A New Entry to the Imidazo[4,5-*d*]pyrimidine System. The Reaction of 1,3-Dimethyl-6-aminouracil with *N,N*-Dimethyldichloromethyleniminium Chloride (Phosgeniminium Chloride) and Trimethylsilyl Azide, A Novel and Convenient "One Pot" Synthesis of 8-*N*-Arylaminotheophyllines (2-*N*-Arylamino-4,6-dimethylimidazo[4,5-*d*]pyrimidine-(4H,6H)-5,7-diones), Starting from 1,3-Dimethyl-6-aminouracil

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1,3-Dimethyl-6-aminouracil **2** was converted into various 8-*N*-arylaminotheophyllines (2-*N*-arylamino-4,6-dimethylimidazo[4,5-*d*]pyrimidine-(4*H*,6*H*)-5,7-diones) **17** through reaction successively, with phosgeniminium chloride (*N,N*-dimethyldichloromethyleniminium chloride) (**1a**), trimethylsilyl azide (**4**) and arylamines. Starting with the synthesis of the *N,N*-dimethyl(1,3-dimethyl-4-aminouracil-5-yl)chloromethyleniminium chloride (amide chloride) **3** this new route to the imidazo[4,5-*d*]pyrimidine skeleton was shown to proceed *via* the formation of a very unstable *N,N*-dimethyl-(1,3-dimethyl-4-aminouracil-5-yl)azidomethyleniminium chloride (amide azide) (**8**) which would undergo an *in situ* rearrangement into very likely, a 4-amino-5-(chloroformamidin-1'-yl)uracil and/or related compounds of types **10**. Depending on reaction conditions, the latter was proved to be a very good precursor of the 8-dimethylaminotheophylline **11** as well.

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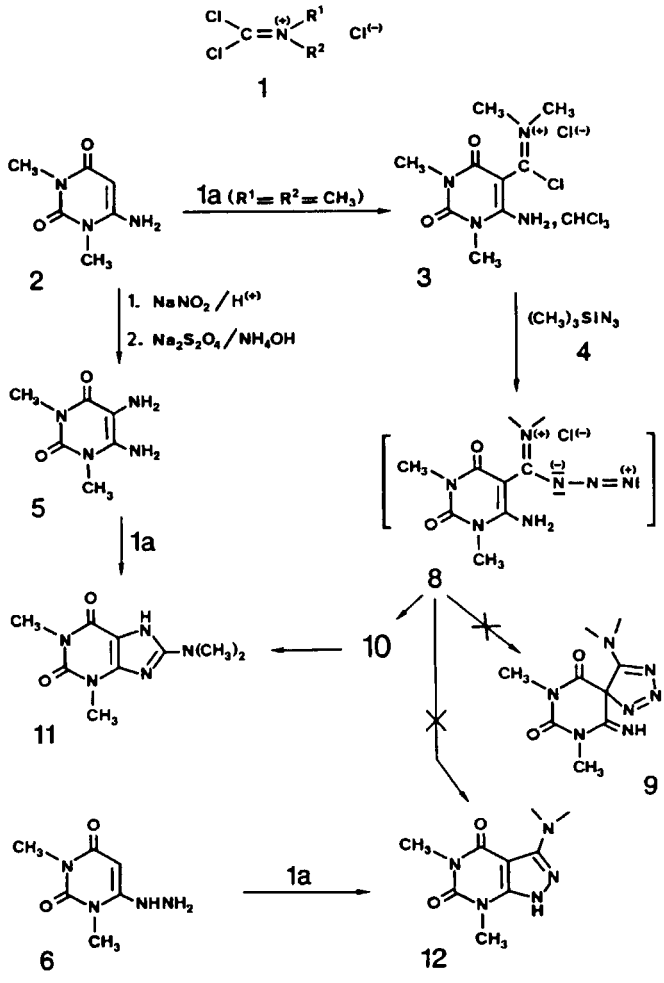
Our longstanding involvement in the use of uracil derivatives as starting materials to prepare new heterocyclic systems of biological interests, led us, some years back, to consider their reaction with *N,N*-dialkyldichloromethyleniminium chlorides (phosgeniminium chlorides) **1** (Scheme 1). At that time, although recently discovered and still strenuously studied by Viehe's group, phosgeniminium chlorides were already known as very useful one carbon atom reagents, condensing with many types of nucleophiles and having, due to the presence in their molecule, of three mobile chlorine atoms, greater synthetic potential than corresponding Vielsmeyer-Haack-Arnold and Mannich reagents [2-6].

Reactions involving the phosgeniminium chlorides **1** and nucleophiles usually afford new electrophilic synthons such as chloromethyleniminium chlorides (amide chlorides), α-chloroenamines, 1,3-dichlorotrimethinecyanines, *etc*, able to react further with nucleophiles and to produce eventually, various types of functionalized 5, 6 and 7 membered ring systems through either intra or extra molecular heterocyclization processes. Accordingly, phosgeniminium chloride (**1a**) ($R^1 = R^2$ = methyl) condenses readily with the 1,3-dimethyl-6-aminouracil **2**, affording the *N,N*-dimethyl(1,3-dimethyl-4-aminouracil-5-yl)chloromethyleniminium chloride (amide chloride) **3** in a very good yield (Scheme 1). This thermally stable and strong electrophilic amide chloride was conveniently converted into various new uracil derivatives and fused pyrimidines including thieno[3,4-*d*], pyrido[2,3-*d*] and pyrimido[4,5-*d*]pyrimidines, pyrido[1,2-*a*]pyrimido-[4,5-*b*]pyrimidines, *etc*, [7-11].

