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]*

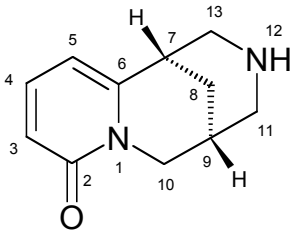
[a]Mechnikov State Medical Academy, St. Petersburg, Russia
e-mail: veselkoff@mail.ru
[b]InterBioScreen Ltd., Chernogolovka, Moscow, Russia
e-mail: vkartsev@ibscreen.chg.ru

Abstract – Three-step transformation of cytisine 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)cytisine (generated upon arylation of cytisine with 2-cloro-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)phenylmethyleno]hexahydro-2,4,6-pyrimidinetrione containing a benzoannelated anagyrine skeleton. Subsequent alkaline hydrolysis of the spiro compound led to cleavage of the spiropyrimidine moiety followed by stereoselective decarboxylation to afford an enantiomerically pure carboxylic acid derivative of the benzoanagyrine series.

INTRODUCTION

Cytisine (**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] Cytisine shows a nicotine-like CNS activity and is being used in medicine as a respiratory stimulant[2], despite its high toxicity (LD_{50} 1.3 mg/kg, mus., ivn.).[3]

The alkaloid anagyrine (**2**), biogenetically close to cytisine (**1**), has been isolated from *Anagyris foetida*, some *Cytisus* species, etc. (*Leguminosae*).[4] Anagyrine is known[5] to act as an anti-arrhythmic, cardiotonic, diuretic, and purgative agent.



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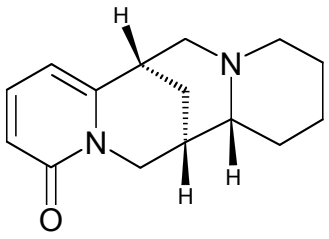

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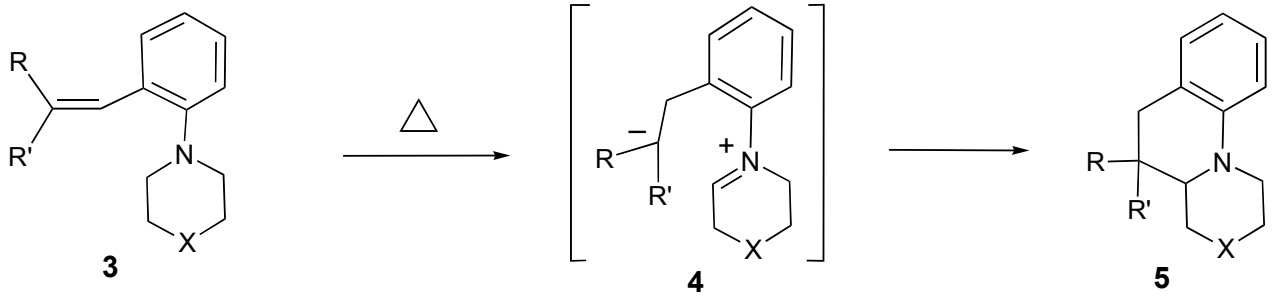
The structural similarity between alkaloids (**1** and **2**) suggests an attractive synthesis of pharmacologically valued anagyrine derivatives from the commercially available cytisine. Until recently, such a transformation of **1** seemed inaccessible by standard methods of synthetic chemistry.

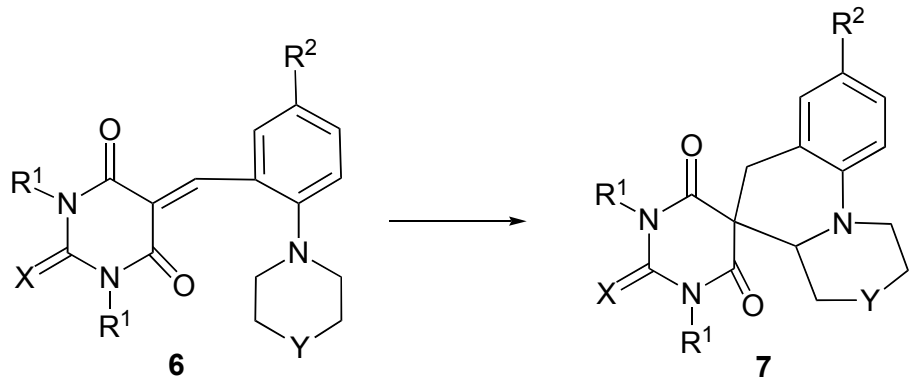
As is known, *o*-vinyl derivatives of tertiary aromatic amines (**3**) may undergo cyclization into respective 1,2,3,4-tetrahydroquinolines (**5**) via the so-called *tert*-amino effect (Scheme 1).[6] Reactions of this type (T-reactions) involve hydrogen detachment from the α-position of the *tert*-amino 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.



