Chemistry of Natural Compounds, Vol. 47, No. 4, September, 2011 [Russian original No. 4, July-August, 2011]

DERIVATIVES OF THE ALKALOID CONVOLVINE AND THEIR PHARMACOLOGICAL ACTIVITY

A. M. Gapparov, I. I. Okhunov, S. F. Aripova,*
A. Nabiev, and V. U. Khuzhaev

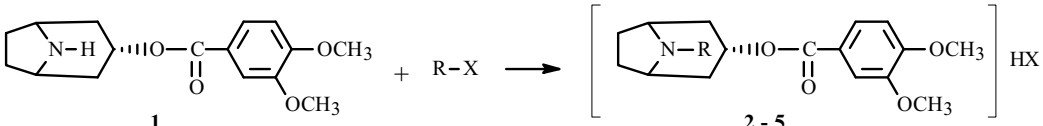
UDC 547.944/945

A series of new convolvine derivatives based on the alkaloid from Convolvulus subhirsutus *and* C. pseudocanthabrica *were synthesized using alkylhalides and aliphatic and aromatic acid chlorides. Results of biological tests showed that convolvine and its derivatives exhibited pronounced antihypoxic, immunomodulating, and anti-inflammatory activity.*

Keywords: convolvine, derivatives, biological activity.

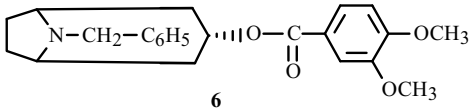
The aerial parts of *Convolvulus subhirsutus* and *C. pseudocanthabrica* growing in Uzbekistan [1] have previously yielded 10 alkaloids [2–7] that were tropane derivatives, the principal ones being convolvine and convolamine with a content of 45–50% of the total alkaloids. A quantitative determination found that the content of the alkaloid mixture in the aerial part was 0.6%; in the roots, 1.6% of the dry plant weight.

The convolvine content in *C. subhirsutus* and *C. pseudocanthabrica* reaches 0.3% in the aerial part; 0.7%, in roots. As a result of the availability of convolvine, a series of its derivatives were prepared. Their pharmacological properties were studied in a search for compounds with valuable pharmacological activity. For this, convolvine (**1**) was reacted with alkyl halides (methyliodide, hexylbromide, amylbromide, nonylbromide, benzylchloride) to produce the corresponding derivatives *N*-methylconvolvine hydroiodide (**2**), *N*-amylconvolvine hydrobromide (**3**), *N*-hexylconvolvine hydrobromide (**4**), *N*-nonylconvolvine hydrobromide (**5**), and *N*-benzylconvolvine (**6**) according to the scheme:



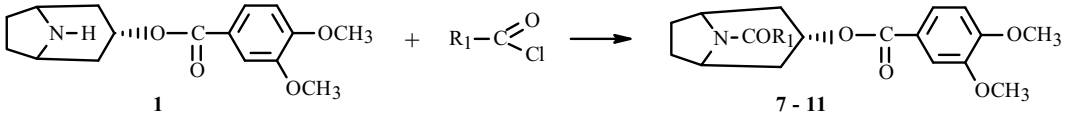
1 **2 - 5**

2: R = CH_3, X = I; **3:** R = C_5H_{11}, X = Br
4: R = C_6H_{13}, X = Br; **5:** R = C_9H_{19}, X = Br



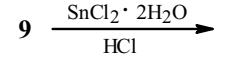
6

Convolvine was also reacted with aliphatic and aromatic acid chlorides to produce *N*-benzoylconvolvine (**7**), *N*-chloroacetylconvolvine (**8**), and *N*-4′-nitrobenzoylconvolvine (**9**), reduction of **9** produced *N*-4′-aminobenzoylconvolvine (**10**), and *N*-naphthoylconvolvine (**11**):



1 **7 - 11**

R_1 = C_6H_5 (**7**); CH_2Cl (**8**); $C_6H_4NO_2$-4 (**9**); $C_6H_4NH_2$-4 (**10**); $C_{10}H_7$ (**11**)



S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences, Republic of Uzbekistan, 100170, Tashkent, fax (99871) 120 64 75, e-mail: salima_aripova@mail.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, July–August, 2011, pp. 539–541. Original article submitted January 31, 2011.

 0009-3130/11/4704-0608

The pharmacological properties of the 10 synthesized convolvine derivatives were studied.

