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(54) Title A NEW PYRROLINONE DERIVATIVE, PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF FOR THE PREPARATION OF TETRAMIC ACID

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The present invention is concerned with a new pyrrolinone derivative, with a process for the preparation thereof and with the use thereof for the synthesis of tetramic acid.

5 Tetramic acid is a valuable starting material for the preparation of β -lactams which, in turn, are used for the preparation of active antibiotics (G. Lowe, J. Chem. Soc., Perkin Trans. I, 1973, 2907).

Hitherto, there has been a lack of advantageous
10 processes for the preparation of tetramic acid.

Thus, it is known (Lowe, J. Chem. Soc., Perkin Trans. I, 1973, 2909) to react monoethyl malonate with ethyl glycinate in the presence of dicyclohexylcarbodiimide to give ethyl N-ethoxy-(carbonylacetyl)-
15 glycinate, in a further step to ring close with a base to give methyl 2,4-dioxopyrrolidine-3-carboxylic acid ethyl ester and finally to decarboxylate to give tetramic acid.

However, an important disadvantage of this process is the extremely high dilution of the reaction solution which is necessary in the last step (3.39 g. to 2.5 litres = 0.1% solution) which excludes an economic process on a larger scale.

Therefore, it is an object of the present invention to provide a process which overcomes these disadvantages.

This object can be achieved in a surprisingly easy way by means of a new and easily obtainable intermediate, the 4-benzyloxy-3-pyrrolin-2-one.

This compound can be prepared by the acid-catalysed transesterification of 4-alkoxy-3-pyrrolin-2-ones with benzyl alcohol.

The 4-alkoxy-3-pyrrolin-2-ones can also be easily prepared by a known process from esters of 4-haloacetoacetic acid (see Patent Specification No. 2161/86), 4-methoxy-3-pyrrolin-2-one preferably being used as the starting material.

As acids for the transesterification, there are preferably used anhydrous inorganic acids, for example sulphuric acid, or sulphonic acids, methanesulphonic acid preferably being used.

The acids are used in catalytic amounts of preferably 5 to 20 mole % and more preferably of 5 to 10 mole %.

The benzyl alcohol is preferably used in an excess of 50 to 200%, referred to the 4-alkoxy-3-pyrrolin-2-one

used, the benzyl alcohol preferably also functioning as a solvent.

The reaction is advantageously carried out at a temperature of from 60 to 100°C. and preferably of from
5 70 to 90°C.

It is preferable to work under reduced pressure, especially of from 1 to 50 mbar, in order to remove from the equilibrium the lower alcohols split off.

After a reaction time of about 20 to 30 hours,
10 the 4-benzyloxy-3-pyrrolin-2-one obtained can be worked up in the usual way, for example by azeotropic evaporation of the excess benzyl alcohol and possibly by subsequent crystallisation.

The 4-benzyloxy-3-pyrrolin-2-one obtained can be
15 converted in a simple way, by catalytic hydrogenolysis, into tetramic acid.

An especially preferred catalyst for this purpose is palladium in an amount of preferably 5 to 20%, applied to charcoal.

20 It is of advantage to work in an anhydrous, polar aprotic solvent, tetrahydrofuran, dioxan or dimethylformamide being preferred.

The reaction temperature is preferably from 0 to 40°C. and the reaction pressure from 1 to 20 bar.

25 After usual working up, which, dependent upon the pressure and temperature used, can take place after 5 to 10 hours, the tetramic acid is obtained in almost

quantitative yield.

The following Example is given for the purpose of illustrating the present invention:

Example.

