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New β-[*o*-(5-oxopyrazol-3-yl)aryl]ethylamines and their unusual metastable betaine form

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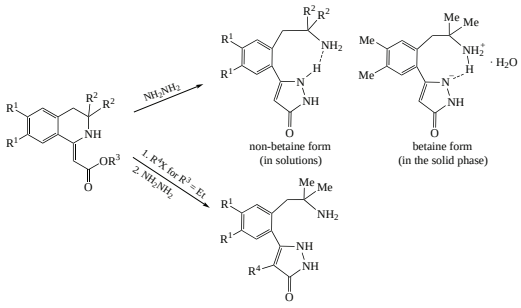
Novel β-arylethylamines bearing 5-pyrazolone substituent in the *ortho*-position of aryl moiety were obtained by the hydrazine-induced recyclization of 1-(alkoxycarbonylmethylidene)-1,2,3,4-tetrahydroisoquinolines. These amines can exist in a highly unstable betaine form in the solid phase.



Keywords: natural β-arylethylamines, 1,2,3,4-tetrahydroisoquinolines, hydrazine, recyclization, 5-pyrazolones, internal salts, metastable structures.

Dedicated to Academician Irina Petrovna Beletskaya on the occasion of her anniversary.

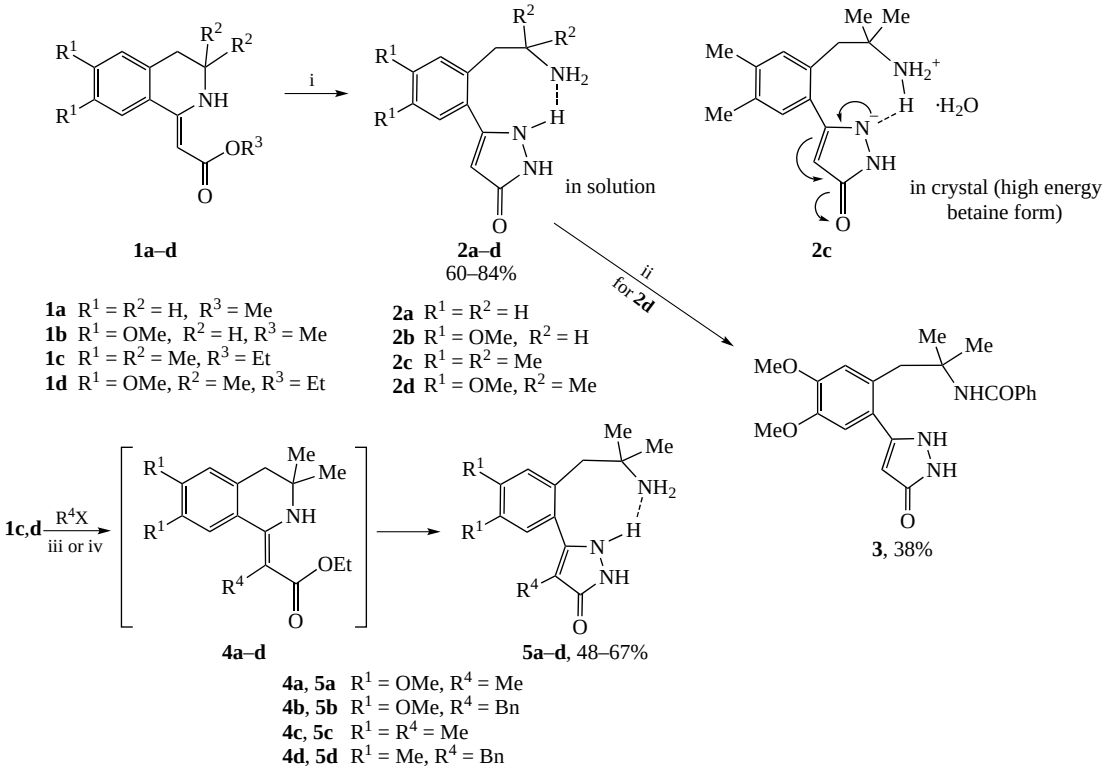
Nitrogen heterocycles[1] are material carriers of the DNA genetic code, cofactors of many biochemical processes, photosynthesis pigments, *etc*. According to the available estimates,[2] over 85% of practically significant biologically active compounds have heterocyclic structures; the majority of privileged scaffolds used in the molecular design of such compounds are also heterocyclic.[3] Synthesis of heterocyclic derivatives of natural compounds should be considered one of the most important approaches to their structural modification. This concept may be related to natural β-(hetero)arylethylamines, primarily biogenic amines such as dopamine, adrenaline, noradrenaline, serotonin, and histamine which ensure the functioning of the nervous and hormonal systems, as well as to the so-called trace amines,[5] in particular, the simplest representative of this series, phenylethylamine, a CNS neuromodulator. Moreover, numerous medicinal agents have been created on the basis of various non-heterocyclic derivatives of β-(hetero)arylethylamines and their analogues.[6–9] Heteroaryl derivatives of β-(hetero)arylethylamines have been studied rather poorly while they may be of interest as potential neuro- and psychotropic agents.[4]