3 **4** **5**

R, R' = CN, COOMe; X = $(CH_2)_{2\text{-}0}$, NMe, O



6 **7**

R^1= H, Me, Ph; R^2 = H, NO_2; X = O, S; Y = $(CH_2)_{0\text{-}3}$, O, NPh, or no bond

Scheme 1

RESULTS AND DISCUSSION

The nucleophilic reaction of the native (7*R*,9*S*) cytisine (**1**) with 2-cloro-5-nitrobenzaldehyde (**8**) was found to afford *N*-(2-formyl-4-nitrophenyl)cytisine (**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)cytisine (**11**) which was then allowed to undergo the T-reaction.

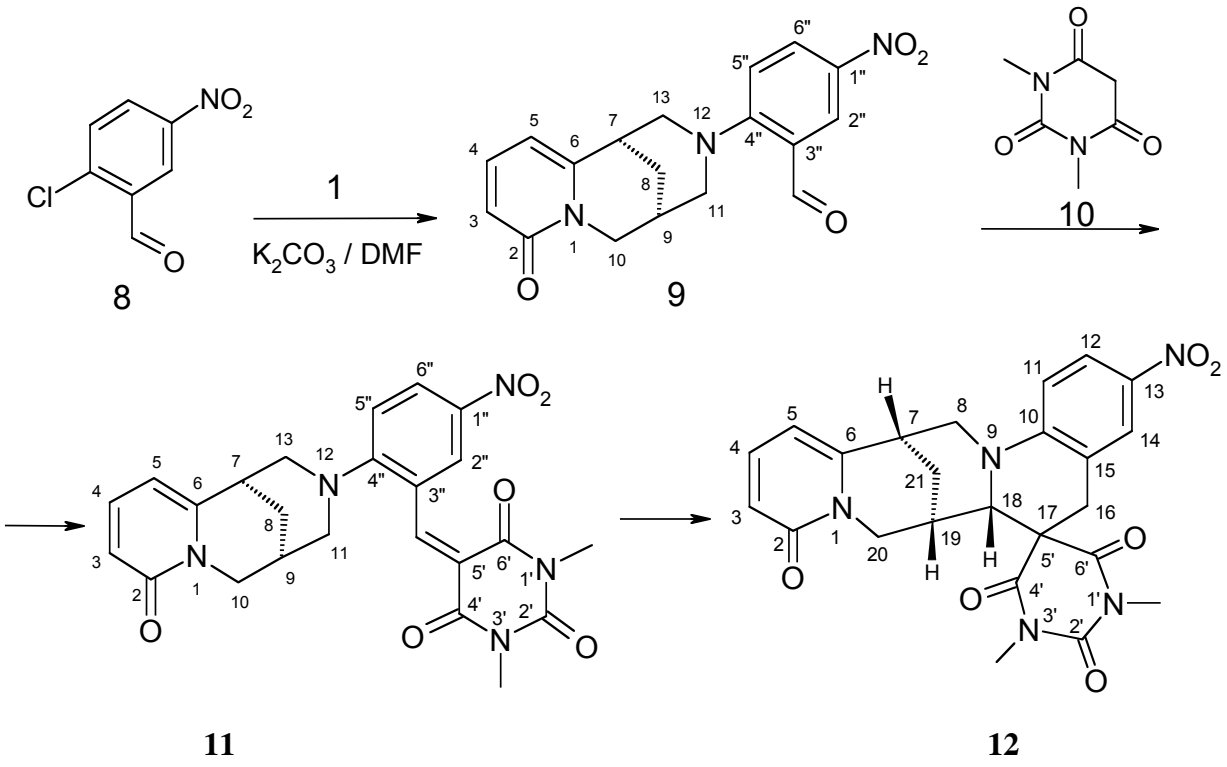
Theoretically, cyclization of the substrate (**11**) may be expected to proceed via attachment of the 11-H_2 or 13-H_2 group from the cytisine moiety and provide four possible isomers (two structural isomers and two diastereomers). We have found that the isomerization of **11** in chloroform, as well as in dimethylacetamide (DMAC), led (according to ^{1}H 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 ^{1}H and ^{13}C NMR (1D and 2D experiments). Established by ^{1}H-^{1}H 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 90º. Considering the data of XRD for N-substituted cytisine derivatives [9], such an angle between vicinal CH appears in the case of their *cis*-relation, whereas the *trans*-related CH forms the dihedral angle of ~140º. 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 anagyrine skeleton incorporated in the synthesized compound (**12**) is similar to those of the natural anagyrine (**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%).

