

HETEROCYCLES, Vol. 71, No. 1, 2007, pp. 19 - 25. © The Japan Institute of Heterocyclic Chemistry
Received, 7th July, 2006, Accepted, 6th November, 2006, Published online, 7th November, 2006. COM-06-10855

STEREOSELECTIVE MODIFICATION OF CYTISINE: T-REACTION FOR CONSTRUCTION OF BENZOANNELATED ANAGYRINE SKELETON

Konstantin A. Krasnov^a and Victor G. Kartsev^{b*}

^aMechnikov State Medical Academy, St. Petersburg, Russia

e-mail: veselkoff@mail.ru

^bInterBioScreen Ltd., Chernogolovka, Moscow, Russia

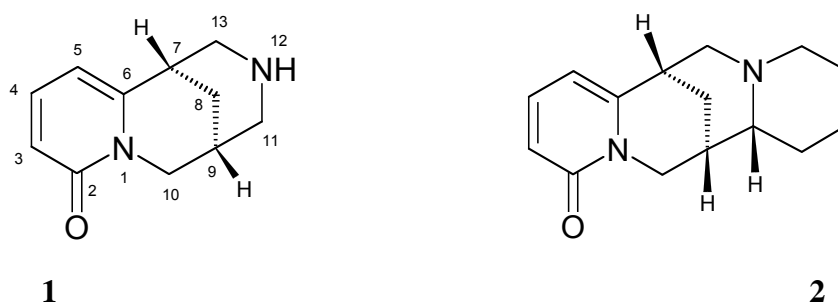
e-mail: vkartsev@ibscreen.chg.ru

Abstract – Three-step transformation of cytosine into a heterocyclic system closely related to the alkaloid anagyrine was achieved by using the T-reaction as a key stage. In this way, *N*-(2-formyl-4-nitro)cytosine (generated upon arylation of cytosine with 2-chloro-5-nitrobenzaldehyde) was condensed with 1,3-dimethylbarbituric acid to obtain a corresponding 5-arylidenebarbiturate. The latter was found to undergo stereoselective cyclization (T-reaction) into 1,3-dimethyl-5,13'-spiro-[5-nitro-2-(6-oxo-7,11-diazatricyclo[7,3,1,0^{2,7}]trideca-2,4-diene-11-yl)phenylmethylene]hexahydro-2,4,6-pyrimidinetrione containing a benzoannelated anagyrine skeleton. Subsequent alkaline hydrolysis of the spiro compound led to cleavage of the spiroimidine moiety followed by stereoselective decarboxylation to afford an enantiomerically pure carboxylic acid derivative of the benzoanagyrine series.

INTRODUCTION

Cytosine (**1**) is known as one of the most widely spread piperidine alkaloids. It has been isolated from *Cytisus laburnum*, other *Cytisus spp.*, from *Baptisia*, *Genista*, *Thermopsis*, etc. (*Leguminosae*).¹ Cytosine shows a nicotine-like CNS activity and is being used in medicine as a respiratory stimulant², despite its high toxicity (LD₅₀ 1.3 mg/kg, mus., ivn.).³

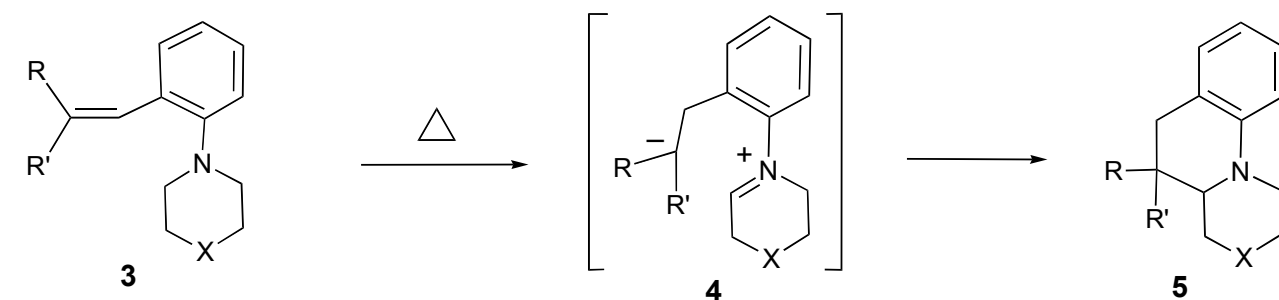
The alkaloid anagyrine (**2**), biogenetically close to cytosine (**1**), has been isolated from *Anagyris foetida*, some *Cytisus* species, etc. (*Leguminosae*).⁴ Anagyrine is known⁵ to act as an anti-arrhythmic, cardiotoxic, diuretic, and purgative agent.



