A HIGH CHEMICAL REACTIVITY OF 5-AZIDOURACILS AND ITS SYNTHETIC APPLICATION: NOVEL SYNTHESIS OF 8-SUBSTITUTED 1,3-DIMETHYLXANTHINE DERIVATIVES

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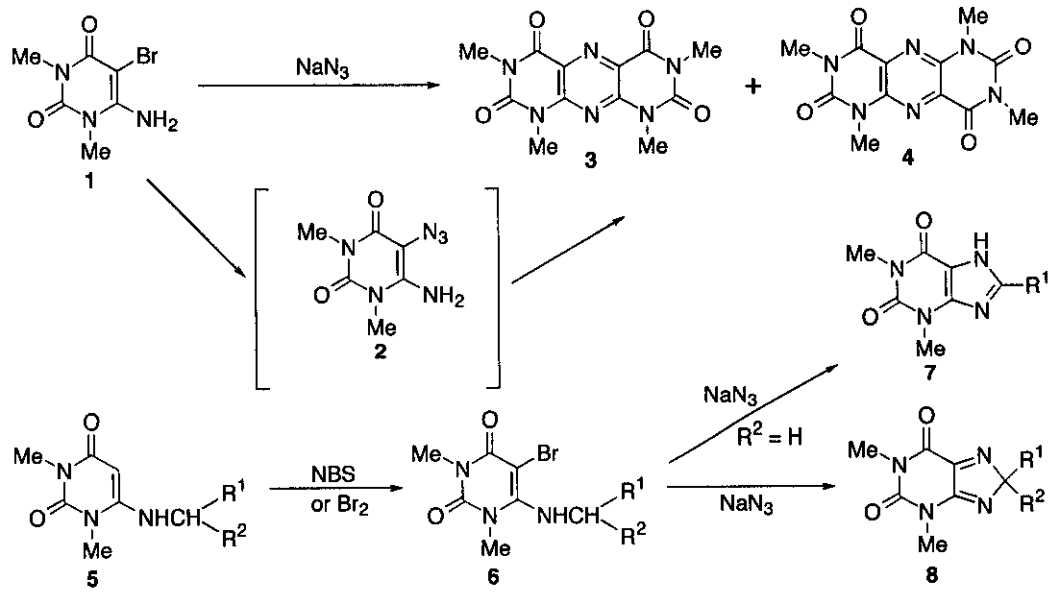
Abstract — A novel method for the preparation of 8-substituted 1,3-dimethylxanthine derivatives (**7** or **8**) is described: treatment of 6-alkylamino-5-bromo-1,3-dimethyluracils (**6a—e**), easily prepared by bromination of the corresponding 6-alkylamino-1,3-dimethyluracils (**5**), with sodium azide in DMF at ambient temperature allowed the direct formation of the 8-substituted 1,3-dimethylxanthines (**7**) proceeding *via* a transient formation of the corresponding 5-azido-1,3-dimethyluracils. The 5-bromo-1,3-dimethyluracils (**6f, g**) possessing an α-branched alkylamino group at the 6-position similarly react with sodium azide to afford 8,8-disubstituted 1,3-dimethyl-8*H*-xanthines (8,8-disubstituted 1,3-dimethyl-3,8-dihydropurine-2,6-diones) (**8**).

We have demonstrated that 6-azido-1,3-dimethyluracil is a useful synthon for the synthesis of fused pyrimidines.[1,2] In the course of our study on synthesis of 5-azidouracils in connection with the intriguing chemical reactivity and utility of the 6-azidouracils,[2] we found a novel method for the synthesis of 8-substituted 1,3-dimethylxanthines.[3]

In order to prepare 5-azido-1,3-dimethyluracil, 5-bromo-1,3-dimethyluracil was allowed to react with sodium azide under various conditions, our attempts for the isolation of the desired azidouracil, however, were unsuccessful because of the high complexity of products in this reaction. Therefore, the reaction of 6-amino-5-bromo-1,3-dimethyluracil (**1**),[4] highly reactive toward nucleophiles such as amines,[5] with sodium azide was examined. Although the treatment of **1** with sodium azide in DMF at ambient temperature did not give the expected 5-azidouracil (**2**), two products, 1,3,7,9-tetramethylpyrimido[5,4-*g*]pteridine-2,4,6,8-(1*H*,3*H*,7*H*,9*H*)-tetrone (**3**)[6,7] and 1,3,6,8-tetramethylpyrimido[4,5-*g*]pteridine-

2,4,7,9-(1*H*,3*H*,6*H*,8*H*)-tetrone (**4**),[8,9] which would be formed *via* **2**, were isolated. This result suggests intermediary formation of the corresponding 5-azidouracil (**2**) followed by the generation of a nitrene.

