

Preparation of Some Imino- and Cyano-imino-substituted Barbiturates

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A number of imino- and cyano-iminobarbituric acid derivatives has been prepared in good yield by gradually adding sodium methoxide — as condensation catalyst — to some substituted cyanoacetic and malonic esters reacting with urea, dicyandiamide and guanidine.

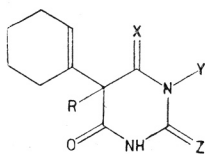
Barbiturates are prepared usually by condensing a substituted cyanoacetic or malonic ester with urea, guanidine or dicyandiamide in the presence of an alkali metal alkoxide as condensation catalyst; the corresponding imino- and cyano-imino-intermediates are then subjected to acid hydrolysis. The condensation is carried out in the presence of an excess of the condensing agent, usually sodium ethoxide, at relatively high concentration of sodium, and high temperatures, and sometimes under pressure. A disadvantage of such procedure resides in the fact that cleavage, mostly decarboxylation of the substituted cyanocetic or malonic ester takes place^{1, 2, 3, 4, 5}, resulting in a decrease of yield due to the formation of undesired byproducts^{4, 6, 7} (e. g. 35% in the case of ethyl ethyl-phenylmalonate and urea⁸). To suppress this ester decomposition catalyzed by sodium ethoxide, the condensation of cyanoacetic or malonic esters with urea or its derivatives was carried out by adding the catalyzing ethanolic sodium ethoxide solution to the reaction mixture gradually, i. e. at a rate at which the condensation occurs and controlling the temperature of reaction^{3, 5}.

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The principle of gradual addition of the condensation catalyst to the reaction mixture was later applied to sodium methoxide, which was used in the condensation of ethyl malonate with urea⁹. The gradual addition of sodium methoxide as condensing agent has now been extended to condensations of some substituted cyanoacetic and malonic esters with urea, guanidine nitrate and dicyandiamide. Thus, a number of imino- and cyano-imino-derivatives was prepared in good yield, which after acid hydrolysis gave the corresponding barbiturates.

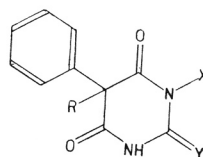
The derivatives prepared are listed below.

* In collaboration with V. Popović from the Chemical Department, Military Technical Institute.



I.

- a) R = CH₃; X = NH; Y = H; Z = O
 b) R = CH₃; X,Z = NH; Y = H
 c) R = CH₃; X,Z = NH; Y = CN
 d) R = CH₃; X,Z = O; Y = H
 e) R = C₂H₅; X = NH; Y = H; Z = O
 f) R = C₂H₅; X,Z = NH; Y = H
 g) R = C₂H₅; X,Z = NH; Y = CN
 h) R = C₂H₅; X,Z = O; Y = H



II.

- a) R = H; X = H; Y = NH
 b) R = H; X = CN; Y = NH
 c) R = CH₃; X = H; Y = O
 d) R = CH₃; X = H; Y = NH
 e) R = CH₃; X = CN; Y = NH
 f) R = CH₃; X = H; Y = O
 g) R = C₂H₅; X = H; Y = NH
 h) R = C₂H₅; X = CN; Y = NH
 i) R = C₂H₅; X = H; Y = O

EXPERIMENTAL*

General procedure:

To a boiling suspension of the ester (0,1 mole) and urea (0,15 mole) in methanol (25 ml), a methanolic solution of sodium methoxide (prepared from 0,22 g-atom sodium and 100 ml. of methanol) was added gradually with stirring over a period of six to eight hours. The mixture was refluxed for additional three hours and the methanol evaporated to dryness under reduced pressure. The residue was dissolved in cold water (150 ml), the solution extracted with ether (40 ml), decolorized with charcoal and gradually acidified with diluted hydrochloric acid (15%) while cooled and agitated. The precipitate was collected on a filter and washed with water.

The imino- and cyano-imino-derivatives (0,1 mole) were hydrolyzed by boiling with diluted sulfuric acid (13 ml of 25%).

