Reaction of *N,N*-Dimethylazidochloromethyleniminium Chloride (Azidophosgeniminium Chloride) with 1,3-Dimethyl-4-aminouracils. A New "One Pot" Synthesis of 3-Aryl-(and 3-alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidines (8-Azatheophyllines) *via* a Diazo Group Transfer Process

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N,N-Dimethylazidochloromethyleniminium chloride (azidophosgeniminium chloride) (**1**) reacts by diazo group transfer with 1,3-dimethyl-4-aryl-(and alkyl)aminouracils **4** to give, under mild "one pot" reaction conditions, a very good yield of 3-aryl-(and 3-alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidines (8-azatheophyllines) **8**. That reaction proceeds, very likely, through formation of non-isolated 4-imino-5-diazouracils **6**.

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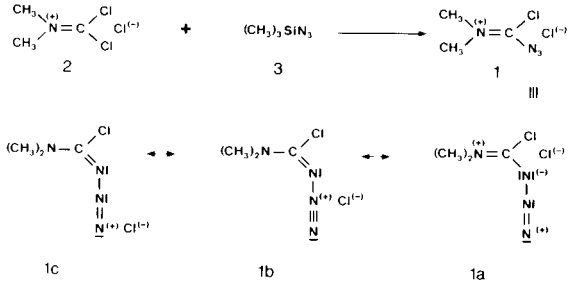
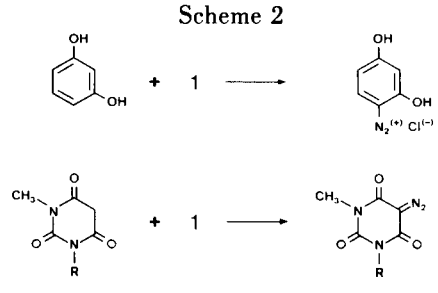
N,N-Dimethylazidochloromethyleniminium chloride (azidophosgeniminium chloride) (**1**) is an easily available new reagent for the transfer of the diazo group [3] readily prepared (Scheme 1) from *N,N*-dimethyldichloromethyleniminium chloride (phosgeniminium chloride) (**2**) and azidotrimethylsilane (**3**) [4,5,6].

Scheme 1



As expected and according to its limiting structures outlined above (Scheme 1), azidophosgeniminium chloride (**1**) exhibits interesting ambident electrophilic properties on either its iminium carbon atom or its azido group. Thus, while it behaves as an iminium salt with water, alcohol and primary amines [4,5,6], **1** reacts by transfer of its diazo group [3] with a variety of CH-acidic compounds such as resorcin and barbituric acids (Scheme 2), dimedon, naphthols, *etc*... [3], affording diazo derivatives or corresponding diazonium salts.

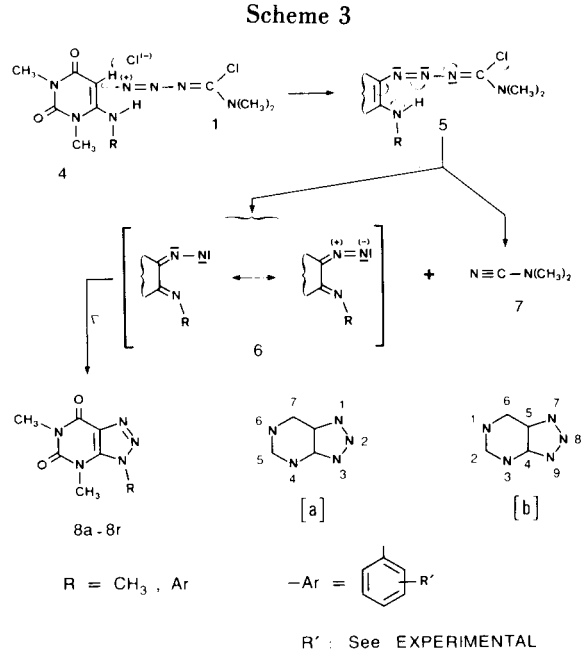
Scheme 2



In connection with our attempts to develop new simple procedures for the preparation of heterocyclic systems of biological interests, we found that **1** reacts with 1,3-dimethyl-4-aminouracils of type **4** as well, producing (Scheme 3), under mild "one pot" reaction conditions, very good yield of 3-aryl-(and 3-alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidines **8** (see [a] Scheme 3) also known as 9-aryl-(and 9-alkyl)-8-azatheophyllines (see [b] Scheme 3).