Scheme 1



In expectation of an intramolecular cyclization between a nitrene generated from the 5-azido group and an appropriate substituent at the 6-position, we synthesized 6-alkylamino-5-bromo-1,3-dimethyluracils (**6**) as the starting materials. 6-Alkylamino-1,3-dimethyluracils (**5**), which were easily prepared by condensation of 6-chloro-1,3-dimethyluracil with various amines according to the synthetic method reported in the literature,[10-12] were treated with NBS in the presence of a catalytic amount of AIBN in THF or with bromine in AcOH at ambient temperature to give the corresponding 6-alkylamino-5-bromo-1,3-dimethyluracils (**6a—g**) in high yields (see Table 1). First, reaction of 5-bromo-1,3-dimethyl-6-methylaminouracil (**6a**) with sodium azide in DMF at ambient temperature did not allow to isolate the corresponding 5-azidouracil and afforded directly 1,3-dimethylxanthine (theophylline) (**7a**) in 47% yield.

Xanthine derivatives, such as theophylline and caffeine, have long been known to cause a variety of physiological actions, *e.g.*, analeptic, cardiotonic, and bronchodilatory actions.[13] The antagonism of adenosine receptors and/or inhibition of *c*-AMP phosphodiesterase accounts for the mechanism of these actions.[13] 8-Substituted xanthine derivatives have been found to be an excellent selective antagonist of adenosine receptors.[14] Therefore, this novel synthetic method was undertaken to explore further synthetic

application of 8-substituted xanthines (**7** and **8**). Analogous treatment of **6b—e** with sodium azide led to the formation of 8-substituted 1,3-dimethylxanthines (**7b-e**). The 5-bromouracils (**6f, g**) possessing an α-branched alkylamino group at the 6-position react with sodium azide to afford 8,8-disubstituted-8*H*-xanthines (**8a, b**).

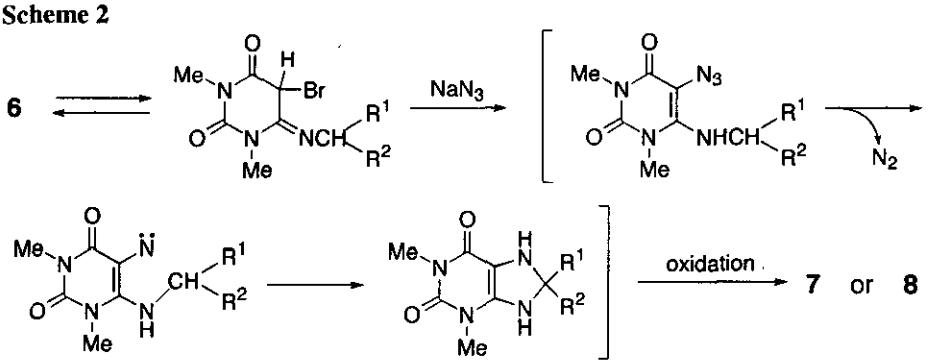
Table 1. Formation of 6-Alkylamino-5-bromo-1,3-dimethyluracils (6), Xanthine (Theophylline) Derivatives (7) and 8*H*-Xanthine Derivatives (8)

R^1	R^2	Product **6**	Yield (%)	Product **7** or **8**	Yield (%)
H	H	**6a**	89	**7a**	47[a]
Me	H	**6b**	92	**7b**	87
Et	H	**6c**	84	**7c**	61
CF_3	H	**6d**	76	**7d**	36[a]
Ph	H	**6e**	83	**7e**	86
Me	Me	**6f**	97	**8a**	78
$-(CH_2)_5-$		**6g**	69	**8b**	66

[a]In these cases any by-products could not be isolated.

