Replacement of hydrogen in the amino-group of (I) by diacetyl (Va) or dichloroacetyl (Vb) reduced the toxicity of the compound considerably (MTD = 3500 mg/kg). In a dose of 200 mg/kg, (Va) showed significant antitumor activity against sarcoma 45 (I% = 58.6, $\alpha > 0.99$), without any marked toxic effects (GC −3.3%). However, (Vb) showed no antiblastic activity against this tumor. Neither compound was active in rats with Pliss lymphosarcoma, and were of low activity (30%) against Walker carcinosarcoma. In a dose of 400 mg/kg, (Va) inhibited the growth of sarcoma 180 by 55.5% ($\alpha > 0.95$). The compounds were ineffective against Ehrlich carcinoma.

Of these spirodihydronaphthalenes, therefore, (IV) and (VIb) show some psychotropic activity. Compound (IV) (a spironaphthalene with an imino-group in the 4-position and bromine in position 3) showed test activity characteristic of compounds which excite the central nervous system, namely excitation of behavior, enhancement of the effects of 5-HT, and antagonism to the effects of reserpine. Replacement of the imino-group in the 4-position by an amide group, and absence of bromine in the 3-position results in the appearance of properties characteristic of compounds which inhibit the central nervous system, such as behavioral depression, hypothermia, extension of hexenal sleep, and antagonism to the effects of 5-HT and apomorphine. Both compounds weakly inhibited the effects of MAO on 5-HT.

These studies have shown that of the three spirodihydronaphthalenes the compound with a diacetyl group (Va) is relatively effective as an antitumor agent.

LITERATURE CITED

1. R. A. Kuroyan, A. I. Markosyan, A. Sh. Oganisyan, and M. G. Oganisyan, Arm. Khim. Zh., No. 8, 527-529 (1989).
2. G. N. Pershin (ed.), Methods of Experimental Chemotherapy [in Russian], 2nd edn., Moscow (1971).
3. R. R. Safrazbekyan and R. S. Sukasyan, Biol. Zh. Armen., 22, No. 10, 43-49 (1969).
4. R. R. Safrazbekyan and É. M. Arzanunts, ibid., 25, 102-106 (1972).
5. R. R. Safrazbekyan and É. M. Arzanunts, ibid., 42-48.
6. R. R. Safrazbekyan and D. Z. Partev, ibid., 37, No. 2, 159-161 (1984).
7. M. Negwer, Organic Chemical Drugs and Their Synonyms, Berlin (1987), Vols. 1-3.

SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMINOACETYL DERIVATIVES OF PYRROLE AND INDOLE

M. V. Mezentseva, I. N. Nesterova, I. S. Nikolaeva, E. G. Golovanova, O. V. Baklanova, and L. N. Filitis

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Acetanilide is known to have a wide spectrum of biological activity [3, 5, 8], including antiviral activity [9]. For this reason we have synthesized derivatives of pyrrole and indole, with alkylaminoacetylamino groups at the 2 and 3 position of the ring, and we have studied the biological activity of these compounds. As starting material we used 2- and 3-aminopyrroles [2, 6, 7], and indoles [1]. Methylation of 2-amino-3-cyano-4,5-tetramethylenepyrrole (I) with dimethylsulfate gave 1-methyl-2-amino-3-cyano-4,5-tetramethylenepyrrole (II). Comparing the PMR spectrum of compound II with the spectrum of the starting material I, the signal of the 2-NH_2 protons is shifted to the stronger field at 3.69 ppm, the signal from the proton at position 1 is absent, and a singlet due to the CH_3 appears at 3.25 ppm. (Formula, top, following page.)

The 2- and 3-aminopyrroles and indoles were converted to the chloroacetyl derivatives (III-X) by reaction with chloroacetylchloride either in benzene or acetone in the presence of an equimolar amount of pyridine or Et_3N at 0-10°C, or in refluxing benzene without an HCl acceptor.

The IR spectra of compounds III-X contain absorptions due to the stretching vibrations of the amide C=O group at 1660-1700 cm^{-1}, while for compounds V, VI, IX, and X the C=O group

S. Ordzhonikidze All-Union Research Institute of Chemistry and Physics, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 6, pp. 21-23, June, 1991. Original article submitted March 11, 1989.

