SYNTHESIS OF 4,5-DIAMINOURACIL DERIVATIVES

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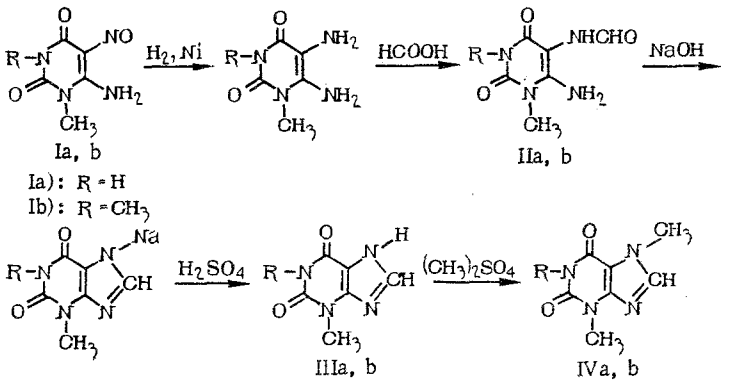
In the manufacture of theophyllin (IIIa), theobromine (IVa), and caffeine (IVb), derivatives of 4,5-diaminouracil are prepared by the reduction of 3-methyl- or 1,3-dimethyl-4-amino-5-isonitrosouracil (Ia or Ib) with zinc dust in a formic acid—sulfuric acid solution [1]. Thereupon the zinc dust is taken in a considerable excess, as a result of which a number of side reactions arise in the main technological process, which impair the quality of the object compound [1-3].

The known means of solving this technological problem by use of ammonium sulfites [4,5], other sulfur-containing compounds [6], or iron in aqueous electrolyte solutions [7, 8] as the reducing agent have a number of their own inherent defects, namely: the presence of harmful exhaust gases in the atmosphere, formation of sludgy masses, low yields of the object compound, laboriousness of the technological operations, appreciable material outlays, limitations on raw material and other materials, and the like.



Ia, b — IIa, b

Ia): R = H

Ib): R = CH_3

IIIa, b — IVa, b

In the present work we present a procedure for preparing 4,5-diaminouracil and its derivative which is free of the deficiencies listed. To reduce the isonitroso compounds (Ia,b) we have used catalytic reduction with hydrogen in aqueous medium over Raney nickel at comparatively low temperatures and pressures, in a flow-type reactor. After separation from the catalyst, the 1,3-dimethyl- and 3-methyl-4,5-diaminouracils obtained in the reduction process are formulated and are isolated in the form of formyl derivatives of 4,5-diaminouracil, which are converted upon further treatment into theophyllin, theobromine, or caffeine which conform to the requirements of the State Pharmacopoeia of the USSR, 10th edition.

EXPERIMENTAL

1,3-Dimethyl-4-amino-5-formylaminouracil (IIb). Into a flow-type reactor are charged an aqueous suspension of 5 kg of Ib, 30 liters of water, and 0.25 kg of Raney nickel.* The reactor is sealed, it is swept with nitrogen, and reduction is conducted at 0.5-4 atm of hydrogen pressure for 4-6 h; the temperature thereupon rises to 40-65°. After absorption of

*The Raney nickel catalyst was prepared by leaching N45A55 alloy (Technical Specification 48-5-76-73) with a 20% sodium hydroxide solution for 3 h at 90-100°. It is possible to use spent catalyst which has undergone passivation and washing for the same purpose.

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hydrogen has ceased, the mixture is allowed to stand for an hour. Filtration of the reaction mixture from catalyst is performed at 96-98°; to the filtrate is added 2-2.5 liters of 85% formic acid (in work with Ia, the formic acid is poured in at a reaction mixture temperature of 25-30°, before filtration of the 4,5-diaminouracil from the catalyst), and formylation is carried out at 70-75° for 1 h; the mixture is cooled to 5-8° and filtered; the solid is washed with 4-5 liters of cold water; and 4.3 kg of dry, ash-free IIb is obtained, which is 87.8% of theory, based on Ia; mp of IIb, 265-267°.

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PREPARATION OF 10β-HYDROXYSTEROIDS BY OXIDATION OF ESTRA-5(0)-ENE-3-ONES WITH THE JONES REAGENT

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The synthesis of 10β-hydroxyestra-4-ene-3-ones presents considerable interest since these compounds have hormonal activity [1] and, moreover, may be used to prepare estradiol derivatives.

We propose a simple means of preparing 10β-hydroxyestra-4-ene-3-ones (II) which consists in the direct oxidation of estra-5(10)-ene-3-ones (I) with the Jones reagent in dimethylformamide or dimethyl sulfoxide. We have prepared the 10β-hydroxy compounds (IIb and c) from compounds Ia-c by this method in yields of 52-60%. The oxidation of 17β-ethylestra-5(10)-ene-17β-ol-3-one (Id) took place less selectively: The corresponding diol (IId) was isolated in 28% yield.

Under the action of mineral acids the diols II easily split out the 10β-hydroxy group and isomerize into the 1,3,5(10)-trienes [2]. Thus, in an attempt to acetylate diol IIc in the presence of zinc chloride and hydrochloric acid [3], we obtained a mixture of three substances: ethynylestradiol 17-monoacetate (IV), ethynylestradiol diacetate (V), and 17α-ethynylestra-4,9-diene-17β-ol-3-one acetate (VI).

The easy dehydration of steroidal 10β-alcohols may be used to go over from 5(10)-ene-3-ones to 1,3,5(10)-triene-3-ones. For example, the diol IIc was converted into mestranol (III) in methanol in the presence of the ion-exchange resin Dowex-50 (in the H^+ form).

Compound IId was investigated with respect to androgenic, anabolic, antiandrogenic, uterotropic, antiestrogenic, gestagenic, antigestagenic, thymolytic, antiinflammatory, mineralocorticoid, and antimineralocorticoid actions.

The methods of investigation have been described previously [4]. In all experiments the substance was introduced subcutaneously in oil solution.

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