*A. Condensation with urea**5-(1-cyclohexenyl)-4-imino-5-methylbarbituric acid [I a]*

Prepared from ethyl cyclohexenyl-methyl-cyanoacetate and urea as described in the General procedure. Yield: 68,4%. White crystalline powder (absolute ethanol), m. p. 247—254° with decomposition. Although the acid was reported earlier, its melting point was not mentioned¹⁰.

Anal. 2,912 mg subst: 0,49 ml N₂ (21°, 762 mm)
 C₁₁H₁₅N₃O₂ (221,26) calc'd: N 19,00%
 found: N 19,19%

Hydrolysis (nine hours) gave *5-(1-cyclohexenyl)-5-methylbarbituric acid [I d]*. Silky needles (water), m. p. 190—200° (205—208° uncorr.).

Anal. 4,020 mg subst.: 0,45 ml N₂ (20°, 750 mm)
 C₁₁H₁₄N₂O₃ (222,24) calc'd: N 12,62%
 found: N 12,64%

5-(1-cyclohexenyl)-5-ethyl-4-iminobarbituric acid [I e]

Prepared from ethyl cyclohexenyl-ethyl-cyanoacetate and urea as described in the General procedure. Yield: 61,7%. White crystalline powder (absolute ethanol), m. p. 259—262° with decomposition. The earlier reported melting point was 265° with decomposition¹¹.

* The melting points were determined with a Kofler micro melting point apparatus unless otherwise indicated.

Hydrolysis (seven hours) gave 5-(1-cyclohexenyl)-5-ethyl-barbituric acid [I h], m. p. 172—175° (uncorr.). The product showed no melting point depression with an authentic sample.

B. Condensation with guanidine nitrate

The procedure was essentially the same as described for urea, with the difference that 1,3 mole of guanidine nitrate and 3,15 g atom sodium in the corresponding excess of methanol per mole of ester were used.

5-(1-cyclohexenyl)-2,4-diimino-5-ethylbarbituric acid [I b]

Prepared from ethyl cyclohexenyl-methyl-cyanoacetate and guanidine nitrate as described in the General procedure with the difference that the residue after evaporation of methanol was insoluble in water. Yield: 79,4%. White powder (since soluble in acids, the product was reprecipitated from 20% hydrochloric acid / 25% aqueous sodium hydroxide solution), m. p. 245—253° with decomposition.

Anal. 1,539 mg subst.: 0,35 ml N₂ (23°, 751 mm)
 C₁₁H₁₆N₄O (220,27) calc'd: N 25,43%
 found: N 25,39%

Hydrolysis (twelve hours) gave 5-(1-cyclohexenyl)-5-methylbarbituric acid [I d], m. p. 205—210° (uncorr.). The product showed no melting point depression with a sample obtained as described earlier.

5-(1-cyclohexenyl)-2,4-diimino-5-ethylbarbituric acid [I f]

Prepared from ethyl cyclohexenyl-ethyl-cyanoacetate and guanidine nitrate as described in the General procedure; the residue after the evaporation of methanol was insoluble in water. Yield: 89%. White powder (since soluble in acids, the product was reprecipitated from 20% hydrochloric acid / 25% aqueous sodium hydroxide solution), m. p. 248—253° with decomposition.*

Anal. 3,590 mg subst.: 0,75 ml N₂ (19°, 751 mm)
 C₁₂H₁₈N₄O (234,29) calc'd: N 23,91%
 found: N 23,68%

Hydrolysis (nine hours) gave 5-(1-cyclohexenyl)-5-ethylbarbituric acid [I h], m. p. 175—176° (uncorr.). The product showed no melting point depression with an authentic sample.

2-imino-5-phenylbarbituric acid [II a]

Prepared from ethyl phenylmalonate and guanidine nitrate as described in the General procedure. Yield: 86%. White powder (reprecipitated from 10% aqueous sodium hydroxide solution / 10% hydrochloric acid), m. p. 333—336° with decomposition.

Anal. 4,144 mg subst.: 0,76 ml N₂ (22°, 750 mm)
 C₁₀H₉N₃O₂ (203,21) calc'd: N 20,68%
 found: N 20,53%

Hydrolysis (eighteen hours) gave 5-phenylbarbituric acid [II c], m. p. 250° with decomposition. The earlier reported melting point was 250°¹². The product showed no melting point depression with a sample prepared from ethyl phenylmalonate and urea.