The activity of alkaloids from *Convolvulus* plants on oxygen metabolism in tissue and oxygen transport *in vivo* was investigated in animals. An oxygen deficiency *in vivo* (hypoxia) was simulated by injection to mice of sodium nitroprusside or sodium nitrite. The activity of *Convolvulus* alkaloids and several of their synthetic derivatives on a hypoxia model induced by sodium nitrite was studied. The results showed that the most active compound from the *Convolvulus* alkaloids was the *bis*-derivative of convolvine convolvidine (60.8%) in addition to convolicine (54.8%), *N*-chloroacetylconvolvine (50.5%), and *N*-benzylconvolvine (50.5%), and then the other alkaloids. Therefore, convolvine derivatives exhibit higher antihypoxic activity than the starting alkaloid.

Several infectious and somatic diseases are known to be associated with lowered resistance to various external factors, including medicines. Therefore, the activity of *Convolvulus* alkaloids and their derivatives was studied with this in mind. Medicinal immunosuppression was induced by a single injection of hydrocortisone to white mice. This induced sharp changes of the thymic-lienal immunity system by the 10^{th} day of treatment. A reliable mass decrease of the thymus gland by 28.6% was found in this series of tests after injection of hydrocortisone (HC) immunosuppressor hormonal preparation by the 10^{th} day of treatment with the tested compounds. Changes were noted in the spleen, kidneys, and adrenals. The bis-derivative of convolvine was the most active with respect to the thymus gland and prevented mass reduction by 24%. The second most active was *N*-chloroacetylconvolvine. It this instance the effect was 8.6%. Next in line was convolvine. Therefore, *Convolvulus* alkaloids and their derivatives exhibited immunostimulating activity against medicinal immunosuppression.

The anti-inflammatory activity of the compounds was studied using the classical inflammation model induced by formalin. The anti-inflammatory activity of the tested compounds used the formalin edema model in mice. The mass volume of the paw increased in this series of tests upon injection of formalin by 67.3% relative to the control. Animals that received *N*-chloroacetylconvolvine, the *bis*-derivative of convolvine, and convolvine had inflammation volumes that decreased by 42.3, 31.0, and 25.0%, respectively. A definite trend was observed with respect to the thymic-lienal immunity system. The most active compound for the formalin model was convolvine, then *N*-chloroacetylconvolvine and the *bis*-derivative of convolvine. A direct correlation was noted with respect to the spleen. In this instance convolvine took first place and then *N*-chloroacetylconvolvine and the *bis*-derivative of convolvine. Therefore, the thymic-lienal immunity system played a significant role in the anti-inflammatory mechanism of action in addition to the local anti-edema activity. Apparently activation of tissue respiration, which was found earlier, was certainly involved in activation of the thymic-lienal system.

Thus, the results showed that convolvine and its derivatives exhibited antihypoxic, immunomodulating, and anti-inflammatory activity.

EXPERIMENTAL

***N*-Methylconvolvine Hydroiodide (2).** Convolvine (0.1 g, 0.34 mmol) in acetone (4 mL) in a round-bottomed flask was treated with methyliodide (0.02 mL, 0.35 mmol). The mixture was heated on a water bath at 60–70°C for 1 h and left at room temperature for 2 h. The resulting precipitate was filtered off and recrystallized from acetone:MeOH (4:1) to afford crystals (0.12 g, 81.5%) with mp 240–241°C, R_f 0.18 (system 1: $CHCl_3$:MeOH, 1:1).

IR spectrum (ν, cm^{-1}): 3426 (NH), 2931, 2906 [CH and CH_2 stretching vibrations (sv)], 2835 (NCH_3 sv), 1698 (O–CO conjugated with an aromatic ring), 1605, 1459 [CH_2 bending vibrations (bv)], 1454 (CH_3 bv), 1347, 865, 814 [3,4-disubstituted benzene ring (dbr)], 757 [CH_2 rocking vibrations (rv)].

PMR spectrum (CD_3OD, δ, ppm): 3.11 (3H, s, NCH_3), 3.81 (3H, s, Ar-OCH_3), 3.85 (3H, s, Ar-OCH_3), 4.53 (2H, m, H-1, 5), 5.25 (1H, t, H-3β), 7.00–7.65 (3H, m, H-Ar).

***N*-Amylconvolvine Hydrobromide (3).** Convolvine (0.1 g, 0.34 mmol) and amylbromide (0.04 mL, 0.33 mmol) under analogous conditions (heating for 3-4 h) afforded crystals (0.14 g, 78.4%) with mp 259–260°C, R_f 0.75 (system 1).

IR spectrum (ν, cm^{-1}): 3384 (NH), 2977 (NCH_2 sv), 2930 (CH and CH_2 sv), 2861 (OCH_3), 1702, 1266 (O–CO), 1595, 1513, 858, 826 (dbr), 762 (CH_2 rv).