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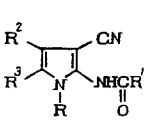
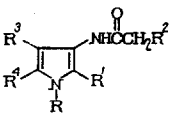


III-VII, XI-XXIII



VIII-X, XXIV-XXVI, XXVII-XXIX

R=H (III, VI — IX, XI — XVI, XVIII — XX, XXIV — XXVI, XXIX), Me (IV, X, XVII, XXI — XXIII, XXVII, XXVIII), Ac (V); R^1=CH_2Cl (III — VII), Ph (VIII, XXIV), (3-cyano-4,5-tetramethylpyrrol-2-yl)aminocarbonyl(XI), COOEt (IX, X, XII, XXV — XXIX); CH_2-morpholino(XIII, XVII, XVIII) CH_2-piperidino(XV, XIX, XXIII); CH_2 (N, N — hexamethylamino) (XX, XXII); $CH_2NHCHMe_2$ (XIV), CH_2NEt_2 (XVI), CH_2NHMe (XXI); R^2=Me (VI, VII, XVIII — XX), Cl (VIII — X), NEt_2 (XXIV, XXV, XXVII), N-phenylpiperazino(XXVI, XXVIII), SPh (XXIX); $R^2+R^3=(CH_2)_4$ (III — V, XI — XVII, XXI — XXIII); R^3=COOEt (VI, XVIII — XX), Me (VII), H (VIII, XXIV); R^4=Ph (VIII, XXIV); $R^3+R^4=(CH)_4$(IX, X, XXV — XXIX).

gives rise to a second peak at 1650-1680 cm^{-1}; the NH group stretching vibrations absorb at 3250-3330 cm^{-1}. For compounds III-VI, the conjugated C=N group absorbs strongly at 2210-2240 cm^{-1}.

The UV spectra of the chloroacetyl derivatives III, V, and VI show strong absorptions at 294-296 nm; for compound IV the absorption maximum undergoes a hypsochromic shift of 32 nm.

Acylation of compound I with oxalylchloride in pyridine gave a product resulting from the simultaneous acylation of two molecules of 2-aminopyrrole by one molecule of oxalylchloride (XI). The structure of this compound was confirmed by elemental analysis and molecular weight data ($M^{+\cdot}$ 376, mass spectrometrically) and from the IR spectrum, which shows a peak at 1660 cm^{-1}, characteristic of the amide carbonyl group. Carrying out the reaction in ether gave the acyl derivative, which reacted with alcohol to give 2-ethoxalylamino-3-cyano-4,5-tetramethylenepyrrole (XII). The IR spectrum of this compound showed absorption bands at 3330, 3300, 3260 cm^{-1} (NH) and at 1730, 1700, 1680 cm^{-1} (C=O).

The reaction of compounds III-X with secondary amines gave aminoacetyl derivatives of pyrrole and indole (XIII-XXVIII). It should be noted that the replacement of the chlorine by an amino group proceeds more readily with the 2-substituted pyrroles than with the 3-substituted compounds. The reaction of compound V with an amine resulted in the removal of the acyl group at position 1. Heating compound IX with thiophenol in alcoholic KOH solution gave thiophenylacetylaminoindole (XXIX).

The work was carried out under the guidance of Professor A. N. Grinev.

EXPERIMENTAL (CHEMICAL)

IR Spectra of the compounds in mineral oil were taken on a Perkin–Elmer 599 (USA), UV spectra on a Perkin–Elmer 575 (Sweden) using alcohol as solvent. PMR spectra were recorded on a Jeol JNM-4H-100 (Japan), internal standard – TMS. Mass spectra were obtained on a Varian MAT-112 (FRG). The course of the reaction was monitored chromatographically using Silufol UV-254 plates developed with 1:1 benzene–ethyl acetate and visualized in UV light.

Physical data for compounds II-VI, VIII-XXIX are given in Table 1.

Elemental analysis and molecular weight data were in good agreement with calculated values.

1-Methyl-2-amino-3-cyano-4,5-tetramethylenepyrrole (II). To a suspension of I (2.83 g, 17 mmole) in dioxane (15 ml) was added a hot solution of NaOH (3.5 g) in water (10 ml). The mixture was stirred for 2-3 min, and dimethylsulfate (3.3 ml, 35 mmole) added dropwise. After mixing for a further 2 h at 20°C it was poured into water, and the oil which separated on cooling recrystallized. IR spectrum, ν_{max}, cm^{-1}: 3410, 3340, 3240, 3180 ($N-H_2$), UV spectrum, λ_{max}, nm (log ε): 267 (3.97). PMR spectrum ($CDCl_3$): 1.75 m (4H, β, γ-CH_2), 2.38 m (4H, α, δ-CH_2), 3.25 s (3H, CH_3), 3.69 s (2H, NH_2).

Derivatives of 2- and 3-Chloroacetylaminopyrrole and Indole (III-VI), (VIII-X)* A. To a stirred solution of the corresponding amine (150 mmole), dry acetone (300 ml), and dry pyri-

*Compound VII was described in [8].

