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LACTAM AND AMIDE ACETALS.

56.* SYNTHESIS OF PYRIMIDINES FROM N-CARBAMOYLAMIDINES

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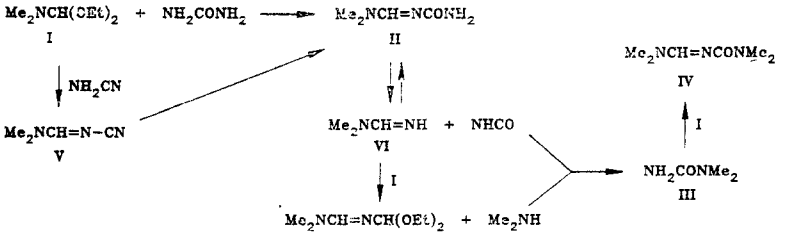
UDC 547.854'421.51'262'495.2.07

N-Carbamoyl-N,N'-dimethylformamidine reacts with ethyl anthranilate to give quinazoline-2,4-dione, and with cyanoacetamide to give 4-amino-5-carbamoylpyrimidin-2-one. The reaction of dimethylacetamide diethyl acetal with urea proceeds via N-carbamoyl-N',N'-dimethylacetamidine with the subsequent formation of 4-dimethylamino-6-methyl-pyrimidin-2-one and 4,6-dimethyl-sym-triazin-2-one

DMF diethylacetal (I) is known to react with urea to give N-carbamoyl-N',N'-dimethylurea (II) [2]. Our attempts to repeat this procedure resulted [2] in the isolation of a compound with a much lower melting point, which according to mass and PMR spectroscopy was a mixture of the amidine (II) and N,N-dimethylurea (III). Separation of (II) from (III) was effected by heating in vacuo, when the dimethylurea sublimed. Comparison of the PMR spectra of the pure (II) and (III) with that of the mixture showed that the ratio of the amidine (II) to the dimethylurea (III) in the mixture was approximately 3:2. The dimethylurea (III) is apparently formed by reversible decomposition of the amidine (II) under the reaction conditions to give N,N-dimethylformamidine and HNCO, as we have previously suggested for the heterocyclization of cyclic amidines [3], as follows:



This reaction pathway is supported by the observation that the mass spectrum of the reaction mixture showed the presence, in addition to compounds (II) and (III), of a compound with M^+ 143, which may be the amidine (IV).

A more suitable preparative method for the N-carbamoylamidine (II) is by reaction of the acetal (I) with cyanamide, followed by acid hydrolysis of the intermediate N-cyanoamide (V). A similar method using lactam acetal has been reported previously by the authors [4]. The unusually facile cleavage of the N-carbamoylamidine (II) to dimethylformamidine (VI) and

*For Communication 55, see [1].

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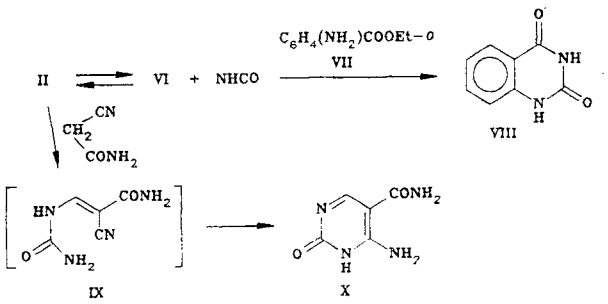
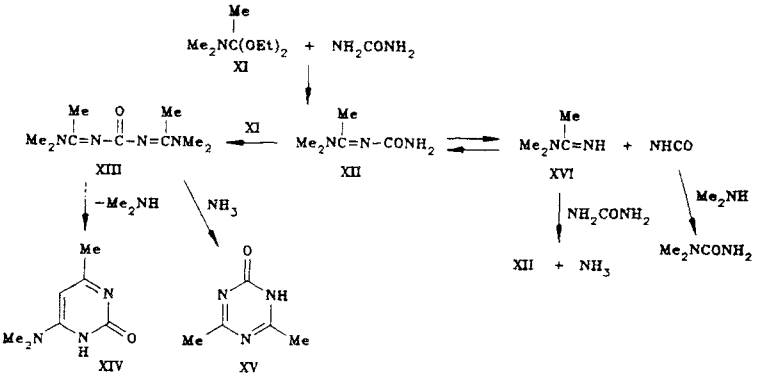
HNCO is confirmed by reaction of the amidine (II) with ethyl anthranilate (VII) to give quinazoline-2,4-dione (VIII), which was identical with an authentic sample [5]. The formation of the bicycle (VIII) is best attributed to the equilibrium (II) ⇄ (IV) + HNCO.

The amidine (II) reacts with cyanoacetamide in a different way, to give the intermediate N-carbamoylamidine (IX), which then cyclizes to 4-amino-5-carbamoylpyrimidin-2-one (X), which has been obtained previously by a more complex method [6].



