THE CHEMISTRY OF BICYCLIC BISUREAS

1. SYNTHESIS OF 2,4,6,8-TETRAAZABICYCLO[3.3.0]OCTANE-3,7-DIONES AND 2,4,6-8-TETRAAZABICYCLO[3.3.1]NONANE-3,7-DIONES BY THE REACTION OF UREAS WITH α- AND β-DICARBONYL COMPOUNDS

V. A. Eres'ko, L. V. Epishina,
O. V. Lebedev, L. I. Khmel'nitskii,
S. S. Novikov, M. V. Povstyanoi,
and A. F. Kulik

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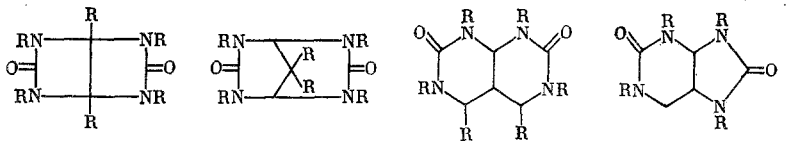
Some derivatives of 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (I) and 2,4,6,8-tetraazabicyclo[3.3.1]-nonane-3,7-dione (II) have been reported to display physiological activity [1] and for this reason the synthesis of a number of saturated bicyclic busureas (BBU) was undertaken. Preliminary pharmacological tests show that the number and nature of the substituents both on the N atoms and in the ring influence the character and degree of activity of the compounds.

Condensed saturated BBU's such as (I)-(IV) have been known for a long time



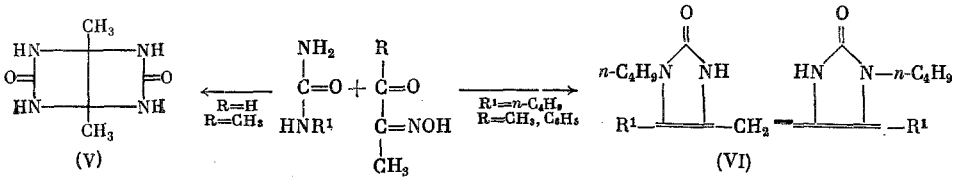
(I) (II) (III) (IV)

The synthesis of the first three types of BBU is based on the condensation of mono- or dicarbonyl compounds with urea [2], a reaction which is generally carried out in acid solution. The fourth type of BBU – the purones (IV) – are obtained by the electrochemical reduction of uric acid and its tetra-N-methyl derivatives [3].

In spite of the relative availability and widespread use of some BBU's [2], there is insufficient available data for the accurate evaluation of the psychotropic activity of these compounds. In this communication we describe a search for new methods of synthesizing BBU's and examine the limitations of known methods of synthesis.

The majority of BBU's of the octyl series (I) were obtained by the reaction of the simplest α-dialdehyde, glyoxal, with substituted and unsubstituted derivatives of urea. With α-aldehydoketones and α-diketones the reaction does not proceed so smoothly and in some cases the BBU is not obtained [2]. Furthermore, some α-dicarbonyl compounds are unstable and hence difficult to separate. For this reason we have studied the possibility of using the more accessible and stable α-isonitrosoketones for the synthesis of octyl BBU's.

The literature contains only one example of the formation of 1,5-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-dione (V) by the condensation of diacetyl monooxime with urea [4]; however, the monooximes of diacetyl and phenylglyoxal give products of a different type (VI) with n-butylene [5]



(V) (VI)

We found that some monooximes of alkyl- and aryl-α-dicarbonyl compounds (VII)-(IX) react with urea in acid solution to give BBU's of the octyl series (X)-(XII) in which the nitrogen atom is unsubstituted

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Kherson Branch, Odessa Technological Institute of the Food Industry. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 5, pp. 1073-1076, May, 1979. Original article submitted January 9, 1978.