In this work we report a synthesis of new derivatives of two natural amines, namely, β-phenylethylamine and β-(3,4-dimethoxyphenyl)ethylamine[10,11] containing *ortho*-positioned pyrazolone substituents in the aryl moiety, and their analogues bearing two methyl groups in the α-position to the amino group. The method is rather simple and does not require any catalysts or reagents that are hard to access. It is based on a new recyclization reaction that 1-alkoxycarbonylmethylidene-1,2,3,4-tetrahydroisoquinolines of type **1** enter upon treatment with hydrazine which occurs at the reactive aminoacrylate moiety (Scheme 1). In fact, this reaction is an extension of the general synthetic approach to *ortho*-heteroaryl(heteroarylmethyl)-containing β-aryl(heteroaryl)ethylamines[12–15] with a new type of *ortho*-heterocyclic groups. Such derivatives are usually accessed by various recyclizations of functionalized hydro heteroarenes when both important 2-aminoethyl and heteroaryl (heteroarylmethyl) moieties are formed simultaneously.[16]

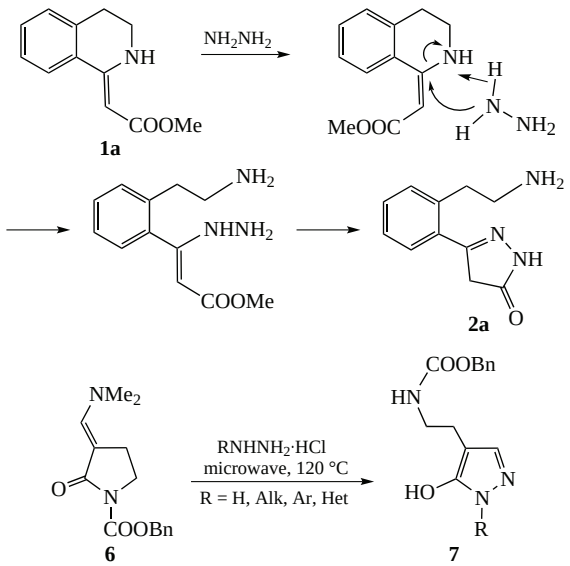
In our experiments, recyclization of isoquinolines **1** with hydrazine was affected only by the nature of the R^3 group (of substituents R^1, R^2 and R^3 present in them). When R^3 = Me (compounds **1a**,**b**), the reaction occurred readily under reflux in EtOH with a small excess of hydrazine hydrate (6 h), whereas the reaction of ethoxycarbonyl analogues **1c**,**d** required the use of higher-boiling methylcellosolve (see Scheme 1). The recyclization products of isoquinolines **1a**–**d**, *i.e*. β-[*o*-(5-oxopyrazol-3-yl)aryl]ethylamines **2a**–**d**, were formed in 60–84% yields. Treatment of representative compound **2d** with benzoyl chloride gave the corresponding benzamide **3**.

Our method was successfully used to convert isoquinolines **1** to amine derivatives **5** with (ar)alkyl groups in position 4 of the pyrazole ring (see Scheme 1). For this purpose, they were first alkylated into intermediate (ar)alkyl derivatives **4**. The latter without isolation were subjected to recyclization with hydrazine without changing the solvent. The yields of desired (ar)alkylated amines **5a**–**d** were 48–67% in the one-pot procedure.

The probable recyclization mechanism (exemplified for compound **1a**, Scheme 2) involves two stages: nucleophilic substitution at the enamine carbon atom with opening of the hetero ring and cyclization of the open forms with the closure of the pyrazolone ring. A similar nucleophilic hydrazino-



Scheme 1 *Reagents and conditions*: i, NH_2NH_2, EtOH (with **1a**,**b**) or $MeO(CH_2)_2OH$ (with **1c**,**d**), reflux, 6 h; ii, PhCOCl, Et_3N, $CHCl_3$, reflux, 5 h, then NH_2NH_2, 6 h; iii, MeI (for **5a**,**c**), $MeO(CH_2)_2OH$, reflux, 10 h, then NH_2NH_2, reflux, 5 h; iv, $PhCH_2Cl$ (for **5b**) or $PhCH_2I$ (for **5d**), EtOH, reflux, 10 h, then NH_2NH_2, reflux, 5 h.



