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Acetylene Chemistry, Part 32 [1]: Alkinylation and Cyclic Rearrangement of Theophylline with Unsaturated Alcohols by Mitsunobu Reaction

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Summary. The reaction of theophylline (**1**) with 2-methyl-3-butyn-2-ol and 1-butyn-3-ol under Mitsunobu conditions gave the respective 9-substituted derivatives 9-[2-(2-methyl-3-butynyl)]-theophylline (**2**) and 9-[2-(3-butynyl)]-theophylline (**3**). On reaction with 2-methyl-3-buten-2-ol, theophylline yielded in addition to the 9-[2-(2-methyl-3-butenyl)]-theophylline (**4**), two more cyclic products, identified as 1,5,5a,8-tetrahydro-1,3,8,8-tetramethyl-2*H*-pyrrolo[1,2-e]purine-2,4(3*H*)-dione (**5**) and 8a,9-dihydro-1,3,6,6-tetramethyl-1*H*-pyrrolo[2,1-f]purine-2,4(3*H*, 6*H*)-dione (**7**).

Keywords. Theophylline; Unsaturated alcohols; Cyclic rearrangement; Mitsunobu reaction.

Acetylenchemie, 32. Mitt.: Alkinylierung und cyclische Umlagerung von Theophyllin mit ungesättigten Alkoholen mittels Mitsunobu-Reaktion

Zusammenfassung. Die Reaktion von Theophyllin (**1**) mit 2-Methyl-3-butin-2-ol und 1-Butin-2-ol unter Mitsunobu-Bedingungen führte zu den 9-substituierten Derivaten 9-[2-(2-Methyl-3-butinyl)]-theophyllin (**2**) bzw. 9-[2-(3-Butinyl)]-theophyllin (**3**). Bei der Reaktion mit 2-Methyl-3-buten-2-ol ergab Theophyllin außer 9-[2-(2-Methyl-3-butenyl)]-theophyllin (**4**) noch zwei weitere cyclisierte Produkte, die als 1,3,8,8-Tetramethyl-1,5,5a,8-tetrahydro-pyrrolo[1,2-e]purin-2,4(3*H*)-dion (**5**) und 1,3,6,6-Tetramethyl-8a,9-dihydro-1*H*,6*H*-pyrrolo[2,1-f]purin-2,4-dion (**7**) identifiziert wurden.

Introduction

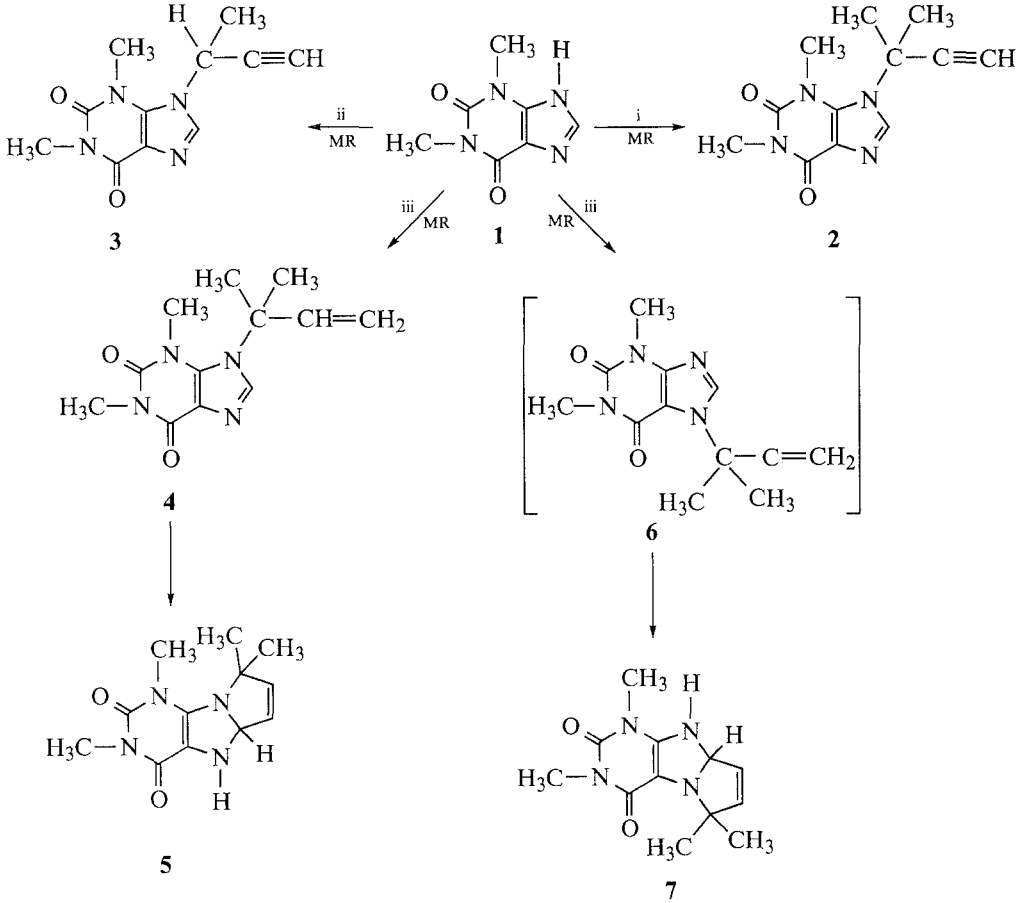
The usefulness of the Mitsunobu reaction [2] in various synthetic procedures can not be overemphasized. Recently we utilized this reaction in synthesizing some heterocyclic derivatives of acridinones [3] and quinazolinones [4] using acetylenic alcohols.