* H. Lund¹¹ obtained this product by the magnesium methoxide catalyzed cyclization of cyclohexenyl-ethyl-cyanoacetyl-guanidine. No melting point has been reported.

2-imino-5-methyl-5-phenylbarbituric acid [II d]

Prepared from ethyl methyl-phenylmalonate and guanidine nitrate as described in the General procedure. Yield: 86%. White powder (reprecipitated from 10% aqueous sodium hydroxide solution/10% hydrochloric acid), m. p. higher than 360° with decomposition (uncorr.).

Anal. 3,778 mg subst.: 0,64 ml N₂ (20°, 750 mm)
 C₁₁H₁₁N₃O₂ (217,24) calc'd: N 19,35%
 found: N 19,11%

Hydrolysis (seven hours) gave *5-methyl-5-phenylbarbituric acid* [II f], m. p. 226°. The melting point reported is 220°¹².

2-imino-5-ethyl-5-phenylbarbituric acid [II g]

Prepared from ethyl ethyl-phenylmalonate and guanidine nitrate as described in the General procedure. Yield: 93,5%. White powder (reprecipitated from 10% aqueous sodium hydroxide solution/10% hydrochloric acid), m. p. 313—315° with decomposition.

Anal. 5,379 mg subst.: 0,87 ml N₂ (21°, 754 mm)
 C₁₂H₁₃N₃O₂ (231,24) calc'd: N 18,16%
 found: N 18,29%

Hydrolysis (twelve hours) gave *5-ethyl-5-phenylbarbituric acid* [II i], m. p. 175—176° (uncorr.). The product showed no melting point depression with an authentic sample.

C. Condensation with dicyandiamide

The procedure was essentially the same as described for urea with the difference, that 1,5 mole of dicyandiamide was used per mole of ester.

1-cyano-5-(1-cyclohexenyl)-2,4-diimino-5-methylbarbituric acid [I c]

Prepared from ethyl cyclohexenyl-methyl-cyanoacetate and dicyandiamide as described in the General procedure. Yield: 85,6%. Crystalline powder (70% ethanol), m. p. 266—272° with decomposition. The earlier reported melting point was 2650^{13*}

Hydrolysis (nine hours) gave *5-(1-cyclohexenyl)-5-methylbarbituric acid* [I d], m. p. 198—202° (uncorr.). The product showed no melting point depression with a sample obtained as described earlier.

1-cyano-5-(cyclohexenyl)-2,4-diimino-5-ethylbarbituric acid [I g]

Prepared from ethyl cyclohexenyl-ethyl-cyanoacetate and dicyandiamide as described in the General procedure. Yield: 87%. Crystalline powder (60% ethanol), m. p. 253—256° with decomposition.

Anal. 10,588 mg subst.: 23,520 mg CO₂ 6,310 mg H₂O
 1,462 mg subst.: 0,343 ml N₂ (22°, 762 mm)
 C₁₃H₁₇N₅O (259,31) calc'd: C 60,21; H 6,61; N 27,01%
 found: C 60,62; H 6,67; N 27,21%

* *Ger. Pat.* 590,175 and *Fr. Pat.* 753,178 describe the same subject. The substance obtained apparently from ethyl cyclohexenyl-methyl-cyanoacetate and dicyandiamide has been referred erroneously as 5-(1-cyclohexenyl)-5-methyl-6-imino-3-cyano-barbituric acid both in *C. A.* 28 (1934) 781 and in *Chem. Zentr.* 1934, I, 894. The correct formula, as described in this paper has been reported in *Chem. Zentr.* 1934, I, 1354.

Hydrolysis (ten hours) gave *5-(1-cyclohexenyl)-5-ethylbarbituric acid* [I h], m. p. 171—174° (uncorr.). The product showed no melting point depression with an authentic sample.

1-cyano-2-imino-5-phenylbarbituric acid [II b]

Prepared from ethyl phenylmalonate and dicyandiamide as described in the General procedure. Yield: 79,5%. White powder (reprecipitated from 15% aqueous sodium hydroxide solution/10% hydrochloric acid), m. p. 280—293° with slow decomposition from 269° on.