Examination of the reaction of urea with N,N-dimethylacetamide diethyl acetal (XI) showed that the presence of a methyl group at the meso-carbon atom of the amidine resulted in the reactions occurring being much more complex. Under mild conditions, a mixture was formed which consisted, according to mass spectroscopy, of three compounds with M+ 129, 198, and 60. Separation of this mixture by column chromatography on silica gel gave the adduct of N-carbamoyl-N',N'-dimethylacetamidine (XII) with urea (M^+ 129 and 60). The PMR spectrum (DMSO-D_6) showed signals for this adduct at 2.05 (C–C_3), 3.00 (NMe_2), 5.76 (C–H), and 10.57 ppm (NH). Column chromatography of the reaction mixture on silica gel afforded a further compound [M^+ 125 and 60, PMR spectrum (DMSO-D_6): 2.26 (C–CH_3) and 5.43 ppm (urea NH_2)], which from these findings and its elemental analysis was assigned the structure of an adduct of the triazinone (XV) with urea.



In addition to these compounds, there was also isolated from the reaction products a mixture of urea and dimethylurea, identified by mass and PMR spectroscopy.

The first step apparently involves condensation of the acetal (XI) with a urea NH_2 group (as with DMF acetal) to give the amidine (XII) as its adduct with urea (for the formation of adducts of amidines and heterocyclic compounds with urea, see [3]). On heating the initial products, the amidine (XII) reacts further with the acetal (XI) to give the bisamidine (XIII), as well as breaking down reversibly to HNCO and N,N-dimethylacetamidine (XVI). Cyclization of the bisamidine (XIII) with elimination of dimethylamine (which reacts with HNCO to give dimethylurea) affords the pyrimidinone (XIV). The acetamidine (XVI) reacts with urea to form the amidine (XII) with evolution of ammonia, which cyclizes the bisamidine (XIII) to the triazinone (XV).*

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 spectrometer (direct introduction) at 70 eV. The ionization chamber temperature was 180°C. IR spectra were recorded on a Perkin-

*Both the dimethylamine and the ammonia probably first react with excess amidine acetal to give aminal ethers and aminals, which are also donors of dimethylamide and amide anions [7], these reacting further with HNCO or the bisamidine (XIII).

Elmer 457 (in Vaseline oil), and PMR spectra on a Varian XL-100 or Varian XL-200 spectrometer, internal standard TMS. The elemental analyses of the products for C, H, and N were in agreement with the calculated values.

N-Carbamoyl-N',N'-dimethylformamidine (II, $C_4H_9N_3O$). A. To 15 g (250 mmole) of urea at 60°C was added dropwise 36.75 g (250 mmole) of the acetal (I). The mixture was stirred for 3 h at 85°C, then cooled, and the solid filtered off and recrystallized from absolute ethanol to give 8.3 g of a mixture of the amidine (II) with dimethylurea (III), mp 135-138°C, M^+ 115 and 88. The mixture of (II) and (III) was sublimed at 6-7 mm for 2 h, and the residue recrystallized from absolute ethanol to give the amidine (II), mp 144-148°C (lit. mp [2] 149°C), M^+ 115. IR spectrum: 1680 (CO), 3190 and 3310 cm^{-1} (NH_2).

B. To a solution of 16.9 g (115 mmole) of the acetal (I) in 45 ml of methanol was added in portions with stirring at 25°C 3.87 g (92 mmole) of cyanamide. The mixture was stirred for 1 h at 20-25°C and evaporated to give 8.85 g (99%) of N,N-dimethylaminomethylenecyanamide (V, $C_4H_7N_3$), mp 72-76°C (from ethyl acetate).

To 0.5 g of the compound (V) was added 3 ml of conc. HCl, a slightly exothermic reaction occurring. The solution was evaporated to dryness, and the residue treated with a solution of sodium ethoxide (from 0.13 g of sodium and 4 ml of ethanol), and the mixture kept for 1 h at 20°C. It was then evaporated, the residue extracted with hot chloroform (3 × 20 ml), and the extract evaporated to give 0.35 g of the amidine (II) (58%), the melting point and IR spectrum of which were identical with those of the compound obtained by method A.

Quinazoline-2,4-dione (VIII). A mixture of 0.3 g (2.6 mmole) of the amidine (II) and 1.3 g (78 mmole) of ethyl anthranilate in 3 ml of glacial acetic acid was boiled for 5 h, cooled, the solid filtered off, and washed with water followed by ethanol and ether to give 0.2 g (47%) of (VIII), mp 350°C, M^+ 162, spectrally identical with the compound obtained as described in [5].

4-Amino-5-carbamoylpyrimidin-2-one (X). A mixture of 1.32 g (11 mmole) of the amidine (II) and 0.92 g (11 mmole) of cyanoacetamide in 15 ml of absolute alcohol was boiled for 3 h, cooled, and filtered to give 0.77 g (44%) of the pyrimidinone (X), mp >320°C, spectrally identical with a sample obtained by direct synthesis [6].