Theophylline (**1**) and its derivatives are well known to exhibit a variety of pharmacological actions including antiasthmatic, diuretic, respiratory stimulant

activities and represent a prototype of a wide range of xanthine antagonists for adenosine receptors [5, 6]. In addition, they could have the potential for the development as research tools as well as clinical agents. 7-[{3-[4-Diphenylmethoxy)-1-piperidinyl}propyl]-3,7-dihydro-1,3-dimethyl-1*H*-pyrine-2,6-dione (WY-49051), a derivative of theophylline, has been recently found to be a potent orally active, non-sedating histamine H_1-receptor antagonist [7, 8]. The syntheses of various 7-substituted theophylline derivatives have been reported earlier [9–12].

Results and Discussion

Under Mitsunobu reaction conditions, using 2-methyl-3-butyn-2-ol and 1-butyn-3-ol as alkylating agents, theophylline (**1**) principally yielded the respective 9-substituted products, 9-[2-(2-methyl-3-butynyl)]-theophylline (**2**) and 9-[2-(3-butynyl)]-theophylline (**3**) (Scheme 1). Anhydrous dioxane was found to be the solvent of choice. The characterisation of these 9-substituted products was based on their ^{1}H- and ^{13}C-NMR data and by comparison with the data of similar derivatives of nucleosides reported in the literature [13–15]. Recent reports also indicated a favoured 9-substitution over the possible 7-substitution while alkylating



Scheme 1. i = HO–C(CH$_3$)$_2$–C≡CH; ii = HO–CH(CH$_3$)–C≡CH; iii = HO–C(CH$_3$)$_2$–CH=CH$_2$; MR = Mitsunobu Reaction: triphenylphosphine, diethylazodicarboxylate, dry dioxane

purine nucleosides using the Mitsunobu reaction [16, 17]. No significant amounts of the corresponding 7-substituted theophylline derivatives or their possible cyclised products were isolated.