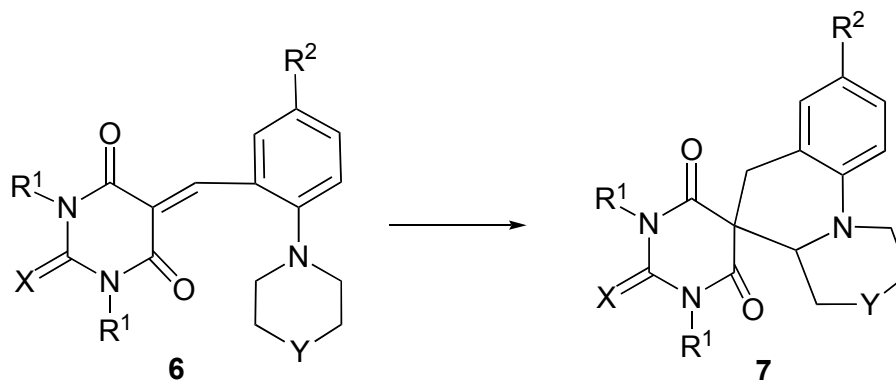
The structural similarity between alkaloids (**1** and **2**) suggests an attractive synthesis of pharmacologically valued anagryne derivatives from the commercially available cytisine. Until recently, such a transformation of **1** seemed inaccessible by standard methods of synthetic chemistry.

As is known, *o*-vinyl derivatives of tertiary aromatic amines (**3**) may undergo cyclization into respective 1,2,3,4-tetrahydroquinolines (**5**) via the so-called *tert*-amino effect (Scheme 1).⁶ Reactions of this type (T-reactions) involve hydrogen detachment from the α -position of the *tert*-amino function followed by cyclization of dipolar intermediate (**4**). Recently, we have found^{7,8} that the T-reaction of 5-arylidenebarbiturates (**6**) readily proceeds even at r.t. to afford spirocyclic derivatives (**7**).

In this work, we attempted to exploit the T-reaction in order to 'build on' a new system to a cytisine moiety.



