INFLUENCE OF THE CONFORMATION OF AMIDE ANALOGS OF ACETYLCHOLINE ON THEIR CHOLINOMIMETIC ACTIVITY

N. V. Khromov-Borisov, L. N. Aleksandrova, A. F. Danilov, and S. A. Shelkovnikov

UDC 615.217.22.015.4.07

Earlier [1] we made a comparative investigation of the nicotinomimetic activity of acetylcholine (I) and its amide analogs: linear (IIb) and circular (IIIb).

According to the data of theoretical conformational analysis, in the amide IIb a trans-conformation of the fragment N–C–C–$\overset{+}{N}$ predominates, while in the amide IIIb this fragment is practically fixed in a gauche conformation.

On the basis of the results obtained we hypothesized that in the interaction of I and its amide analogs IIb and IIIb with nicotine cholinoreceptors, the gauche-conformation of the fragments O–C–C–$\overset{+}{N}$ (in I) and N–C–C–$\overset{+}{N}$ (in IIb and IIIb) is active.

Continuing investigations along this line, we synthesized other linear and circular compounds with various acyl radicals (IIa, c, d and IIIa, c, d).

$$\underset{\text{IV}}{Me_2NCH_2CH_2NH_2} \longrightarrow \underset{\text{VI a-d}}{Me_2NCH_2CH_2NHCOR} \longrightarrow \underset{\text{II a-d}}{I^-Me_3\overset{+}{N}CH_2CH_2NHCOR}$$

$$\underset{\text{V}}{MeN(CH_2CH_2)_2NH} \longrightarrow \underset{\text{VII a-d}}{MeN(CH_2CH_2)_2NCOR} \longrightarrow \underset{\text{III a-d}}{I^-Me_2\overset{+}{N}(CH_2CH_2)_2NCOR}$$

a: R = H; b: R = Me; c: R = Et; d: R = Pr

Compounds IIa, c, d and IIIa, c, d were produced analogously to the diamine (IV) and N-methylpiperazine (V) AcOCHO or acid chlorides, followed by quaternization of the intermediate amides (VIa-d and VIIa-d) MeI.

The methiodides IIa-d and IIIa-d were tested for nicotinomimetic and muscarinomimetic activity.

A comparison of the cholinomimetic activity of IIa-d and IIIa-d with the same acyl radicals can be used to study the active conformation of the N–C–C–$\overset{+}{N}$ fragment of cholinomimetics.

EXPERIMENTAL CHEMISTRY

Dimethyl-β-formylaminoethylamine (VIa) and N-Methyl-N'-formylpiperazine (VIIa). To 0.1 M IV or V, 2.65 M 85% HCOOH is added gradually with mixing, and then over a period of 10 min, 0.4 M Ac_2O. The reaction mixture is exposed at 80-90°C for 1 h. The excess HCOOH and Ac_2O are distilled off. The residue is extracted with $CHCl_3$ and dried with $MgSO_4$. After the removal of $CHCl_3$, the residue is redistilled under vacuum. Yield 9.7 g (85%) VIa, bp 129-132°K/8 mm, and 10.8 g (83%) VIIa, bp 118-120°C/17 mm.

Dimethyl-β-propionylaminoethylamine (VIc), N-Methyl-N'-propionylpiperazine (VIIc), Dimethyl-β-butyrylaminoethylamine (VId), and N-Methyl-N'-butyrylpiperazine (VIIb). To a solution of 0.2 M IV or V in anhydrous toluene, a solution of 0.2 M propionyl chloride or, correspondingly butyryl chloride in anhydrous toluene is added with mixing over a period of 30 min. The mixing is continued for another 1 h. The hydrochloride salts formed are filtered off. The bases are isolated by the addition of a saturated solution of potash to an aqueous solution of the hydrochlorides, separated, and dried over alkali. They are redistilled under vacuum. Yield 19.5 g (67.7%) VIc, bp 135-136°C/8 mm; 18.6 g (60%) VIIc, bp 130-132°C/10 mm; 19.3 g (61%) VId, bp 137-188°C/10 mm; and 20.9 g (61.5%) VIId, bp 132-134°C/8 mm.

