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Mendeleev Commun., 2008, **18**, 213–214
Mendeleev Communications

Synthesis of 3-substituted 1,5-dinitro-3-azabicyclo-[3.3.1]nonanes containing a pyrazole fragment

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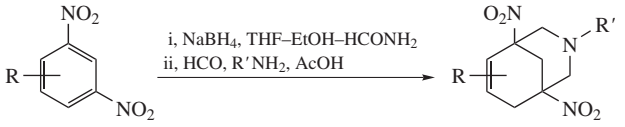
DOI: 10.1016/j.mencom.2008.07.016

3-R-1,5-Dinitro-3-azabicyclo[3.3.1]nonanes fused with a pyrazole ring were synthesised based on isomeric 4,6-dinitro-1- and 2-phenylindazoles.

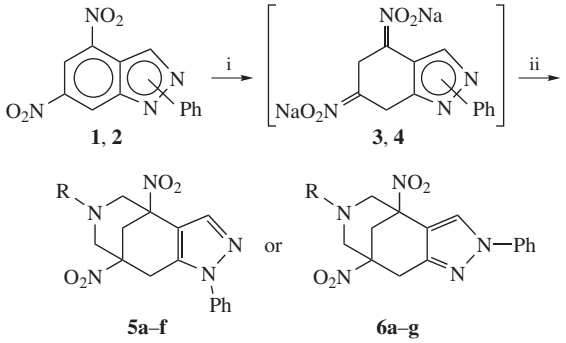
Heteroanalogues of bicyclo[3.3.1]nonanes are contained in terpene alkaloids and used as biologically active compounds.[1] Recently, an efficient antiarrhythmic activity was found in 1,5-dinitro-3-azabicyclo[3.3.1]nonenes.[2] Many of them were synthesised earlier[2–5] on the basis of substituted 1,3-dinitrobenzenes (Scheme 1). This synthesis involves the reduction of carbon–carbon bonds of the benzene ring activated by meta-arranged nitro groups under the action of $NaBH_4$ or KBH_4 and further double Mannich reaction with formaldehyde and primary amines. There are a few examples of the synthesis of such compounds containing heteroaromatic fragments.[5,6] However, there is no information on the synthesis of 3-azabicyclo[3.3.1]-nonanes fused with five-membered heterocycles.



R = OH, Alk, Hal, OAlk, COOH R′ = Alk, $(CH_2)_nCOOH$

Scheme 1

We found 4,6-dinitrobenzoannelated five-membered aromatic heterocycles to be suitable precursors for the synthesis of 3-R-1,5-dinitro-3-azabicyclo[3.3.1]nonanes containing a hetero-aromatic fragment.



1, **3** 1-Ph
2, **4** 2-Ph

5, **6** **a** R = Me
b R = CH_2COOH
c R = $(CH_2)_2COOH$
d R = CH(Me)COOH
e R = Pr^i
f R = $(CH_2)_3COOH$
g R = $(CH_2)_2Cl$

Scheme 2 *Reagents and conditions*: i, $NaBH_4$ (5.6 equiv.), THF–EtOH–$HCONH_2$, 10 °C, 1 h; ii, HCHO (30% aqueous solution) (12 equiv.), RNH_2 (12 equiv.), AcOH–H_2O.

Here, we report the synthesis of 3-R-1,5-dinitro-3-azabicyclo-[3.3.1]nonanes fused with a pyrazole ring. Starting materials in the synthesis of the above compounds are isomeric 4,6-dinitro-1- and 2-phenylindazoles **1** and **2**, which can be prepared from 2,4,6-trinitrotoluene (TNT).[7,8]

Thus, the interaction of dinitroindazoles **1** and **2** with $NaBH_4$ gave rise to hydride adducts **3** and **4**,[9] on treatment of which with formaldehyde solution and primary amine tricyclic derivatives are formed – 1,5-dinitro-3-azabicyclo[3.3.1]nonanes **5a–f** and **6a–g**, annulated with a pyrazole ring at the C(7)–C(8) bond (Scheme 2). Alkylamines and amino acids were used as primary amines.

The structures of compounds **5** and **6** were supported by NMR and IR spectroscopy and elemental analysis.†

The steric structures of 1,5-dinitro-3-azabicyclo[3.3.1]nonane derivatives **5** and **6** were studied using compound **5a** as an

† Compounds synthesised were characterised by ^{1}H NMR spectroscopy and elemental analysis. ^{1}H NMR spectra (in [$^2H_6$]DMSO) were recorded on a Bruker AM-300 spectrometer.