R, R' = CN, COOMe; X = (CH₂)₂₋₀, NMe, O



R¹ = H, Me, Ph; R² = H, NO₂; X = O, S; Y = (CH₂)_{0,3}, O, NPh, or no bond

Scheme 1

RESULTS AND DISCUSSION

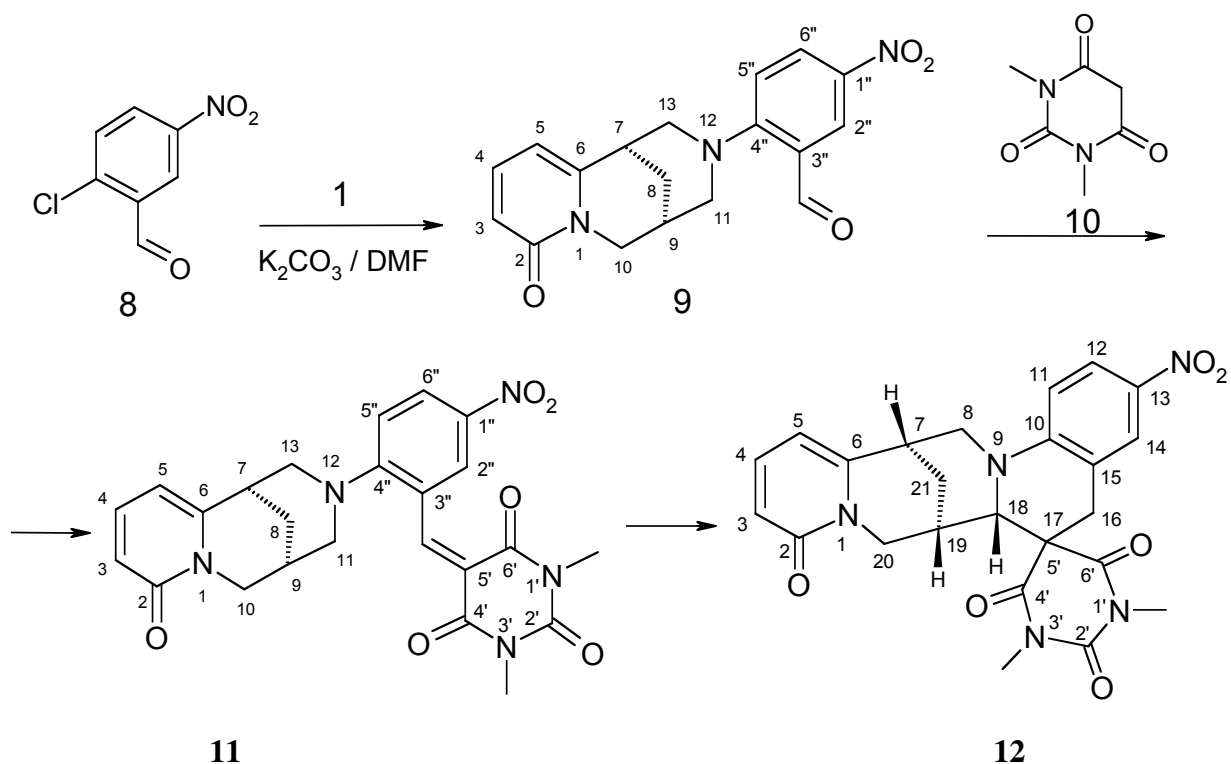
The nucleophilic reaction of the native (7*R*,9*S*) cytosine (**1**) with 2-chloro-5-nitrobenzaldehyde (**8**) was found to afford *N*-(2-formyl-4-nitrophenyl)cytosine (**9**) in a high yield. The Knoevenagel condensation of aldehyde (**9**) with 1,3-dimethylbarbituric acid (**10**) yielded *N*-(2-[2,4,6-trioxo-1,3-dimethylhexahydro-pyrimidino-5-methylene]-4-nitrophenyl)cytosine (**11**) which was then allowed to undergo the T-reaction. Theoretically, cyclization of the substrate (**11**) may be expected to proceed via attachment of the 11-H₂ or 13-H₂ group from the cytosine moiety and provide four possible isomers (two structural isomers and two diastereomers). We have found that the isomerization of **11** in chloroform, as well as in dimethylacetamide (DMAC), led (according to ¹H NMR and MS data) to a mixture of three isomers (all with M⁺ 477). In this mixture, compound (**12**) was predominant (77%), while minor products were present in amounts of 14 and 9%, respectively. The skeletal structure of compound (**12**) (isolated upon recrystallization) was confirmed by ¹H and ¹³C NMR (1D and 2D experiments). Established by ¹H-¹H COSY spectra, the coupling constant J^{18-19} (2.2 Hz) indicate that the dihedral angle between 18-H and 19-H in the compound (**12**) is close to 90°. Considering the data of XRD for *N*-substituted cytosine derivatives⁹, such an angle between vicinal CH appears in the case of their *cis*-relation, whereas the *trans*-related CH forms the dihedral angle of ~140°. This means that a new asymmetry center in **12** (carbon 18) has the absolute *S*-configuration, and consequently the compound (**12**) is defined as *S,S,S*-enantiomer.

Therefore, the stereochemistry of anagryne skeleton incorporated in the synthesized compound (**12**) is similar to those of the natural anagryne (**2**). Since the T-reaction of substrate (**11**) is highly regio- and stereoselective, the pure product (**12**) can be obtained in preparative amounts by applying a simple procedure of recrystallization.