Interestingly, a similar reaction between theophylline and 2-methyl-3-buten-2-ol resulted in a mixture [17], which on chromatographic separation yielded three compounds. The tlc of the mixture appeared as a single spot in methanol:methylene chloride (2:98) mixture. However, their separation was possible using ethyl acetate: methylene chloride (15:85) as solvent system. The expected open-chain derivative, 9-[2-(2-methyl-3-butenyl)]-theophylline (**4**) was one of them. The other two were found to be either isomeric or cyclised derivatives of **4**; their mass spectra showed the molecular ion at $m/z = 248$ with relative intensities of 18% and 15%, respectively. The IR spectrum of **5** indicated a sharp absorption at 3450 cm^{-1} which is diagnostic of a NH group. In the ^{1}H-NMR spectrum, two different signals appeared at $\delta = 5.12$ and 5.19 ppm as two doublets corresponding to one proton each with coupling constants $J = 5.5$ Hz and 0.8 Hz, respectively. Another proton signal was found further down field at $\delta = 6.15$ ppm as a doublet of a doublet as a result of coupling with the other two. This was suggestive of cyclization of the 9-alkylated product, **4**. The corresponding NH appeared as a broad signal at $\delta = 11.32$ ppm. This downfield shift could be due to the hydrogen bonding between 6-carbonyl and 5-NH. The doubly bound 7 and 8 carbon signals in ^{13}C-NMR spectrum were recorded at $\delta = 138.9$ and 142.0 ppm, respectively. Based on these data, **5** was identified as 1,5,5a,8-tetrahydro-1,3,8,8-tetramethyl-2*H*-pyrrolo[1,2-e]purine-2,4(3*H*)-dione.

The ^{1}H-NMR spectrum of the third product was similar to the one of **5**, except the shift of the NH signal to $\delta = 7.71$ as a singlet. This data was indicative of the formation of another cyclised product, 8a,9-dihydro-1,3,6,6-tetramethyl-1*H*-pyrrolo-[2,1-f]purine-2,4(3*H*,6*H*)-dione (**7**). The reaction apparently resulted essentially in the formation of a 9-substituted derivative of theophylline, **4**. The compound **5** is a cyclised product of **4**. The formation of **7**, another cyclised product could have only resulted from the alkylation at the 7-position on theophylline, followed by a concommittant cyclisation. The respective open chain precursor **6** was not isolated. All compounds were unequivocally characterized by their spectroscopic data, supported by high resolution mass spectral analyses.

Experimental Part

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. IR spectra were taken on a Shimadzu IR-470 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer. All NMR spectra were recorded using deutereochloroform with tetramethylsilane as the internal standard. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV and high resolution mass spectra on a Finnigan MAT 312. Silica gel 60 F_{254} (precoated, aluminum sheets, 0.2 mm thickness, Merck 5549) were used for analytical tlc and 60 F_{254} (glass plates, 0.25 mm thickness, Merck 5715) for preparative work. Column chromatography was carried out on silica gel 60 (particle size 0.063–0.200 mm, Merck 7734).

Reaction of Theophylline (**1**) *with Unsaturated Alcohols Under Mitsunobu Conditions*

To a stirred solution of theophylline, unsaturated alcohol, triphenyl phosphine (*TPP*) in anhydrous dioxane was added diethylazadicarboxylate (*DEAD*) drop-wise over a period of 15 min. The slightly

warmed reaction mixture was heated under reflux for 3 h. After the removal of dioxane in vacuo, the syrupy reaction product was subjected to successive extraction with toluene:petroleum ether (40–60 °C) mixture (1:1) such that a large part of the white crystalline triphenylphosphine oxide, which was formed in the process of the reaction, was left behind. Column chromatography, using methanol:methylene chloride (2:98) was used for the separation of the products and further purification was carried out with preparative plate chromatography whenever necessary.

7-[2-(2-Methyl-3-butynyl)]-theophylline (**2**)