N-Carbamoyl-N',N'-dimethylaminoacetamidine (XII). To a mixture of 1.5 g (25 mmole) of urea and 15 ml of absolute ethanol was added dropwise at 20°C 4.025 g (25 mmole) of the acetal (XI). The mixture was stirred for 3 min at 35-40°C until all the urea had dissolved, cooled, 15 ml of dry ether added, and the solid which separated filtered off to give 1.87 g of a mixture, the mass spectrum of which showed molecular ions M^+ 129, 198, and 60. The mixture was chromatographed on a column (silica gel L 40/100, methanol) to give a first fraction (1.31 g) consisting of an adduct of the amidine (XII) with urea ($C_5H_{11}N_3O \cdot CH_4N_2O$), mp 100-104°C (from 2-propanol), M^+ 129 and 60.

4-Dimethylamino-6-methylpyrimidin-2-one (XIV, $C_7H_{11}N_3O$). To 3.0 g (50 mmole) of urea was added dropwise at 60°C 8.05 g (50 mmole) of the acetal (XI), and the mixture was then heated slowly to 76-78°C and boiled for 3 h. It was then cooled, and the solid filtered off and washed with ethanol to give 1.53 g of a mixture (M^+ 60, 88, and 153), 0.5 g of which was sublimed at 120-130°C (3 mm) for 5 h, leaving 0.21 g of the pyrimidinone (XIV), mp 264-165°C (from ethanol), M^+ 153.

The filtrate was evaporated under reduced pressure, kept in a refrigerator for one week, and the solid which separated filtered off and washed with heptane to give 0.46 g of a mixture of urea and dimethylurea (M^+ 60 and 88). The remaining filtrate was evaporated under reduced pressure, and chromatographed on a column (silica gel L 40/100, methanol), the first fraction being collected (0.44 g of the adduct of 4,6-dimethyl-sym-triazin-2-one (XV) with urea ($C_5H_7N_3O \cdot CH_4N_2O$), mp 184-185°C, M^+ 184-185°C, M^+ 125 and 60).

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HETEROARYLATION OF ACETONITRILES.

3.* HETEROARYLATION OF PYRIDIN-2-YL AND QUINOLIN-2-YLACETONITRILES BY CHLOROQUINOXALINES

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F. S. Babichev, and V. K. Promonenkov

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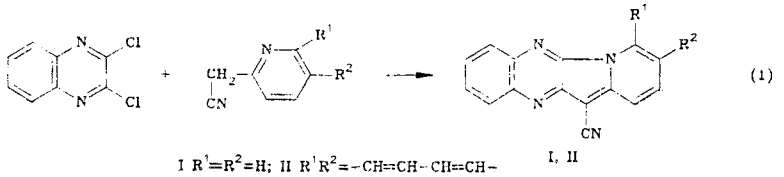
It has been shown that α-chloroquinoxalines heteroarylate pyridin-2-yl and quinolin-2-ylacetonitriles primarily at the methylene group. A method has been developed for synthesizing 1-R-2-amino-3-heteroarylpyrrolo[2,3-b]quinoxalines permitting the preparation of compounds containing the pyridine and quinoline nuclei.

We have previously shown that ambident carbanions formed from benzimidazol-2-yl, benzothiazol-2-yl, and 4-methylthiazol-2-yl-acetonitriles are heteroarylated by 2,3-dichloroquinoxaline in the presence of potassium carbonate at the methylene group carbon [1, 2]. In a similar reaction, pyridin-2-ylacetonitrile forms the product of heteroarylation at both nucleophilic centers, i.e., the methylene group and the exocyclic nitrogen atom [3].

As in the pyridine case, quinolin-2-ylacetonitrile reacts with 2,3-dichloroquinoxaline at both nucleophilic centers (I) in spite of the substantial steric hindrance to nucleophilic attack at the quinoline ring nitrogen atom arising from the hydrogen at position 8 [4].



(1)

I $R^1=R^2=H$; II $R^1R^2=-CH=CH-CH=CH-$ I, II

Heteroarylation of I by 2-chloro-3-methylquinoxaline (2) leads to the product of reaction at the methylene group in high yield, as shown by the presence of an exchangeable NH proton signal at 17 ppm in the NMR spectrum. The presence of a strong C≡N stretching vibration at 2200 cm^{-1} in the infrared spectrum indicates that it is conjugated to the double bond. Hence both in solution and in the solid state, compound III exists in one of the tautomeric forms IIIb or IIIc or as a mixture of these forms.

Thus reaction of α-chloroquinoxalines with ambident carbanions initially forms products of C-heteroarylation. This has allowed us to develop a new synthesis of 1-R-2-amino-3-heteroarylpyrrolo[2,3-b]quinoxalines containing the pyridine and quinoline rings and unavailable by the use of previously reported methods [1, 2].

The benzimidazole, benzothiazole, and thiazole derivatives made in this way were identical to previously reported compounds [1, 2] according to elemental analytical and spectroscopic data and melting points.

The IR and PMR data for the pyridines and quinolines given in the experimental section confirm their proposed structures.

EXPERIMENTAL

PMR Spectra were recorded on a Bruker WP-100SY spectrometer using TMS as internal standard and IR spectra on a Pye-Unicam SP3-300 in KBr tablets. Melting points are uncorrected.

*For Communication 2, see [1].

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