SYNTHESIS OF DERIVATIVES OF 4-ALKYLTHIOURACIL, CYTOSINE, PYRIDO[2,3-d]PYRIMIDINE, AND PYRIMIDO[4,5-d]PYRIMIDINE FROM THE N,S- AND N,N-ACETALS OF DIACETYLKETENE AND ISOCYANATES

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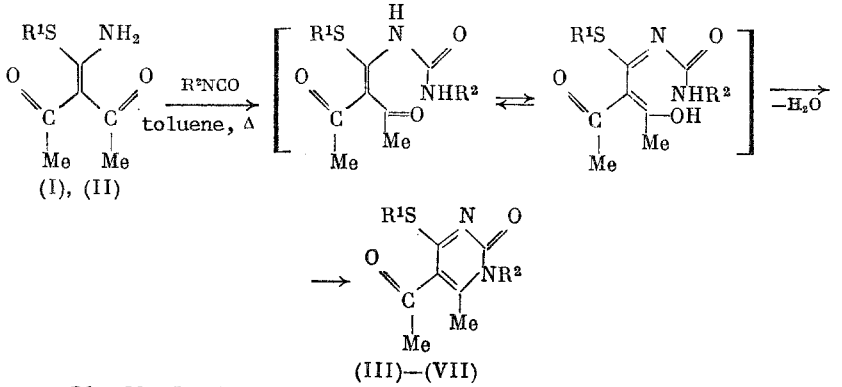
The action of alkyl and aryl isocyanates on the N,S-acetals of diacetylketene leads to the formation of 4-alkylthio-5-acetyl-1-alkyl(aryl)-6-methyl-1H-pyrimidin-2-ones (derivatives of 4-alkylthiouracils). The reaction of the synthesized thiouracils with amines or the reaction of the N,N-acetals of diacetylketene (N,N-ADK) with an equimolar amount of aryl isocyanates leads to the formation of substituted 4-amino-5-acetyl-1H-pyrimidin-2-ones (derivatives of cytosine). From the latter and isocyanates or directly from N,N-ADK and an excess of the isocyanate, derivatives of 4-methylene-1H,3H,4H-pyrimido[4,5-d]pyrimidine-2,7-dione were obtained. The exception was the condensation of 3-[N-(4,6-dimethyl-2-pyrimidinyl)diaminomethylene]pentane-2,4-dione with aryl isocyanates, which led to 3H,8H-pyrido[2,3-d]pyrimidine-2,5-diones.

The S,S-, S,N-, and N,N-acetals of ketenes are used as reagents for the synthesis of various heterocyclic compounds and of pyrimidine derivatives in particular [1-5]. Recently we discovered simple methods for the production of the N,S- and N,N-acetals of diacyl- and alkoxycarbonyl(acyl)ketenes containing a free NH_2 group [6-8]. It was proposed to use a compound of this type for the synthesis of functionally substituted pyridines [4].

In a continuation of these researches we investigated the heterocyclization of the N,S- and N,N-acetals of diacetylketene (N,S- and N,N-ADK) with isocyanates (see also the preliminary communication [10]). It is known that enamino ketones react with isocyanates in the presence of sodium hydride with the formation of 1-substituted 1H-pyrimidin-2-ones [11]. As found, the reaction of N,S-ADK (I, II) with isocyanates takes place in the absence of bases and gives 4-alkylthio-5-acetyl-1-alkyl(aryl)-6-methyl-1H-pyrimidin-2-ones (derivatives of 4-alkylthiouracil) (III-VII) with yields of 78-88% (scheme 1).



(I), (II)

(III)–(VII)

(1)

$R^1 = Me$ (I); Et (II): $R^1 = Me$, $R^2 = Ph$ (III), 2-naphthyl (IV), Et (VII); $R^1 = Et$, $R^2 = Ph$ (V); $R^1 = R^2 = Me$ (VI).

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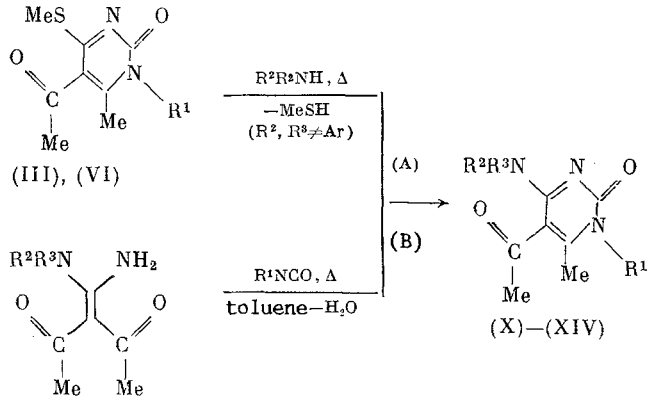
The process (1) clearly involves the initial formation of the corresponding ureas, the cyclization of which with the elimination of water leads to compounds (III-VII). The structure of compounds (III-VII) was confirmed by spectral data (IR, ^1H and ^{13}C NMR, mass spectrometry, see the experimental section).