A plausible mechanism of this reaction is illustrated in Scheme 2. This reaction constitutes formation of the corresponding 5-azidouracil intermediate *in situ*. The subsequent generation of a nitrene intermediate, followed by its intramolecular C-H insertion and oxidation, would give the 8-substituted xanthines (**7** and **8**).

Scheme 2



As disclosed above, we have succeeded in development of a convenient synthetic method of 8-substituted xanthine derivatives (**7** and **8**). The key active species of this synthetic system would be a nitrene generated from the 5-azido group. Workup of the simple reaction mixture and purification of the product (**7** or **8**) are very easy, because the reaction proceeds at ambient temperature.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All column chromatography was carried out with silica gel (Wakogel, C-300). All thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F254, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer FT IR-1640 or Hitachi Model 215 spectrophotometer, using KBr pellet. ^{1}H NMR spectra were determined with a JEOL GX-270, JEOL EX-400 or Hitachi Perkin-Elmer R-20B spectrometer using tetramethylsilane (TMS) in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in DMSO-d_6 as an internal standard. Coupling constants (J) are reported in hertz (Hz). Mass spectra (MS) were obtained in a JEOL JMS-D 300 machine operating at 70 eV. UV spectra were obtained from EtOH on a Shimadzu UV-260 spectrophotometer. Microanalyses were carried out at the Microanalytical Laboratory of our university.

Reaction of 6-Amino-5-bromo-1,3-dimethyluracil (1) with Sodium Azide. A mixture of **1**[5] (1.42 g, 6.1 mmol) and sodium azide (0.59 g, 9.1 mmol) in DMF (30 mL) was stirred at ambient temperature for 5 h. DMF was removed *in vacuo*, and the residue was triturated with water to give a complex solid mass. It was purified by silica gel column chromatography ($CHCl_3$: MeOH = 100 : 1) to afford 1,3,7,9-tetramethylpyrimido[5,4-*g*]pteridine-2,4,6,8-(1*H*,3*H*,7*H*,9*H*)-tetrone (**3**) (0.28 g, 15%) and 1,3,6,8-tetramethylpyrimido[4,5-*g*]pteridine-2,4,7,9-(1*H*,3*H*,6*H*,8*H*)-tetrone (**4**) (0.24 g, 13%), respectively. These products were identified with authentic samples by comparison of their IR spectra.[7,8]

General Procedure for the Synthesis of 6-Alkylamino-5-bromo-1,3-dimethyluracil Derivatives (6a, b, d—g). A suspension of the 6-alkylamino-1,3-dimethyluracil (**5a, b** or **d—g**)[10-12] (1 eq), NBS (1 eq) and AIBN (trace amount) in THF (4 mL/mmol) was stirred at ambient temperature. The progress of the reaction was monitored by TLC. THF was removed *in vacuo*, and the residue was

triturated with water. The resulting precipitate was recrystallized from an appropriate solvent to give the pure product. When the product could not be solidified in water, the mixture was extracted with $CHCl_3$. After the extract was dried over Na_2SO_4, concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography to isolate the desired product.

5-Bromo-1,3-dimethyl-6-methylaminouracil (6a): Recrystallized from AcOEt. 89%: mp 160—162 ℃; IR 3650—3050 (br), 1685, 1625, 1595, 1500, 1425, 1235, 1155, 760, 735 cm^{-1}; MS (EI^+) m/z 247 (M^+-1) and 249 (M^++1); ^1H NMR ($CDCl_3$) δ 2.97 (d, 3H, J = 4.8 Hz), 3.32 (s, 3H), 3.46 (s, 3H), 4.68 (br, 1H). *Anal.* Calcd for $C_7H_{10}N_3O_2Br$: C, 33.89; H, 4.06; N, 16.94. Found: C, 33.77; H, 4.00; N, 16.94.

