N-Acetyl-2-(p-phenetidino)-3-cyano-5,6,7,8-tetrahydroquinoline (IIIg). A mixture of 1.92 g (0.01 mole) of (I) and 0.01 mole of N-acetyl-p-phenetidine was heated for 6 h at 190°C, treated with hot water, and the solid filtered off and crystallized from ethanol to give 1.21 g (63%) of product, mp 115-117°C. Found: C 71.7; H 6.2; N 12.4%. $C_{20}H_{21}N_3O_2$. Calculated: C 71.6; H 6.3; N 12.5%.

Similarly, the nitrile (I) and acetanilide gave 76% of (IIIa). A mixed melting point with (IIIa) obtained from (IIa) and acetic anhydride gave no depression.

2-Substituted 1-Aryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones (IVa-f). Dry hydrogen chloride was passed for 3 h into a solution of 0.01 mole of (IIIa-f) in 40 ml of anhydrous ethanol, and the solid which separated was filtered off, treated with aqueous sodium acetate, and crystallized from ethanol to give (IVa-f).

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ACETALS OF LACTAMS AND ACID AMIDES.

51.* CYCLIZATION OF α-CYANO-β-PHENYLAMINO-N-DIMETHYLAMINOMETHYLENEACRYLAMIDE TO PYRIMIDO[5,4-c]QUINOL-4-ONE

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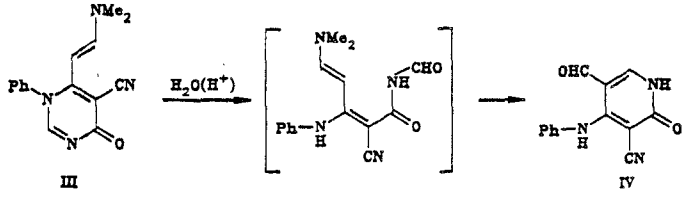
UDC 547.831.6'298'836.7'854.2.07:542.951.2:543.422'51

Cyclization of α-cyano-β-phenylamino-N-dimethylaminomethyleneacrylamide to pyrimido[5,4-c]quinol-4-one proceeds via the intermediate formation of 1-phenyl-5-cyano-1,4-dihydropyrimidin-4-one and α-cyano-β-phenyl-amino-N-formylacrylamide.

We have recently found that α-cyano-β-phenylamino-N-dimethylaminomethyleneacrylamide (I) cyclizes on boiling in acetic acid to give high yields of pyrimido[5,4-c]quinol-4-one [2]. Bearing in mind that enamidoacylamidines such as (I) are readily convertible into pyrimidin-4-ones [2], it would be expected that this stage would mediate in the conversion of (I) into (II). It is also known that acid hydrolysis of 1-phenyl-5-cyano-6-β-dimethylaminovinyl-1,4-dihydropyrimidin-4-one (III) gives 3-cyano-4-phenylamino-5-formylpyrid-2-one (IV), which clearly calls for the intermediate formation of the N-formyl derivative [3]:



III IV

In 1-phenyl-5-cyano-1,4-dihydropyrimidin-4-one (V) [2], the complicating factor present in the pyrimidinone (III), namely the presence of the dimethylaminomethylene group, is absent. Consequently, it was possible to attempt to isolate the intermediate α-cyano-β-phenylamino-N-formylacrylamide (VI), which is the second likely stage in the formation of the tricycle (II) from the acylamidine (I).

*For Communication 50, see [1].

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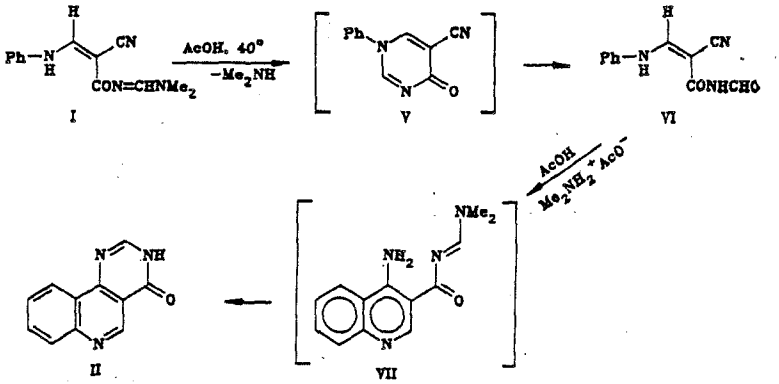
Heating the enaminoacylamide (I) in acetic acid at 40°C did not give the pyrimidinone (V), but led directly to the formation of the formylamide (VI). The mass spectrum of this compound showed a molecular ion peak $M^{+\cdot}$ 215, together with the following ion peaks (m/z): 197 $[M^{+\cdot} - H_2O]^{+\cdot}$, 187 $[M - CO]^{+\cdot}$, 170 $[M - CO - OH]^{+\cdot}$, 104 $[PhN{\equiv}CH]^{+\cdot}$, 77 $[Ph]^{+\cdot}$. The PMR spectrum of the amide (VI) in DMSO-D_6 contained the signals: 7.47 (5H, m, Ph), 8.59 (1H, d, $^3J_{CH,NH}$ = 31.1 Hz, CH), 9.09 (1H, d, $^3J_{CHO,NH}$ = 8.9 Hz, CHO), 10.61 (1H, d, $^3J_{NH,CH}$ = 13.1 Hz, NHCH), 11.10 ppm (1H, d, $^3J_{NH,CHO}$ = 8.9 Hz, NHCHO). These results, in addition to the IR spectral data [1620, 1670 (CO), 2190 (CN), 3290, 3310 cm^{-1} (NH)] and the elemental analysis, were in agreement with the structure (VI).