This reaction proceeds, very likely, *via* formation of thermally unstable triazenes **5** as intermediates. The latter undergo rearrangement through N-N bond cleavage to give both 1,3-dimethyl-4-imino-5-diazouracils **6**, which cyclise on heating, and the dimethylcyanamide (**7**) as a by-product.

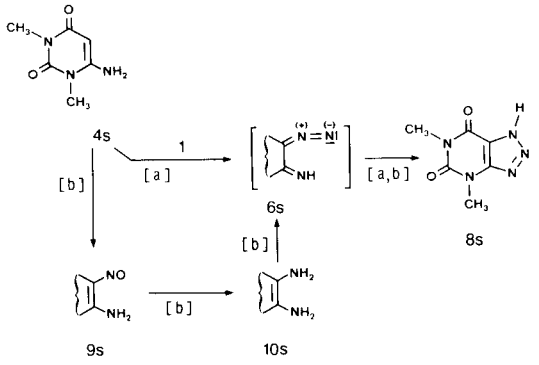
Scheme 3



The conversion of 4-aminouracils **4** into 8-azatheophyllines **8** was achieved in dry dichloromethane exclusively.

It should be noted that 1,3-dimethyl-4-aminouracil (**4s**) leads as expected (see path [a] Scheme 4) to 8-azatheophylline (**8s**) which was identified to an authentic sample obtained independently according to the Traube's procedure [7] by a 3 steps synthesis also starting from 1,3-dimethyl-4-aminouracil (**4s**) (see path [b] Scheme 4).

Scheme 4



Since their discovery by Curtius in 1883 [8], both, properties of diazo compounds and methods for their preparation have been very well studied and reviewed [9a-b,10].

Alternative routes to prepare diazo compounds can be ranged, depending on starting material, in several classes including methods: 1) by which the diazo group is either built up from simple fonctional groups such as primary amines (diazotation) and oximes (Foster reaction) or produced by alteration of fonctional group already containing two adjacent nitrogen atoms such as primary hydrazones, alkysulfonylhydrazones and *N*-nitrosocarboxamides; 2) based upon the transformation, by fonctionalisation (nitration, halogenation, metallation, *etc*...) or cleavage of diazo group containing compounds, without alteration of the diazo group itself; 3) allowing finally, the direct introduction of the diazo group by its transfer from an azide, reaction known as "diazo group transfer process".

Among the many methods described so far, the very well documented diazo group transfer process, is doubtless one of the most useful. As we mentioned above, this method unlike the others, allows the direct introduction of the entire diazo group, by its transfer from a molecule called "diazo group donor" to CH-acidic or activated double and triple bond containing molecules.

The diazo group transfer has been described first by Dimorth in 1910 [11] and investigated afterwards by several other groups [12,13]. However, it has been known as a general method through further intensive work, much of it by Regitz [9a-b,10], only in the late fifties, early sixties.

Until now, the very well known, stable and commercially available tosyl azide has been almost exclusively used as diazo group donor. It usually works in basic medium (triethylamine, alcoholates, *etc*...) with CH-acidic compounds and under neutral and acidic conditions with activated olefins and acetylenes. To our knowledge, beside that "overused" tosyl azide and the "new comer" in that field, the azidophosgeniminium chloride (**1**), which efficacy as a diazo group donor has been shown just a few years ago [3], only one other reagent, the 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate (**11**) made by Balli [14-18] has been used so far as a diazo group transfer reagent (Scheme 5).

