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CHEMICAL MODIFICATION OF PLANT ALKALOIDS. 6. T-REACTIONS OF ANABASINE DERIVATIVES

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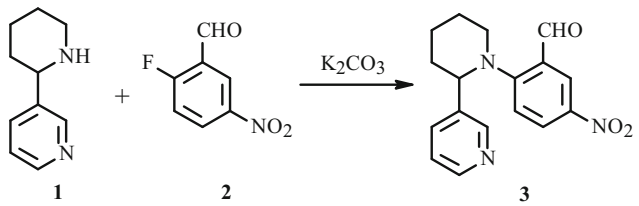
T-reactions of anabasine derivatives were performed for the first time. Condensation of 5-nitro-2-[2-(3-pyridyl)piperidino]benzaldehyde with 1,3-dimethylbarbituric acid formed an annelated tetrahydroquinoline system containing a spiropyrimidine moiety as the T-reaction product. Condensation of this same aldehyde with Meldrum's acid was accompanied by recyclization that led to opening of the piperidine ring and closing of the tetrahydroquinolone system. A third version of the T-reaction that also led to opening of the piperidine ring but without recyclization was the condensation with dimedone.

Keywords: anabasine, 1,3-dimethylbarbituric acid, Meldrum's acid, dimedone, *tert*-amino effect, T-reaction, cyclization, recyclization.

Anabasine (**1**) is the principal alkaloid of *Anabasis aphylla* L. and is used to battle agricultural pests [1]. Many anabasine derivatives also exhibit pronounced biological activity [2–6]. This stimulates interest in the preparation of new synthetic anabasine derivatives and the search for new methods of modifying its structure. As a rule, anabasine derivatives are synthesized using a limited number of methods such as alkylation, acylation, and other electrophilic reactions of **1** at the secondary piperidine amine [2–6]. Nevertheless, the chemical properties of anabasine enable it to be used in other chemical processes.

We applied a new approach that featured the use of T-reactions for the modification of the anabasine structure. The general principles of converting secondary amines into substrates for T-reactions have been published [7, 8]. As applied to the chemistry of alkaloids, we used previously an analogous strategy in the enantioselective synthesis from cytisine of a derivative of the alkaloid anagyrine [9]. Such transformations are based on manifestation of the *tert*-amine effect, which has been reviewed [10].

Anabasine was modified in the present work in two steps. In the first, anabasine was arylated by 2-fluoro-5-nitrobenzaldehyde (**2**) to produce the corresponding *ortho*-substituted benzaldehyde derivative **3** in about 70% yield (Scheme 1). In contrast with most secondary amines, anabasine turned out to be difficult to arylate because of steric hindrance. Whereas cyclic and acyclic secondary amines could be arylated in high yields by 2-chloro-5-nitrobenzaldehyde [6, 8–10], anabasine under standard conditions did not undergo such a reaction. Thus, the use of highly reactive 2-fluoro-5-nitrobenzaldehyde turned out to be the only method for preparing derivative **3**.



1 **2** **3**

Scheme 1

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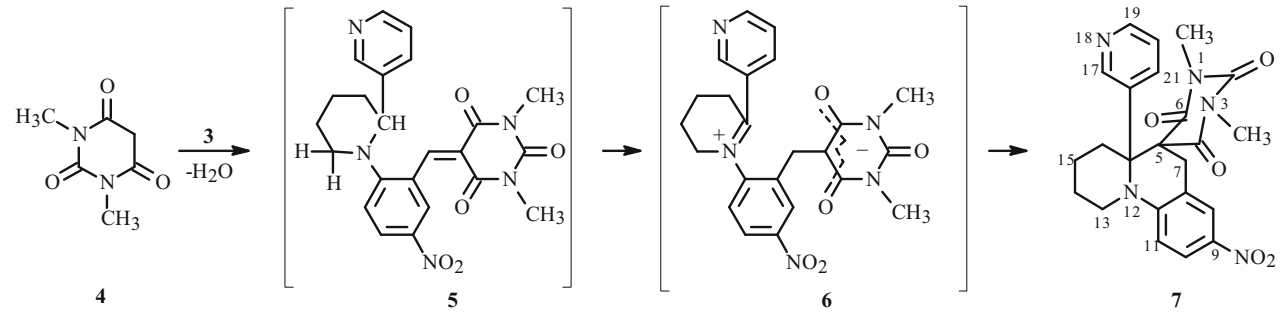
In the second step, the resulting anabasine derivative **3** was condensed with cyclic 1,3-dicarbonyl compounds. This initiated T-reactions in the anabasine fragment of derivative **3**.