In order to throw further light on the mode of formation of the tricycle (II) from the amine (I), the previously-described [2] pyrimidinone (V) was boiled in 99.6% acetic acid. The expected pyrimidoquinolone (II) was not however formed under these conditions, a mixture of the starting pyrimidinone (V) and the formylamide (VI) being obtained in a ratio of 64:36 (UV spectrum). In other words, the formylamide (VI) is not converted into the tricycle (II) under these conditions, nor was (VI) converted into the tricycle (II) even on prolonged boiling in acetic acid.

Consideration of the mode of cyclization of the enaminoacylamidine (I) shows that this reaction results in the elimination of dimethylamine. It seems likely that the resulting dimethylamine acetate catalyzes the cyclization. In fact, on boiling either the pyrimidinone (V) or the N-formylamidine (VI) in acetic acid in the presence of dimethylamine acetate, pyrimido[5,4-c]quinol-4-one (II) is formed smoothly, in high yields. It may therefore be assumed that on boiling α-cyano-β-phenylamino-N-dimethylaminomethyleneacrylamide (I) in acetic acid, cyclization to (V) occurs, this then undergoing hydrolysis to the formylamide (VI). The latter undergoes successive cyclizations to the 4-aminoquinoline (VII) and then to the tricyclic compound (II).



It should be pointed out that the cyclization of (VI) to the tricycle (II) requires a basic catalyst, provided in this instance by ammonium acetate.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 spectrometer with direct introduction of the sample into the ion source. The ionization chamber temperature was 180°C, and the ionizing electron energy 70 eV. PMR spectra were recorded on a Varian XL-200 spectrometer in DMSO-D_6, internal standard TMS. IR spectra were obtained on a Perkin-Elmer 457 instrument in Vaseline oil, and UV spectra on an M-40 spectrophotometer in ethanol.

β-Anilino-α-cyano-α-N-formylacrylamide (VI). A solution of 1 g (4.13 mmole) of the formylamide (I) in 8 ml of glacial acetic acid was heated for 1 h at 40°C, evaporated, the residue triturated with water, and the solid filtered off to give 0.75 g (84%) of (VI), mp 206-208°C (from ethanol). Found: C 61.4; H 4.1; N 19.7%. $C_{11}H_9N_3O_2$. Calculated: C 61.4; H 4.2; N 19.5%.

Mixture of β-Anilino-α-cyano-α-N-formylacrylamide (VI) and 1-phenyl-5-cyano-1,4-dihydropyrimidin-4-one (V). A solution of 0.8 g (4.06 mmole) of (V) in 8 ml of glacial acetic acid was boiled for 3 h, evaporated, and the residue triturated with water, and filtered to give 0.6 g of a mixture of (V) [UV spectrum, λ_{max} (log ε): 207 (4.24), 255 (4.21), 295 nm (3.91)] and (VI) [UV spectrum, λ_{max} (log ε): 228 (4.25), 335 nm (4.46)]. From the UV spectrum, the proportions of (V):(VI) were calculated to be 64:36.

Pyrimido[5,4-c]quinol-4-one (II). A. To a solution of 0.5 g (2.58 mmole) of the pyrimidone (V) in 5 ml of glacial acetic acid was added 0.3 ml of a 10% solution of dimethylamine in dry benzene, and the mixture was boiled for 4 h, evaporated, triturated with water, and the (II) (0.37 g, 74%) filtered off, mp 359-361°C (from DMF); literature value [2], mp 360-362°C.

B. To a solution of 0.8 g (3.74 mmole) of (VI) in 8 ml of glacial acetic acid was added 0.3 ml of a 10% solution of dimethylamine in dry benzene. The mixture was boiled for 4 h, evaporated to 2/3 of its volume, cooled, and the solid which separated was filtered off to give 0.55 g (75%) of (II), mp 360-361°C (from DMF).

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ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF CHIRAL 1,5-DIHYDROXY-4-METHYL-3-OXAPENT-2-YL DERIVATIVES OF URACIL

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A convenient method has been developed for the synthesis of optically active 1-[1,5-dihydroxy-4-(R)-methyl-3-oxapent-2(R and S)-yl]uracils. 5'-Deoxyuridine is obtained from 2',3'-O-isopropylideneuridine, and its periodate oxidation followed by reduction with sodium tetrahydroborate leads to the desired 4(R), 2(R)-isomer. The acetonide of α-uridine is converted into the 4(R),2(S)-isomer analogously.

Interest in acyclic analogs of nucleosides is due to the fact that some of them possess unique antiviral properties [1, 2]. However, only a few syntheses of chiral acyclic nucleoside derivatives have been described: so-called oxidized-reduced derivatives of ribonucleosides (without the $C_{(2')}$–$C_{(3')}$ bond, 2',3'-seco-nucleosides) [3], 3',4'-seco-nucleosides [4], and 1',2'-seco-nucleosides [5] containing all the functional groups of the natural compounds. Oligonucleotides based on acyclic derivatives possess increased resistance to the action of nucleases [6, 7].

The present paper is devoted to a development of methods for the synthesis of 1,5-dihydroxy-4(R)-methyl-3-oxapent-2(R and S)-yl derivatives of nucleic bases, using uridine bases as examples. The initial compounds that we selected were the readily accessible 2',3'-O-isopropylideneuridine (Ia) [8] and its α anomer (Ib) [9].

The hydroxymethyl group was converted into a methyl group by chlorination with a mixture of CCl_4 and Ph_3P [10], followed by reduction with tributyltin hydride [11]. The isopropylidene protective group was eliminated by boiling in water in the presence of Dowex-50 in the H^+ form [12]. The 5'-deoxyuridines (IVa, b), obtained in high yields, were oxidized with sodium periodate and reduced with sodium tetrahydroborate [3]. The acyclic analogs (Va, b) were isolated by chromatography on silica gel.

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