# New functional glycoluril derivatives

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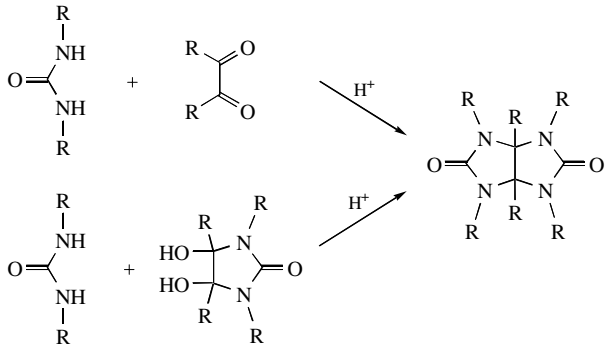
Functional glycoluril (2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione) derivatives containing 2-hydroxyethyl, carboxyl and amino groups were synthesised.

It is well known that glycoluril derivatives (2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones, TABODs) show a wide range of biological activity,[1,2] for example, 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione is used in clinical practice as the tranquilliser Mebicar.[3] The capability of TABODs to exhibit simultaneously both hydrophilic and lipophilic properties is responsible for the physiological action of these compounds. On the one hand, they can easily penetrate into the body and, on the other hand, readily overcome the hemato-encephalic barrier. It is interesting to perform a combinatorial synthesis of TABODs with other known classes of biological substances in order to refine the mechanism of biological effects. To solve this problem, we prepared functional TABOD derivatives containing amino, 2-hydroxyethyl and carboxyl groups for the first time.

The addition of functional groups to nitrogen atoms of TABODs was almost not described in the literature. Only particular examples of *N*-hydroxymethyl derivatives, which were prepared by the reaction of TABODs with an alkaline formaldehyde solution, are known.[4] For the most part, di-*N*-hydroxymethyl and tetra-*N*-hydroxymethyl derivatives of TABODs were synthesised.

Two approaches may be suggested to prepare TABOD derivatives of interest. One of them consists in the introduction of a functional group into a completed TABOD molecule, which is used for the hydroxymethyl derivatives of TABODs. The other uses a bicyclization reaction involving specially synthesised ureas containing functional groups at nitrogen atoms. We decided on the latter method because the nitrogen atoms of TABODs exhibit a weak nucleophilicity.

It is well known that TABODs can be prepared by the reaction of ureas with α-dicarbonyl compounds or 4,5-dihydroxyimidazolidin-2-ones in aqueous or aqueous-ethanol media in the presence of acids[5] (Scheme 1).

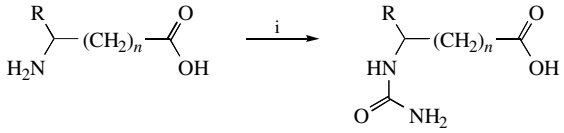


**Scheme 1**

The syntheses of ureas containing amino acid units starting from amino acid esters are known.[6,7] We developed a simple procedure for preparing ureas directly from relevant amino acids **1a**–**c** (Scheme 2).

With the use of *S*(+)-α-alanine, the *S*(–) isomer of **1c** was isolated, as found by polarimetry ($[\alpha]_D^{23}$ –8.25°, *c* = 2, $H_2O$).

Other ureas **1d** and **1e** containing 2-(*N*-acetyl)aminoethyl and 2-hydroxyethyl groups, respectively, were prepared according to standard procedures.[8,9]

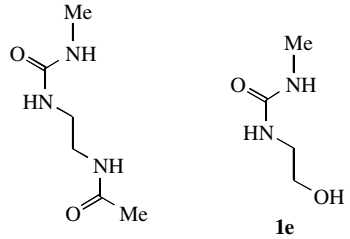


**1a** *n* = 1, R = H
**1b** *n* = 0, R = H
**1c** *n* = 0, R = Me

**Scheme 2** *Reagents and conditions*: i, $H_2O$, KCNO, reflux for 20 min, addition of HCl to pH 3.

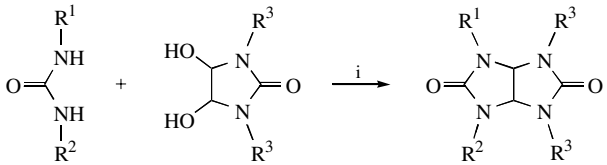
Ureas **1a**–**e** were entered into a bicyclization reaction with dihydroxyimidazolidin-2-ones **2a**,**b**. As a result, new functional TABOD derivatives **3a**–**g** were obtained (Scheme 3).