Scheme 5

11

Balli's reagent has been found to work as a diazo group donor with CH-acidic containing compounds in aqueous alcoholic medium at a *p*H ranging from 0 to 8 [9a-b]. Those specific conditions were actually widening the preparative scope of diazo group transfer reactions, because precisely of the *p*H limitation which are required when using tosyl azide.

As far as we know, the azidophosgeniminium chloride (**1**), more readily available than the Balli's reagent, works very well even at room temperature, in dry dichloromethane in which it is very soluble. It offers, therefore, additional possibilities to achieve the diazo group transfer reaction under experimental conditions which could not be used with either tosyl azide or Balli's reagent.

Heterocyclisation of *o*.diazoimines into 1,2,3-triazole derivatives is well known [9a-b,10,19]. To begin with, nitrosation of the 4,5-diaminouracil **10s** which gives (Scheme 4) the triazolopyrimidine **8s** by the Traube's procedure [7] is a good example of that type of reaction since **8s** is made at room temperature *via* the non-isolated *o*-diazoimine **6s**. Many examples of that kind are described in the literature. However, to our knowledge, it seems that no 8-azatheophylline has ever been made through a diazo group transfer process.

8-Azapurines occur in microorganisms. They have been of great interest in cancer research, and on account of the high antitumor activity of the 2-amino-6-hydroxy-8-azapurine, present in "*Streptomyces albus*" [20-24], a wide variety of 1,2,3-triazolo[4,5-*d*]pyrimidines have been prepared and their biological properties evaluated [25-28]. However, while theophyllines themselves were extensively studied, it seems that much less attention was being paid to their 8-aza analogues. The latter can be built up from

substituted pyrimidines and from substituted 1,2,3-triazoles as well, involving, respectively, 1,2,3-triazole and pyrimidine ring closure processes.

The first synthesis of an 8-azapurine have been done in 1900 by Traube [7]. It corresponds, as a matter of fact, to the original preparation of the 8-azatheophylline (**8s**). Traube's procedure is still the main route to be used in that field for preparing 8-azapurines which are 9-substituted or not substituted on the triazole ring and/or having widely diversified substituents on the pyrimidine ring [26,27,29-32].

Other methods dealing with a 1,2,3-triazole ring closure process starting from pyrimidines bearing many kinds of *N*- and *C*-substituents, include: 1) reaction of sodium azide with 5-bromouracils [33] and 5-nitrouracils [34,35]; 2) oxidative cyclisation of 4-amino-5-arylazouracils by copper sulfate [36] or lead tetracetate [37]; 3) nitrosative cyclisation of 4-(α-methylalkylidenehydrazino)uracils [38]; 4) catalytic reduction followed by nitrosation, of 4-arylamino-5-phenylazouracils [39].

Methods to prepare 8-azapurines from 4- and 5-appropriately functionalized 1,2,3-triazoles *via* a pyrimidine ring closure process, are very useful for the synthesis of 7- and 8-substituted derivatives [40-44] which are not available by the Traube's procedure. They are relatively recent [45] and they mostly correspond to methods usually suitable for the preparation of purines and xanthines, starting from imidazoles [28].

Quite unexpectedly, although they are of biological interest as potential antitumor, antiallergic, antiviral, antibacterial, diuretic agents, *etc*...[26-28] as well as potential xanthine oxydase and phosphodiesterase inhibitors [28,46], the only two 9-aryl-8-azatheophyllines **8a** (aryl = phenyl) and **8l** (aryl = 4'-chlorophenyl) were described so far [39].

The 9-methyl-8-azatheophylline (**8r**) has been known for about 20 years [32] and made by the Traube's procedure. That compound has been shown [47] to exhibit an interesting radioprotective activity towards mice lethaly irradiated by X-rays.