Anal. 1,806 mg subst.: 0,39 ml N₂ (22°, 759 mm)

C₁₁H₈N₄O₂ (228,20) calc'd: N 24,55%

found: N 24,44%

Hydrolysis (eleven hours) gave *5-phenylbarbituric acid* (II c), m. p. 248—252° (uncorr.). The product showed no melting point depression with a sample obtained as described earlier.

1-cyano-2-imino-5-methyl-5-phenylbarbituric acid [II e]

Prepared from ethyl methyl-phenylmalonate and dicyandiamide as described in the General procedure. Yield: 89,5%. White crystalline powder (80% ethanol), m. p. 236—241° with decomposition.

Anal. 1,845 mg subst.: 0,37 ml N₂ (19°, 763 mm)

C₁₂H₁₀N₄O₂ (242,23) calc'd: N 23,13%

found: N 23,15%

Hydrolysis (eleven hours) (25% hydrochloric acid) gave *5-methyl-5-phenylbarbituric acid* [II f], m. p. 226—228° (uncorr.). The product showed no melting point depression with a sample obtained as described earlier.

1-cyano-2-imino-5-ethyl-5-phenylbarbituric acid [II h]

Prepared from ethyl ethyl-phenylmalonate and dicyandiamide as described in the General procedure. Yield: 86%. White crystalline powder (50% ethanol), m. p. 220—225° with decomposition. The melting point reported is 223°^{13, 14}.

Hydrolysis (ten hours) gave *5-ethyl-5-phenylbarbituric acid* [II i], m. p. 177° (uncorr.). The product showed no melting point depression with an authentic sample.

The microanalyses and melting point determinations were carried out by N. Manger from our Microchemical laboratory and by Prof. L. Filipović from the Chemical Institute, Faculty of Science, Zagreb.

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IZVOD

Priprema nekih imino- i cijano-imino-supstituiranih barbiturata

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Barbiturati se obično pripremaju kondenzacijom supstituiranih cijanoctenih ili malonskih estera s ureom ili njenim derivatima uz neki alkoxid alkalnih metala kao kondenzaciono sredstvo i naknadnu hidrolizu imino- i cijano-imino-intermedijera. Obično se kondenzacije vrše suviškom kondenzacionog sredstva, najčešće natrium etoksida, uz relativno veliku koncentraciju natriuma, kod povišene temperature, pa i pod tlakom. Vršenje kondenzacije pod takvim uvjetima dovodi do cijepanja, obično dekarboksilacije supstituiranih cijanoctenih ili malonskih estera^{1, 2, 3, 4, 5}, tj. do pada iskorištenja, jer se stvaraju neželjeni sporedni produkti^{4, 7, 8}. Da se cijepajuće djelovanje natrium etoksida smanji, kondenzacija nekih cijanoctenih i malonskih estera vršena je tako, da se etanolna otopina natrium etoksida dodavala reakcionoj smjesi postepeno, tj. brzinom, kojom se vrši kondenzacija^{3, 5}. Princip postepenog dodavanja kondenzacionog sredstva primijenjen je i na natrium metoksid kod kondenzacije etil malonata s ureom⁹. U ovoj radnji proširen je princip postepenog dodavanja natrium metoksida kao kondenzacionog sredstva na kondenzacije nekih supstituiranih cijanoctenih i malonskih estera s ureom, guanidin nitratom i dicitandiamidom, pa je s dobrim iskorištenjem priređeno nekoliko imino- i cijano-imino-derivata, koji su hidrolizom u kiselom mediju prevedeni u odgovarajuće barbiturate.

Kod izrađivanja eksperimentalnog dijela surađivao je ing. V. Popović iz Tehnološkog odjela Vojno-tehničkog instituta.

Mikroanalize su izvršili ing. N. Manger (u našem mikroanalitičkom laboratoriju) i prof. L. Filipović (u Kemijskom institutu Prirodoslovno-matematičkog fakulteta u Zagrebu). Tališta je odredio ing. N. Manger prema mikroskopskoj metodi po Kofleru.

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