It is well known that the MeS group in the pyrimidine ring can be substituted by N-nucleophiles such as amines [4]. Accordingly, the substituted 4-amino-5-acetyl-1H-pyrimidin-2-ones (5-acetylcytosines) (X-XII) were obtained with high yields by heating 4-methylthiouracils (III), (IV) with an excess of benzylamine or morpholine (scheme 2, method A).

The cyclization of N,N-ADK (VIII, IX) with aryl isocyanates, which takes place when an equimolar mixture of the reagents in toluene is boiled (scheme 2, method B), was also used for the synthesis of the cytosine derivatives (XII-XIV). In this way it was possible to obtain cytosines both with alkyl and with aryl substituents at the exocyclic nitrogen atom, whereas substitution of the MeS group in (III-VII) by the action of weakly nucleophilic aromatic amines was difficult.



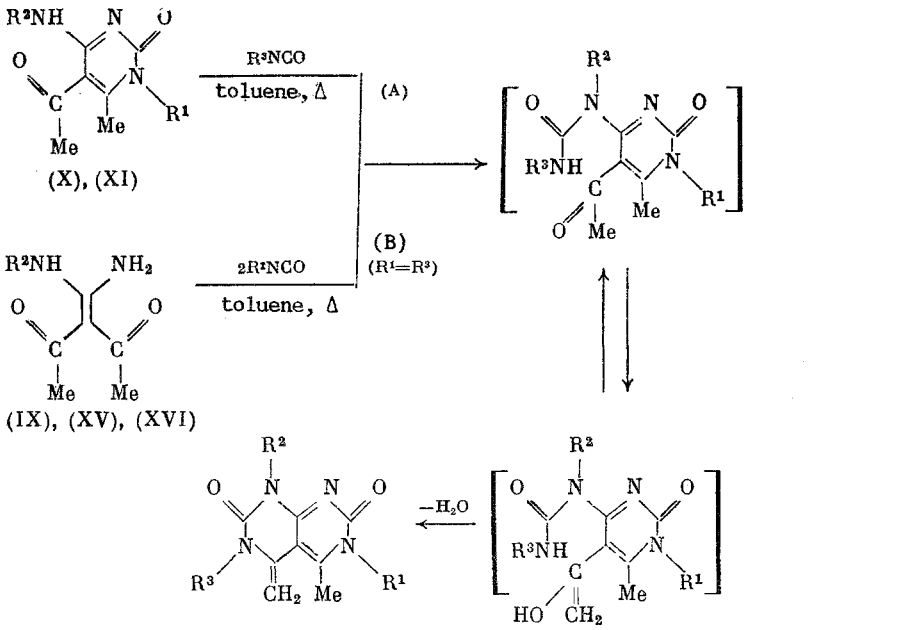
(2)

(VIII), (IX)

$R^2 + R^3 = -(CH_2)_2O(CH_2)_2-$ (VIII); R^2 = Ph, R^3 = H (IX);
R^1 = Ph, R^2 = $PhCH_2$, R^3 = H (X); R^1 = Me, R^2 = $PhCH_2$,
R^3 = H (XI); R^1 = Ph, $R^2 + R^3 = -(CH_2)_2O(CH_2)_2-$ (XII);
$R^1 = R^2$ = Ph, R^3 = H (XIII); R^1 = 2-naphthyl, R^2 = Ph, R^3 = H (XIV).

Cytosines containing a partially substituted exocyclic nitrogen atom (R^3 = H) can be regarded as convenient starting reagents for the construction of the bicyclic systems. It was found that they are in turn capable of entering into heterocyclization with isocyanates with the formation of derivatives of 1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (PPD). Thus, the bicyclic compounds (XVII-XIX) with an exomethylene group were synthesized from (X, XI) (scheme 3, method A). The process probably involves the addition of the cytosines (X, XI) to the isocyanate with the formation of the respective ureas, the intramolecular cyclization of which gives the PPD.

The synthesis of PPD can also be realized directly by the reaction of N,N-ADK (IX, XV, XVI) with the isocyanates in a ratio of 1:2 (scheme 3, method B), bypassing the isolation of the cytosines. (To increase the yield of the PPD it is better to use not less than 3-4 equivalents of the isocyanate in the reaction.) In this way the PPD (XVII, XX) was obtained with yields of 64 and 71% respectively. If N,N-ADK containing the weakly nucleophilic PhNH fragment is used, annellation of the second pyrimidine ring takes place less readily, and the corresponding PPD (XXI, XXII) is obtained with low yields (21-28%). The presence of the exomethylene group in the PPD synthesized according to scheme 3 is confirmed by the PMR and ^{13}C NMR spectra. Thus, for example, in the PMR spectrum of compound (XVII) the methylene protons correspond to the signals of an AB system (δ_A 4.38 and δ_B 4.28 ppm), while the C atom of the methylene group in the ^{13}C NMR spectrum gives a triplet at δ 99.22 ppm ($^1J_{C,H}$ = 162.40 Hz).