Scientific-Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR. I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR, Leningrad. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 6, pp. 689-691, June, 1984. Original article submitted June 14, 1983.

0091-150X/84/1806-0401$08.50

Production of Methiodides (IIa, c, d, and IIIa, c, d). To 0.03 M tertiary base VIa, VIIa, d in anhydrous ethanol, the base VIc, VIIc in anhydrous MeOH, or the base VId in anhydrous ether, 0.06 M MeI is added. The mixture is left overnight at room temperature. The precipitates formed are filtered and crystallized.

Dimethyl-β-formylaminoethylamine Methiodide (IIa). Yield 67%, mp 210-212°C (from MeOH). Found, %: C 27.91; H 5.65; N 10.87; I 49.14. $C_6H_{15}N_2IO$. Calculated, %: C 27.91; H 5.86; N 10.85; I 49.19.

N-Methyl-N'-formylpiperazine Methiodide (IIIa). Yield 70%, mp 208-209°C (from MeOH). Found, %: C 30.85; H 5.58; N 10.33; I 47.19. $C_7H_{15}N_2IO$. Calculated, %: C 31.11; H 5.60; N 10.37; I 47.00.

Dimethyl-β-propionylaminoethylamine Methiodide (IIc). Yield 77%, mp 97-98°C (from anhydrous ethanol). Found, %: C 33.82; H 6.59; H 9.91; I 44.20. $C_8H_{19}N_2IO$. Calculated, %: C 33.57; H 6.69; N 9.79; I 44.37.

N-Methyl-N'-propionylpiperazine Methiodide (IIIc). Yield 73%, mp 230-232°C (from MeOH). Found, %: C 36.11; H 6.39; N 9.29; I 42.88. $C_9H_{19}N_2IO$. Calculated, %: C 36.24; H 6.43; N 9.39; I 42.58.

Dimethyl-β-butyrylaminoethylamine Methiodide (IId). Yield 96%, mp 77-79°C (from anhydrous ethanol). Found, %: C 36.46; H 7.25; N 9.06; I 41.87. $C_9H_{21}N_2IO$. Calculated, %: C 36.00; H 7.05; N 9.33; I 42.29.

N-Methyl-N'-Butyrylpiperazine Methiodide (IIId). Yield 87%, mp 165-168°C (from anhydrous ethanol). Found, %: C 38.74; H 6.92; N 8.96; I 40.82. $C_{10}H_{21}N_1IO$. Calculated, %: C 38.46; H 6.78; N 8.97; I 40.67.

EXPERIMENTAL PHARMACOLOGY

In experiments on the rectus abdominis muscle of the frog *Rana temporaria*, the N-cholinomimetic activity of the compounds was determined by the method of recording the cumulative concentration versus effect curves [2] in an isotonic system. The average value of the maximum activity (ME; "internal" activity according to Ariens), i.e., the ratio of the height of its maximum possible contraction (according to KCl), was calculated according to the results of experiments on 10 muscles. The average value of EK_{50}, the concentration of the substance under the action of which contraction of the muscle to an extent of 50% of the maximum induced by the same substance was observed, was also calculated.

The muscarinomimetic activity was determined in experiments on the longitudinal muscle of the small intestine of a guinea pig by the method of recording discrete curves in an isometric system. The nicotine cholinoreceptors of the intestine were blocked with hexonium in a concentration of $2 \cdot 10^{-4}$ M. The ME and EK_{50} were calculated according to the results of experiments on four mice. The effect of all the investigated substances in the experiments on the intestines was competitively blocked by atropine. This served as evidence that their effect is due to an action on the muscarine receptors, and not some other receptors.

The results of the pharmacological investigations are cited in Table 1.

RESULTS AND DISCUSSION

The results obtained show that both for linear compounds IIa-d and for circular compounds IIIa-d the activity changes appreciably with changing acyl radical. In this case the greatest activity is possessed by the acetyl derivative with a piperazine ring (IIIb), in which, just as in I, R = Me. This pertains both to the nicotine and to the muscarine activities.