In chloroform at 20°C, the isomerization of substrate (**11**) was slow: the extent of conversion attained a value of only 14% in 72 h. At 65°C in chloroform, the 95% conversion of the starting material was achieved in 20 h, while at 110°C (in DMAC), the reaction was accomplished in 20 min. In the latter case, yield of **12** was somewhat lower because of formation of high-molecular by-products (in amounts up to 15%).

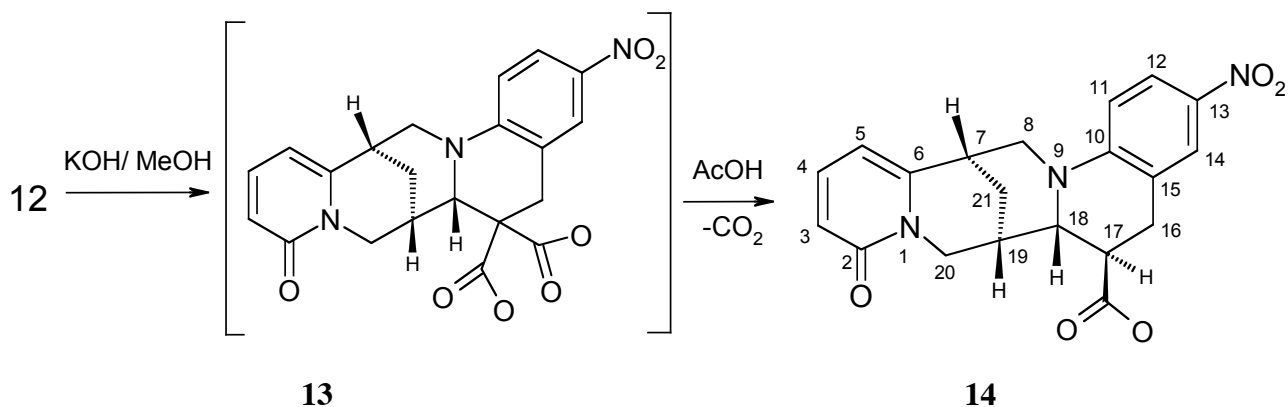
These data show that the rate of isomerization of **11** is markedly (by three–four orders of magnitude) lower than that for related derivatives of the cycloalkylamine series. So, 5-arylidenebarbiturate (**6**) (R₁=Me, R₂=NO₂, X=O, Y=CH₂, Scheme 1) underwent a rapid T-reaction (in several min at r.t.⁷) to give the respective spiro derivative (**7**). Such a differences can be explained by the steric hindrance caused by the cytosine skeleton in **11**.

Further modification of system (**12**) opens up new horizons for synthesis of alkaloid-like compounds containing a benzoannelated anagryne moiety.



Scheme 2

Treatment of spirobarbiturate (**12**) with KOH in methanol (Scheme 3) was found to cause hydrolysis of the spiropyrimidine moiety to give the dicarboxylic acid derivative (**13**). Acidification of the reaction mixture with acetic acid at rt followed by stereoselective decarboxylation of **13** afforded the enantiomerically pure monocarboxylic acid derivative (**14**). The stereochemistry of a new asymmetry center (carbon 17) in the acid (**14**) was established by 2D 1H NMR (COSY and NOESY) experiments. The configuration between the 17- and 18-H was suggested to be *trans* from the coupling constant (6.7 Hz) and confirmed finally by Overhauser effect measurement; the correlations of 17-H/18-H, 18-H/19-H and 17-H/19-H gave a NOE of 25%, 45% and 10%, respectively. This indicates a *R*-configuration of the carbon 17, and consequently the compound (**14**) was defined as 7*S*,17*R*,18*S*,19*S*-enantiomer.



Scheme 3

In conclusion, we have to state that T-reactions have not been involved in similar modification of alkaloids so far. Moreover, until recently T-reactions have remained virtually unclaimed by the chemistry of alkaloids (rare exceptions are the synthesis¹⁰ of the antibiotic mitomycin and the transformation¹¹ of cotarnine under the action of acid **10**). Conceptually, the strategy suggested in this communication can also be applied to modification of other alkaloids containing a secondary amino group. Mild conditions and stereoselectivity of T-reactions make them attractive for the chemistry of natural compounds.