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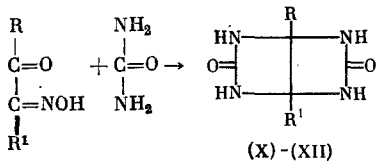
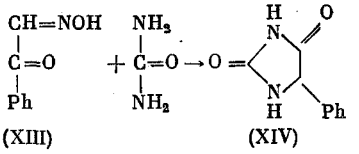


(X)-(XII)

(VII)—(IX)

R=H, R^1=CH_3 (VII), (X); R=CH_3, R^1=C_6H_5 (VIII), (XI); R=CH_3, R^1=n-C_3H_7 (VIII), (XII)

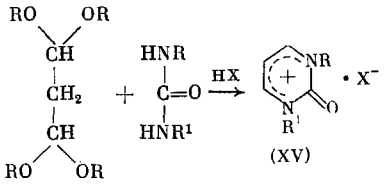
However, with phenylglyoxal monooxime (XIII), as also with phenylglyoxal itself [6], 5-phenylhydantoin (XIV) was obtained



(XIII) (XIV)

The reaction between methylurea and dimethylurea, and the monooximes (VII)-(IX) and (XIII) does not give bicyclic products; instead only very small amounts of the dioxime of the corresponding α-dicarbonyl compounds were isolated from the reaction mixture.

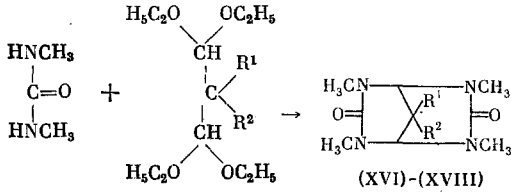
The formation of nonyl BBU's (II) by the condensation of malonic anhydride derivatives with both unsubstituted and monosubstituted ureas has been reported [2]. With the disubstituted ureas, instead of the BBU (II) the quaternary salt of 2-pyrimidine (XV) is formed [7].



(XV)

R and R' can be the same or different alkyl groups

We also made a more detailed study of the reaction between the β-dicarbonyl compound and N,N'-dimethylurea and we developed a method of preparing nonyl BBU's using this reaction



(XVI)-(XVIII)

R^1=R^2=H (XVI); R^1=R^2=CH_3 (XVII); R^1=H, R^2=Br

In contrast to the synthesis of the 2-pyrimidone salts [7], this reaction should be carried out at low temperatures.

The structures of the compounds were confirmed by elemental analysis and IR and PMR spectroscopy.

EXPERIMENTAL

Spectral measurements were obtained on a UR-10 spectrometer (in KBr pellets), PMR spectra on a Perkin-Elmer spectrometer (60 MHz), and mass spectra on a Varian MAT CH-6. The course of the reaction and the purity of compounds were checked by the TLC using silica gel L 5/40 μm plates which were developed in iodine vapor.

The starting and end products had constants in agreement with those in the literature [1, 6, 8].

1-Methyl-2,4,6,8-tetraazabicyclo[3.3.0] octane-3,7-dione (X). To a stirred mixture of 50.9 g (0.58 mole) of methylglyoxal monooxime (VII) [9] and 104 g (1.74 mole) of urea in 170 ml of water at 25°C was added dropwise 4 ml of concentrated HCl. The temperature was raised to 28°C, the mixture maintained at this temperature for 4 h, cooled, the precipitate of (X) filtered off, washed with methanol (~ 50 ml), and dried in air. A yield of 20 g (23%) of (X) with mp 274°C (from aqueous acetone) was obtained; R_f 0.54 (butanol:methanol:water = 3:1:1); cf. [8].

1-Methyl-5-phenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (XI). A mixture of 6 g (0.1 mole) of urea and 1.4 g (0.008 mole) of methylphenylglyoxal monooxime (VIII) [9] in 39 ml of 70% methanol was heated to 95°C and 2 ml of concentrated H_2SO_4 added. After 4 h, the reaction mixture was cooled and left at ~20°C for 2 days. The precipitated material was washed with water, acetone, and dried in air to give 0.2 g (10.5%) of (XI), mp 340°C (from AcOH). IR spectrum (ν, cm^{-1}): 1690 (C=O), 3250 (NH). Found: C 55.58; H 5.36; N 23.60%. $C_{11}H_{12}N_4O_2 \cdot 0.3\ H_2O$. Calculated: C 55.70; H 5.32; N 23.62%.