It is interesting to note that the reaction of *S*(–) **1c** with **2a** is diastereoselective. The $^1$H NMR spectrum of **3e** exhibits signals due to protons of two diastereoisomers. An analysis of the most



**1d** **1e**

informative portion of the $^1$H NMR spectrum (the range 4.0–4.5 ppm of signals due to CH protons) indicated that according to integral intensities the ratio between diastereoisomers in the reaction mixture is 2:5. This ratio remained almost unchanged in the course of isolation of **3e**.†



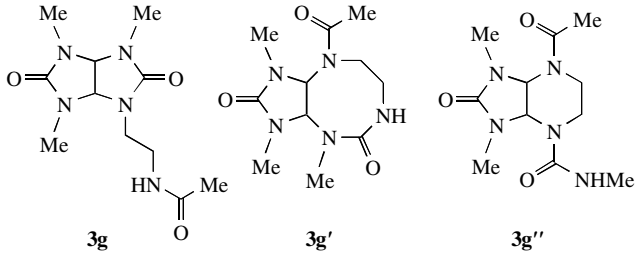
**1** **2** **3**

**1**: **a** $R^1$ = H, $R^2$ = $CH_2CH_2COOH$
**b** $R^1$ = H, $R^2$ = $CH_2COOH$
**c** $R^1$ = H, $R^2$ = CH(Me)COOH
**d** $R^1$ = Me, $R^2$ = $CH_2CH_2NHCOMe$
**e** $R^1$ = Me, $R^2$ = $CH_2CH_2OH$
**2**: **a** $R^3$ = H
**b** $R^3$ = Me
**3**: **a** $R^1$ = $R^3$ = H, $R^2$ = $CH_2CH_2COOH$
**b** $R^1$ = H, $R^2$ = $CH_2CH_2COOH$, $R^3$ = Me
**c** $R^1$ = $R^3$ = H, $R^2$ = $CH_2COOH$
**d** $R^1$ = H, $R^2$ = $CH_2COOH$, $R^3$ = Me
**e** $R^1$ = $R^3$ = H, $R^2$ = CH(Me)COOH
**f** $R^1$ = Me, $R^2$ = $CH_2CH_2OH$, $R^3$ = H
**g** $R^1$ = $R^3$ = Me, $R^2$ = $CH_2CH_2NHCOMe$

**Scheme 3** *Reagents and conditions*: i, $H_2O$, pH 1, 90 °C, 1 h.

It would be expected that not only compound **3g**, but also alternative compounds **3g′** and **3g″** result from the reaction between **1d** and **2b**.

The structure of **3g** was supported by $^{15}$N NMR spectroscopy. Thus, in an INEPT experiment adjusted to the direct coupling constant $^{15}$N–$^{1}$H, the $^{15}$N NMR spectrum exhibited a doublet of the NH group at –266.8 ppm with the constant $^{1}J(^{15}\text{N}–^{1}\text{H})$ = 91.9 Hz. On the selective polarisation transfer from the protons of the MeCO group (1.72 ppm in the $^{1}$H NMR spectrum), the $^{15}$N NMR signal was observed with the same chemical shift and splitting due to direct NH coupling, $J$ 91.9 Hz, and antiphase splitting, $J$ 2.0 Hz, due to long-range coupling with Me protons. This is indicative of the presence of the MeCONH unit in the molecule of only compound **3g**.



**3g** **3g′** **3g″**

Compounds **3a**–**g** are of special interest as biologically active substances, and the introduced functional groups make it possible to combine TABODs with a wide variety of natural compounds.

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## References

1 O. V. Lebedev, L. I. Khmel'nitskii, L. V. Epishina, L. I. Suvorova, I. V. Zaikonnikova, I. E. Zimakova, S. V. Kirshin, A. M. Karpov, V. S. Chudnovskii, M. V. Povstyanoi and V. A. Eres'ko, in *Tselenapravlennyi poisk novykh neirotropnykh preparatov* (*Directed Search for Novel Neurotropic Drugs*), Zinatne, Riga, 1983, p. 81 (in Russian).
2 *Uspekhi khimii v sozdanii novykh biologicheski aktivnykh soedinenii* (*Chemical Advances in the Development of New Biologically Active Compounds*), ed. A. A. Bakibaev, Tomsk Polytechnic University, Tomsk, 1998, p. 67 (in Russian).
3 M. D. Mashkovskii, *Lekarstvennye sredstva* (*Drugs*), Meditsina, Moscow, 1993, p. 99 (in Russian).
4 H. Petersen, *Text. Res. J.*, 1971, **41**, 239.
5 H. Petersen, *Synthesis*, 1973, 243.
6 C. Harries and M. Weiss, *Liebigs Ann. Chem.*, 1903, 355.
7 H. Knolker and T. Braxmeier, *Synlett*, 1997, 925.
8 T. L. Davis and K. C. Blachard, *J. Am. Chem. Soc*., 1923, **45**, 1818.
9 F. Arndt, C. R. Noller and J. Georgsteinsson, *Org. Synth*., 1953, **15**, 48.