EXPERIMENTAL

¹H NMR and ¹³C NMR spectra were taken with a Bruker AM-500 spectrometer (500 and 125 MHz), and mass spectra with a MKh-1303 instrument. Assignment of signals in ¹H NMR spectra was accomplished by using the D2 experiments (¹H-¹H COSY and NOESY), the multiplicities of ¹³C signals were determined by DEPT-135.

Pharmaceutical cytosine (**1**) (above 99% pure) isolated from *Chamaecytisus austriacus*) was used in our experiments.

N-(2-Formyl-4-nitrophenyl)cytosine (9). To a solution of 2-chloro-5-nitrobenzaldehyde (**8**, 9.3 g, 50 mmol) in 30 mL of DMF, added were anhydrous K₂CO₃ (8.3 g, 60 mmol) and cytosine (**1**, 10.3 g, 55 mmol). The mix was stirred at 120°C for 2.5 h. Upon cooling down, 250 mL of water was added. A precipitate was filtered out, washed with water, and dissolved in 10% HCl. Undissolved matter was taken off and thrown away. The filtrate was diluted with water and neutralized with ammonia. A precipitate was filtered out, washed with water, dried at 20°C under reduced pressure to obtain compound (**3**) as yellow crystals. Yield 15.4 g (91%), mp 249–250°C (MeOH).

¹H MNR (AM-500 Bruker, CDCl₃) *J*, Hz, δ, ppm: 2.08 m (2H, AB-system, C8H₂, *J* 12.6), 2.68 br. s (1H, C9H), 3.17 br. s (1H, C7H), 3.36–3.51 m (4H, 2NCH₂), 3.90 q (1H, C10H_{ax}, *J*¹ 15.6, *J*² 6.0), 4.22 d (1H, C10H_{eq}, *J* 15.6), 6.14 d (1H, C5H, *J* 6.9), 6.50 d (1H, H_{arom}, *J* 9.1), 6.96 d (1H, C3H, *J* 8.8), 7.37 dd (1H, C4H, *J*¹ 8.8, *J*² 6.9), 8.22 dd (1H, H_{arom}, *J*¹ 9.1, *J*² 2.5), 8.48 d (1H, H_{arom}, *J* 2.5), 9.29 s (1H, CHO). Anal. Calcd for C₁₈H₁₇N₃O₄ (%): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.83; H, 5.01; N, 12.24.

N-(2-(1,3-Dimethyl-2,4,6-trioxoperhydropyrimidinylmethylene)-4-nitrophenyl)cytosine (11). To a solution of aldehyde (**9**) (3.37 g, 10 mmol) in 15 mL of chloroform, added were 1,3-dimethylbarbituric acid (**10**, 1.56 g, 10 mmol) and 1 g anhydrous Na₂SO₄. The mix was held at 50°C for 5 min and allowed to stay at 20°C overnight. A precipitate was filtered out, washed with 5 mL of chloroform, and combined solution is evaporated under reduced pressure. A dry residue was washed with 20 mL of 50% EtOH and dried at 20°C *in vacuo* to obtain compound (**11**) as yellow crystals. Yield 4.4 g (93%), mp 252–253°C.

¹H NMR (AM-500 Bruker, CDCl₃) *J*, Hz, δ, ppm: 1.98 m (2H, AB-system, C8H₂, *J* 12.7), 2.59 br. s (1H, C9H), 3.09 br. s (1H, C7H), 3.22 m (2H, C13H₂), 3.23 s (3H, NCH₃), 3.47 m (2H, C11H₂), 3.49 s (3H,

NCH₃), 3.89 q (1H, C10H_{ax}, J^1 15.9, J^2 6.1), 4.22 d (1H, C10H_{eq}, J 15.9), 5.94 d (1H, C5H, J 6.1), 6.38 d (1H, H_{arom}, J 9.7), 6.96 d (1H, C3H, J 8.5), 7.20 dd (1H, C4H, J^1 8.5, J^2 6.1), 8.17 m (3H, =CH+2H_{arom}). Anal. Calcd for C₂₄H₂₃N₅O₆ (%): C, 60.37; H, 4.87; N, 14.67. Found: C, 60.21; H, 4.84; N, 14.55.