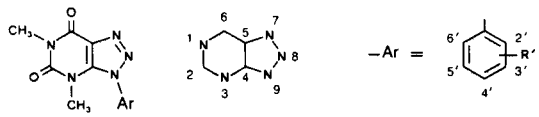
EXPERIMENTAL

Melting points were taken on a Kofler bench and are uncorrected. The ^{1}H nmr spectra have been recorded on a Hitachi Perkin-Elmer 60 MHz spectrometer using chloroform-d or dimethylsulfoxide-d_6 or mixture of chloroform-d and dimethylsulfoxide-d_6 as solvent (see [a] and [b] in Table 1) and tetramethylsilane as internal reference. Chemical shifts are given in ppm and coupling constants in Hz. The following abbreviation are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet.

The ir spectra have been recorded on a Perkin-Elmer spectrometer P.E. 225. Elemental analysis have been performed by the "Service Central d'Analyse du C.N.R.S.", Vernaison, France and Mass spectra by the "Laboratoire de Chimie Organique Structurale de l'Université P. et M. Curie", Paris, France.

Table 1

^{1}H-NMR Data (60 MHz, δ (ppm), J Hz) of 9-Aryl-8-azatheophyllines **8a-q**



8a - 8q

	R'		R'		R'
8a	H	8g	4'-OCH_3	8l	4'-Cl
8b	3'-CH_3	8h	3',4'-$(CH_3)_2$	8m	2',3'-Cl_2
8c	4'-CH_3	8i	3',4',5'-$(OCH_3)_3$	8n	2',4'-Cl_2
8d	4'-C_2H_5	8j	2'-Cl	8o	2',5'-Cl_2
8e	2'-OCH_3	8k	3'-Cl	8p	3',4'-Cl_2
8f	3'-OCH_3			8q	3',5'-Cl_2

^{1}H-NMR Values (ppm)

No. **8**	1-CH_3 s, 3H	3-CH_3 s, 3H	Other values (Ar, including R')
a	3.20	3.45	7.60 (s, 5H, 2', 3', 4', 5' and 6'-H)
b	3.15	3.40	2.50 (s, 3H, 3'-CH_3), 7.35 (m, 4H, 2', 4', 5' and 6'-H)
c	3.15	3.40	2.50 (s, 3H, 4'-CH_3), 7.35 (s, 4H, 2', 3', 5' and 6'-H)
d	3.15	3.35	1.25 (t, 3H, 4'-CH_2CH_3, J = 8 Hz), 2.80 (q, 2H, 4'-CH_2CH_3, J = 8.0 Hz), 7.35 (s, 4H, 2', 3', 5' and 6'-H)
e	3.20	3.45	3.85 (s, 3H, 2'-OCH_3), 7.35 (m, 4H, 3', 4', 5' and 6'-H
f	3.20	3.40	3.95 (s, 3H, 3'-OCH_3), 7.25 (m, 4H, 2', 4', 5' and 6'-H)
g	3.15	3.40	3.85 (s, 3H, 4'-OCH_3), 7.25 (2d, 4H, 2', 3', 5' and 6'-H, J = 9.0 Hz)
h	3.15	3.40	2.35 (s, 6H, 3' and 4'-CH_3), 7.20 (s, 3H, 2', 5' and 6'-H)
i	3.20	3.30	3.85 (s, 9H, 3', 4' and 5'-OCH_3), 6.75 (s, 2H, 2' and 6'-H)
j	3.15	3.40	7.60 (s, 4H, 3', 4', 5' and 6'-H)
k [b]	3.25	3.45	7.60 (m, 4H, 2', 4', 5' and 6'-H)
l [b]	3.20	3.45	7.55 (s, 4H, 2', 3', 5' and 6'-H)
m	3.15	3.40	7.65 (m, 3H, 4', 5' and 6'-H)
n	3.20	3.40	7.60 (m, 3H, 3', 5' and 6'-H)
o [a]	3.05	3.30	7.80 and 8.00 (2 m, 3H, 3', 4' and 6'-H)
p	3.25	3.40	7.55 (m, 3H, 2', 5' and 6'-H)
q [a]	3.10	3.30	7.9 (s, 3H, 2', 4' and 6'-H)

[a], [b]: Solvent (TMS): deuteriochloroform or [a] DMSO-d_6 or [b] mixture DMSO-d_6/deuteriochloroform. s (singlet); d (doublet); t (triplet); q (quadruplet); m (multiplet).