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† The $^{1}$H, $^{13}$C and $^{15}$N NMR spectra of solutions in [$^{2}H_6$]DMSO were recorded on a Bruker AM 300 spectrometer. Chemical shifts were measured with reference to the signals of the solvent at $\delta$ 2.50 ppm ([$^{2}H_6$]DMSO, $^{1}$H NMR) and 39.50 ppm ($^{13}$C NMR) or with the use of an external standard ($MeNO_2$, $^{15}$N NMR). The structures of new compounds were confirmed by elemental analysis.

**1a**: yield 96%, mp 180–182 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 2.30 (t, 2H, $CH_2$), 3.17 (q, 2H, $CH_2$), 5.70 (s, 2H, $NH_2$), 6.22 (t, 1H, NH).

**1b**: yield 98%, mp 193–195 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 3.65 (d, 2H, $CH_2$), 5.69 (s, 2H, $NH_2$), 6.22 (t, 1H, NH).

**1c**: yield 84%, mp 224–226 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 1.22 (d, 3H, Me), 4.05 (m, 1H, CH), 5.57 (s, 2H, $NH_2$), 6.22 (d, 1H, NH), 12.0–12.8 (br. s, 1H, COOH).

**1d**: yield 76%, mp 155–157 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 1.76 (s, 3H, MeCO), 2.43 (s, 3H, Me), 3.02 (m, 4H, $2CH_2$), 5.48 (s, 2H, $NH_2$), 6.01 (d, 1H, NH).

**1e**: yield 93%. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 2.48 (d, 3H, Me), 3.01 (q, 2H, $CH_2$), 3.35 (t, 2H, $CH_2$), 4.4 (br. s, OH), 5.05 (d, H, CH), 6.0 (br. s, 2H, 2NH).

**3a**: yield 58%, mp 215–217 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 2.3–2.6 (m, 2H, $CH_2$), 2.9–3.3 (m, 2H, $CH_2$), 5.12 (d, 1H, CH), 5.23 (d, 1H, CH), 7.11 (s, 1H, NH), 7.20 (s, 1H, NH), 7.28 (s, 1H, NH).

**3b**: yield 28%, mp 187–191 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 2.35–2.60 (m, 2H, $CH_2$), 2.64 (s, 3H, Me), 2.83 (s, 3H, Me), 3.20–3.60 (m, 2H, $CH_2$), 5.09 (d, 1H, CH), 5.22 (d, 1H, CH), 7.68 (s, 1H, NH), 12.2–12.4 (br. s, 1H, COOH).

**3c**: yield 60%, mp 273–275 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 3.62 (d, 1H, $CH_2$), 3.97 (d, 1H, $CH_2$), 5.28 (s, 2H, CH–CH), 7.29 (s, 2H, 2NH), 7.51 (s, 1H, NH).

**3d**: yield 31%, mp 258–260 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO): 2.66 (s, 3H, Me), 2.76 (s, 3H, Me), 3.83 (d, 1H, $CH_2$), 4.03 (d, 1H, $CH_2$), 5.14–5.23 (m, 2H, CH–CH), 7.90 (s, 1H, NH).

**3e**: yield 37%. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: diastereomer 1: 1.38 (d, 3H, Me), 4.02 (q, 1H, CH), 5.21 (d, 1H, CH), 5.30 (d, 1H, CH), 7.19 (s, 1H, NH), 7.23 (s, 1H, NH), 7.41 (s, 1H, NH); diastereomer 2: 1.41 (d, 3H, Me), 4.31 (q, 1H, CH). $^{13}$C NMR: diastereomer 1: 14.66 (Me), 51.82 (CH), 62.68 (CH), 67.68 (CH), 158.73 (CO), 160.95 (CO), 172.05 (COOH); diastereomer 2: 15.83 (Me), 51.96 (CH), 62.80 (CH), 67.08 (CH), 159.35 (CO), 161.21 (CO), 172.38 (COOH).

**3f**: yield 21%, mp 142–144 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 2.66 (s, 3H, Me), 3.05–3.25 (m, 2H, $CH_2$), 3.46 (t, 2H, $CH_2$), 5.21 (d, 1H, CH), 5.29 (d, 1H, CH), 7.25–7.50 (br. s, 2H, NH).

**3g**: yield 34%, mp 127–130 °C. $^{1}$H NMR ([$^{2}H_6$]DMSO) $\delta$: 1.72 (s, 3H, COMe), 2.68 (s, 3H, Me), 2.71 (s, 3H, Me), 2.75 (s, 3H, Me), 2.95–3.15 (m, 2H, $CH_2$), 3.28–3.42 (m, 2H, $CH_2$), 4.78 (d, 1H, CH), 5.06 (d, 1H, CH), 7.18 (t, H, NH). $^{13}$C NMR, $\delta$: 22.15 (Me), 37.31 ($CH_2$), 42.41 ($CH_2$), 68.88 (CH), 71.91 (CH), 158.35 (CO), 158.76 (CO), 170.07 (CO).