(S,S,S)-1,3-Dimethyl-5-[5-nitro-2-(6-oxo-7,11-diazatricyclo[7,3,1,0^{2,7}]trideca-2,4-dien-11-yl)phenyl-methylene]hexahydro-2,4,6-pyrimidinetrione (12). To a mix of 25 ml dimethylacetamide with 30 mL of chloroform, added was the compound (**11**) (4.77 g, 10 mmol). The mixture was refluxed until dissolution. Chloroform was evaporated. The mix was held at 110°C for 20 min. Upon cooling down, the solution was diluted with a double amount of 94% EtOH and held at 10°C for 2 h. A solid precipitate was filtered out, diluted with 200 mL of water, and allowed to stay at 10°C overnight. Then a precipitate was separated, washed with water, and dried to obtain 3.4 g of a mixture containing about 77% compound (**12**) (according to ¹H NMR). The crude product is treated with 20 mL of EtOH at 20°C. In 2 h, 1 g silica gel was added, intermixed, and taken off. Upon dropwise addition of 30 mL of water, the filtrate was allowed to stay at 10°C overnight. A precipitate was separated, washed with water, and dried at 20°C *in vacuo* to obtain 1.35 g (28%) of compound **12** as yellow crystals. An additional amount (0.38 g) of **12** was obtained by evaporation of 10 mL from the mother solution and recrystallization of the formed precipitate from EtOH 40%. The overall yield of **12** was 36%, mp 304–306°C.

¹H NMR (CDCl₃) J , Hz, δ , ppm: 2.13 m (2H, AB-system, C21H₂, J 13.0), 2.46 br. s (1H, C19H, J^{19-18} 2.2), 3.23 and 3.42 d (1H+1H, AB-system, C16H₂, J 16.0), 3.24 m (1H, C7H), 3.31 s (3H, NCH₃), 3.37 and 4.26 m (1H+1H, AB-system, NC8H₂, J^1 12.7), 3.39 s (3H, NCH₃), 3.43 and 4.15 m (1H+1H, AB-system, C20H₂, J^1 16.8), 4.05 d (1H, C18H, J 2.2), 6.10 d (1H, C5H, J 6.9), 6.33 d (1H, C11H, J 9.7), 6.66 d (1H, C3H, J 9.1), 7.23 dd (1H, C4H, J^1 9.1, J^2 6.9), 7.79 d (1H, C14H, J 2.4), 7.90 dd (1H, C12H, J^1 9.1, J^2 2.4).

¹³C NMR (CDCl₃), δ , ppm: 28.21 C21H₂, 29.18 C19H, 29.37 NCH₃, 29.46 NCH₃, 34.04 C7H, 37.39 C16H₂, 44.40 C8H₂, 49.93 C5', 56.50 C20H₂, 64.04 C18H, 104.92 C5H, 111.99 C14H, 117.94 C4H, 119.49 C15, 124.06 C_{arom}H, 124.60 C_{arom}H, 138.69 C3H, 147.75 C13, 149.96 C10, 150.25 C2'O, 162.41 and 169.63 C4'O and C6'O, 166.16 C2O.

MS: M⁺ 477. Calcd for C₂₄H₂₃N₅O₆ (%): C, 60.37; H, 4.87; N, 14.67. Found: C, 60.26; H, 4.82; N, 14.59.