(3)

(X), (XI)

(IX), (XV), (XVI)

(XVII)—(XXII)

$R^2 = PhCH_2$ (XV); R^2 = 4,6-dimethyl-2-pyrimidinyl (XVI); $R^1 = R^3 = Ph$, $R^2 = PhCH_2$ (XVII); $R^1 = Me$, $R^2 = PhCH_2$, $R^3 = Ph$ (XVIII); $R^1 = Ph$, $R^2 = PhCH_2$, $R^3 = Me$ (XIX); $R^1 = R^3 = Me$, R^2 = 4,6-dimethyl-2-pyrimidinyl(XX); $R^1 = R^2 = R^3 = Ph$ (XXI); $R^1 = R^3 = Me$, $R^2 = Ph$ (XXII).

Compounds (XVII-XXII) are white or light-yellowish crystalline substances soluble in chloroform, acetone, and ethanol but insoluble in hexane.

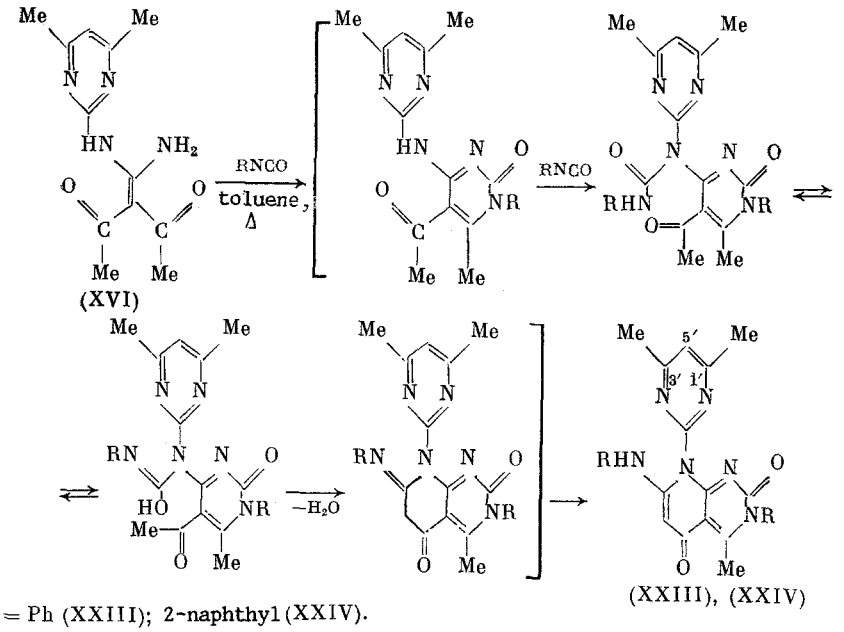
As seen from the presented examples, the PPDs cannot be synthesized from the various N,N-ADKs and the isocyanates of the aliphatic or aromatic series. It was found unexpectedly that the N,N-ADK (XVI) reacts differently with aryl isocyanates (scheme 4). Whereas this ketene aminal gives the PPD (XX) with methyl isocyanate, as indicated above, the products from its reaction with phenyl and 2-naphthyl isocyanates are derivatives of 3H,8H-pyrido-[2,3-d]pyrimidine-2,5-dione (XXIII, XXIV), the yields of which are 64 and 74% respectively.

The intermediates in the synthesis of (XXIII, XXIV) are clearly also the ureido derivatives of the cytosines analogous with those presented in scheme 3. However, the overall effect of the aryl and heteryl substituents probably stabilizes the imidoyl form of the carbamide fragment, making it possible for it to participate in the condensation (scheme 4), whereas the weaker nucleophilicity of the ArNH group compared with MeNH reduces the probability of heterocyclization according to scheme 3.

Compounds (XXIII, XXIV) are white crystalline substances readily soluble in chloroform and poorly soluble in other organic solvents. Their PMR spectra contain the characteristic signal of the methine proton at δ 5.5 ppm (in the ^{13}C NMR spectra a doublet at δ 9.87 ppm). Thus, the syntheses of the functionally substituted pyrimido[4,5-d]-pyrimidines and pyrido[2,3-d]pyrimidines show that the N,N-ADKs containing additional nucleophilic and electrophilic reaction centers compared with simple enamino ketones are prospective reagents for the construction of condensed heterocyclic systems.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WM-250 instrument in deuterochloroform (δ, ppm). The ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer in deuterochloroform (δ, ppm, J, Hz). The spin–spin coupling constants are indicated in cases where they are required for assignment of the signals. The IR spectra were recorded on a UR-20 instrument



(4)

R = Ph (XXIII); 2-naphthyl (XXIV).

(ϑ, cm^{-1}). The mass spectra were obtained on Varian MAT CH-6 and Varian MAT-311A spectrometers [m/z (I, %)]. The initial compounds (I, II) were obtained by the method in [6], and compounds (VIII, IX, XVI) by the method in [6,8].

3-[Benzylamino(amino)methylene]pentane-2,4-dione (XV). The compound was obtained from N,S-ADK (I) and benzylamine by analogy with [6]. Compound (XV) was isolated by column chromatography on silica gel with chloroform as eluant in the form of an oil and was then used without further purification. The yield was 87%. PMR spectrum: 11.67 br.s (NH), 10.70 br.s (NH), 7.40-7.22 m (Ph), 5.17 br.s (NH), 4.34 d (CH_2, J = 5.5 Hz), 2.37 s (2Me).