1-Methyl-5-n-propyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (XII). To a mixture of 2.4 g (0.04 mole) of urea and 1.7 g (0.013 mole) of methylpropylglyoxal monooxime (IX) [9] in 7 ml of water at 50°C was added 0.5 ml of concentrated HCl. This was then heated for 1 h at 90°C cooled, and neutralized with $NaHCO_3$ to pH 7. The precipitate of (XII) was washed with acetone (3 × 10 ml), and dried in air to give 0.3 g (11%) of (XII) mp 312-312.5°C (from methanol). IR spectrum (ν, cm^{-1}): 1730 (C=O), 3290 (NH). Found: C 48.53; H 7.08; N 28.36%; mol. wt. $C_8H_{14}N_4O_2$. Calculated: C 48.47; H 7.12; N 28.27%; mol. wt. 198.

5-Phenylhydantoin (XIV). A mixture of 12 g (0.2 mole) of urea, 6.25 g (0.025 mole) of phenylglyoxal monooxime (XIII), [9] and 4 ml of concentrated HCl in 30 ml of 80% aqueous methanol was refluxed for 3 h, cooled, and neutralized with $NaHCO_3$ (pH 7). The precipitated material was washed with 10 ml of water and dried in air to give 2.9 g (66%) of (XIV), mp 182°C; cf. [6].

2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (XVI). A mixture of 30 g (0.32 mole) of N,N'-dimethylurea in 100 ml of water and 5 ml of concentrated HCl was maintained at 30-35°C for 6 h, while 17.7 g (0.08 mole) of the tetraethylacetal of malonic dialhyde was added dropwise. The solution was maintained at 20°C for 3 h and the solvent evaporated in vacuum until crystals started to form; the mother liquor was cooled to 0°C. The precipitate of (XVI) was washed with 10 ml of acetone, and ether (3 × 10 ml), and dried in air to give 4 g (25%) of (XVI), mp 320-321°C (from water); cf. [1].

2,4,6,8,9,9-Hexamethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (XVII). To a solution of 19 g (0.22 mole) of N,N'-dimethylurea in 75 ml of water was added dropwise 1.5 ml of concentrated HCl, the solution kept at 60°C for 1.5 h and 19 g (0.06 mole) of the β,β-dimethyltetraethylacetal of malonic dialdehyde added [10]. The reaction mixture was maintained for 1 h at 20°C and then neutralized with 20% aqueous NaOH. The solvent was evaporated in vacuum until crystals started to appear, the precipitate of (XVII) dried in air (9.7 g), and the filtrate extracted with CH_2Cl_2 to give a further 4.8 g of (XVII). The precipitates were combined and recrystallized from a mixture of acetone and methylene chloride to give 13.5 g (92%) of (XVII) mp 285-286°C; cf. [1].

2,4,6,8-Tetramethyl-9-bromo-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (XVIII). To 5 g (0.057 mole) of N,N'-dimethylurea in 25 ml of water was added 2.5 ml of concentrated HCl and after 30 min at 80°C, 3 g (0.01 mole) of the β-bromotetraethylacetal of malonic dialdehyde [10] was added dropwise. The reaction mixture was heated on the water bath, cooled, and extracted with CH_2Cl_2 (5 × 20 ml). The extract was evaporated until crystals started to appear and the precipitate of (XVIII) washed with acetone, ether, and dried in air to give 0.2 g (7%) of (XVIII), mp 239-239.5°C (with decomp., from a mixture of methanol and acetone), R_f 0.67 (ethanol). IR spectrum (ν, cm^{-1}): 1648 (C=O), 3005-2970-2915 (N=CH_3). Found: C 37.65; H 5.26%. $C_6H_{15}BrN_4O_2$. Calculated: C 37.13; H 5.19%.