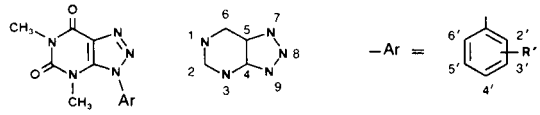
Compounds **8a** to **8s** are numbered as 8-azatheophillines (see [b] Scheme 3).

1,3-dimethyl-4-aminouracils **4** [53].

Aminouracils **4** were prepared according to the literature [48-52] from

Table 2

Analytical Data of 9-Aryl-8-azatheophyllines **8a-q**



8a - 8q

	R′		R′		R′
8a	H	8g	4′-OCH_3	8l	4′-Cl
8b	3′-CH_3	8h	3′,4′-$(CH_3)_2$	8m	2′,3′-Cl_2
8c	4′-CH_3	8i	3′,4′,5′-$(OCH_3)_3$	8n	2′,4′-Cl_2
8d	4′-C_2H_5	8j	2′-Cl	8o	2′,5′-Cl_2
8e	2′-OCH_3	8k	3′-Cl	8p	3′,4′-Cl_2
8f	3′-OCH_3			8q	3′,5′-Cl_2

No. 8	Formula (M^+)	Mp °C	Analysis (%): Found/Calcd. C	H	Cl	N	O
a [e]	$C_{12}H_{11}N_5O_2$ (257)	196 [a]	– – – –	– – – –	Lit. [39]	– – – –	– – – –
b	$C_{13}H_{13}N_5O_2$ (271)	184 [b]	57.57	4.78		25.70	12.07
			57.56	4.79		25.83	11.80
c	$C_{13}H_{13}N_5O_2$ (271)	258 [a]	57.38	4.59		25.93	11.90
			57.56	4.79		25.83	11.80
d	$C_{14}H_{15}N_5O_2$ (285)	254 [b]	59.05	5.27		24.58	11.35
			58.94	5.26		24.56	11.22
e	$C_{13}H_{13}N_5O_3$ (287)	226 [b]	54.14	4.51		24.73	16.76
			54.35	4.52		24.39	16.72
f	$C_{13}H_{13}N_5O_3$ (287)	184 [b]	54.08	4.54		24.50	
			54.35	4.52		24.39	
g [e]	$C_{13}H_{13}N_5O_3$ (287)	242 [b]	54.52	4.49		24.36	16.97
			54.35	4.52		24.39	16.72
h	$C_{14}H_{15}N_5O_2$ (285)	252 [b]	58.83	5.23		24.75	11.43
			58.94	5.26		24.56	11.22
i	$C_{15}H_{17}N_5O_5$ (347)	238 [b]	51.99	5.00		19.77	22.72
			51.87	4.89		20.17	23.05
j [e]	$C_{12}H_{10}ClN_5O_2$ (291)	138 [a]	49.48	3.49	12.16	24.20	10.98
			49.48	3.43	12.02	24.05	10.99
k	$C_{12}H_{10}ClN_5O_2$ (291)	212 [a]	49.52	3.45	12.68	24.40	10.84
			49.48	3.43	12.02	24.05	10.99
l [e]	$C_{12}H_{10}ClN_5O_2$ (291)	230 [a]	– – – –	– – – –	Lit. [39]	– – – –	– – – –
m [e]	$C_{12}H_9Cl_2N_5O_2$ (325)	228 [c]	43.93	2.71	21.92	21.48	9.72
			44.30	2.76	21.53	21.53	9.84
n	$C_{12}H_9Cl_2N_5O_2$ (325)	232 [c]	44.25	2.61	21.93	21.64	10.00
			44.30	2.76	21.53	21.53	9.84
o	$C_{12}H_9Cl_2N_5O_2$ (325)	246 [c]	44.05	2.73	21.77	21.55	10.00
			44.30	2.76	21.53	21.53	9.84
p	$C_{12}H_9Cl_2N_5O_2$ (325)	224 [c]	44.32	2.81	21.71	21.53	9.87
			44.30	2.76	21.53	21.53	9.84
q	$C_{12}H_9Cl_2N_5O_2$ (325)	248 [c]	44.45	2.71	21.72	21.41	9.78
			44.30	2.76	21.53	21.53	9.84