4-Methylthio-5-acetyl-1-phenyl-6-methyl-1H-pyrimidin-2-one (III). A mixture of 1.73 g (10 mmoles) of (I) and 1.2 ml (11 mmoles) of phenylisocyanate in 35 ml of toluene was boiled under argon for 2.5 h. After the reaction mixture had cooled to ~20°C 35 ml of hexane was added. The precipitate was filtered off and washed with a 1:2 mixture of ether and hexane (2 × 30 ml), and 2.13 g (78%) of (III) was obtained; mp 165-166°C (1:1 benzene–hexane). Mass spectrum: 274 (5) $[M]^{+\cdot}$, 259 (100) $[M - Me]^+$, 241(6) $[M - HS]^+$. Found %: C 61.21; H 5.20; N 10.05; S 11.73. $C_{14}H_{14}N_2O_2S$. Calculated %: C 61.29; H 5.14; N 10.21; S 11.69. IR spectrum (carbon tetrachloride): 1690, 1680 (CO), 1605, 1585, 1487. PMR spectrum: 7.53–7.38 m (3H, Ph), 7.16 m (2H, PH), 2.56 s (Me), 2.55 s (Me), 1.86 s (Me). ^{13}C NMR spectrum 199.78 q (CO, $^2J_{C,H}$ = 5.0), 173.44 q (C^4, $^2J_{C,H}$ = 3.0), 153.10 (C^2), 152.21 q (C^6, $^2J_{C,H}$ = 6.0), 136.94; 129.63; 128.91; 127.27 (Ph), 118.54 (C^5), 32.01 (COMe), 18.42 (Me), 12.95 (SMe).

4-Methylthio-5-acetyl-1-(2-naphthyl)-6-methyl-1H-pyrimidin-2-one (IV). Compound (IV) was obtained from (I) and 2-naphthyl isocyanate by analogy with (III). It was isolated from the reaction mixture by column chromatography on silica gel with gradient elution from benzene to 10:1 benzene–ethanol. The yield was 85%; mp 227-228°C (1:2 benzene–hexane). Mass spectrum: 324(20) $[M]^{+\cdot}$, 309(100) $[M - Me]^+$, 291(11) $[M - HS]^+$. Found %: C 66.71; H 4.88; N 8.40; S 9.84. $C_{18}H_{16}N_2O_2S$. Calculated %: C 66.64; H 4.97; N 8.64; S 9.88. IR spectrum (methylene chloride): 1675, 1670 (CO), 1590, 1585 sh, 1490. PMR spectrum 7.97 m (1H), 7.92-7.78 m (2H, naphthyl), 7.68 m (1H, naphthyl), 7.60-7.49 m (2H, naphthyl), 7.26 m (1H, naphthyl), 2.62 s (Me), 2.60 s (Me), 1.92 s (Me).

4-Ethylthio-5-acetyl-1-phenyl-6-methyl-1H-pyrimidin-2-one (V). The compound was obtained from (II) and phenyl isocyanate by analogy with (III). The yield of compound (V) was 88%; mp 168-169°C (benzene). Mass spectrum: 288(5) $[M]^{+\cdot}$, 273(8) $[M - Me]^+$, 259(100) $[M - C_2H_5]^+$, 255(16) $[M - HS]^+$. Found %: C 62.51; H 5.52; N 9.94; S 11.30. $C_{15}11_{16}N_2O_2S$. Calculated %: C 62.48; H 5.59; N 9.71; S 11.12. IR spectrum (methylene chloride): 1680, 1670 (CO), 1605, 1585. PMR spectrum 7.57–7.42 m (3H, Ph), 7.19 d (2H, Ph), 3.28 q (CH_2), 2.58 s (Me), 1.87 s (Me), 1.36 t (MeCH$_2$).

4-Methylthio-5-acetyl-1,6-dimethyl-1H-pyrimidin-2-one (VI). A mixture of 0.423 g (2.5 mmoles) of (I) and 0.16 ml (2.75 mmoles) of methyl isocyanate in 8 ml of toluene was heated in a sealed tube at 100-105°C for 5 h. The solvent was evaporated under vacuum, the residue

was chromatographed on a column of silica gel (eluant chloroform), and 0.404 g (78%) of (VI) was obtained; mp 119-120°C (1:1 benzene–hexane). Mass spectrum: 212(10) $[M]^{+\cdot}$, 197(100) $[M - Me]^+$, 179(23) $[M - HS]^+$, 155(13) $[M - MeNCO]^+$. Found %: C 51.10; H 5.75; N 13.61; S 14.92%. $C_9H_{12}N_2O_2S$. Calculated %: C 50.92; H 5.70; N 13.20; S 15.11%. IR spectrum (methylene chloride): 1670, 1660 (CO), 1595, 1505. PMR spectrum: 3.50 s (NMe), 2.53 s (2 Me), 2.26 s (Me). ^{13}C NMR spectrum: 199.89 (CO), 171.50 (C^4), 153.54 (C^2), 152.17 (C^6), 118.57 (C^5), 3.83(CO<u>Me</u>) and (NMe), 17.31 (Me), 12.60 (SMe).