Of particular interest, is the reaction of **3** with the trimethylsilyl azide **4** producing, very likely, the expected *N,N*-dimethyl(1,3-dimethyl-4-aminouracil-5-yl)azidomethyleniminium chloride (amide azide) **8**. The latter undergoes an *in situ* rearrangement into an uracil derivative of type **10** (Schemes 1 and 4), which depending on the work up conditions, can be readily converted into the 2-*N,N*-dimethylamino-4,6-dimethylimidazo[4,5-*d*]-pyrimidine-(4*H*,6*H*)-5,7-dione (8-dimethylaminotheophylline) **11** (Scheme 1). This imidazo[4,5-*d*]pyrimidine ring system formation, seems to be a very selective process since neither the more or less first expected conversion of **8** into the 1*H*-3-*N,N*-dimethylamino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-(5*H*,7*H*)-4,6-dione **12**, independently available starting from the 1,3-dimethyl-6-hydrazinouracil **6** and phosgeniminium chloride (**1a**) [11,12], nor its cyclization into a spiro uracil derivative of type **9**, as it is sometimes the case when dealing with barbituric acids and related compounds [11], were ever observed (Scheme 1). The 8-dimethylaminotheophylline **11** was positively identified to an authentic sample prepared from the 1,3-dimethyl-4,5-diaminouracil **5** [13,14] and **1a** [11,12], and its structure proved by X-ray crystallography of its perchloric acid salt **11a** [15] also prepared starting from **10**.

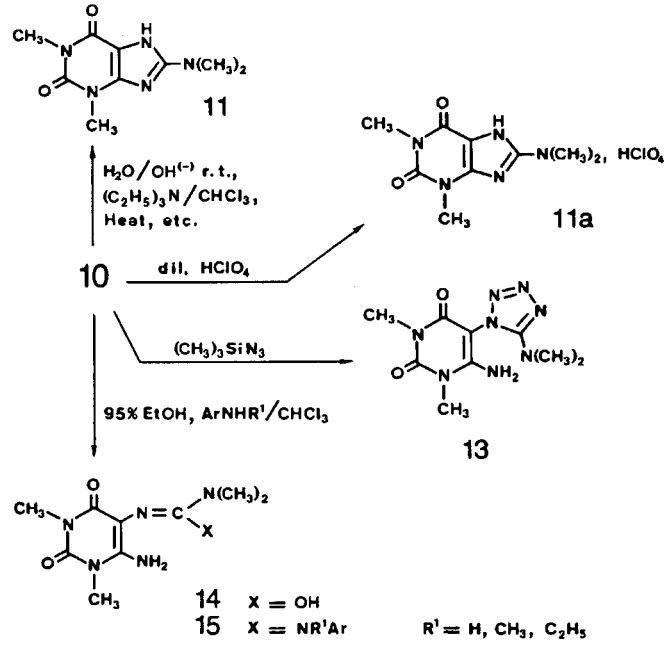
Scheme 1



The compound we assume to be the amide azide **8** is readily formed when the trimethylsilyl azide **4** is added to a clear solution of the amide chloride **3** in dry chloroform cooled in an iced water bath, but cannot be isolated since it cleanly decomposes *in situ*, soon after its formation and while the temperature of the cooling system is still at 0°, into nitrogen and the molecule **10** which separates slowly from the reaction mixture as a slightly hygroscopic white solid. Very soluble in water, **10** was found to be either insoluble at room temperature or unstable when heated, in dry organic solvents, and to react with inorganic and organic bases in aqueous and non aqueous conditions, while releasing one equivalent of hydrochloric acid. As a matter of fact, all our attempts to purify and to make an unambiguous identification of **10** using standard procedures, have, as of yet, failed. However, insights into its structure, could tentatively be deduced from some of its properties and the nature of its hydrolysis and/or aminolysis reaction products.

Thus, while **10** is readily converted into the only 8-*N*,*N*-dimethylaminotheophylline **11** vhen treated at room temperature with a base in aqueous solution, or when dissolved in dimethyl sulfoxide-d_6 or in trifluoroacetic acid to perform ^{1}H nmr spectra, it gives the same theophylline **11** when heated extensively in dry chloroform or dichloroethane, and the corresponding perchloric acid salt **11a** when dissolved at room temperature in diluted perchloric acid. Furthermore, **10** was shown to condense slowly with the azide group, when heated in dry chloroform in the presence of an excess of trimethylsilyl azide, affording the tetrazole **13** in moderate yield, and with water, when stirred at room temperature in 95% ethanol or in aqueous acetonitrile, to give rather low yields of the urea **14**. Similarily, **10** reacts with primary and secondary anilines in dry dichloromethane or dry chloroform, to produce the guanidines **15** (Scheme 2). Unlike anilines, aliphatic amines used in similar conditions do not condense with **10** but provoke the formation of **11**. The compounds **13** and **14**, are usually obtained competitively with more or less important quantity of **11** while the presence of the latter is seldom observed into the reaction mixtures corresponding to the preparation of the guanidines **15**. The structure of the tetrazole **13** was proved by X-ray crystallography [16, 17].

Scheme 2



When heated in the presence of a strong inorganic base in aqueous solution, the guanidines **15** undergo an intramolecular imidazole ring closure affording the corresponding 8-arylaminotheophyllines **17** in very good yield, while one equivalent of dimethylamine is expelled from the starting molecules. We assume that the reaction pro-