[a], [b], [c], [d]: Recrystallisation from [a] pure 2-propanol; [b] mixture of 2-propanol (95%)/water (5%); [c] mixture dioxane (90%)/water (10%), [d] water. [e] Two equivalents of **1** are required (see [53] and [54]).

1,3-dimethyl-4-chlorouracil and primary amines. The 1,3-dimethyl-4-aminouracil (**4s**) was obtained by the Traube's procedure [7,31] from 1,3-dimethylurea and cyanacetic acid.

N,N-Dimethylazidochloromethyleniminium Chloride (Azidophosgeniminium Chloride (**1**) [3-6].

Azidotrimethylsilane (**3**) (13.8 g, 0.12 mole) in dry dichloromethane (100 ml) was added dropwise (during 3-4 hours) to a stirred suspension of phosgeniminium chloride (**2**) (16.1 g, 0.10 mole) in dry dichloromethane (300 ml) kept at −5° and in dry atmosphere.

The reaction mixture was then, allowed to stand at room temperature for 3-4 hours and the solvent removed *in vacuo* at room temperature. The residue was washed 3-4 times with dry ether (50 ml) and dried *in vacuo* at room temperature, yield 90-92%.

9-Aryl-8-azatheophyllines **8a-q**. General Procedure.

To a solution of azidophosgeniminium chloride (**1**) (0.85 g, 0.005 mole [53,54] and see [e] in Table 2) in dry dichloromethane (40 ml) was added 0.004 mole of 1,3-dimethyl-4-*N*-arylaminouracil **4**. The stirring mixture, protected from moisture, was allowed to stand at room temperature for 2 hours and then refluxed for 2-3 hours.

The reaction mixture was filtered off if necessary and the filtrate evaporated *in vacuo*. Water (20 ml) was added to the residue. The precipitate of nearly pure 9-aryl-8-azatheophylline was isolated by suction, washed with water and dried *in vacuo*, yield 86-88%; ir (potassium bromide): 1580-1620 cm^{-1} (−C=N), 1680-1720 cm^{-1} (−C=O); ^1H nmr: See Table 1; *Anal.*: see Table 2.

9-Methyl-8-azatheophylline (**8r**).

The title compound was prepared from 1,3-dimethyl-4-*N*-methylaminouracil (**4r**), using 2 equivalents of azidophosgeniminium chloride (see footnote [e] in Table 2) and in the same manner as compounds **8a-q**, yield 60-62%, mp 222° (2-propanol); nmr (mixture of DMSO-d_6 and deuteriochloroform): 3.30 (s, 3H, 1-CH_3), 3.70 (s, 3H, 3-CH_3), 4.30 (s, 3H, 9-CH_3); ms: (70 eV, electron impact) m/e 195 (M^+). *Anal.* [32].

8-Azatheophylline (**8s**).

A stirring mixture of azidophosgeniminium chloride (**1**) (1.70 g, 0.010 mole), 1,3-dimethyl-4-aminouracil (**4s**) (0.62 g, 0.004 mole) and dry dichloromethane (40 ml), protected from moisture, was allowed to stand at room temperature for 2 hours and then refluxed for 2-3 hours.