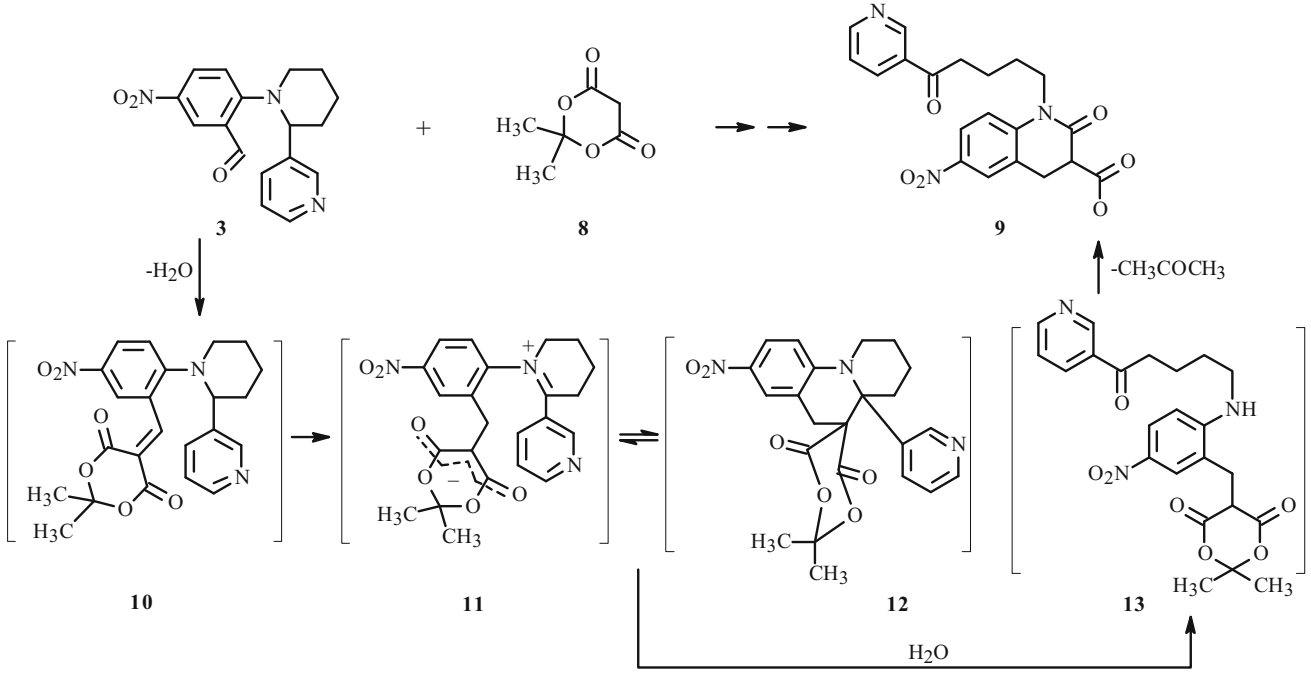
Reaction of **3** with 1,3-dimethylbarbituric acid (**4**) at room temperature in CH_2Cl_2:MeOH formed spiro-cyclic derivative **7** (Scheme 2), which was isolated in 61% yield. The structure of **7** was proved using PMR spectral data.



Scheme 2

Scheme 2 shows the formation mechanism of **7**. It could be explained by the occurrence of two reactions in succession. Obviously the first reaction involved a typical Knoevenagel reaction of **3** and **4** to form intermediate **5**, which was unstable and cyclized through a T-reaction mechanism through Zwitter-ion **6** into the final product **7**. The mechanism of this reaction is based on activation of the H atom in intermediate **5** with a subsequent hydride shift and cyclization [8]. (All H atoms shown in **5** are potentially susceptible to a hydride shift. In actuality, H cleavage occurs only from the tertiary C atom.) An example of such a transformation is the isomerization of 5-(2-*N*-piperidinobenzylidene)barbituric acid and its analogs that, like **5**, are active T-intermediates that isomerize into the corresponding spiro-cyclic systems at room temperature [6].

Cyclization of **5** occurred regioselectively. Of the two theoretically possible products, the sterically more strained isomer **7** formed. We did not observe even traces of the alternate isomer, i.e., the product of cyclization at the NCH_2 group, during a study of the reaction mixture by TLC and PMR methods. This indicated that the NCH group in intermediate **5** was a much more active hydride donor than the NCH_2 group and that the T-reaction was kinetically controlled.