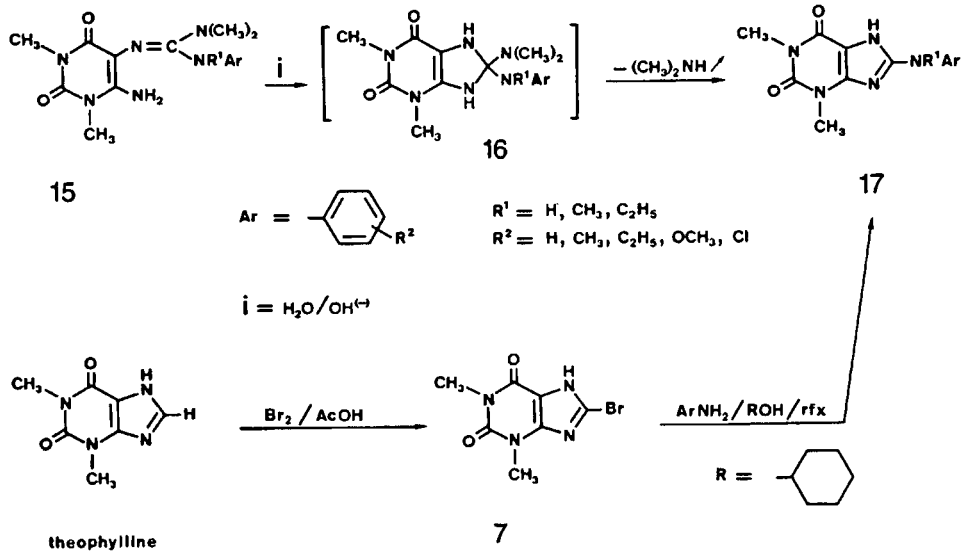
ceeds probably, through the formation first of 8-dimethylamino-8-arylamino derivatives of types **16** (Scheme 3).

The 8-arylaminotheophyllines **17a**, **17b**, **17c**, **17e**, and **17i** were identified to samples independently prepared by heating the 8-bromotheophylline **7** in refluxing cyclohexanol in the presence of the corresponding anilines (Scheme 3). The 8-bromotheophylline **7** was obtained according to the literature, starting from the commercially available theophylline *via* reaction with bromine in acetic acid [18,19].

The conversion of **10** into the 8-dimethylaminotheophylline **11** when dissolved in a potassium hydrogen carbonate aqueous solution, and into the perchloric acid salt **11a** when treated with diluted perchloric acid, could allow the visualization of that molecule as the hydrochloride form of **11** which would give back the latter when treated with an aqueous base and undergo an anion exchange into **11a** in the presence of perchloric acid.

The other results however, suggest otherwise. As a matter of fact, the xanthine skeleton being a very stable system,

Scheme 3



The guanidines **15** can be isolated and purified using standard procedures. However, the tediousness of the corresponding work-ups, leading eventually to rather low yields of not so pure and often hygroscopic material, prompted us to perform their cyclization into the 8-arylaminotheophyllines **17**, without further purification, using the crude oily residue which is left after the treatment of **10** with anilines in chloroform or dichloromethane and the evaporation of the solvent *in vacuo*.

Similarily, although the amide chloride **3** [7] and the compound **10**, which are both prepared in dry chloroform, can be isolated and stored at room temperature under inert atmosphere, we found much easier to carry out their transformation into the amide azide **8** and the guanidines **15**, respectively, without prior isolation and purification, that is to say *in situ*, using the respective crude reaction mixtures as starting materials. Consequently, we could conveniently perform the five step conversion of the 6-aminouracil **2** into the 8-arylaminotheophyllines **17** under mild "one pot" reaction conditions and isolate the final products through a single very easy work up.

it is unlikely that the azide group in refluxing chloroform or water in ethanol or anilines in dichloromethane at room temperature would ever condense with the π-excessive imidazole ring of **11** and provoke its cleavage to afford such compounds as the tetrazole **13**, the urea **14** and the guanidines **15**. Therefore, **10** would rather be seen as a 4,5-disubstituted uracil derivative, which would act as an open precursor of **11**, than as the corresponding hydrochloride of the 8-dimethylaminotheophylline **11** itself.

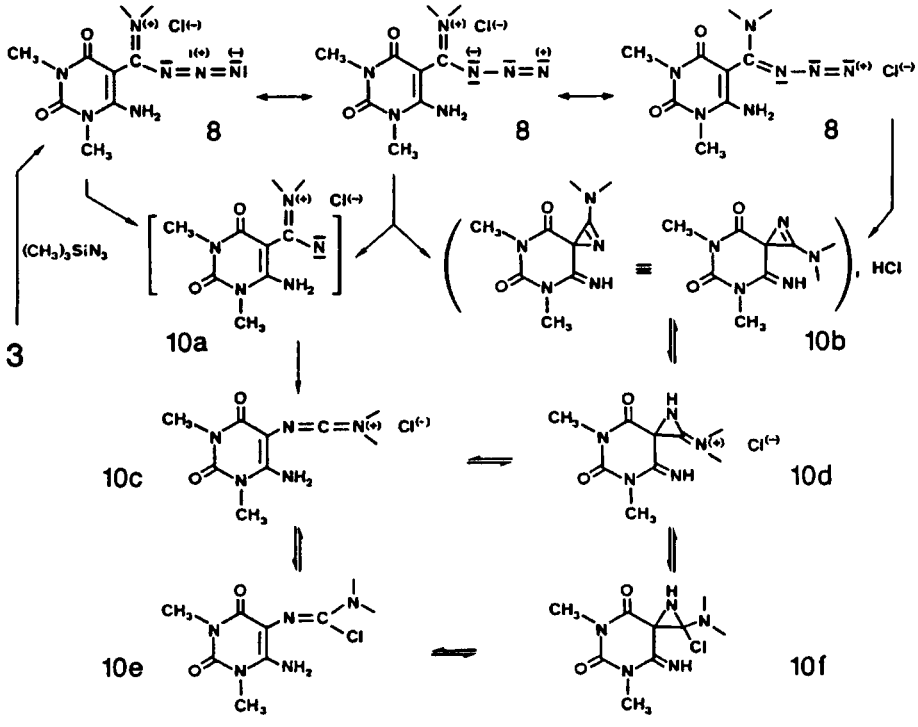
The main aspect of the conversion mechanism of the amide chloride **3** into compounds such as **11**, **13**, **14**, **15** and eventually **17** after reacting with the trimethylsilyl azide to form **8**, is the fact that the reaction starts with a 4,5-disubstituted uracil 5-bonded to the carbon atom of an amide chloride group and ends up with molecules in which this specific C-C bond has been changed into a C-N bond. This, obviously, means that 1) a molecular rearrangement has taken place and 2) the corresponding process involves necessarily the 5-position of the pyrimidine moiety. Accordingly, as outlined below (Scheme 4), the thermal decomposition and rearrangement of **8** could

