with the valence oscillation of the C=O at 1720-1730 cm^{-1} include the "amide I" absorption band at 1640-1660 cm^{-1}. The valence oscillations of the C≡N in the spectra of aminonitrile XXII and its hydrochloride XXIII were found at 2260 cm^{-1}. Since the absorption band for the ν_{NH_2} in the aminonitrile XXIV overlaps the valence oscillations of the associated hydroxyl group in the 3300-3400 cm^{-1} region, the IR spectrum of its N,O-diacetate was recorded. The latter was characterized by the presence of absorption bands at 1630 and 1740 cm^{-1}, corresponding to the $\nu_{C=O}$ of the amide and the ester.

The synthesized isomeric phthalates V-XII and XXVI and the carbamates XIII-XXI were tested for their antimicrobial and antiphagal activity.

Significantly more attention is merited by the results of antiphagal activity tests. Compounds V, VI, XI-XVI, XVIII-XX, and XXVI possessed expressed antiphagal activity which exceeded or compared with the activity of such antitumor antibiotics as rubomycin and bleomycin with respect to both DNA(T_6)- and RNA (MS_2)-containing intestinal phages (Table 2). For example, compounds VI and XXIII inhibited the reproduction of phages by 41-45%.

On the basis of the data obtained, it is difficult to carry out a correlation between structure and biological activity. However, the influence on antiphagal activity by both the acidic and aminoalcohol fragments of the molecules should be noted. Among the isomeric phthalates of the cycloalkyl[b]pyrrolidine alcohols, isophthalate VI was the most active. Exchange of the methyl group on the nitrogen atoms by γ-dimethylaminopropyl(compound (XXVI) promotes an increase in the antiphagal activity. The acute toxicities of compounds V, VI, and XI-XIII were determined: their LD_{50} by intraperitoneal injection was found to be about 100 μg/kg.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on an UR-20 spectrometer (GDR) as suspensions in Vaseline oil or hexachlorobutadiene and as capillary films.

The cycloalkyl[b]pyrrolidine alcohols I-IV were obtained by methods in the literature [6, 7].

Bis{3-[1-methyl-2-cyclopenta[b]pyrrolidinyl]-1-propyl}terephthalate Dihydrochloride (V). Upon mixing solutions of 1 g (0.0054 mole) of aminoalcohol I in 20 ml of absolute ether and 0.55 g (0.0027 mole) of terephthaloyl chloride in 10 ml of absolute ether, the dihydrochloride V was obtained in the form of a white precipitate in 80% yield (Table 1).

TABLE 1. Derivatives of the Cycloalkyl[b]pyrrolidinylalkanols I-IV

Compound	Yield, %	T_{mp}, °C or T_{bp}, °C (mm Hg)	Empirical formula
V	80	140—143	$C_{30}H_{46}N_2O_4Cl_2$
VI	55	112—115	$C_{30}H_{46}N_2O_4Cl_2$
VII	77	59—61	$C_{30}H_{46}N_2O_4Cl_2$
VIII	70	79—82	$C_{32}H_{50}N_2O_4Cl_2$
IX	92	72—75	$C_{32}H_{50}N_2O_4Cl_2$
X	75	54—56	$C_{32}H_{50}N_2O_4Cl_2$
XI	92	68—70	$C_{34}H_{54}N_2O_4Cl_2$
XII	73	61—63	$C_{34}H_{54}N_2O_4Cl_2$
XIII	68	112—115	$C_{19}H_{29}N_2O_2Cl$
XIV	75	144—146	$C_{20}H_{31}N_2O_2Cl$
XV	50	110—111	$C_{16}H_{30}N_2O_2$
XVI	50	97—99	$C_{19}H_{28}N_2O_2$
XVIII	50	99—100	$C_{20}H_{30}N_2O_2$
XIX	79	102—103	$C_{19}H_{29}N_2O_2Cl$
XX	85	113—115	$C_{17}H_{33}N_2O_2I$
XXI	51	74—77	$C_{18}H_{35}N_2O_2I$
XXIII	57	146—147	$C_{14}H_{25}N_2OCl$
XXIV[a]	58	191—196 (5)	$C_{14}H_{25}N_2O$
XXV[b]	40	172—175 (2)	$C_{16}H_{32}N_2O$
XXVI	50	89—91	$C_{40}H_{68}N_4O_4Cl_2$

Note. The elemental analysis data satisfied the calculated values.

TABLE 2. Antiphagal Activity of Derivatives of Cycloaklyl[b]pyrrolidine Alcohols (at a concentration of 100 μg/ml)

Compound	% Phage inactivation	
	T_4	MS_2
V	17	28
VI	41	44
XI	20	27
XII	10	4
XIII	29	37
XIV	22	37
XV	22	33
XVI	22	33
XVIII	28	19
XIX	29	25
XX	10	4
XXVI	44	45
Rubomycin	14	39
Belomycin	29	32

The acetylation of aminoalcohols I, III, and XXV was carried out in an analogous manner with ortho-, iso-, and terephthaloyl chlorides. The characteristics of the isomeric phthalates VI-XII and XXVI are given in Table 1.

3-{1-Methyl-2-octahydroindolyl}-1-propyl-N-benzyl Carbamate (XVIII). To a solution of 5.5 g (0.028 mole) of aminoalcohol III in 45 ml of absolute toluene heated to boiling was slowly added a solution of 3.8 g (0.028 mole) of benzylisocyanate in 25 ml of absolute toluene with vigorous stirring. The reaction mixture was cooled to room temperature, 6-10 ml of distilled water was added and the mixture was vigorously shaken and kept for 12 h. The toluene solution was washed with distilled water (2 × 20 ml) and 2 N HCl (3 × 20 ml). The acidic layers were combined, neutralized with 20% K_2CO_3 solution and extracted with chloroform. The chloroform extract was dried with calcined $MgSO_4$, the solvent was distilled, and the residue, a viscous oil, was crystallized from absolute ether to give carbamate XVIII in a yield of 50% (Table 1).