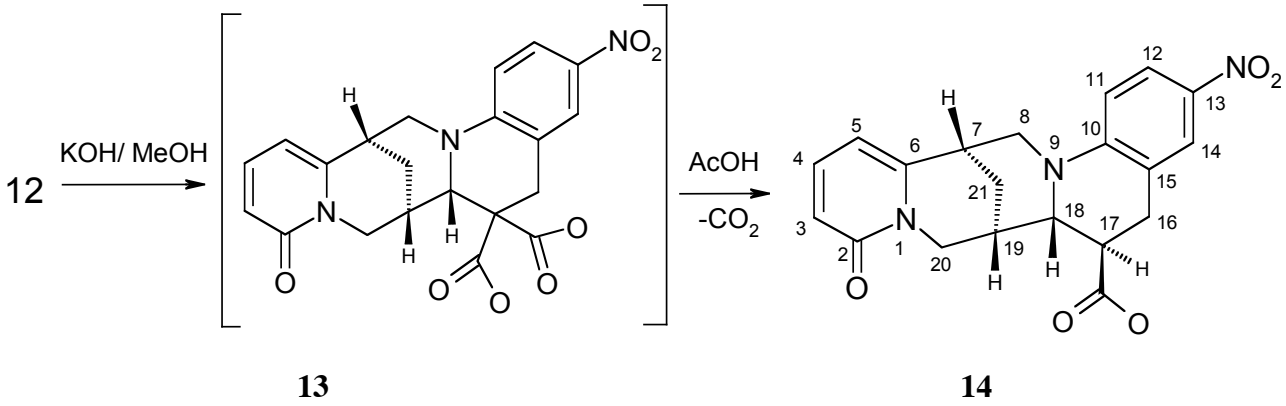
These data show that the rate of isomerization of **11** is markedly (by three–four orders of magnitude) lower than that for related derivatives of the cycloalkylamine series. So, 5-arylidenebarbituirate (**6**) (R1=Me, R2=NO_2, X=O, Y=CH_2, Scheme 1) underwent a rapid T-reaction (in several min at r.t.[7]) to give the respective spiro derivative (**7**). Such a differences can be explained by the steric hindrance caused by the cytisine skeleton in **11**.

Further modification of system (**12**) opens up new horizons for synthesis of alkaloid-like compounds containing a benzoannelated anagyrine 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 ^{1}H 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 synthesis[10] of the antibiotic mitomycin and the transformation[11] 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

^{1}H NMR and ^{13}C 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 ^{1}H NMR spectra was accomplished by using the D2 experiments (^{1}H-^{1}H COSY and NOESY), the multiplicities of ^{13}C signals were determined by DEPT-135.

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

***N*-(2-Formyl-4-nitrophenyl)cytisine** (**9**). To a solution of 2-chloro-5-nitrobenzaldehyde (**8**, 9.3 g, 50 mmol) in 30 mL of DMF, added were anhydrous K_2CO_3 (8.3 g, 60 mmol) and cytisine (**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).

^{1}H MNR (AM-500 Bruker, $CDCl_3$) *J*, Hz, δ, ppm: 2.08 m (2H, AB-system, C8H_2, *J* 12.6), 2.68 br. s (1H, C9H), 3.17 br. s (1H, C7H), 3.36–3.51 m (4H, 2NCH_2), 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 $C_{18}H_{17}N_3O_4$ (%): 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)cytisine** (**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 Na_2SO_4. 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.

^{1}H NMR (AM-500 Bruker, $CDCl_3$) *J*, Hz, δ, ppm: 1.98 m (2H, AB-system, C8H_2, *J* 12.7), 2.59 br. s (1H, C9H), 3.09 br. s (1H, C7H), 3.22 m (2H, C13H_2), 3.23 s (3H, NCH_3), 3.47 m (2H, C11H_2), 3.49 s (3H,

NCH_3), 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 $C_{24}H_{23}N_5O_6$ (%): 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)phenylmethyleno]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 ^{1}H 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.

^{1}H NMR ($CDCl_3$) J, Hz, δ, ppm: 2.13 m (2H, AB-system, C21H_2, J 13.0), 2.46 br. s (1H, C19H, $J^{19–18}$ 2.2), 3.23 and 3.42 d (1H+1H, AB-system, C16H_2, J 16.0), 3.24 m (1H, C7H), 3.31 s (3H, NCH_3), 3.37 and 4.26 m (1H+1H, AB-system, NC8H_2, J^1 12.7), 3.39 s (3H, NCH_3), 3.43 and 4.15 m (1H+1H, AB-system, C20H_2, 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).

^{13}C NMR ($CDCl_3$), δ, ppm: 28.21 C21H_2, 29.18 C19H, 29.37 NCH_3, 29.46 NCH_3, 34.04 C7H, 37.39 C16H_2, 44.40 C8H_2, 49.93 C5', 56.50 C20H_2, 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 $C_{24}H_{23}N_5O_6$ (%): C, 60.37; H, 4.87; N, 14.67. Found: C, 60.26; H, 4.82; N, 14.59.

(7*S*,17*R*,18*S*,19*S*)-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.).

^{1}H NMR (DMSO-d_6) *J*, Hz, δ, ppm: 2.09 br. s (2H, CH$\underline{CH_2}$CH), 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, N9CH_2, *J* 12.9), 3.52 and 4.12 dd (1H+1H, AB-system, N1CH_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 C21H_2, 29.53 C16H_2, 30.53 C19H, 33.53 C7H, 42.41 C17H, 43.45 C8H_2, 54.81 C20H_2, 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 $C_{20}H_{19}N_3O_5$ (%): 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, 'Lekarstvennye 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. Dijksman, 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.