5-Bromo-6-ethylamino-1,3-dimethyluracil (6b): Recrystallized from ligroin. 92%: mp 107—109 ℃; IR 3450—2850 (br), 1690, 1630, 1595, 1230, 1200, 1145, 1050, 810, 755, 745 cm^{-1}; MS (EI^+) m/z 261 (M^+-1) and 263 (M^++1); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.4 Hz), 3.14 (q, 2H, J = 7.4 Hz), 3.31 (s, 3H), 3.43 (s, 3H), 4.33 (br, 1H). *Anal.* Calcd for $C_8H_{12}N_3O_2Br$: C, 36.70; H, 4.61; N, 16.03. Found: C, 36.95; H, 4.61; N, 16.12.

5-Bromo-6-(2,2,2-trifluoroethyl)amino-1,3-dimethyluracil (6d): Purified by silica gel column chromatography ($CHCl_3$: acetone = 30 : 1). 76%: MS (EI^+) m/z 315 (M^+-1) and 317 (M^++1); ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H), 3.53 (s, 3H), 3.82 (m, 2H), 4.80 (br t, 1H, J = 7.1 Hz).

6-Benzylamino-5-bromo-1,3-dimethyluracil (6e): Recrystallized from benzene. 83%: mp 147—149 ℃; IR 3300, 1700, 1640, 1590, 1505, 1430, 1350, 1215, 1100, 755, 735, 695 cm^{-1}; MS (EI^+) m/z 323 (M^+-1) and 325 (M^++1); ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H), 3.56 (s, 3H), 4.34 (d, 2H, J = 6.0 Hz), 4.74 (br, 1H), 7.25—7.55 (m, 5H). *Anal.* Calcd for $C_{13}H_{14}N_3O_2Br$: C, 48.16; H, 4.35; N, 12.96. Found: C, 48.41; H, 4.37; N, 12.99.

5-Bromo-6-isopropylamino-1,3-dimethyluracil (6f): Purified by silica gel column chromatography (AcOEt : benzene = 7 : 3). 97%: IR 3350, 2960, 1700, 1650, 1590, 1530, 1490, 1420, 1390, 1370, 1215, 1120, 1015, 830, 750 cm^{-1}; MS (EI^+) m/z 275 (M^+-1) and 277 (M^++1); ^1H NMR ($CDCl_3$) δ 1.20 (s, 1H), 1.30 (s, 1H), 3.30—3.63 (m, 1H), 3.31 (s, 3H), 3.41 (s, 3H). *Anal.* Calcd for $C_9H_{14}N_3O_2Br$: C, 39.15; H, 5.11; N, 15.22. Found: C, 39.10; H, 4.96; N, 15.15.

5-Bromo-6-cyclohexylamino-1,3-dimethyluracil (6g): Purified by silica gel column chromatography (AcOEt : benzene = 7 : 3). 69%: IR 3300, 2925, 2850, 1710, 1690, 1600, 1550, 1430, 1365, 1300, 1250, 1210, 1145, 1000, 780, 760, 755 cm^{-1}; MS (EI^+) m/z 315 (M^+-1) and 317 (M^++1); ^1H NMR ($CDCl_3$) δ 1.10—2.63 (m, 10H), 3.23—3.68 (m, 1H), 3.31 (s, 3H), 3.43 (s, 3H), 4.29 (br d, 1H, J = 10.5 Hz). *Anal.* Calcd for $C_{12}H_{18}N_3O_2Br$: C, 45.58; H, 5.74; N, 13.29. Found: C, 45.29; H, 5.75; N, 13.17.

5-Bromo-1,3-dimethyl-6-propylaminouracil (6c): To a stirred solution of the 1,3-dimethyl-6-propylaminouracil (**1c**)[11] (1.00 g, 5.1 mmol) in AcOH (12 mL) was added dropwise a solution of bromine (0.81 g, 5.1 mmol) in AcOH (2 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 3 h and AcOH was removed *in vacuo*. The residue was triturated with water and the resulting precipitate was purified by recrystallization from EtOH to give 1.17 g of **6c** (84 %): mp 107—108 ℃; IR 3340, 1700, 1630, 1590, 1540, 1460, 1425, 1380, 1225, 1000, 1050, 795, 745, 740 cm^{-1}; MS (EI^+) m/z 275 (M^+-1) and 277 (M^++1). *Anal.* Calcd for $C_9H_{14}N_3O_2Br$: C, 39.15; H, 5.11; N, 15.33. Found: C, 39.25; H, 5.11; N, 15.33.