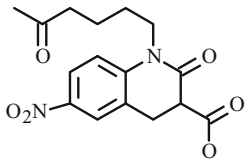
Scheme 3

The stereoselectivity of the cyclization is noteworthy. We used anabasine of relatively low enantiomeric purity {α^{25} of a solution in MeOH (1%) was –9.5 whereas the pure (*S*)-enantiomer of anabasine had α^{25} –79 [1]}. Compound **7** was optically active [α^{25} of a solution in DMSO (1%) was +3.5], i.e., the T-reaction leading to its formation occurred stereoselectively. Apparently this should be explained by the high rate of the cyclization. Although cleavage of the hydride ion in **5** and

formation of Zwitter-ion **6** was accompanied by loss of the initial asymmetric center, the mutual orientation of the piperidine and pyrimidine rings was probably not disrupted. Therefore, intramolecular addition of the C-nucleophile to the $^{+}$C=N bond in Zwitter-ion **6** occurred stereoselectively from one side, leading primarily to the formation of one of the two possible enantiomers.

Furthermore, we found that the structures of the products from reaction of aminoaldehyde **3** with 1,3-dicarbonyl reagents depended in principle on the nature of the used reagent. A derivative of tetrahydroquinolin-2-one-3-carboxylic acid (**9**) was isolated in about 60% yield from the condensation of **3** with Meldrum's acid (**8**) under conditions identical to those mentioned above (Scheme 3).

The structure of **9** was established using mass spectral, PMR, and ^{1}H–^{1}H COSY methods and by comparison with spectra of model compound **14**, which we prepared earlier [11].



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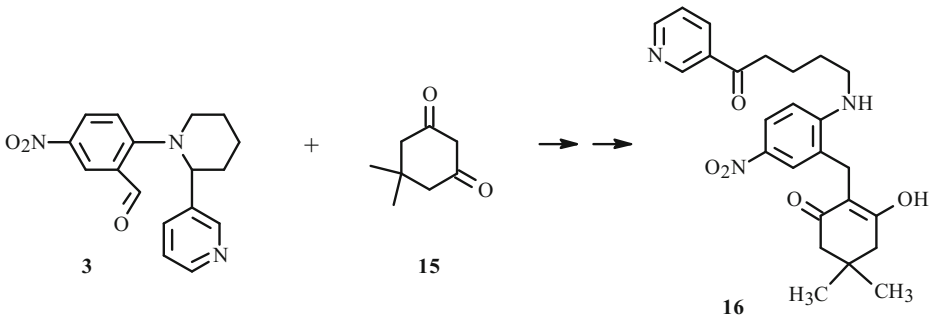
The formation of **9** from starting materials **3** and **8** indicated that a complicated multi-step process occurred. During its course, hydrolytic opening of the piperidine and 1,3-dioxane rings and formation of a tetrahydroquinolin-2-one system occurred. Scheme 3 shows what in our opinion is the most probable sequence of transformations. In the first step, **3** and **8** obviously underwent a Knoevenagel reaction with loss of water and formation of arylidene derivative **10**. Considering that derivatives of Meldrum's acid are as a rule about as active in T-reactions as their barbituric acid analogs, it could be expected that intermediate **10** and its analog **5** in Scheme 2 should quickly cyclize through the T-reaction mechanism through Zwitter-ion **11** into the spiro-cyclic system (**12**). This probably also occurred in this instance. However, the spiro-cyclic system of **12** was destabilized by steric hindrance and could equilibrate with starting Zwitter-ion **11** because the T-reaction is reversible in principle [12]. The equilibrium Zwitter-ion **11**, being a quaternary Schiff base, could easily be hydrolyzed by water with opening of the piperidine ring to give **13**, in which conditions for a new cyclization arose. This was intramolecular attack of the secondary amine at the carbonyl C atom to close into a quinolin-2-one system. Opening of the 1,3-dioxane ring with loss of acetone and formation of quinolin-2-one **9** occurred simultaneously with this. Compound **9** was isolated as the final product.

A study of the reaction of **3** and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**15**) revealed another example of a T-reaction, the direction of which differed from the two reactions examined above. The reaction could be carried out at 120°C, i.e., under more forcing conditions than in the previous examples. Obviously the dimedone derivative was much more reactive in T-reactions than the corresponding analogs of barbituric acid and Meldrum's acid. As a result, compound **16** was isolated. Its hypothetical formation pathway is shown in Scheme 4.