TABLE 1. Physical Characteristics for Compounds II-VI, VIII-XXIX

Compound	Yield[a], %	MP, °C	Empirical formula
II	87	140—1	$C_{10}H_{13}N_3$
III	82	234—5	$C_{11}H_{12}ClN_3O$
IV	48	179—80	$C_{12}H_{14}ClN_3O$
V	63,5	118—20	$C_{13}H_{14}ClN_3O_2$
VI	95,7	195—6	$C_{11}H_{12}ClN_3O_3$
VIII	78,9	158—60	$C_{16}H_{15}ClN_2O$
IX	80	187—8	$C_{13}H_{13}ClN_2O_3$
X	84	182—3	$C_{14}H_{15}ClN_2O_3$
XI	25,4	>360	$C_{20}H_{20}N_6O_2$
XII	50	160—1	$C_{13}H_{15}N_3O_3$
XIII	88	168—70	$C_{15}H_{20}N_4O_2$
XIV	64,7	137—8	$C_{14}H_{20}N_4O_2$
XV	78,5	205—6	$C_{16}H_{22}N_4O$
XVI	60,7	132—3	$C_{15}H_{22}N_4O$
XVII	88,8	164—5	$C_{16}H_{22}N_4O_2$
XVIII	71,9	128—9	$C_{18}H_{20}N_4O_4$
XIX	90,3	168—9	$C_{16}H_{22}N_4O_3$
XX	97,3	140—2	$C_{17}H_{24}N_4O_3$
XXI	80,8	135—6	$C_{13}H_{18}N_4O$
XXII	90,7	109—10	$C_{18}H_{26}N_4O$
XXIII	85,6	119—20	$C_{17}H_{24}N_4O$
XXIV	100	272—4 (with decomp.	$C_{22}H_{25}N_3O \cdot HCl$
XXV	50	242 with decomp.	$C_{17}H_{22}N_3O_3 \cdot HCl$
XXVI	100	235 with decomp.	$C_{23}H_{25}N_4O_3$
XXVII	20	160—1	$C_{18}H_{25}N_3O_3 \cdot HCl$
XXVIII	100	131—2	$C_{24}H_{27}N_4O_3$
XXIX	70	176—7 (with decomposition)	$C_{19}H_{18}N_2O_3S$

*Compounds were recrystallized as follows: II and XXIX from aqueous alcohol, III-VI, XVIII-XXIII from ethyl acetate, VIII from benzene, IX from a 1:1 mixture of acetone and water, X from acetone, XI from DMF, XII from alcohol, XIII, XIV, XVI from a mixture of benzene and hexane, XVII from a mixture of ethyl acetate and hexane, XXIV, XXV, XXVII from a mixture of acetone, MeOH, and ether, XXVI, XXVIII from MeOH.

dine (150 mmole) at 0°C was added dropwise chloroacetyl chloride (180 mmole). The mixture was maintained at this temperature for 20 min followed by 30 min at 20°C, and then poured into water to give III, IV, VI, IX, and X.

B. To a stirred solution of the amine (20 mmole) [2] in dry acetone (200 ml) and Et_3N (20 mmole) at 10°C, chloroacetylchloride (20 mmole) was added dropwise. The mixture was maintained for 1 h at 20°C, followed by 1 hour at reflux temperature, then cooled, and poured into water to give VIII.

C. To a stirred solution of the corresponding amine (30 mmole) [6, 7] in dry benzene (150 ml) was added chloroacetylchloride (33 mmole). The mixture was then refluxed for 3 h, the solvent evaporated, the residue filtered to give V and VI.

N,N-bis(3-cyano-4,5-tetramethylenepyrrole-2-yl)oxalylamine (XI). To a solution of I (3.22 g, 24 mmole) in dry pyridine (25 ml) with cooling and mixing, oxalylchloride (3.2 g, 24 mmole) was slowly added dropwise at 7-10°C. The precipitated material was filtered and washed with methanol to give XI.

2-Ethoxalylamino-3-cyano-4,5-tetramethylenepyrrole (XII). To a solution of I (1.61 g, 10 mmole) in dry ether (200 ml) at 0-5°C was added dropwise oxalyl chloride (1.99 g, 15 mmole) in dry ether (30 ml). The reaction mixture was left for 20 h at 20°C, and the solvent evaporated. The residue was refluxed in alcohol for 20 min to give XII.