General procedure for the preparation of compounds **5**, **6** and **8**. To a solution of 0.48 g (1.7 mmol) of compound **1** or **2** in a mixture of 2 ml of THF, 6 ml of EtOH and 4 ml of formamide 0.36 g (9.5 mmol) of $NaBH_4$ were added portionwise over 20 min at a temperature below 10 °C. After 30 min, 7 ml of water was added followed by an addition of the mixture of 2 ml of 30% aqueous solution of RNH_2, 2 ml of water and 2 ml of 30% aqueous solution of formaldehyde, and then 2 ml of glacial AcOH. After stirring for 30 min at room temperature, the reaction mixture was poured into 150 ml of water, the precipitate was collected by filtration and dried in air.

5a: yield 48%, mp 152–154 °C (EtOH). ^{1}H NMR, δ: 2.34 (s, 3H, NMe), 2.55 (d, 1H, *J* 10.2 Hz), 2.60 (d, 1H, *J* 10.9 Hz), 2.80 (d, 1H, *J* 11.8 Hz), 3.09 (d, 1H, *J* 11.8 Hz), 3.27 (d, 1H, *J* 10.2 Hz), 3.31 (d, 1H, *J* 10.9 Hz), 3.41 (d, 1H, *J* 16.6 Hz), 3.47 (d, 1H, *J* 16.7 Hz), 7.43 (m, 1H, Ph), 7.49–7.51 (m, 4H, Ph), 7.69 (s, 1H, Pz).

5b: yield 70%, mp 154–155 °C. ^{1}H NMR, δ: 2.92 (d, 1H, *J* 12.8 Hz), 3.08 (d, 1H, *J* 12.9 Hz), 3.23–3.57 (m, 7H), 3.74 (d, 1H, *J* 16.2 Hz), 7.44 (t, 1H, *p*-Ph, *J* 8.1 Hz), 7.52–7.65 (m, 5H, Pz, Ph).

5c: yield 80%, mp 208–210 °C. ^{1}H NMR, δ: 2.24 (t, 2H, CH_2, *J* 5.1 Hz), 2.60–3.53 (m, 9H), 3.72 (d, 1H, *J* 16.2 Hz), 7.41–7.64 (m, 6H, Pz, Ph).

5d: yield 68%, mp 193–194 °C. ^{1}H NMR, δ: 0.89, 1.04 [2d, 3H, Me (mixture of diastereomers), *J* 7.6 Hz], 2.92–3.53 (m, 8H), 3.73 (d, 1H, *J* 16.1 Hz), 7.43–7.62 (m, 6H, Pz, Ph).

5e: yield 72%, mp 96–98 °C. ^{1}H NMR, δ: 0.88 (d, 3H, Me, *J* 8.6 Hz), 1.06 (d, 3H, Me, *J* 8.6 Hz), 2.91–3.67 (m, 9H), 7.38–7.63 (m, 6H, Pz, Ph).

5f: yield 75%, mp 79–81 °C. ^{1}H NMR, δ: 1.46 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 2.41 (m, 2H, CH_2), 2.68 (d, 1H, *J* 10.7 Hz), 2.75 (d, 1H, *J* 10.7 Hz), 2.94 (d, 1H, *J* 10.7 Hz), 3.10 (t, 2H, *J* 12.9 Hz), 3.32 (d, 2H, *J* 17.5 Hz), 3.79 (d, 1H, *J* 17.5 Hz), 7.42–7.63 (m, 6H, Pz, Ph).

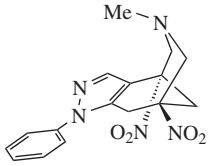


Figure 1 Steric structure of **5a**.

example. The data of NMR experiments (^{1}H, ^{13}C, COSY, 2D-NOESY, HSQC and HMBC) showed that the piperidine ring in the molecule of **5a** has the 'chair' conformation, although the cyclohexene ring is approximately planar (Figure 1).

These data are analogous to published data[10,11] obtained for 7-polyfluoroalkoxy-1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes.

On interaction of 3-cyano-4,6-dinitro-1-(4-nitrophenyl)indazole **7** prepared by the nitration of a corresponding N-phenyl derivative[12] with $NaBH_4$ the reduction proceeds selectively (only at the dinitrophenyl fragment) and further double Mannich reaction with formaldehyde and glycine gives tricyclic derivative **8**† in a good yield (Scheme 3).

Thus, based on isomeric 4,6-dinitro-1- and 2-phenylindazoles, a general method was developed for the synthesis of 3-R-1,5-dinitro-3-azabicyclo[3.3.1]nonanes fused with a pyrazole ring, a new type of 1,5-dinitro-3-azabicyclo[3.3.1]nonanes.