<u>4-Methylthio-5-acetyl-1-ethyl-6-methyl-1H-pyrimidin-2-one (VII).</u> The compound was synthesized from compound (I) and ethyl isocyanate by analogy with compound (VI). The yield of (VII) was 82%; mp 99-100°C (1:2 benzene–hexane). Mass spectrum: 226(11) $[M]^{+\cdot}$, 211(100) $[M - Me]^+$, 193(21) $[M - HS]^+$, 183(26) $[M - COMe]^+$. Found %: C 53.41; H 6.31; N 12.31; S 14.03. $C_{10}H_{14}N_2O_2S$. Calculated %: C 53.07; H 6.24; N 12.38; S 14.17. IR spectrum (methylene chloride): 1670, 1660 (CO), 1590, 1505. PMR spectrum: 3.86 q (CH_2), 2.36 s (Me), 2.35 s (Me), 2.14 (SMe), 1.13 t (<u>Me</u>CH_2).

<u>4-Benzylamino-5-acetyl-1-phenyl-6-methyl-1H-pyrimidin-2-one (X).</u> A mixture of 0.274 g (1 mmole) of the pyrimidine (III) and 0.22 ml (2 mmoles) of benzylamine in 4 ml of toluene was boiled for 6 h. The solvent was evaporated under vacuum, the residue was chromatographed on a column of silica gel with chloroform as eluant, and 0.25 g (75%) of (X) was obtained; mp 167-168°C (1:2 benzene–hexane). Mass spectrum: 333(100) $[M]^{+\cdot}$, 318(31) $[M - Me]^+$, 290(9) $[M - COMe]^+$, 242(17) $[M - CH_2Ph]^+$. Found %: C 72.29; H 5.91; N 12.94. $C_{20}H_{19}N_3O_2$. Calculated %: C 72.05; H 5.74; N 12.60. IR spectrum (methylene chloride): 3440-3210 (NH), 1680, 1645 (CO), 1610, 1590, 1560, 1498. PMR spectrum: 8.60 br.s (NH), 7.62-7.10 m (2 Ph), 4.73 d (CH_2, J = 4.9), 2.48 s (Me), 2.17 s (Me). ^{13}C NMR spectrum: 199.99 (CO), 160.54, (C^4), 159.36 q (C^6, $^2J_{C,H}$ = 5.4), 154.87 (C^2), 138.12, 137.78, 129.83, 128.96, 128.63, 128.07, 127.84, 127.38 (2 Ph), 107.17 (C^5), 44.85 (CH_2), 33.05 (CO<u>Me</u>), 21.84 (Me).

<u>4-Benzylamino-5-acetyl-1,6-dimethyl-1H-pyrimidin-2-one (XI).</u> The compound was obtained from the pyrimidine (VI) and benzylamine by analogy with (X). The reaction time was 11 h. The yield of (XI) was 86%; mp 170-171°C (4:1 benzene–hexane). Mass spectrum: 271 (100) $[M]^{+\cdot}$, 256 (45) $[M - Me]^+$. Found %: C 66.42; H 6.39; N 15.31. $C_{10}H_{17}O_2N_3$. Calculated %: C 66.40; H 6.32; N 15.49. IR spectrum (methylene chloride): 3440-3200 (NH), 1670, 1640 (CO), 1600, 1565, 1505. PMR spectrum: 8.33 br.s (NH), 7.37-7.15 m (Ph), 4.65 d (CH_2, J = 5.0), 3.49 s (NMe), 2.48 s (Me), 2.43 s (Me).

<u>4-Morpholino-5-acetyl-1-phenyl-6-methyl-1H-pyrimidin-2-one (XII). Method A.</u> The compound was obtained from pyrimidine (III) and morpholine by analogy with (X). It was isolated by column chromatography with gradient elution with benzene and ethanol from 100:1 to 25:1. The yield was 82%; mp 206-207°C (1:1 benzene–hexane). Mass spectrum: 313 (54) $[M]^{+\cdot}$, 298 (100) $[M - Me]^+$. Found %: C 65.41; H 6.37; N 13.55. $C_{17}H_{19}N_3O_3$. Calculated %: C 65.16; H 6.11; N 13.41. IR spectrum (methylene chloride): 1690 sh, 1667 (CO), 1605, 1585, 1498, 1488. PMR spectrum: 7.55-7.33 m (3H, Ph), 7.17 m (2H, Ph), 3.72 t (2 CH_2), 3.59 t (2 CH_2), 2.39 s (Me), 1.92 s (Me). ^{13}C NMR spectrum: 200.05 (CO), 163.41 (C^4), 156.00 q (C^6, $^2J_{C,H}$ = 5.7), 154.64 (C^2), 137.72, 129.47, 128.64, 127.67 (Ph), 108.88 (C^5), 66.20 t (2 CH_2, $^1J_{C,H}$ = 144.0), 47.81 t (2 CH_2, $^1J_{C,H}$ = 142.0), 30.64 (<u>Me</u>CO), 18.03 (Me).