Aminoacetyl Derivatives of Pyrrole and Indole (XIII-XXVIII). A. To a suspension of the corresponding compound III-VI (6 mmole) in dry benzene (10 ml) was added the amine (12 mmole). After 20 hours at room temperature, the precipitated material was filtered off, and the mother liquor evaporated under vacuum. Water was added to the residue, and the precipitate filtered, and washed with water to yield XIII-XXIII.

B. A mixture of VIII, IX, or X (0.8 mmole) in dry benzene (20 ml) and the corresponding amine (1.6 mmole) was refluxed for 5 h. The precipitated material was filtered off, the mother liquor evaporated under vacuum. The precipitate was recrystallized to give XXVI and XXVIII. Compounds XXV, XXVII were isolated as the hydrochlorides in the usual manner.

2-Ethoxycarbonyl-3-phenylthioacetylaminoindole (XXIX). To a mixture of KOH (0.56 g, 1 mmole) in alcohol (10 ml) and thiophenol (0.51 ml, 0.5 mmole) was added 2-ethoxycarbonyl-3-chloroacetylaminoindole IX (1.2 g, 0.5 mmole) in alcohol (20 ml). After 1 h at 20°C and 1 h under reflux, the mixture was cooled, and the precipitate filtered off to give XXIX.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activity of the compounds against influenza A virus A/PR8/34 (HONI) was studied. The virucidal action of the compound on the influenza virus was studied by mixing equal volumes of solutions or suspensions of the compounds with 1, 10, and 100% embryonic infecting doses (EID_{100}). The mixture was kept at 14°C for 1 h and then injected into the allantoic cavity of 9-day-old chick embryos in 0.2 ml amounts. These were kept in a thermostat for 48 h at 37°C and the activity of the compound on the allantoic fluid of the chick embryos was determined by titration of the virus using the hemagglutination reaction. The activity of the compounds was expressed by the quantity of neutralized EID_{100} of the influenza virus.

Compound VIII exhibited weak virucidal activity – it reduced the infection titer of the virus by 1.0 log EID_{100} when used in concentrations of 1000 μg/ml. The remaining compounds were found to be inactive.

The antibacterial and antifungal activities of the compounds were tested in vitro as described in [4] against Gram-positive and Gram-negative bacteria and pathogenic fungii. These studies showed that compound VIII in concentrations of 15.6 μg/ml inhibited the growth of staphylococcus aureus and hemolytic streptococcus. Compound XXII in concentrations of 62.5 μg/ml suppressed the growth of acid-resistant tuberculosis mycobacteria (type $H_{37}R_V$). Compounds III, V, and VII, at concentrations of 31.2-62.5 μg/ml, exhibited moderate activity against dermatophytic fungii.

Compounds III and VII showed high bacteriostatic activity against tuberculosis bacilli, with a minimum suppressing concentration of 2.0-0.12 and 0.06-0.5 μg/ml in a series of serial dilutions in Soton's medium. On addition to the medium of 10% horse serum, the activity of these compounds was lowered to 64 and 125 μg/ml respectively. Tolerance of compounds III and VII was determined by a single daily injection into the stomach of white non-pedigree male mice weighing 18-20 g over a period of 5 days. It was determined that the maximum endurable dose for mice for compound III was 1000 mg/kg, and for compound VII – >2000 mg/kg.

LITERATURE CITED

1. O. N. Boyarintseva, Dissertation for the Degree of Candidate in Chemistry, Moscow (1976).
2. A. N. Grinev, M. V. Mezentseva, E. F. Kuleshova, and L. M. Alekseeva, Khim. Geterosikl. Soedinen., No. 3, 612-615 (1986).
3. V. Ya. Grinshtein, A. A. Prikulis, and B. A. Grinberg, Khim.-farm. Zh., No. 2, 51-54 (1977).
4. Methods of Experimental Chemotherapy [in Russian], G. N. Pershin (ed.), 2nd edn., Moscow (1971), p. 100.
5. E. M. Cherkasova, N. T. Pryanishnikova, S. V. Bogatkov, and G. S. Erkomaishvili, Usp. Khim., 42, 1892-1919 (1973).
6. V. I. Shvedov, M. V. Mezentseva, L. B. Altukhova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 3, 380-382 (1974).
7. V. I. Shvedov, M. V. Mezentseva, A. N. Grinev, and A. M. Ermakov, ibid., No. 12, 1677-1681 1681 (1976).
8. R. W. Johnson, T. H. Keenan, J. W. Kosh, and J. W. Sowell, J. Pharm. Sci., 68, No. 3, 317-324 (1979).
9. F. M. Schabel, W. Lacter, R. Brockman, and H. Skipper, Proc. Soc. Exp. Biol., (N.Y.), 83, 1-9 (1953).