possibly give rise first to the nitrene **10a** and/or to the uracilspiro-1*H*-azirine derivative **10b** and then to other systems such as **10c** to **10f** for instance. The solubility of **10** in water and conversely, its insolubility in dry inert organic solvents, as well as its mass spectrum which 1) does not suggest that a chlorine atom is attached to the molecule *via* a covalent bond and 2) exhibits an M^+ value in accord with the molecular weight, either calculated or analytically found through acidimetric titration, minus one equivalent of hydrogen chloride, seem however more consistent with the salt forms **10b**, **10c** and **10d** than with the corresponding covalent forms **10e** and **10f**. On the other hand, on the issue of these various proposed structures for the molecule **10** and although to our knowledge, no uracilspiroazirine derivative have, as of yet, been described in the literature, the formation of such a compound as **10b** would also be in accord with the propensity of barbituric acids and related compounds to produce 5-spiro derivatives [20,21], let alone the fact that stable 3,3-dimethyl-2-dimethylamino-1-azirines are readily available starting from α-chloroenamines and sodium azide [22-25]. Finally, the fact that strong inorganic bases or aliphatic amines in aqueous solution would induce an imidazole ring closure process to produce the theophylline **11** while anilines and trimethylsilyl azide in chloroform or water in ethanol and acetonitrile would rather behave as nucleophiles and afford such derivatives as **13**, **14** and **15** (Scheme 2), is also in agreement with the structures we are suggesting for the molecule **10**.

Considering the conversion of the 6-aminouracil **2** into the amide azide **8** when using successively, as described above, the two reagents **1a** and **4**, we thought it reasonable to assume that a similar transformation might occur, should the aminouracil **2** be treated with the *N,N*-dimethylazidochloromethyleniminium chloride (azidophosgeniminium chloride) **1b**, which is readily obtained by reaction between **1a** and **4** [26] (Scheme 5). Curiously, when reacting with **1b**, under similar solvent and temperature reaction conditions than before when preparing **8**, the 6-aminouracil **2** affords, *via* a diazo group transfer process, the corresponding 4,6-dimethyl-1,2,3-triazolo[4,5-*b*]pyrimidine-5,7-dione (8-azatheophylline) **20** in very good yield and with no trace of the 8-dimethylaminotheophylline **11**, through formation very likely, of such intermediates as the thermally unstable triazene **18** and 1,3-dimethyl-4-imino-5-diazouracil **19** (Scheme 5) [11,27]. As a matter of fact, the compound **1b** which is now known to exhibit interesting ambident electrophilic properties, was proved to react as an imminium salt with water, alcohols and primary amines, and as a diazo group transfer reagent with various CH-acidic compounds, including resorcin, barbituric acids, dimedon, naphtols, *etc*, [11,26,27].

Purines and related compounds, which are imidazo[4,5-*d*]-

Scheme 4



Scheme 5

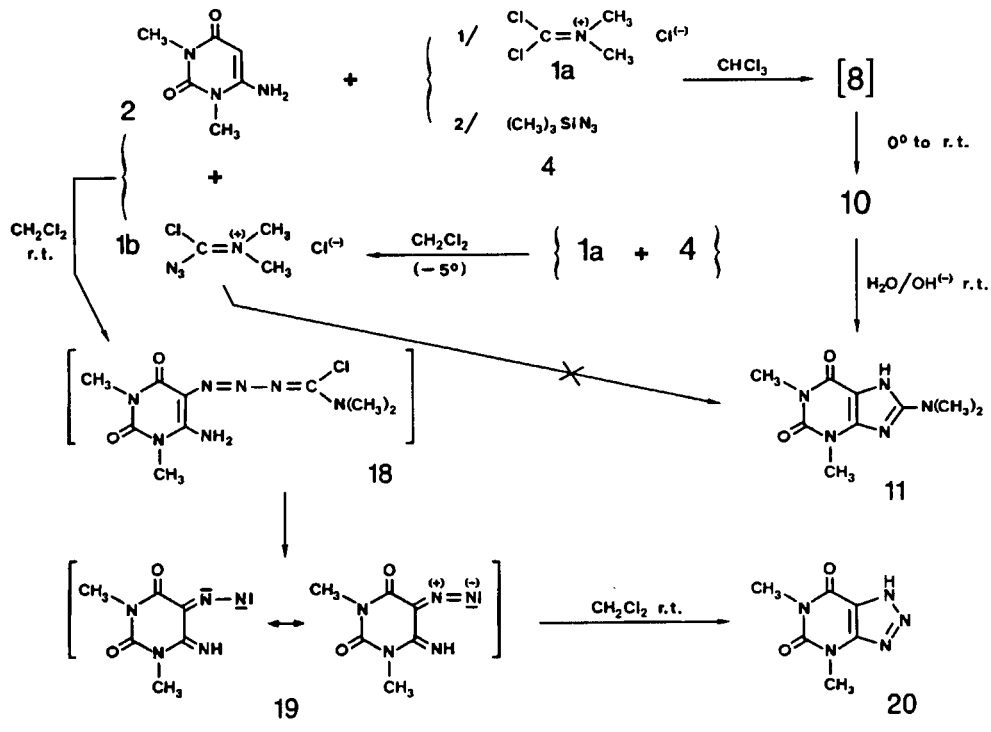


Table 1

Analytical Data of 8-Arylaminotheophyllines (**17**)