<u>Method B.</u> A mixture of 0.424 g (2 mmoles) of N,N-ADK (VIII) and 0.24 ml (2.2 mmoles) of phenyl isocyanate in 8 ml of toluene was boiled under argon for 6 h. The solvent was distilled under vacuum, the residue was chromatographed on a column of silica gel with chloroform as eluant, and 0.29 g (47%) of compound (XII) was obtained.

<u>4-Phenylamino-5-acetyl-1-phenyl-6-methyl-1H-pyrimidin-2-one (XIII).</u> The compound was synthesized from (IX) and phenyl isocyanate by analogy with (XII) (method B). The solvent was removed from the reaction mixture under vacuum, and the residue was crystallized from a 1:1 mixture of benzene and hexane. Compound (XIII) was obtained with a yield of 64%; mp 182-183°C (1:1 benzene–hexane). Mass spectrum: 319 $[M]^{+\cdot}$, 318 $[M - H]^+$. Found %: C 71.33; H 5.25; N 13.17. $C_{19}H_{17}N_3O_2$. Calculated %: C 71.45; H 5.37; N 13.16. IR spectrum (chloroform): 3400-2950 (NH, CH), 1682, 1648 (CO), 1615, 1590, 1569, 1557. PMR spectrum: 10.36 br.s (NH), 7.75 m (2H, Ph), 7.60-7.40 m (3H, Ph), 7.34 m (2H, Ph), 7.21 m (2H, Ph), 7.12 m (1H, Ph), 2.53 s (Me), 2.19 s (Me). ^{13}C NMR spectrum: 200.52 (CO), 160.28 q (C^6, $^2J_{C,H}$ = 5.8), 158.71, 154.12 (C^2, C^4), 137.88, 137.75, 129.73, 128.88, 128.61, 127.89, 124.30, 122.06 (2 Ph), 107.25 (C^5), 33.01 (CO<u>Me</u>), 21.99 (Me).

<u>4-Phenylamino-5-acetyl-1-(2-naphthyl)-6-methyl-1H-pyrimidin-2-one (XIV).</u> The compound was obtained from (IX) and 2-naphthyl isocyanate by analogy with (XII) (method B). The yield of (XIV) was 50%; mp 139-140°C (1:1 benzene–hexane). Mass spectrum: 369 $[M]^{+\cdot}$, 368

$[M - H]^+$. Found %: C 74.44; H 5.55; N 11.31. $C_{23}H_{19}N_3O_2$. Calculated %: C 74.78; H 5.18; N 11.38. IR spectrum (chloroform): 3400-2950 (NH, CH), 1681, 1647 (CO), 1610, 1590, 1569, 1555. PMR spectrum: 10.40 br.s (NH), 7.99 m (1H), 7.96-7.75 m (4H), 7.72 m (1H), 7.60-7.50 m (2H), 7.40-7.25 m (3H), 7.15 m (1H arom).

4-Methylene-1-benzyl-3,6-diphenyl-5-methyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XVII). Method A. A mixture of 0.167 g (0.5 mmole) of pyrimidine (X) and 0.11 ml (1 mmole) of phenyl isocyanate in 4 ml of toluene was boiled under argon for 3 h. The solvent was removed under vacuum, the residue was chromatographed on a column of silica gel with benzene and then with a 3:2 mixture of benzene and ether as eluant (to separate the diphenylurea) and then with chloroform as eluant. An oil was obtained. It was dissolved in benzene, and compound (XVII) was precipitated with hexane. The yield was 75% (0.163 g); mp 188-189°C. Mass spectrum 434 (40) $[M]^{+\cdot}$, 344 (34), 343 (100) $[M - CH_2Ph]^+$. Found %: C 74.44; H 5.08; N 13.24. $C_{27}H_{22}N_4O_2$. Calculated %: C 74.64; H 5.10; N 12.90. IR spectrum (methylene chloride): 1695, 1680 (CO), 1615, 1598, 1535. PMR spectrum: 7.68-7.18 m (3 Ph), 5.44 s (CH_2), 4.38 d (1H, CH_2=, J = 2.1) and 4.28 d (1H, CH_2=, J = 2.1), 2.21 s (Me). ^{13}C NMR spectrum 158.70; 155.20; 150.19 (C^2, C^7, C^{8a}), 154.30 q (C^5, $^2J_{C,H}$ = 6.4), 138.37, 138.25, 137.27, 130.19, 129.90, 129.67, 129.35, 129.00, 128.54, 128.34, 127.92, 127.50 (C^4 and 3 Ph), 100.64 (C^{4a}), 99.22 t (CH_2=, $^1J_{C,H}$ = 162.40), 44.98 (CH_2), 21.18 (Me).

Method B. A mixture of 0.23 g (1 mmole) of (XV) and 0.43 ml (4 mmoles) of phenyl isocyanate in 4 ml of toluene was boiled under argon for 4 h. By analogy with method A we isolated 0.28 g (64%) of compound (XVII).