We should make special note of the fact that in all cases, regardless of the size of the radical R, closing of the piperazine ring (transition from trans- to gauche-conformation of the fragment $N-C-C-\overset{+}{N}$) leads to an extremely substantial increase in the nicotine and muscarine activities (by one and two orders of magnitude).

Thus, on the basis of the results obtained, we can hypothesize that the gauche-conformation of the fragment $N-C-C-\overset{+}{N}$ is optimum both for nicotine and for muscarine cholinomimetics.

The significance of the gauche-conformation for the nicotine activity increases with increasing size of the radical R; the ratio of the activities increases from 44 (at R = H) to 315 (at R = Pr).

TABLE 1. Nicotino- and Muscarinomimetic Activity of Compounds IIa-d and IIIa-d

Compound	N-Mimetic activity		M-Mimetic activity	
	EK_{50}, moles/liter	activity ratio*	EK_{50}, moles/liter	activity ratio*
IIa	$2{,}0\cdot10^{-4}$	44	$6{,}0\cdot10^{-4}$	3
IIIa	$4{,}5\cdot10^{-6}$		$2{,}0\cdot10^{-4}$	
IIb	$1{,}3\cdot10^{-4}$		$1{,}0\cdot10^{-4}$	100
IIIb	$1{,}1\cdot10^{-6}$	118	$1{,}0\cdot10^{-6}$	
IIc	$2{,}8\cdot10^{-4}$	175	$2{,}0\cdot10^{-4}$	10
IIIc	$1{,}6\cdot10^{-6}$		$2{,}0\cdot10^{-5}$	
IId	$6{,}3\cdot10^{-4}$	315	$3{,}0\cdot10^{-4}$	60
IIId	$2{,}0\cdot10^{-6}$		$5{,}0\cdot10^{-6}$	

*The activity ratio of the circular compound IIIa-d to the activity of the linear compound IIa-d with the same acyl radicals.

The conformational influence on the muscarinomimetic activity is a maximum at R = Me; in the sequence from compound IIa to compound IIIa there is a 100-fold increase in the muscarinomimetic activity.

LITERATURE CITED

1. N. V. Khromov-Borisov, A. F. Danilov, L. N. Aleksandrova, et al., Dokl. Akad. Med. Nauk SSSR, 230, No. 5, 1250-1253 (1976).
2. E. I. Ariens, Arch. Int. Pharmacodynam., 99, 32 (1954).
3. C. C. Price, G. Kabas, and J. Naketa, J. Med. Chem., 8, 650 (1965).

β-AMINO KETONES — α-AMINO ACID DERIVATIVES.

IV. AMINOMETHYL DERIVATIVES OF ACETOPHENONES AND THEIR BIOLOGICAL ACTIVITY

A. G. Agababyan, G. A. Gevorgyan, L. K. Durgaryan, É. V. Vlasenko, R. V. Agababyan, Yu. Z. Ter-Zakharyan, A. E. Tumadzhyan, N. A. Apoyan, and O. L. Mndzhoyan

UDC 615.274+615.212.3+615.281]:547.477.5

As we have previously shown [1], many β-amino ketones — derivatives of α-amino acids — display antiinflammatory, antipyretic, and bactericidal properties. In a continuation of our research on the synthesis and study of the biological activity of amino ketones — α-amino acid derivatives [2-4] — we have obtained a number of β-amino ketones, viz., serine, threonine, valine, and leucine derivatives, and have studied their antibacterial, local-anesthetic,and antiinflammatory properties.

The hydrochlorides of N-[β(p-substituted benzoyl)ethyl] amino acids (I-VI) and ethyl esters (VII, VIII) were obtained via the Mannich reaction [2, 4].

$$n\text{-}RC_6H_4COCH_2CH_2A$$

I—VIII

I: R = H; K = NHCH(COOH)$CH(CH_3)_2$; II: R = CH_3O; A = = NHCH(COOH)$CH(CH_3)_2$; III: R = H; NHCH(COOH)$CH_2CH(CH_3)_2$; IV: R = CH_3O;

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan.

Translated from Khimiko-farmetsevticheskii Zhurnal, Vol. 18, No. 6, pp. 691-697, June, 1984. Original article submitted August 22, 1983.

0091-150X/84/1806-0403$08.50