No	R^1	R^2	Formula	Mp	Analysis (%) Calcd./Found C	H	N
17a [a]	H	H	$C_{13}H_{19}N_5O_2$	> 280	57.56 57.66	4.79 4.61	25.83 25.78
17b [a]	H	3'-CH3	$C_{14}H_{15}N_5O_2$	> 280	58.94 58.96	5.26 5.48	24.56 24.29
17c [a]	H	4'-CH3	$C_{14}H_{15}N_5O_2$	>280	58.94 58.76	5.26 5.29	24.56 24.78
17d	H	3'-C_2H_5	$C_{15}H_{17}N_5O_2$	268	60.20 60.16	5.68 6.01	23.41 23.03
17e [a]	H	4'-C_2H_5	$C_{15}H_{17}N_5O_2$	>280	60.20 60.45	5.68 5.73	23.41 23.10
17f	H	2'-OCH_3	$C_{14}H_{15}N_5O_3$	>280	55.81 55.91	4.98 5.19	23.25 22.99
17g	H	3'-OCH_3	$C_{14}H_{15}N_5O_3$•0.5 H_2O	272	54.19 53.80	5.16 5.17	22.58 22.55
17h	H	4'-OCH_3	$C_{14}H_{15}N_5O_3$	>280	55.81 55.90	4.98 4.76	23.25 23.00
17i [a]	H	3',4'-$(CH_3)_2$	$C_{15}H_{17}N_5O_2$	>280	60.20 60.21	5.68 5.93	23.41 23.41
17j	H	3'-Cl	$C_{13}H_{12}ClN_5O_2$	>280	51.06 51.17	3.92 3.84	22.91 22.64
17k	H	4'-Cl	$C_{13}H_{12}ClN_5O_2$	>280	51.06 51.21	3.92 3.98	22.91 22.75
17l	CH_3	H	$C_{14}H_{15}N_5O_2$	268	58.94 59.19	5.26 5.54	24.56 24.65
17m	C_2H_5	H	$C_{15}H_{17}N_5O_2$	204	60.20 60.08	5.68 5.80	23.41 23.26
17n	C_2H_5	3'-CH_3	$C_{16}H_{19}N_5O_2$	176	61.34 60.60	6.07 6.21	22.36 22.26

[a] Also prepared starting from the 8-bromotheophylline **7** (see procedure 2).

Table 2

^{1}H-NMR Data of 8-Arylaminotheophyllines **17** [a]

No	R^1	R^2	
17a	H	H	3.25 (s, 3H), 3.45 (s, 3H), 7.18 (m, 5H), 9.41 (s, 1H), 11.80 (br s, 1H)
17b	H	3'-CH_3	2.30 (s, 3H), 3.26 (s, 3H), 3.46 (s, 3H), 7.10 (m, 4H), 9.30 (s, 1H), 11.80 (br s, 1H)
17c	H	4'-CH_3	2.26 (s, 3H), 3.25 (s, 3H), 3.46 (s, 3H), 7.10 (d, 2H, J = 9.0), 7.50 (d, 2H, J = 9.0), 9.28 (s, 1H), 11.70 (br s, 1H)
17d	H	3'-C_2H_5	1.20 (t, 3H, J = 7.50), 2.60 (q, 2H, J = 7.50), 3.25 (s, 3H), 3.45 (s, 3H), 7.08 (m, 4H), 9.31 (s, 1H), 11.78 (br s, 1H)
17e	H	4'-C_2H_5	1.16 (t, 3H, J = 7.50), 2.55 (q, 2H, J = 7.50), 3.23 (s, 3H), 3.45 (s, 3H), 7.13 (d, 2H, J = 9.0), 7.50 (d, 2H, J = 9.0), 9.30 (s, 1H), 11.78 (br s, 1H)
17f [b]	H	2'-OCH_3	
17g	H	3'-OCH_3	3.23 (s, 3H), 3.45 (s, 3H), 3.76 (s, 3H), 6.89 (m, 4H), 9.40 (s, 1H), 11.86 (br s, 1H)
17h	H	4'-OCH_3	3.25 (s, 3H), 3.45 (s, 3H), 3.75 (s, 3H), 6.88 (d, 2H, J = 9.0), 7.50 (d, 2H, J = 9.0), 9.16 (s, 1H), 11.63 (br s, 1H)
17i	H	3',4'-$(CH_3)_2$	2.17 (s, 3H), 2.21 (s, 3H), 3.23 (s, 3H), 3.45 (s, 3H), 7.18 (m, 3H), 9.20 (s, 1H), 11.70 (br s, 1H)
17j	H	3'-Cl	3.26 (s, 3H), 3.45 (s, 3H), 6.43 (m, 4H), 9.63 (s, 1H), 12.25 (br s, 1H)
17k	H	4'-Cl	3.25 (s, 3H), 3.46 (s, 3H), 7.31 (d, 2H, J = 9.0), 7.65 (d, 2H, J = 9.0), 9.55 (s, 1H), 12.29 (br s, 1H)
17l	CH_3	H	3.23 (s, 3H), 3.35 (s, 3H), 3.45 (s, 3H), 7.29 (m, 5H), 11.80 (br s, 1H)
17m	C_2H_5	H	1.15 (t, 3H, J = 7.50), 3.23 (s, 3H), 3.36 (s, 3H), 3.90 (q, 2H, J = 7.50), 7.38 (m, 5H), 11.75 (br s, 1H)
17n	C_2H_5	3'-CH_3	1.13 (t, 3H, J = 7.50), 2.33 (s, 3H), 3.20 (s, 3H), 3.35 (s, 3H), 3.88 (q, 2H, J = 7.50), 7.13 (m, 4H), 11.76 (br s, 1H)

[a] In dimethyl sulfoxide-d_6, [b] Not analyzed because of its insolubility.

pyrimidines, are often prepared *via* an imidazole ring closure process starting from 4,5-diaminopyrimidines. Thus 4,5-diaminouracils which are precursors of xanthines, including theophyllines, condense readily with various one carbon atom reagents such as amides, acyl halides, ureas, *etc*, affording first, usually thermally unstable open intermediates which result of reactions involving the 5-amino group of the 4,5-diaminouracils, and which cyclize *in situ* when heated [13,14,28-30].