The reaction mixture was filtered off and the residue dried *in vacuo*. Another fraction of 8-azatheophylline (**8s**) was isolated from the filtrate partially evaporated off *in vacuo*, yield 65-68%, mp 253° (water); nmr (DMSO-d_6): 3.20 (s, 3H, 1-CH_3), 3.40 (s, 3H, 3-CH_3); ms: (70 eV, electron impact) m/e 181 (M^+). *Anal.* [7,31].

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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] Undergraduate student at the "Institut Universitaire de Technologie" Orsay, France.

[3] B. Kokel and H. G. Viehe, *Angew. Chem.*, **92**, 754 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 716 (1980).

[4] H. G. Viehe and P. George, *Chimia*, **29**, 209 (1975).

[5] Z. Janouzek and H. G. Viehe, "Chemistry of dichloromethyleniminium Salts (Phosgeniminium Salts)", "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, Sidney, Toronto, 1976, p 343 and references cited therein.

[6] P. George, Dissertation, Louvain-La-Neuve, Belgique, 1978.

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

[8] T. Curtius, *Ber.*, **16**, 2230 (1883).

[9] M. Regitz, [a] *Angew. Chem.*, **79**, 786 (1967) and references cited therein; *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967); [b] *Synthesis*, 351 (1972) and references cited therein.

[10] B. Eistert, M. Regitz, G. Heck and H. Schwall, "Herstellung und Umvandlung von aliphatischen Diazoverbindungen", "Houben-Weyl, Methoden der Organischen Chemie", Vol **10/4**, E. Müller, ed, Georg Thieme Verlag, Stutgart, 1968, p 473 and references cited therein.

[11] O. Dimroth, *Ann. Chem.*, **373**, 356 (1910).

[12] T. Curtius and W. Klavehn, *J. Prakt. Chem.*, **112**, 65 (1926).

[13] W. E. Doering and C. H. De Puy, *J. Am. Chem. Soc.*, **75**, 5955 (1953).

[14] H. Balli and F. Kersting, *Ann. Chem.*, **647**, 1 (1961).

[15] H. Balli, *Ann. Chem.*, **647**, 11 (1961).

[16] H. Balli and V. Müller, *Angew. Chem.*, **76**, 573 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 644 (1964).

[17] H. Balli and R. Gipp, *Ann. Chem.*, **699**, 133 (1966).

[18] H. Balli and R. Low, *Tetrahedron Letters*, 5821 (1966).

[19] T. L. Gilchrist and G. E. Gymer, "1,2,3-Triazoles", "Advances in Heterocyclic Chemistry", Vol **16**, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, London, 1974, p 33 and references cited therein.

[20] A. Gellhorn, M. Engelman, D. Shapiro, S. Graff and H. Gillespie, *Cancer Res.*, **10**, 170 (1950).

[21] H. E. Skipper, J. A. Montgomery, J. R. Thomson and F. M. Shabel, Jr., *Cancer Res.*, **19**, 425 (1959).

[22] R. W. Brockman, C. Sparks, D. J. Hutchison and H. E. Skipper, *Cancer Res.*, **19**, 177 (1959).

[23] G. C. Armistead, Jr., J. H. Burchenal, D. A. Karnofski and C. M. Southam, *Cancer*, **2**, 1087 (1949).

[24] A. Gellhorn, *Cancer*, **6**, 1030 (1953).

[25] D. S. Bariana, *J. Med. Chem.*, **14**, 543 (1971).

[26] C. J. Coulson, R. E. Ford, E. Lunt, S. Marshall, D. L. Pain, I. H. Rogers and K. R. H. Wooldridge, *Eur. J. Med. Chem.*, **9**, 313 (1974).

[27] B. J. Broughton, P. Chaplen, P. Knowsles, E. Lunt, S. M. Marshall, D. L. Pain and K. R. H. Wooldridge, *J. Med. Chem.*, **18**, 1117 (1975).

[28] E. Lunt, "Purines and Analogues", "Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds", "Heterocyclic Compounds", Vol **4**, D. Barton, W. D. Ollis, P. G. Sammes, eds, Pergamon Press, Oxford, New York, Toronto, Sidney, Paris, Frankfurt, 1979, p 493 and references cited therein.