6a: yield 29%, mp 127–129 °C (EtOH). ^{1}H NMR, δ: 2.26 (s, 3H, NMe), 2.52, 2.60, 2.72 (3d, 1H, *J* 10.1 Hz), 2.92, 3.05 (2d, 1H, *J* 11.1 Hz), 3.17 (d, 1H, *J* 8.9 Hz), 3.35–3.54 (m, 2H), 7.31 (t, 1H, *p*-Ph, *J* 8.1 Hz), 7.48 (t, 2H, *m*-Ph, *J* 8.1 Hz), 7.85 (d, 2H, *o*-Ph, *J* 8.0 Hz), 8.42 (s, 1H, Pz).

6b: yield 82%, mp 88–90 °C. ^{1}H NMR, δ: 2.92 (d, 1H, *J* 13.3 Hz), 3.02–3.54 (m, 9H), 7.28 (t, 1H, *p*-Ph, *J* 8.2 Hz), 7.45 (t, 2H, *m*-Ph, *J* 8.2 Hz), 7.80 (d, 2H, *o*-Ph, *J* 8.3 Hz), 8.43 (s, 1H, Pz).

6c: yield 76%, mp 92–94 °C. ^{1}H NMR, δ: 2.25 (t, 2H, CH_2, *J* 6.6 Hz), 2.65–3.62 (m, 10H), 7.28 (t, 1H, *p*-Ph, *J* 8.0 Hz), 7.46 (t, 2H, *m*-Ph, *J* 8.1 Hz), 7.82 (d, 2H, *o*-Ph, *J* 8.1 Hz), 8.38 (s, 1H, Pz).

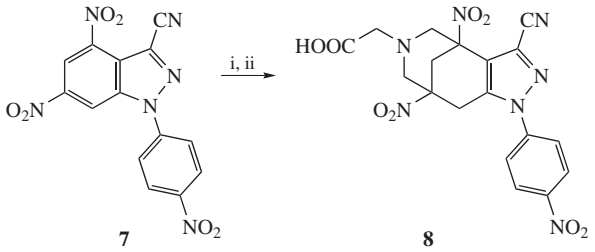
6d: yield 76%, mp 188–190 °C. ^{1}H NMR, δ: 0.88, 1.08 [2d, 3H, Me (mixture of diastereomers), *J* 8.6 Hz], 2.95–3.58 (m, 9H), 7.29 (t, 1H, *p*-Ph, *J* 8.5 Hz), 7.47 (t, 2H, *m*-Ph, *J* 8.6 Hz), 7.83 (d, 2H, *o*-Ph, *J* 8.6 Hz), 8.41 (s, 1H, Pz).

6e: yield 83%, mp 139–141 °C. ^{1}H NMR, δ: 0.81 (d, 3H, Me, *J* 8.6 Hz), 0.90 (d, 3H, Me, *J* 8.6 Hz), 2.80–3.52 (m, 9H), 7.28 (t, 1H, *p*-Ph, *J* 8.1 Hz), 7.47 (t, 2H, *m*-Ph, *J* 8.1 Hz), 7.83 (d, 2H, *o*-Ph, *J* 8.0 Hz), 8.37 (s, 1H, Pz).

6f: yield 75%, mp 75 °C. ^{1}H NMR, δ: 1.48 (m, 2H, CH_2), 1.86 (m, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.73–3.30 (m, 5H), 3.34–3.62 (m, 3H), 7.29 (t, 1H, *p*-Ph, *J* 8.5 Hz), 7.48 (t, 2H, *m*-Ph, *J* 8.4 Hz), 7.80 (d, 2H, *o*-Ph, *J* 8.6 Hz), 8.35 (s, 1H, Pz).

6g: yield 16%, mp 65–67 °C. ^{1}H NMR, δ: 2.71–3.10 (m, 6H), 3.23–3.58 (m, 6H), 7.30 (t, 1H, *p*-Ph, *J* 8.1 Hz), 7.47 (t, 2H, *m*-Ph, *J* 8.1 Hz), 7.82 (d, 2H, *o*-Ph, *J* 8.2 Hz), 8.42 (s, 1H, Pz).

8: yield 75%, mp 178–180 °C. ^{1}H NMR, δ: 2.95–3.45 (m, 8H), 3.60 (d, 1H, *J* 18.6 Hz), 3.93 (d, 1H, *J* 18.6 Hz), 8.00 (d, 2H, 4-$NO_2C_6H_4$, *J* 9.4 Hz), 8.43 (d, 2H, 4-$NO_2C_6H_4$, *J* 9.4 Hz).



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This work was supported by the Russian Foundation for Basic Research (grant no. 07-03-00414).

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Received: 14th March 2008; Com. 08/3102