The acylation of aminoalcohol I with benzyl- and butyl-isocyanate, and aminoalcohol III with butylisocyanate was carried out analogously. Characteristics of carbamates (XV and XVI) are given in Table 1. Carbamate XVII was identified in the form of its methiodide XXI.

3-{1-Methyl-2-octahydroindolyl}-1-propyl-N-butyl Carbamate Methiodide(XXI). Carbamate XVII (2 g, 0.0068 mole) was heated with 4 g (0.03 mole) of CH_3I for 3 h. The excess CH_3I was distilled and the residue, a viscous oil, was crystallized from absolute ether by cooling. The yield of methiodide XXI was 51% (cf. Table 1). Compound XX was prepared analogously (Table 1).

3-[1-Methyl-2-cyclopenta[b]pyrrolidinyl]-1-propyl-N-methyl-N-phenyl Carbamate Hydrochloride (XIII). A mixture of 0.5 g (0.0027 mole) of aminoalcohol I and 0.68 g (0.0041 mole) of N-methyl-N-phenylcarbamoyl chloride was heated for 4 h at 110-120°C. After cooling the reaction mixture was treated with absolute ether to remove excess carbamoyl chloride and to crystallize the hydrochloride XIII. The latter was obtained in a yield of 68% (Table 1).

The synthesis of 3-[1-methyl-2-cyclopenta[b]pyrrolidinyl]-1-propyl-N-ethyl-N-phenyl carbamate hydrochloride XIV was carried out analogously (Table 1).

3-[1-{β-Cyanoethyl}-2-octahydroindolyl]propan-1-ol (XXII). To a mixture of 1.26 g (0.038 mole) of acrylonitrile, stabilized by addition of a small quantity of hydroquinone, and 0.18 ml (0.0036 mole) of acetic anhydride was added in small portions with vigorous stirring 3.5 g (0.019 mole) of aminoalcohol II. The reaction mixture was stirred for 1 h at room temperature and 2 h at 80-85°C. The excess acrylonitrile and acetic anhydride were removed at reduced pressure, and the viscous oily residue was converted to its hydrochloride XXIII for identifica-

tion by adding absolute ether and saturating with HCl (Table 1). The aminonitrile XXII was used in succeeding reactions without further purification.

3-[1-{γ-Aminopropyl}-2-octahydroindolyl]propan-1-ol (XXIV). To a 250-ml autoclave was added 16 g (0.065 mole) of aminonitrile XXII, 120 ml of methanol saturated with ammonia (25 g, 1.47 mole), and about 2 g of Raney nickel. The initial hydrogen pressure was 100 atm, and the temperature was 100°C. The reaction was finished in 6-7 h, judging by the absorption of the calculated amount of hydrogen; 46 atm (0.13 mole). The catalyst was filtered off, the methanol was removed at reduced pressure, and the residue was distilled under vacuum to give aminoalcohol XXIV in 58% yield (Table 1).

3-[1-(γ-Dimethylaminopropyl)-2-octahydroindolyl]-propan-1-ol (XXV). A mixture of 2.5 g (0.014 mole) of aminoalcohol XXIV, 9.8 ml of 85% formic acid and 8 ml of 35% formalin was stirred in a water bath for 10 h. Concentrated HCl (1.2 ml) was added to the reaction mixture and the unreacted starting materials were removed under reduced pressure. To the residue was added a saturated solution of KOH until the separation of an oily layer, which was removed. The aqueous layer was then extracted with ether. Removal of the ether and distillation of the residue under vacuum gave compound XXV in 40% yield (Table 1).

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity was determined by the serial dilution method in Hottinger broth at pH 7.2 - 7.4 relative to the test microbes S. aureus 209p, E. coli 675, P. vulgaris 38, P. aeruginosa 165, and C. albicans 45.

The antiphagal activity of the synthesized compounds was studied in the system phage/bacteria compared to DNA (T_6)- and RNA (MS_2)-containing intestinal phages. E. coli "B" and "Hfrc," respectively, served as indicators. The quantity of intestinal phage particles was determined by the agar layer method of Gratia. The antiphagal activity was expressed in % inactivation, calculated by the formula [1]:

$$\% \text{ inactivation} = \left(1 - \frac{N_0}{N_K}\right) \cdot 100,$$

where N_0 = number of surviving corpuscles of phage in the experiment: N_K = number of surviving corpuscles of phage in the control (Table 2). The LD_{50} was determined on non-inbred white mice by intraperitoneal injection by the method of V. B. Prozorov.

LITERATURE CITED

1. D. M. Gold'farb, Bacteriophages [in Russian], Moscow (1961), p. 125.
2. A. P. Kriven'ko, T. G. Nikolaeva, A. A. Espenbetov, et al., Khim. Geterotsilk. Soedin., No. 1, 66-70 (1985).
3. A. P. Kriven'ko, T. G. Nikolaeva, N. T. Komyagin, et al., ibid., 71-75.
4. US 3104241 (1963), Chem. Abstr., 61, 6993 (1964).
5. Swiss 359442 (1962), ibid, 58, 3331 (1963).
6. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, Khim. Geterotsikl. Soedin., No. 5, 850-856 (1967).
7. V. G. Kharchenko, A. P. Kriven'ko, and T. G. Nikolaeva, ibid., No. 11, 1561-1562 (1983).