General Procedure for the Preparation of Xanthine (Theophylline) Derivatives (7) and 8*H*-Xanthine Derivatives (8). A mixture of the 6-alkylamino-5-bromo-1,3-dimethyluracil (**6**) (1 eq) and sodium azide (1.5 eq) in DMF (4 mL/mmol) was stirred at ambient temperature. The progress of the reaction was monitored by TLC. DMF was removed *in vacuo*, and the residue was triturated with water. The resulting precipitate was recrystallized from an appropriate solvent to give the pure product. When the product could not be solidified in water, the mixture was extracted with $CHCl_3$. After the extract was dried over Na_2SO_4, concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography to isolate the desired product.

1,3-Dimethylxanthine (Theophylline) (7a): Recrystallized from EtOH. 47%: mp 276 ℃ (*lit.*,[11] 273—274 ℃); IR 3200—2200 (br), 1720, 1670, 1570, 1450, 1395, 985, 745 cm^{-1}; MS (EI^+) m/z 180 (M^+); ^1H NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.67 (s, 3H), 7.84 (s, 1H). This product was identified with a commercial sample by comparison of its spectra.[11]

1,3,8-Trimethylxanthine (8-Methyltheophylline) (7b): Recrystallized from EtOH. 87%: mp >300 ℃ (*lit.*,[11] 329 ℃); IR 3600—2800 (br), 1720, 1640, 1510, 1375, 1220, 985, 735 cm^{-1}; MS (EI^+) m/z

194 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.48 (s, 3H), 3.63 (s, 3H). This product was identified with the authentic compound by comparison of its spectra.[11]

8-Ethyl-1,3-dimethylxanthine (8-Ethyltheophylline) (7c): Recrystallized from EtOH. 61%: mp 273 ℃ (*lit.*,[11] 277—277.5 ℃); IR 3300—2700 (br), 1710, 1645, 1515, 1405, 1380, 985, 760, 750 cm^{-1}; MS (EI^+) m/z 208 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.0 Hz), 2.90 (q, 2H, J = 7.0 Hz), 3.46 (s, 3H), 3.63 (s, 3H). This product was identified with the authentic compound by comparison of its spectra.[11]

1,3-Dimethyl-8-trifluoromethylxanthine (8-Trifluoromethyltheophylline) (7d). Purified by silica gel column chromatography ($CHCl_3$: acetone = 7 : 3). Recrystallized from AcOEt. 36%: mp 266—268 ℃; IR 3700—2400, 1727, 1654, 1561, 1423, 1364, 1268, 1156, 984, 812, 753 cm^{-1}; MS (EI^+) m/z 248 (M^+); UV λ_{max}(EtOH) 275 (ε 10800), 211(ε 20400); ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 3H), 3.51 (s, 3H). *Anal.* Calcd for $C_8H_7N_4O_2F_3$: C, 38.72; H, 2.84; N, 22.58. Found: C, 38.74; H, 2.91; N, 22.39.

1,3-Dimethyl-8-phenylxanthine (8-Phenyltheophylline) (7e): Recrystallized from DMF. 86%: mp >300 ℃ (*lit.*,[11] >360 ℃); IR 3340—2750 (br), 1695, 1650, 1530, 1475, 1360, 1235, 1060, 990, 785, 760, 710 cm^{-1}; MS (EI^+) m/z 256 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 3H), 3.31 (s, 3H), 7.50—7.70 (m, 3H), 8.10—8.35 (m, 2H), 13.85 (br, 1H). This product was identified with the authentic compound by comparison of its spectra.[11]

1,3,8,8-Tetramethyl-8*H*-xanthine (8a). Purified by silica gel column chromatography (AcOEt : Benzene = 7 : 3). Recrystallized from ligroin. 78%: mp 142—144 ℃ (*lit.*,[12] 148—149 ℃); IR 3420, 2980, 1745, 1685, 1660, 1595, 1425, 1380, 1300, 1215, 1075, 885, 740 cm^{-1}; MS (EI^+) m/z 208 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 6H), 3.46 (s, 3H), 3.51 (s, 3H). This product was identified with the authentic compound by comparison of its spectra.[12]