The 8-aminotheophyllines can be obtained *via* condensation of amines with the 8-bromotheophylline **7**. The latter being very stable, the use of a sealed tube is generally required, especially when condensing low boiling point primary and secondary amines. In our hands, 8-arylaminotheophyllines such as **17** could be prepared as mentioned earlier, by heating mixtures of the 8-bromotheophylline **7** and anilines in refluxing cyclohexanol [18,19]. As already seen, the 4,5-diaminouracil **5** was proved, when treated with **1a**, to be a very suitable starting material for the direct preparation of the 8-dimethylaminouracil **11** which happens to be available as well, starting from 4-amino-5-arylazouracils [31].

The compounds **17a**, **17f**, **17g**, **17h** and **17j**, selected by the National Cancer Institute of the N.I.H. as potential chemotherapeutic agents, have been confirmed inactive against the Human Immunodeficiency Virus (H.I.V.). They are presently evaluated as potential anti-tumor agents.

EXPERIMENTAL

Melting points were taken with a Kofler bench and are uncorrected. The ^{1}H nmr have been recorded on a R 24 Hitachi Perkin-Elmer 60 MHz spectrometer and/or an E.M.390 Varian 90 MHz spectrometer (Institut Curie, Section de Biologie) using dimethyl sulfoxide-d_6 as solvent (see Table 2) and tetramethylsilane as internal reference. Chemical shifts are given in ppm and coupling constants in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad. Elemental analysis have been performed by the "Service central d'analyse du C.N.R.S.", Vernaison, France. Mass Spectra have been obtained on a Nermag R 10-10C mass spectrometer by the "Service de Spectrometrie de Masse de l'Ecole Nationale Supérieure de Chimie de Paris (E.N.S.C.P.), Université P. et M. Curie, Paris, France.

The 1,3-dimethyl-6-aminouracil **2**, 1,3-dimethyl-4,5-diaminouracil **5**, 1,3-dimethyl-6-hydrazinouracil **8** and 8-bromotheophylline **7**, were prepared according to the literature [11,13,14,18,19,28-30,32].

2-*N*-Arylamino-4,6-dimethylimidazo[4,5-*d*]pyrimidine-(4*H*,6*H*)-5,7-diones (8-Arylaminotheophyllines) **17** (Procedures 1 and 2).

Procedure 1 (General Procedure).

A stirring mixture of 1,3-dimethyl-6-aminouracil (**2**) (1.55 g, 0.01 mole), phosgeniminium chloride (**1a**) (2.0 g, approximately 0.012 mole) and dry chloroform (50 ml), protected from atmospheric moisture was allowed to stand at room temperature for one hour and then heated at reflux until the evolution of hydrogen chloride had ceased (5-6 hours) and a clear solution was obtained:

reaction mixture 1A containing the amide chloride **3** [7]. After cooling at 0° in an iced water bath, trimethylsilyl azide (1.5 g, 0.015 mole) diluted with dry chloroform (10 ml), was added dropwise over a period of 40-45 minutes. The cooling at 0° was discontinued after the evolution of nitrogen had ceased (4-5 hours) and the resulting heterogeneous mixture warmed gradually at room temperature and stirred overnight (12-13 hours): reaction mixture 1B containing the compound **10**. An excess of arylamine (0.03 mole) diluted with dry chloroform (20 ml), was then added dropwise at room temperature and over a period of 30 minutes. The resultant clear solution was allowed to stand at room temperature for 4-5 hours and heated at reflux for 2 hours. The solvent was removed *in vacuo,* the oily residue mixed with a 20% potassium hydrogen carbonate aqueous solution (20 ml) and the mixture heated at reflux until the evolution of dimethylamine had ceased. After cooling at room temperature, the usually heterogeneous mixture was slowly neutralized with a 20% acetic acid aqueous solution and the 8-arylaminotheophylline **17** collected by suction using a glass filter, washed with water (3 x 20 ml) and dried *in vacuo*, yield 81-85% (Tables 1 and 2).

Procedure 2.

A stirring mixture of 8-bromotheophylline (**7**) (1.29 g, 0.005 mole), arylamine (0.01 mole) and cyclohexanol (10 ml), was heated at reflux overnight (14-15 hours). After cooling, the heterogeneous mixture was filtered, using a glass filter, and the 8-arylaminotheophylline washed with ether (1 x 30 ml) then with water (4 x 20 ml) and dried *in vacuo* at room temperature, yields: 74% **17a**, 91% **17b**, 78% **17c**, 80% **17e** and 76% **17i**.

2-*N*,*N*-Dimethylamino-4,6-dimethylimidazo[4,5-*d*]pyrimidine-(4*H*,6*H*)-5,7-dione (8-*N*,*N*-Dimethylaminotheophylline) (**11**) (Procedures 3, 4 and 5).

Procedure 3.