5 Preparation of 4-benzyloxy-3-pyrrolin-2-one

5.7 g. (50 mMole) 4-methoxy-3-pyrrolin-2-one and 10.8 g. (100 mMole) benzyl alcohol were mixed with 0.4 g. (4 mMole) methanesulphonic acid and stirred for 24 hours at 80°C. and 20 mbar. Subsequently, the
10 reaction solution was mixed with 50 ml. ice water and 100 ml. methylene chloride and neutralised with 4 ml. of a saturated aqueous solution of sodium bicarbonate. The aqueous phase was then extracted twice with, in each case, 50 ml. methylene chloride. After drying the
15 organic phase over anhydrous sodium sulphate and distilling off the solvent, the residue was mixed with 150 ml. ice water, heated to 100°C. and 100 ml. water-benzyl alcohol distilled off azeotropically. The crystals precipitating out upon cooling were
20 recrystallised from 50 ml. hot toluene to give 6.7 g. of white, crystalline product; m.p. 147 - 148°C.

NMR: (300 MHz, DMSO-d₆) δ in ppm

7.38 (m, 5H), 6.20 (br. s, 1H), 5.16 (s, 1H),

4.98 (s, 2H), 3.98 (s, 2H).

25 MS (70 eV): 189 (M⁺, 40), 172 (18), 132 (51), 91 (100).

Preparation of 2,4-dioxopyrrolidine (tetramic acid)

1.0 g. (5.3 mMole) 4-Benzyloxy-3-pyrrolin-2-one

was dissolved in 50 ml. tetrahydrofuran and hydrogenated in the presence of 100 mg. of 5% palladium/charcoal for 6 hours at ambient temperature and 10 bar. Subsequently, the catalyst was filtered off and the
5 filtrate evaporated to dryness on a rotary evaporator to give 500 mg. of white, crystalline product; m.p. 120°C. (above 120°C., it again became solid).

NMRL (300 MHz, DMSO-d₆) δ in ppm

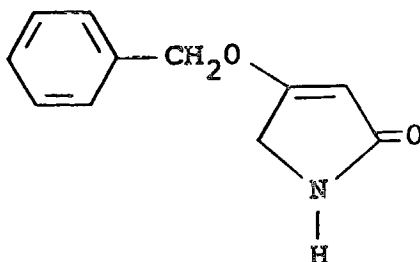
enol form: 11.28 (s, 1H), 7.11 (br.s, 1H), 4.76 (s, 1H),
10 3.74 (s, 2H).

keto form: 8.25 (br.s, 1H), 3.78 (s, 2H), 2.93 (s, 2H).

MS (70 eV): 99 (M⁺, 32), 71 (78), 43 (58), 42 (100).

Patent Claims

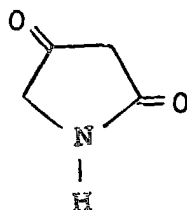
1. 4-Benzoyloxy-3-pyrrolin-2-one of the formula



2. Process for the preparation of the compound
5 according to claim 1, wherein 4-alkoxy-3-pyrrolin-2-one
is reacted with benzyl alcohol with acid catalysis.
3. Process according to claim 2, wherein the acid
used is a sulphonic acid or an anhydrous inorganic
acid.
- 10 4. Process according to claim 2 or 3, wherein the
reaction is carried out at a temperature of from 60
to 100°C.
5. Process according to claim 4, wherein the reaction
is carried out at a temperature of from 70 to 90°C.
- 15 6. Process according to any of claims 2 to 5, wherein
the reaction is carried out under reduced pressure.
7. Process according to claim 6, wherein the reaction
is carried out at a pressure of from 1 to 5 mbar.
8. Process for the preparation of the compound accord-
20 ing to claim 1, substantially as hereinbefore described
and exemplified.
9. The compound according to claim 1, whenever

prepared by the process according to any of claims
2 to 8.

10. Use of the compound according to claim 1 or 9
for the preparation of tetramic acid of the formula



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wherein said compound is subjected to a catalytic
hydrogenolysis.

11. Use according to claim 10, wherein palladium is
used as catalyst.

10 12. Use according to claim 10 or 11, wherein the
hydrogenolysis is carried out at a temperature of from
0 to 40°C. and at a pressure of from 1 to 20 bar.

13. Use according to any of claims 10 to 12,
substantially as hereinbefore described and exemplified.

15 14. Tetramic acid, whenever obtained according to
any of claims 10 to 13.

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