4-Methylene-1-benzyl-3-phenyl-5,6-dimethyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XVIII). Compound (XVIII) was obtained from the pyrimidine (XI) and phenyl isocyanate by analogy with (XVII) (method A). The yield of (XVIII) was 72%; mp 229-230°C. Mass spectrum 372 (48) $[M]^{+\cdot}$, 282 (26), 281 (100) $[M - CH_2Ph]^+$. Found %: C 71.07; H 5.53; N 14.78. $C_{22}H_{20}N_4O_2$. Calculated %: C 70.95; H 5.41; N 15.05. IR spectrum (methylene chloride): 1695, 1680 (CO), 1615, 1595, 1530. PMR spectrum: 7.63-7.15 m (2 Ph), 5.35 s (CH_2), 4.34 d (1H, CH_2=, J = 2.1) and 4.25 d (1H, CH_2=, J = 2.1), 3.58 s (NMe), 2.55 s (Me).

4-Methylene-1-benzyl-6-phenyl-3,6-dimethyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XIX). A mixture of 0.167 g (0.5 mmole) of the pyrimidine (X) and 0.06 ml (1 mmole) of methyl isocyanate in 5 ml of toluene was heated in a sealed tube at 110-115°C for 5 h. The solvent was evaporated under vacuum, the residue was chromatographed on a column of silica gel with chloroform as eluant, and an oil was obtained. It was dissolved in benzene, and compound (XIX) was precipitated with hexane. The yield was 0.11 g (59%); mp 193-194°C. Mass spectrum 372 (18) $[M]^{+\cdot}$, 282 (19), 281 (100) $[M - CH_2Ph]^+$. Found %: C 71.06; H 5.42; N 14.80. $C_{22}H_{20}N_4O_2$. Calculated %: C 70.95; H 5.41; N 15.05. IR spectrum (methylene chloride): 1695, 1680 (CO), 1615. 1595, 1530. PMR spectrum: 7.62-7.05 m (2 Ph), 5.37 s (CH_2), 4.82 d (1H, CH_2=, J = 2.5) and 4.41 d (1H, CH_2=, J = 2.5), 3.28 s (NMe), 2.21 s (Me).

1-(4,6-Dimethyl-2-pyrimidinyl)-4-methylene-3,5,6-trimethyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XX). The compound was obtained from 1 mmole of (XVI) and 4 mmoles of methyl isocyanate by analogy with (XIX). The mixture was left at ~20°C for 12 h. The precipitate was separated by decantation, dissolved in chloroform, and chromatographed on a column of silica gel with a 100:1 mixture of chloroform and ethanol as eluant. The solvent was evaporated, and compound (XX) was obtained with a 71% yield; mp 307-308°C. Mass spectrum: 326 (100) $[M]^{+\cdot}$, 311 (5) $[M - Me]^+$, 298 (7) $[M - CO]^+$, 297 (10) $[M - CO - H]^+$. Found %: C 58.48; H 5.56; N 25.94. $C_{16}H_{18}N_6O_2$. Calculated %: C 58.88; H 5.56; N 25.75. IR spectrum (methylene chloride): 1705, 1668 (CO), 1615, 1600, 1540. PMR spectrum: 7.07 s ($H^{5'}$), 4.88 d (1H, CH_2=, J = 2.4) and 4.45 d (1H, CH_2=, J = 2.4), 3.53 s and 3.23 s (2NMe), 2.60 s (Me), 2.50 s (2Me). ^{13}C NMR spectrum: 169.48 ($C^{4'}$, $C^{6'}$), 157.65, 155.45, 155.16, 154.73, 149.92 ($C^{2'}$, C^2, C^5, C^7, C^{8a}), 137.23 (C^4), 120.25 d ($C^{5'}$, $^1J_{C,H}$ = 165.0), 99.85 (C^{4a}), 96.06 t (CH_2=, $^1J_{C,H}$ = 162), 33.10 and 31.78 (2NMe), 23.73 (2Me), 19.29 (Me).

4-Methylene-1,3,6-triphenyl-5-methyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XXI). The compound was obtained from (IX) and phenyl isocyanate by analogy with (XVII) (method B). By column chromatography we isolated successively the pyrimidine (XIII) (62%) and compound (XXI) (21%); mp 159-160°C. Mass spectrum 420 (100) $[M]^{+\cdot}$, 391 (88) $[M - CO - H]^+$. Found %: C 74.23; H 4.88; N 12.92. $C_{26}H_{20}N_4O_2$. Calculated %: C 74.27; H 4.79; N 13.33. IR spectrum: (methylene chloride): 1710, 1680 (CO), 1615, 1595, 1530. PMR spectrum: 7.60-7.18 m (3Ph), 4.53 d (1H, CH_2=, J = 2.3) and 4.45 d (1H, CH_2=, J = 2.3), 2.27 s (Me).