(7S,17R,18S,19S)-7-Nitro-18-oxo-11,15-diazapentacyclo[11,7,1,0^{2,11},0^{5,10},0^{14,19}]genicosa-5(10),6,8,14,16-pentaene-3-carboxylic acid (14). To a solution of KOH (0.336 g, 6 mmol) in 30 mL of abs. MeOH, added was the compound (**12**) (0.477 g, 1 mmol). The mix was heated (for 5 min) under stirring until complete dissolution, and then held at rt for 1 h. Solvent was evaporated at 30°C under reduced pressure. A solid residue was dissolved in 20 mL of water and filtered. The filtrate was acidified with 50% AcOH (added dropwise under stirring) to pH 5 and allowed to stay at 10°C for 1 h. A precipitate was filtered out, washed with water, and dried at 20°C *in vacuo* to obtain compound (**14**) as pale yellow crystals. Yield 0.34 g (89%), mp 272–273°C (with decomp.).

^1H NMR (DMSO- d_6) J , Hz, δ , ppm: 2.09 br. s (2H, CHCH_2CH), 2.46 br. s (1H, C19H), 2.85 and 2.96 dd (1H+1H, AB-system, ArCH_2 , J 10.5), 2.86 m (1H, C3H, J^{19-18} 6.7), 3.27 m (1H, C7H), 3.44 and 4.06 dd (1H+1H, AB-system, N^9CH_2 , J 12.9), 3.52 and 4.12 dd (1H+1H, AB-system, N^1CH_2 , J^1 15.1), 3.72 dd (1H, NCH, J^{18-17} 6.7, J^{18-19} 2.3), 6.17 d (1H, C11H, J 8.5), 6.28 d (1H, C5H, J 7.8), 6.43 d (1H, C3H, J 8.6), 7.36 dd (1H, C4H, J^1 8.6, J^2 7.8), 7.78 dd (1H, C12H, J^1 8.6, J^2 2.5), 7.85 d (1H, C14H, J 2.5), 13.00 br. s (1H, COOH).

^{13}C NMR (DMSO- d_6), δ , ppm: 26.23 C21H₂, 29.53 C16H₂, 30.53 C19H, 33.53 C7H, 42.41 C17H, 43.45 C8H₂, 54.81 C20H₂, 60.95 C18H, 104.39 C5H, 111.16 C11H, 115.90 C3H, 123.22 C15, 123.80 C12H, 124.06 C14H, 136.78 C13, 138.88 C4H, 149.86 C10, 151.01 C6, 161.88 C2O, 173.64 COOH.

MS: M^+ 381. Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5$ (%): C, 62.99; H, 5.02; N, 11.02. Found: C, 62.76; H, 5.10; N, 10.88.

REFERENCES (AND NOTES)

1. H. R. Ing, *J. Chem. Soc.*, 1932, 2778; S. W. Pelletier, 'Alkaloids; Chemical and Biological Properties,' Vol. 2, New York, 1984, pp. 105-148.
2. M. D. Mashkovskii, 'Lekarstvennyye Sredstva,' Vol. 1, Novaya Volna, Moscow, 2000, pp. 129-130.
3. R. J. Lewis, 'Sax's Dangerous properties of Industrial materials,' 8-th edn., ed. by V. N. Reinhold, 1992.
4. J. F. Couch, *J. Am. Chem. Soc.*, 1939, **61**, 3327.
5. W. H. Lewis and M. P. F. Elvin-Lewis, 'Medical Botany,' Wiley, New York, 1977.
6. O. Meth-Cohn, *Adv. Heterocycl. Chem.*, ed. by A. R. Katritzky, 1996, **65**, 1.
7. K. A. Krasnov and V. G. Kartsev, *Russ. J. Org. Chem.*, 2005, **41**, 920.
8. K. A. Krasnov, V. G. Kartsev, and V. N. Khrustalev, *Mendeleev Commun.*, 2006, **16**, 52.
9. K. A. Krasnov, V. G. Kartsev, A. S. Gorovoi, and V. N. Khrustalev, *Chemistry of natural compounds*, 2002, **38**, 450.
10. W. C. Dijkman, W. Verboom, R. J. M. Egberink, and S. Harkema, *J. Org. Chem.*, 1985, **50**, 3791.
11. K. A. Krasnov, V. G. Kartsev, and V. N. Khrustalev, *Russ. J. Org. Chem.*, 2002, **38**, 457.