An excess of triethylamine (4.04 g, 0.04 mole) diluted with chloroform (20 ml) was added dropwise over a period of 10 minutes to the stirring heterogeneous reaction mixture 1B containing the compound **10** (see procedure 1) and the resultant clear solution allowed to stand at room temperature for one hour and heated at reflux for one hour. The solvent was removed *in vacuo,* the oily residue mixed with water and the precipitate of nearly pure 8-dimethylaminotheophylline **11**, isolated by suction using a glass filter, washed with water and dried *in vacuo,* yield 1.85 g, 83%, mp >280° (water); ^{1}H nmr (dimethyl sulfoxide-d_6): 3.05 (s, 6H), 3.20 (s, 3H), 3.38 (s, 3H), 11.35 (br s, 1H).

Anal. Calcd. for $C_9H_{13}N_5O_2$ (M^+ = 223): C, 48.43; H, 5.82; N, 31.39. Found: C, 48.36; H, 5.84; N, 31.34.

Procedure 4.

The solvent of the reaction mixture 1B containing the compound **10** (see procedure 1) was removed *in vacuo* at room temperature, the oily residue mixed with water (30 ml) and then with potassium hydrogen carbonate, added slowly until the evolution of carbon dioxide had ceased. The precipitate which is the 8-dimethylaminotheophylline **11**, was treated as before in procedure 3, yield 1.92 g, 86%.

Procedure 5. From the 1,3-Dimethyl-4,5-diaminouracil **5** and Phosgeniminium Chloride **1a**.

A stirring mixture of 1,3-dimethyl-4,5-diaminouracil hydrate (**5**) (0.94 g, 0.005 mole), phosgeniminium chloride (**1a**) (2.0 g, 0.012 mole) and dry dichloromethane (50 ml) protected from atmospheric moisture, was allowed to stand at room temperature for 5 hours and then heated at reflux until the evolution of hydrogen chloride had ceased (5-6 hours). After cooling at room temperature, the heterogeneous mixture solvent was removed *in vacuo* and the residue mixted with water (30 ml) and then with potassium hydrogen carbonate added slowly until the evolution of carbon dioxide had ceased. The resultant 8-dimethylaminotheophylline **11** was then treated as before in procedures 3 and 4, yield 0.88 g, 79%.

3-*N*,*N*-Dimethylamino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-(5*H*,7*H*)-4,6-dione (**12**) from 1,3-Dimethyl-6-hydrazinouracil (**8**) and Phosgeniminium Chloride (**1a**).

Procedure 6.

A stirring mixture of 1,3-dimethyl-6-hydrazinouracil (**8**) (0.85 g, 0.005 mole), phosgeniminium chloride (**1a**) (1.0 g, approximately 0.006 mole) and dry chloroform (50 ml) protected from atmospheric moisture was allowed to stand at room temperature for 3 hours and then heated at reflux until the evolution of hydrogen chloride had ceased (5-6 hours). After cooling, the solvent was removed *in vacuo* and the oily residue mixed with water (30 ml) and then with potassium hydrogen carbonate, added slowly until the evolution of carbon dioxide had ceased. The precipitate of nearly pure 3-dimethylamino-5,7-dimethylpyrazolo[3,4-*d*]-pyrimidine **12** was isolated by suction using a glass filter, washed with water (2 x 20 ml) and dried *in vacuo,* yield 0.90 g, 81%, mp = 265° (water); ^{1}H nmr (dimethyl sulfoxide-d_6): 3.10 (s, 6H), 3.15 (s, 3H), 3.27 (s, 3H), 11.90 (br s, 1H).

Anal. Calcd. for $C_9H_{13}N_5O_2$ (M^+ = 223): C, 48.43; H, 5.82; N, 31.39. Found: C, 48.47; H, 5.84; N, 31.32.

1,3-Dimethyl-4-amino-5-[5'-(dimethylamino)-1',2',3',4'-tetrazol-1'-yl)uracil (**13**) (Procedures 7 and 8).

Procedure 7.

To the stirring clear mixture 1A (see procedure 1) protected from atmospheric moisture and cooled in an iced water bath, trimethylsilylazide (3.90 g, 0.033 mole) diluted with dry chloroform (20 ml) was added dropwise over a period of 1 hour. The cooling at 0° was discontinued after the evolution of nitrogen had ceased (4-5 hours) and the resulting heterogeneous mixture warmed gradually at room temperature, stirred overnight (12-13 hours) and finally heated at reflux for 12 hours. After cooling the heterogeneous mixture at room temperature, the tetrazole **13** was isolated by suction using a glass filter, washed with chloroform (2 x 20 ml) and dried at room temperature, yield 1.98 g, 72%, mp 272-274° (water); X ray crystallography [16,17]; ^{1}H nmr (dimethyl sulfoxide-d_6): 2.90 (s, 6H), 3.10 (s, 3H), 3.13 (s, 3H), 7.32 (br s, 2H).

Anal. Calcd. for $C_9H_{14}N_8O_2 \cdot 0.5\ H_2O$ (M = 275, M^+ ($-N_2$) = 238): C, 39.27; H, 5.45; N, 40.72. Found: C, 38.57; H, 5.56; N, 40.05.

The filtrate was evaporated in *vacuo* and the residue treated with water (30 ml) and an excess of potassium hydrogen carbonate, added slowly until the evolution of carbon dioxide had ceased. The heterogeneous mixture containing the 8-dimethylaminotheophylline **11** was then treated as before in procedures 2-4, yield 0.38 g, 17%.

Procedure 8.

To the stirring heterogeneous reaction mixture 1B (see procedure 1) protected from atmospheric moisture, trimethylsilylazide

(2.80 g, 0.024 mole) diluted with dry chloroform (10 ml) was added dropwise at room temperature and over a period of 10 minutes. The resulting mixture was allowed to stand at room temperature for 3 hours, heated at reflux for 12 hours and treated as before in procedure 7, yield for **13**, 1.90 g, 69%, yield for **11**, 0.42 g, 19%.

Compound **10**.

Procedure 9.