CONCLUSIONS

1. The monooximes of alkyl- and aryl-α-dicarbonyl compounds gave 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione only with the unsubstituted urea.

2. The most favorable conditions for the preparation of tetra-N-methyl derivatives of 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-diones by the condensation of N,N'-dimethylurea with malonic aldehyde tetraacetal and its substituted derivatives were established.

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SYNTHESIS OF 4-SUBSTITUTED THIACYCLOHEXANES

N. P. Volynskii and L. P. Shcherbakova

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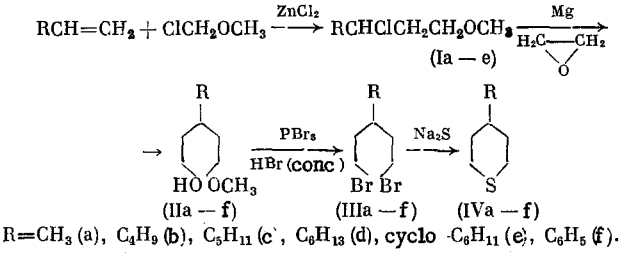
Few good methods of synthesizing 4-substituted thiacyclohexanes have been developed. Until now, 4-methyl- [1, 2] and 4-t-butylthiacyclohexane [2] have been obtained by various methods, and a general method for the preparation of 4-alkylthiacyclohexanes starting from 4-thiacyclohexanes has been reported [3].

We offer a four-stage scheme for the synthesis of 4-substituted thiacyclohexanes, starting from α-olefins.



R=CH_3 (a), C_4H_9 (b), C_5H_{11} (c), C_6H_{13} (d), cyclo-C_6H_{11} (e), C_6H_5 (f).

Alkoxymethylation of olefins in the presence of $ZnCl_2$ is described in [4-7]. The 3-chloroalkyl ether which is obtained reacts with Mg and ethylene oxide to give the 3-R-substituted 5-methoxypentanol, which on bromination gives a quantitative yield of the corresponding 1,5-dibromoalkane, a reaction which occurs without any tarring. Treatment of the 1,5-dibromoalkane with an aqueous alcoholic solution of Na_2S, using a modification of the method given in [1], yields the 4-substituted thiacyclohexane. The moderate yields obtained in the first two stages of the process are compensated for by the simplicity of the reaction, and by the ready availability of the starting compounds. When methyl-2-chloroethyl ether was used in place of ethylene oxide, reaction with the Grignard reagent resulted in loss of HCl to give methyl vinyl ether instead of the expected increase in length of carbon chain.*

4-Cyclohexylthiacyclohexane (IVe) was synthesized in two ways – from vinylcyclohexane and from styrene; the latter method involves an additional step in which the intermediate 3-phenyl-5-methoxypentanol (IIf) is hydrogenated in the presence of Raney nickel. All the sulfides were oxidized to the corresponding sulfones (Va-f). The yields and properties of the compounds are presented in Tables 1 and 2.

EXPERIMENTAL

Methyl 3-Chlorobutyl Ether (Ia). Hydrogen chloride was passed through a gently stirred mixture of 600 g (20 moles) of paraformaldehyde and 810 ml (20 moles) of CH_3OH at 0-15°C until the solution was saturated. The lower aqueous-acidic layer was separated with a syphon and Na_2SO_4 was added to remove the remaining moisture. The dissolved HCl was driven off by heating to 50-55°C.

The $ClCH_2OCH_3$ obtained was warned to 30-40°C, 200 g of $ZnCl_2$ added, and the solution saturated with propylene (3-4 h). A Tishchenko flask (~10 mm of mercury) was attached to the upper end of the condenser and the reaction was carried out with vigorous stirring and periodic cooling with water. After the passage of propylene was complete, 1 liter of water was added, the aqueous layer separated, and the product dried with Na_2SO_4. Distillation gave 1000 g (Ia) with bp 122-127°C (see Table 1).

*The author of [6] stages that according to [8], a halogen atom β to the alkoxy group is extremely inert. However, [8] contains no such assertion.

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