We suppose that **16** could be formed via processes analogous to those shown in Scheme 3. The Knoevenagel intermediate produced in the first step underwent a hydride shift. The resulting Zwitter-ion was hydrolyzed with opening of the piperidine ring. However, in contrast with the preceding example, the process in Scheme 4 did not lead to formation of the quinolin-2-one system so that the cyclic 1,3-dicarbonyl moiety was retained in final product **16**.



3 **15** **16**

Scheme 4

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer at operating frequency 500 MHz. Mass spectra were measured on an MX-1303 instrument with direct sample introduction into the ion source at 150°C with ionizing potential 70 eV. The purity of the products was monitored using TLC on Silufol UV-254 plates and $CHCl_3$:EtOAc:CH_3CO_2H (3:2:0.1) or DMF (R_f values are not given because the final products, in contrast with the starting compounds, form broad bands in the chromatograms), PMR spectra, and elemental analyses.

5-Nitro-2-[2-(3-pyridyl)piperidino]benzaldehyde (3). Freshly distilled anabasine base (**1**, 8.1 g, 0.05 mol) was treated with 2-fluoro-5-nitrobenzaldehyde (**2**, 3.38 g, 0.02 mol) and freshly calcined potash (2.76 g, 0.02 mol). The mixture was heated to 75°C and stirred at that temperature for 2 h. The resulting homogeneous mixture was cooled, poured into aqueous HCl (100 mL, 5%), stirred with silica gel (1 g), stored for 30 min, and filtered. The filtrate was made basic with aqueous ammonia (25%) until the pH was 9. The resulting precipitate was separated on a filter and washed with water. The crude product was purified by dissolving in HCl (70 mL, 2%) with added activated carbon (0.5 g), stirring, and filtering. The filtrate was made basic with aqueous ammonia (5%) until the pH was 9. The resulting precipitate was separated on a filter, washed with aqueous alcohol (10%) and water, and dried in a vacuum desiccator over KOH to afford **3** (4.4 g) as yellowish-brown crystals, yield 71%, mp 99–100°C. $C_{17}H_{17}N_3O_3$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.64-2.08 (6H, m, $3CH_2$), 3.05 (1H, m, $^1J = 12.6$, $^2J = 6.4$, NCH_2), 3.40 (1H, dd, $^1J = 12.6$, $^2J = 6.0$, NCH_2), 4.37 (1H, dd, $^1J = 6.9$, $^1J = 5.0$, NCH), 7.05 (1H, d, J = 9.2, ArH), 7.13 (1H, dd, $^1J = 6.9$, $^2J = 5.7$, PyH), 7.50 (1H, d, J = 6.9, PyH), 8.11 (1H, d, J = 9.2, ArH), 8.39 (1H, d, J = 5.7, PyH), 8.50 (1H, s, ArH), 8.57 (1H, s, PyH), 10.45 (1H, s, CHO).

1,3-Dimethyl-2,4,6-trioxospiro-(perhydropyrimidino-5,6′)-3′-nitro-7′-(3-pyridino)-6′,6a,7′,8′,9′,10′-hexahydro-5*H*-pyrido[1,2-*a*]quinoline (7). Aldehyde **3** (0.622 g, 0.02 mol) was dissolved in $CHCl_3$ (6 mL), treated at room temperature with 1,3-dimethylbarbituric acid (**4**, 0.312 g, 0.02 mol) in MeOH (9 mL), stirred, and stored for 1 d at room temperature. The solvent was evaporated to dryness in *vacuo* without heating. The solid was dissolved in MeOH (15 mL) and left for 6 h at room temperature. The resulting precipitate was filtered off, washed with cold MeOH, and dried in a vacuum desiccator over KOH to afford **7** (0.59 g, 66%), as yellowish-gray crystals, mp 243–244°C (MeOH). $C_{23}H_{23}N_5O_5$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz) (for atom numbering, see Scheme 2): 1.40 (1H, m, CH_2-14), 1.58 (2H, m, CH_2-15), 1.80 (1H, m, CH_2-14), 2.03 (1H, m, CH_2-16), 2.55 (1H, dd, $^1J = 15.1$, $^2J = 5.0$, NCH_2), 2.93 (3H, s, NCH_3), 3.03 (1H, d, J = 17.2, CH_2-7), 3.13 (3H, s, NCH_3), 3.14 (1H, m, C_6H_2-16), 3.89 (1H, d, J = 17.2, CH_2-7), 4.08 (1H, dd, $^1J = 15.1$, $^2J = 4.6$, NCH_2), 7.08 (1H, d, J = 9.2, CH-11), 7.37 (1H, dd, $^1J = 6.4$, $^2J = 6.4$, CH-20), 7.51 (1H, br.s, CH-21), 8.01 (1H, s, CH-8), 8.10 (1H, d, J = 9.2, CH-10), 8.40 (1H, br.s, CH-17), 8.60 (1H, d, J = 4.7, CH-19).