PMR spectrum (CD_3OD, δ, ppm, J/Hz): 2.15 (3H, t, J = 5, $CH_2C\underline{H}_3$), 2.40 (3H, m, $C\underline{H}_2CH_3$), 3.24 (4H, $2CH_2$), 3.82 (3H, s, Ar-OCH_3), 3.85 (3H, s, Ar-OCH_3), 4.03 (2H, d, J = 6, NCH_2), 4.23 (2H, m, H-1, 5), 5.23 (1H, t, J = 2, H-3β), 6.98–7.62 (3H, m, H-Ar).

***N*-Hexylconvolvine Hydrobromide (4).** Convolvine (0.1 g, 0.34 mmol) and hexylbromide (0.05 mL, 0.34 mmol) under analogous conditions (heating for 2-3 h) afforded crystals (0.11 g, 82.0%) with mp 226–227°C, R_f 0.70 (system 1).

IR spectrum (ν, cm^{-1}): 3485 (NH), 2958, 2933 (CH and CH_2 sv), 2861 (OCH_3 sv), 1703, 1595, 1513, 1462, 1348 (CH_2 bv), 1267 (O–CO), 875, 826 (dbr), 763 (CH_2 rv). PMR spectrum (CD_3OD, δ, ppm, J/Hz): 2.16 (3H, t, J = 3, $CH_2C\underline{H}_3$), 2.36 (3H, m, $C\underline{H}_2CH_3$), 3.25 (6H, $3CH_2$), 3.82 (3H, s, Ar-OCH_3), 3.85 (3H, s, Ar-OCH_3), 4.01 (2H, m, NCH_2), 4.26 (2H, m, H-1, 5), 5.22 (1H, t, J = 4, H-3*β*), 7.00-7.62 (3H, m, H-Ar).

***N*-Nonylconvolvine Hydrobromide (5).** Convolvine (0.1 g, 0.34 mmol) and nonylbromide (0.06 mL, 0.34 mmol) under analogous conditions (heating for 3–4 h) afforded crystals (0.12 g, 72.0%) with mp 264–265°C, R_f 0.45 (system 1).

IR spectrum (ν, cm^{-1}): 3414 (NH), 2930, 2876 (CH and CH_2 sv), 1702, 1600, 1509, 1459, 1443, 1375 (CH_2 bv), 1265 (O–CO), 872, 825 (dbr), 761 (CH_2 rv).

PMR spectrum (CD_3OD, δ, ppm, J/Hz): 2.18 (3H, t, J = 4, $CH_2C\underline{H}_3$), 2.38 (3H, m, $C\underline{H}_2CH_3$), 3.25 (6H, $3CH_2$), 3.82 (3H, s, Ar-OCH_3), 3.85 (3H, s, Ar-OCH_3), 4.02 (2H, m, NCH_2), 4.26 (2H, m, H-1, 5), 5.21 (1H, m, H-3*β*), 7.01–7.60 (3H, m, H-Ar).

***N*-Benzylconvolvine (6).** A mixture of convolvine (0.15 g) and benzylchloride (0.1 mL) was left at room temperature for 2 d. After this time the product was separated by treatment with acetone and purified over a column of Al_2O_3 to afford crystals (0.15 g, 78.9%) with mp 88–89°C.

IR spectrum (ν, cm^{-1}): 1746, 1602, 1583, 876, 829. PMR spectrum (CD_3OD, δ, ppm): 1.69–2.17 (8H, m, $4CH_2$), 3.18 (2H, m, H-1, 5), 3.48 (2H, s, CH_2), 3.74 (3H, s, Ar-OCH_3), 3.77 (3H, s, Ar-OCH_3), 5.12 (1H, t, H-3*β*), 6.89–7.58 (8H, m, H-Ar).

***N*-Benzoylconvolvine (7).** A mixture of convolvine (0.15 g) and benzoylchloride (0.1 g, 0.05 mL) was left at 5–10°C for 2 d and at room temperature for 1 d. The resulting precipitate was washed with benzene and purified over a column of Al_2O_3. Yield 0.16 g (80%), mp 138–139°C.

IR spectrum (ν, cm^{-1}): 1751, 1601, 1543, 878, 823.

PMR spectrum (CD_3OD, δ, ppm, J/Hz): 1.80–2.35 (8H, m, $4CH_2$), 4.06 and 4.78 (1H each, m, H-1, 5), 3.81 (2H, d, J = 3, CH_2), 3.84 (3H, s, Ar-OCH_3), 3.87 (3H, s, Ar-OCH_3), 5.30 (1H, t, H-3*β*), 6.98–7.62 (8H, m, H-Ar).