1,3-Dimethyl-8,8-pentamethylene-8*H*-xanthine (8b). Purified by silica gel column chromatography (AcOEt : Benzene = 7 : 3). Recrystallized from ligroin. 66%: mp 112—113 ℃ (*lit.*,[12] 115—116.5 ℃); IR 3425, 2940, 2855, 1735, 1685, 1650, 1590, 1425, 1375, 1295, 1250, 1125, 1075, 745 cm^{-1}; MS (EI^+) m/z 248 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 6H), 1.90 (m, 4H), 3.46 (s, 3H), 3.50 (s, 3H). This product was identified with the authentic compound by comparison of its spectra.[12]

REFERENCES AND NOTES

1. H. Wamhoff, J. Dzenis, and K. Hirota, 'Advances in Heterocyclic Chemistry', Vol. 55, ed. by A. R. Katritzky, Academic Press, Inc., San Diego, 1992, pp. 130-259.
2. S. Senda, K. Hirota, M. Suzuki, T. Asao, and K. Maruhashi, *J. Chem. Soc., Chem. Commun.*, 1976, 731; S. Senda, K. Hirota, T. Asao, and K. Maruhashi, *J. Am. Chem. Soc.*, 1977, **99**, 7358; S. Senda, K. Hirota, T. Asao, K. Maruhashi, and N. Kitamura, *Tetrahedron Lett.*, 1978, 367; S. Senda, K. Hirota, T. Asao, and K. Maruhashi, *J. Chem. Soc., Chem. Commun.*, 1978, 1531; S. Senda, K. Hirota, T. Asao, and K. Maruhashi, *J. Am. Chem. Soc.*, 1978, **100**, 7661; K. Hirota, K. Maruhashi, T. Asao, and S. Senda, *Heterocycles*, 1981, **15**, 285; K. Hirota, K. Maruhashi, T. Asao, and S. Senda, *Chem. Pharm. Bull.*, 1982, **30**, 3377; K. Hirota, K. Maruhashi, T. Asao, N. Kitamura, Y. Maki, and S. Senda, *Chem. Pharm. Bull.*, 1983, **31**, 3959; K. Hirota, K. Maruhashi, N. Kitamura, T. Asao, Y. Maki, and S. Senda, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1719.
3. Reviews on the synthetic methods of xanthine derivatives: see J. H. Lister, 'Fused Pyrimidines, Part II: Purines', Wiley Interscience., New York, 1971; J. H. Lister and M. D. Fenn, 'The Purines Supplement 1', John Wiley & Sons, Inc., New York, 1996.
4. E. F. Schroeder, *U.S. Patent*, 2,731,465, 1956 (*Chem. Abstr.*, 1957, **51**, 1257).
5. M. Sako, Y. Kojima, K. Hirota, and Y. Maki, *Heterocycles*, 1984, **22**, 1021.
6. E. C. Taylor, C. K. Chain, and H. M. Loux, *J. Am. Chem. Soc.*, 1954, **76**, 1874.
7. K. Hirota, K. Maruhashi, T. Asao, and S. Senda, *Chem. Pharm. Bull.*, 1982, **30**, 3377.
8. W. Pfleiderer, K. H. Schundehutte, and H. Ferch, *Liebigs Ann. Chem.*, 1958, **615**, 57.
9. F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.*, 1971, **19**, 1060.
10. G. Strauss, *Liebigs Ann. Chem.*, 1960, **638**, 205.
11. H. Goldner, G. Dietz, and E. Carstens, *Liebigs Ann. Chem.*, 1966, **691**, 142.
12. H. Goldner, G. Dietz, and E. Carstens, *Liebigs Ann. Chem.*, 1966, **692**, 134.
13. M. Williams, *Med. Research Rev.*, 1989, **9**, 219.
14. K. A. Jacobson, P. J. M. van Galen, and M. Williams, *J. Med. Chem.*, 1992, **35**, 407.

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