4-Methylene-1-phenyl-3,5,6-trimethyl-1H,3H,6H-pyrimido[4,5-d]pyrimidine-2,7-dione (XXII). Compound (XXII) was obtained from 1 mmole of (IX) and 4 mmoles of methyl isocyanate

by analogy with compound (XIX). The yield of compound (XXII) was 28%; mp 250-251°C. Mass spectrum 296 (100) $[M]^{+\cdot}$, 281 (16) $[M - Me]^+$, 268 (16) $[M - CO]^+$, 267 (81) $[M - CO - H]^+$. Found %: C 64.39; H 5.51; N 19.00. $C_{16}H_{16}N_4O_2$. Calculated %: C 64.85; H 5.44; N 18.91. IR spectrum (methylene chloride): 1700, 1670 (CO), 1615, 1600, 1540. PMR spectrum: 7.48-7.30 m (3H, Ph), 7.15 m (2H, Ph), 4.88 d (1H, CH_2=, J = 2.4) and 4.47 d (1H, CH_2=, J = 2.4), 3.50 s and 3.26 s (2 NMe), 2.57 s (Me).

8-(4,6-Dimethyl-2-pyrimidinyl)-7-phenylamino-3-phenyl-4-methyl-3H,8H-pyrido[2,3-d]-pyrimidine-2,5-dione (XXIII). A mixture of 0.496 g (2 mmoles) of (XVI) and 0.87 ml (8 mmoles) of phenyl isocyanate in 10 ml of toluene was boiled under argon for 4 h, cooled to ~20°C, and left for 8 h. The precipitate was filtered off and washed from the diphenyl urea impurity with ether (3 × 40 ml), and 0.66 g (73%) of compound (XXIII) was obtained; mp 325-327°C (benzene, decomp.). Mass spectrum: 450 (65) $[M]^{+\cdot}$, 449 (100) $[M - H]^+$. Found %: C 68.97: H 4.84; N 18.63. $C_{26}H_{22}N_6O_2$. Calculated %: C 69.32; H 4.92; N 18.66. IR spectrum: 1715, 1665 (CO), 1625, 1605, 1592, 1540. PMR spectrum: 13.66 br.s (NH), 7.72-7.36 m (6H), 7.30 m (2H), 7.15 m (2H) (2Ph), 6.80 s ($H^{5'}$), 5.51 s (H^6), 2.89 s (Me), 2.50 s (2Me). ^{13}C NMR spectrum: 167.78 ($C^{4'}$, $C^{6'}$, q $^2J_{C,H}$ = 6, d, $^2J_{C,H}$ = 3), 164.12, 162.32 ($C^{2'}$, C^5), 155.75 q (C^4, $^2J_{C,H}$ = 7.5), 151.41, 148.05 (C^2, C^{8a}), 150.11 d (C^7, $^2J_{C,H}$ = 3.0), 138.31, 135.55, 130.41, 130.08, 129.63, 129.28, 128.89, 127.79 (2Ph), 115.56 ($C^{5'}$, d, $^1J_{C,H}$ = 166.0, qq, $^2J_{C,H}$ = 4.0), 100.26 (C^{4a}), 98.71 d (C^6, $^1J_{C,H}$ = 170.0), 24.05 (2Me), 23.04 (Me).

8-(4,6-Dimethyl-2-pyrimidinyl)-7-(2-naphthylamino)-3-(2-naphthyl)-4-methyl-3H,8H-pyrido[2,3-d]pyrimidine-2,5-dione (XXIV). A mixture of 0.248 g (1 mmole) of compound (XVI) and 0.676 g (4 mmoles) of 2-naphthyl isocyanate in 5 ml of toluene was boiled under argon for 5 h. The mixture was cooled to ~20°C, and 10 ml of chloroform was added to the precipitate. The insoluble dinaphthylurea impurity was filtered off, the solution was evaporated, and 0.23 g of compound (XXIV) was obtained. An additional quantity of compound (XXIV) (0.12 g) was isolated from the filtrate by column chromatography on silica gel with chloroform as eluant. The overall yield was 63%; mp 341-343°C (benzene, decomp.). Mass spectrum: 550 (100) $[M]^{+\cdot}$, 549 (88) $[M - H]^+$. Found %: C 74.31; H 4.70; N 15.45. $C_{34}H_{26}N_6O_2$. Calculated %: C 74.16; H 4.76; N 15.26. IR spectrum (chloroform): 1715, 1663 (CO), 1620, 1595, 1550, 1540. PMR spectrum: 13.70 br.s (NH), 8.06 m (2H, naphthyl), 8.00-7.85 m (5H, naphthyl), 7.70 m (1H, naphthyl), 7.67-7.54 m (4H, naphthyl), 7.41 m (1H, naphthyl), 7.28 m (1H, naphthyl), 6.81 s ($H^{5'}$), 5.61 s (H^6), 2.99 s (Me), 2.55 s (2Me). ^{13}C NMR spectrum: 167.76 ($C^{4'}$, $C^{6'}$), 164.16, 162.45 ($C^{2'}$, C^5), 155.95 (C^4), 151.42, 148.18 (C^{8a}, C^2), 150.29 (C^7), 135.63, 133.91, 133.62, 133.42, 133.20, 132.78, 130.63, 130.19, 128.34, 128.22, 127.93, 127.37, 127.24, 126.92, 126.86, 125.77, 125.14 (2-naphthyl), 115.53 ($C^{5'}$), 100.44 (C^{4a}), 98.79 (C^6), 23.96 (2Me), 23.16 (Me).

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