The heterogeneous reaction mixture 1B (see procedure 1) was filtered *in vacuo* under inert atmosphere using a glass filter, and the white residue washed with dry chloroform (3 x 30 ml) then with dry ether (3 x 20 ml), dried *in vacuo* at room temperature and stored without purification under nitrogen, yield 2.31 g, 89%, mp >280; ^{1}H nmr (dimethyl sulfoxide-d_6): 3.05 (s, 6H), 3.20 (s, 3H), 3.38 (s, 3H).

Anal. Calcd. for $C_9H_{14}ClN_5O_2$ or $C_9H_{13}N_5O_2$•HCl, M^+ = 223, (-HCl): Cl, 13.68; N, 26.97. Found: Cl (HCl titration), 13.48; N, 27.12.

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REFERENCES AND NOTES

[1] Researcher at the "Institut National de la Santé et de la Recherche Médicale (I.N.S.E.R.M.)".

[2] Z. Janousek, Dissertation, U.C.L., Louvain-la-Neuve, Belgique, 1972.

[3] Z. Janousek and H. G. Viehe, Chemistry of dichloromethyleniminium salts (Phosgeniminium salts) in Iminium salts in Organic Chemistry, Advances in Organic Chemistry Vol **9**, Part **1**, H. Böhme and H. G. Viehe, eds, John Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1976, p 343 and references cited therein.

[4] H. G. Viehe and Z. Janousek, *Angew. Chem.*, **85**, 837 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 806 (1973).

[5] H. G. Viehe, *Chem. Ind.*, 386 (1077).

[6] [a] V. P. Kukhar and V. I. Pasternak, *Synthesis*, 611 (1972); [b] V. P. Kukhar and V. I. Pasternak, *Synthesis*, 563 (1974).

[7] B. Kokel, C. Lespagnol and H. G. Viehe, *Bull. Soc. Chem. Belg.*, **89**, 651 (1980).

[8] B. Kokel, R. Royer, J. P. Declercq, G. Germain and M. Van Meerssche, *Tetrahedron Letters*, 449 (1981).

[9] B. Kokel, J. Guillaumel and R. Royer, *J. Heterocyclic Chem.*, **20**, 575 (1983).

[10] B. Kokel, G. Menichi, M. Hubert-Habart and J. Mercier, 8th International Symposium on Medicinal Chemistry, Uppsala, Sweden, August 27-31, 1984, Proceedings, **2**, 483 (1985).

[11] B. Kokel, Thèse de Doctorat ès Sciences Physiques, Paris, France, 1987.

[12] B. Kokel, N. Boussouira, G. Menichi and M. Hubert-Habart, 10th International Congress of Heterocyclic Chemistry, University of Waterloo, Ontario, Canada, August 11-16, 1985, Proceedings, P5-166 (1985).

[13] W. Traube, *Chem. Ber.*, **33**, 3035 (1900).

[14] F. F. Blicke and H. G. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954).

[15] To be published.

[16] B. Kokel, M. Hubert-Habart, A. Cousson and B. Bachet, 14th European Colloquium on Heterocyclic Chemistry, Toledo, Spain, October 1-3, 1990. Proceedings, 222 (1990).

[17] A. Cousson, J. Proust, B. Bachet, B. Kokel and M. Hubert-Habart, *Acta Cryst.*, **C48**, 76 (1992).

[18] A. Lespagnol and A. Gaumeton, *Bull. Soc. Chem. France*, 253 (1951).

[19] A. Martine, Thèse de Doctorat de Troisième Cycle, Lille, France, 1974, and references cited therein.

[20] [a] H. H. Otto and J. Triepel, *Liebigs Ann. Chem.*, 1982 (1976); [b] H. H. Otto and J. Triepel, *Liebigs Ann. Chem.*, 1809 (1978).

[21] B. Kokel, H. G. Viehe, J. P. Declercq, G. Germain and M. Van Meerssche, *Tetrahedron Letters*, 3799 (1980).

[22] L. Ghosez and J. Marchand-Brynaert, α-Haloenamines and Ketenimínium salts in Iminium salts in Organic Chemistry, Advances in Organic Chemistry, Vol **9**, Part **1**, H. Böhme and H. G. Viehe, eds, John Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1976, p 482.

[23] [a] M. Rens, Dissertation, U.C.L. Louvain, 1973; [b] M. Rens and L. Ghosez, *Tetrahedron Letters*, 3765 (1970).

[24] L. Ghosez, A. Demoulin, M. Henriet, E. Sonveaux, M. Van Meerssche, G. Germain and J. P. Declercq, *Heterocycles*, **7**, 896 (1978).

[25] M. Henriet, M. Houtckie, B. Techy, R. Touillaux and L. Ghosez, *Tetrahedron Letters*, 223 (1980).

[26] [a] H. G. Viehe and P. George, *Chimia*, **29**, 209 (1975); [b] P. George, Dissertation, U.C.L., Louvain La Neuve, Belgique, 1978, and references cited therein.

[27] B. Kokel and N. Boussouira, *J. Heterocyclic Chem.*, **24**, 1493 (1987), and references cited therein.

[28] B. Kokel, Thèse de Doctorat de Troisième Cycle, Lille, France, 1975, and references cited therein.

[29] J. H. Speer and A. Raymond, *J. Am. Chem. Soc.*, **75**, 114 (1953).

[30] H. Bredereck and A. Edenhofer, *Chem. Ber.*, **88**, 1306 (1955).

[31] F. Yoneda, M. Higuchi and T. Nagamatsu, *J. Am. Chem. Soc.*, **96**, 5607 (1974).

[32] [a] W. Pfleiderer and K. H. Schündehütte, *Liebigs Ann. Chem.*, **612**, 158 (1958); [b] H. Goldner, G. Dietz and E. Carstens, *Liebigs Ann. Chem.*, **691**, 142 (1966).