Scheme 2

deamination is also typical of linear aminomethylene-3-oxoalkanoates.[17–21] The reduced reactivity of isoquinolines **1c**,**d** can be explained within the framework of this mechanism by the steric effect of the ethyl group at the rate-limiting stage, *i.e.*, cyclization of open forms. Bearing this in mind, compounds with more sterically hindered attack at the CO group in the alkoxycarbonyl substituent and compounds with one or two additional competitive electrophilic reaction centres may be considered as possible limitations on the use of this recyclization.

The reaction described above resembles the recyclization of pyrrole **6** into β-heteroarylethylamines **7**[22] (see Scheme 2) as it also results in the generation of 2-aminoethyl and heteroaryl groups in the products. It also occurs due to the existence of a two-centred reaction unit >NCH=CHCO– in the substrate, though this unit is incorporated into the hetero ring in a different way.

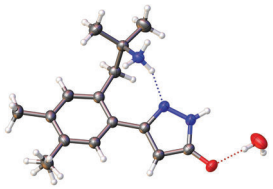


Figure 1 Molecular structure of pyrazolonyl derivative hydrate **2c** (from methyl cellosolve; the thermal ellipsoids are shown at 50% level).

The structures of the resulting compounds were confirmed by ^1H and ^{13}C NMR spectra and by single-crystal X-ray diffraction for compound **2c** (Figure 1).[†] Interestingly, in the solid phase the pyrazolone derivative **2c** has rather an unusual structure of the internal salt monohydrate corresponding to formation of betaine of an untypical pyrazolone N(1)H,N(2)H-tautomer due to migration of the N(2)-proton to the amino group through the internal hydrogen bond existing between the two nitrogen atoms.

A quantum-chemical calculation (B3LYP/6-311G**) showed that both betaine **2c** itself and its simpler analogue without methyl groups are absolutely unstable, since they pass into non-betaine forms through a barrier-free process with a large energy gain ($\Delta E_{tot} \approx -25$ kcal mol^{-1} for both betaines; the energy of unstable betaine forms is given for partially optimized structures with $d^{N—H} = 1.00$ Å). The fact that compound **2c** exists in crystals in betaine form is due to the greater polarity of this form ($\mu_{calc} = 10.8$ D, against 6.6 D for the non-betaine form) and its

[†] *Crystal data for* **2c**. $C_{15}H_{23}N_3O_2$ ($M = 277.36$ g mol^{-1}): monoclinic, space group $P2_1/c$ (no. 14), $a = 13.0630(3)$, $b = 9.6899(2)$ and $c = 12.6477(3)$ Å, $\beta = 108.487(3)°$, $V = 1518.32(6)$ Å^3, $Z = 4$, $T = 293(2)$ K, μ(CuKα) = 0.656 mm^{-1}, $d_{calc} = 1.213$ g cm^{-3}, 16441 reflections measured ($7.136° \leqslant 2\theta \leqslant 152.378°$), 3167 unique ($R_{int} = 0.0249$, $R_{sigma} = 0.0163$) which were used in all calculations. The final R_1 was 0.0391 [$I > 2\sigma(I)$] and wR_2 was 0.1148 (all data).

CCDC 2193910 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

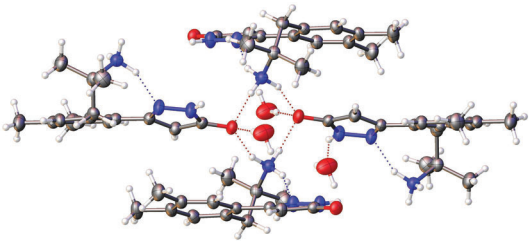


Figure 2 The tetrameric fragment of the crystal packing of pyrazonyl derivative **2c**.

strong intermolecular association resulting in a hydrogen-bound polymer structure whose tetrameric part is shown in Figure 2. The four betaine molecules of the tetramer form an eight-membered hydrogen-bonded cycle through two $^{+}NH_3$ groups and two carbonyl oxygen atoms, where each oxygen would form a trifurcated H-bond resembling that in *p*-bromophenylurea because of additional binding to a water molecule.[23]

In conclusion, an efficient synthetic approach to derivatives of natural β-arylethylamines containing *ortho*-positioned 5-pyrazolone substituents in the aryl moieties and their analogues has been suggested.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.017.

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