***N*-Chloroacetylconvolvine (8).** A mixture of convolvine (0.64 g) and chloroacetylchloride (0.2 g, 0.18 mL) was left at room temperature for 1 d. The resulting precipitate was washed with benzene and purified over a column of Al_2O_3. Yield 0.68 g (87.5%), mp 211–212°C.

IR spectrum (ν, cm^{-1}): 1704, 1600, 1514, 874, 829.

PMR spectrum (CD_3OD, δ, ppm, J/Hz): 1.77–2.27 (8H, m, $4CH_2$), 3.87 (3H, s, Ar-OCH_3), 3.89 (3H, s, Ar-OCH_3), 3.98 (2H, d, J = 3, CH_2), 4.24 and 4.65 (1H each, m, H-1, 5), 5.31 (1H, t, H-3*β*), 6.84–7.60 (3H, m, H-Ar).

***N*-(4′-Nitrobenzoyl)convolvine (9).** A mixture of convolvine (0.78 g) in acetone (4 mL) and *p*-nitrobenzoylchloride (0.48 g) was heated on a boiling-water bath for 2-3 h and cooled. The resulting precipitate was separated and purified over a column of Al_2O_3. Yield 0.074 g (67.2%), mp 175–177°C.

IR spectrum (ν, cm^{-1}): 1713, 1699, 1602, 1590, 1517, 1370, 880, 864.

PMR spectrum (CD_3OD, δ, ppm): 1.84–2.44 (8H, m, $4CH_2$), 4.12 and 4.65 (1H each, m, H-1, 5), 3.70 (3H, s, Ar-OCH_3), 3.78 (3H, s, Ar-OCH_3), 5.10 (1H, t, H-3*β*), 6.87–7.53 (7H, m, H-Ar).

***N*-(4′-Aminobenzoyl)convolvine (10).** A mixture of *N*-(4′-nitrobenzoyl)convolvine (0.078 g), $SnCl_2 \cdot 2H_2O$ (0.31 g), and conc. HCl (1 mL) was held at room temperature for 1 d. The resulting precipitate was separated and purified over a column of Al_2O_3. Yield 0.068 g (72.0%), R_f 0.7 ($CHCl_3$:MeOH, 20:1).

IR spectrum (ν, cm^{-1}): 3380, 1710, 1600, 1520, 1260, 885, 865.

PMR spectrum (CD_3OD, δ, ppm): 1.82–2.45 (8H, m, $4CH_2$), 4.11 and 4.63 (1H each, m, H-1, 5), 3.72 (3H, s, Ar-OCH_3), 3.80 (3H, s, Ar-OCH_3), 5.12 (1H, t, H-3*β*), 6.80–7.45 (7H, m, H-Ar).

***N*-Naphthoylconvolvine (11).** Convolvine (0.15 g) in acetone (3 mL) was treated with naphthoylchloride (0.095 g), heated on a boiling-water bath for 2-3 h, and cooled. The resulting precipitate was separated and purified over a column of Al_2O_3. Yield 0.152 g (78.0%) of amorphous product, R_f 0.65 (system 2).

IR spectrum (ν, cm^{-1}): 1775, 1707, 1630, 1510, 940 [sic], 881.

PMR spectrum (CD_3OD, δ, ppm): 1.72–2.36 (8H, m, $4CH_2$), 3.78 (3H, s, Ar-OCH_3), 3.81 (3H, s, Ar-OCH_3), 4.78 and 4.98 (1H each, m, H-1, 5), 5.97 (1H, t, H-3*β*), 6.96–7.94 (10H, m, H-Ar).

REFERENCES

1. *Flora of Uzbekistan* [in Russian], Vol. 5, Izd. Akad. Nauk UzSSR, Tashkent, 1961.
2. A. M. Gapparov, N. A. Razzakov, and S. F. Aripova, *Khim. Prir. Soedin.*, 242 (2007).
3. A. M. Gapparov, S. F. Aripova, N. A. Razzakov, and V. U. Khuzhaev, *Khim. Prir. Soedin.*, 601 (2008).
4. S. F. Aripova, E. G. Sharova, S. Yu. Yunusov, and A. Dzhabbarov, *Khim. Prir. Soedin.*, 245 (1983).
5. E. G. Sharova, S. F. Aripova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 672 (1980).
6. J. Parello, P. Longevialle, W. Vetter, and J. A. McLoskey, *Bull. Chim. Fr.*, **12**, 2787 (1963).
7. S. F. Aripova, V. M. Malikov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 290 (1977).