6-Nitro-2-oxo-1-[5-oxo-5-(3-pyridyl)pentyl]-1,2,3,4-tetrahydro-3-quinoline Carboxylic Acid (9). Aldehyde **3** (0.622 g, 0.02 mol) was dissolved in $CHCl_3$ (3 mL), treated at room temperature with Meldrum's acid (**8**, 0.288 g, 0.02 mol) in MeOH (3 mL), stirred, and stored for 1 d at room temperature. The resulting crystalline precipitate was separated, washed with MeOH (15 mL) and $CHCl_3$ (15 mL), and dried in a vacuum desiccator to afford **9** (0.57 g, 59%) as large dark red crystals, mp 171–172°C (dec.). $C_{20}H_{19}N_3O_6$.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.75 (4H, m, CH_2–CH_2), 3.10 (2H, t, J = 7.2, $COCH_2$), 3.24 (1H, dd, $^1J = 16.4$, $^2J = 6.3$, $ArCH_2$), 3.29 (1H, dd, $^1J = 16.4$, $^2J = 6.6$, $ArCH_2$), 3.58 (1H, t, J = 6.6, CHCOO), 4.00 (1H, ddd, $^1J = 12.1$, $^2J = 6.5$, $^3J = 6.5$, NCH_2), 4.06 (1H, ddd, $^1J = 12.1$, $^2J = 6.5$, $^3J = 6.5$, NCH_2), 7.33 (1H, d, J = 9.4, ArH), 7.46 (1H, dd, $^1J = 8.3$, $^2J = 7.1$, PyH), 8.12 (2H, m, 2ArH), 8.25 (1H, d, J = 8.3, PyH), 8.71 (1H, br.s, PyH), 9.11 (1H, br.s, PyH), 12.65 (1H, br.s, COOH).

Mass spectrum (*m*/*z*, I_{rel}, %): 397 (1) $[M]^+$, 353 (20), 336 (35), 335 (35), 318 (7), 229 (18), 215 (10), 205 (15), 177 (60), 162 (37), 148 (35), 131 (50), 122 (40), 106 (100).

3-Hydroxy-5,5-dimethyl-2-{5-nitro-2-[5-oxo-5-(3-pyridyl)pentylamino]benzyl}-2-cyclohexen-1-one (16). Aldehyde **3** (0.622 g, 0.02 mol) and dimedone (**15**, 0.28 g, 0.02 mol) were dissolved in dimethylacetamide (5 mL), heated to 120°C, held at that temperature for 10 min, cooled to room temperature, stirred, and treated dropwise aqueous alcohol (15 mL, 50%). The resulting dark resinous precipitate was separated. The solution was stored for 1 d at 10°C. The resulting crystalline precipitate was separated, washed with aqueous ammonium acetate (30 mL, 5%) and water (30 mL), and dried in a vacuum desiccator to afford **16** (0.42 g, 47%) as yellowish-brown needle-like crystals, mp 133–134°C (alcohol). $C_{25}H_{29}N_3O_5$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.04 (6H, s, $2CH_3$), 1.80 (2H, m, CH_2), 1.91 (2H, m, CH_2), 2.32 (4H, m, $2CH_2$), 3.12 (2H, t, J = 7.0, $COCH_2$), 3.24 (2H, t, J = 7.1, NCH_2), 3.53 (2H, s, $ArCH_2$), 6.42 (1H, d, J = 9.3, ArH), 6.44 (1H,

br.s, NH), 7.46 (1H, dd, ^{1}J = 8.0, ^{2}J = 4.9, PyH), 7.98 (1H, d, J = 9.3, ArH), 8.21 (1H, s, ArH), 8.27 (1H, d, J = 8.0, PyH), 8.77 (1H, d, J = 4.9, PyH), 9.17 (1H, s, PyH).

Mass spectrum (m/z, I_{rel}, %): 451 (3) $[M]^+$, 433 (20), 423 (5), 345 (16), 327 (30), 318 (5), 312 (11), 285 (20), 275 (9), 270 (35), 243 (7), 164 (45), 151 (17), 148 (30), 122 (60), 106 (100).

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