[29] S. Gabriel and J. Colman, *Ber.*, **34**, 1235 (1901).

[30] R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **67**, 290 (1945).

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

[32] G. Nübel and W. Pflederer, *Chem. Ber.*, **98**, 1060 (1965).

[33] T. Sasaki, K. Minamoto, M. Kino and T. Mizuno, *J. Org. Chem.*, **41**, 1100 (1976).

[34] H. U. Blank and J. J. Fox, *J. Am. Chem. Soc.*, **90**, 7175 (1968).

[35] H. U. Blank, I. Wempen and J. J. Fox, *J. Org. Chem.*, **35**, 1131 (1970).

[36] F. R. Benson, L. W. Hartzel and W. L. Savell, *J. Am. Chem. Soc.*, **72**, 1816 (1950).

[37] Y. Maki and E. C. Taylor, *Chem. Pharm. Bull.*, **20**, 605 (1972).

[38] K. Senga, Y. Kanamori, S. Nishigaki and F. Yoneda, *Chem. Pharm. Bull.*, **24**, 1917 (1976).

[39] K. Senga, Y. Kanamori and S. Nishigaki, *Heterocycles*, **9**, 1437 (1978).

[40] A. Albert and K. Tratt, *J. Chem. Soc. (C)*, 344 (1968).

[41] A. Albert, [a] *J. Chem. Soc. (C)*, 2076 (1968); [b] *ibid.*, 152

(1969).

[42] A. Albert and H. Taguchi, *J. Chem. Soc., Perkin Trans. I*, 449 (1972).

[43] A. Albert and D. Thacker, *J. Chem. Soc., Perkin Trans. I*, 468 (1972).

[44] A. Albert, [a] *J. Chem. Soc., Perkin Trans. I*, 461 (1972); [b] *ibid.*, 345 (1975).

[45] A. Dornow and J. Helberg, *Chem. Ber.*, **93**, 2001 (1960).

[46] M. S. Amer and W. E. Kreighbaum, *J. Pharm. Sci.*, **64**, 1 (1975).

[47] G. N. Krutovskikh, A. M. Rusanov, G. F. Gornaeva, L. P. Vartanyan, M. R. Kolesova, Kh. L. Muravich-Aleksandr, N. V. Smirnova and S. S. Sherkazova, *Khim.-Farm. Zh.*, **11**, 82 (1977); *Chem. Abstr.*, **86**, 182955W (1977).

[48] H. Biltz and H. Wittek, *Ber.*, **54**, 1035 (1921).

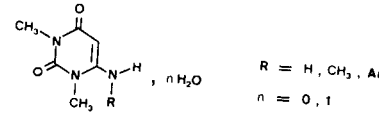
[49] W. Pfleiderer and K. H. Schündehütte, *Ann. Chem.*, **612**, 158 (1958).

[50] H. Goldner, G. Dietz and E. Carstens, [a] *Ann. Chem.*, **691**, 142 (1966); [b] *ibid.*, **694**, 142 (1966).

[51] Y. Sakuma, S. Matsumoto, T. Nagamatsu and F. Yoneda, *Chem. Pharm. Bull.*, **24**, 338 (1976).

[52] F. Yoneda, Y. Sakuma, M. Ichiba and K. Shinomura, *J. Am. Chem. Soc.*, **98**, 830 (1976).

[53] 1,3-Dimethyl-4-aminouracils **4** may contain one equivalent of water (n = 1) which has to be taken into account when calculating the quantity of azidophosgeniminium chloride (**1**) to be used for the formation of 8-azatheophyllines **8** (see [54] and [e] in Table 2).



4a - 4s

[54] Quantity of azidophosgeniminium chloride suitable only for non-hydrated aminouracils (n = 0). When n = 1, another equivalent of **1** (0.85 g, 0.005 mole) is required (see [e] in Table 2).