2-Methyl-3-butyn-2-ol (0.17 g, 2.0 mmol), **1** (0.3 g, 1.70 mmol) in 10 ml of anhydrous dioxane in the presence of *TPP* (0.655 g, 2.5 mmol) was added *DEAD* (0.435 g, 2.5 mmol) as in the general procedure to give **2** from methylene chloride:petroleum ether (40–60 °C) (3:7) as colourless needles (0.170 g, 30%), m.p. 136–140 °C. IR (KBr): 3320 (C=C), 2945 (C–H), 2125 (C=C), 1704 (C=O), 1662 (C=O), 1219 (C=N) cm^{-1}; ^{1}H-NMR: $\delta = 2.05$ (s, 6H, 2 × CH_3), 2.87 (s, 1H, C=CH), 3.44 (s, 3H, 3-CH_3), 3.61 (s, 3H, 1-CH_3), 8.24 (s, 1H, 8-H); ^{13}C-NMR: $\delta = 28.6$ (3-CH_3), 29.7 (1-CH_3), 29.9 (2 × CH_3), 55.9 (C-1'), 75.8 (C-3'), 84.1 (C-2'), 107.4 (C-5), 140.8 (C-8), 151.3 (C-4), 151.5 (C-2), 154.4 (C-6). EI-MS: *m/z* (%): 247 (3) [$M^+ + 1$], 246 (15) [M^+], 245 (3) [$M^+ - 1$], 180 (100) [$M^+ - C_5H_7$], 151 (6), 123 (28), 104 (5), 95 (55), 86 (30), 67 (37), 53 (15); HRMS: Calcd. for $C_{12}H_{14}N_4O_2$ 246.1116; found 246.11116.

7-[2-(3-Butynyl)]-theophylline (**3**)

3-Butyn-2-ol (0.14 g, 2.0 mmol), **1** (0.3 g, 1.70 mmol) in 10 ml of anyhydrous dioxane in the presence of *TPP* (0.655 g, 2.5 mmol) was added *DEAD* (0.435 g, 2.5 mmol) as in the general procedure to give **3** from methylene chloride:petroleum ether (40–60 °C) (3:7) as colourless needles (0.125 g, 28%), m.p. 144–148 °C. IR (KBr): 3280 (C=C), 2960 (C–H), 2130 (C=C), 1720 (C=O), 1670 (C=O), 1229 (C=N) cm^{-1}; ^{1}H-NMR: $\delta = 1.78$ (d, $J = 6.8$ Hz, 3H, 1'-CH_3), 2.69 (d, $J = 2.4$ Hz, 1H, 3'-H), 3.42 (s, 3H, 3-CH_3), 3.60 (s, 3H, 1-CH_3), 5.77 (m, 1H, 1'-H), 7.97 (s, 1H, 8-H); ^{13}C-NMR: $\delta = 24.5$ (1'-CH_3), 28.1 (3-CH_3), 29.7 (1-CH_3), 44.9 (1'-C), 75.5 (3'-C), 79.9 (2'-C), 106.2 (C-5), 139.4 (C-8), 149.3 (C-4), 151.7 (C-2), 155.1 (C-6). EI-MS: *m/z* (%): 232 (26), [M^+], 231 (12) [$M^+ - 1$], 207 (10) [$M^+ - (C{=}CH)$], 180 (24), 175 (14), 147 (15), 123 (32), 95 (70), 67 (63), 53 (100); HRMS: Calcd. for $C_{11}H_{12}N_4O_2$ 232.09602; found 232.09553.

7-[2-(2-Methyl-3-butenyl)]-theophylline (**4**)

2-Methyl-3-buten-2-ol (0.174 g, 2.0 mmol), **1** (0.3 g, 1.70 mmol) in 10 ml of anhydrous dioxane in the presence of *TPP* (0.655 g, 2.5 mmol) was added *DEAD* (0.435 g, 2.5 mmol) as in the general procedure to give **4** from methylene chloride:petroleum ether (40–60 °C) (3:7) as colourless needles (0.063 g, 15%), m.p. 118–121 °C. IR (KBr): 2915 (C–H), 1693 (C=O), 1649 (C=O), 1248 (C=N), 1023 (C=C) cm^{-1}; ^{1}H-NMR: $\delta = 1.80$ (d, $J = 1.3$ Hz, 6H, [1'-(2 × CH_3)], 3.42 (s, 3H, 3-CH_3), 3.59 (s, 3H, 1-CH_3), 4.92 (d, $J = 6.9$ Hz, 2H, 3'-H), 5.43 (m, 1H, 2-H), 7.54 (s, 1H, 8-H); ^{13}C-NMR $\delta = 25.6$ [1'-(2 × CH_3)], 27.9 (3-CH_3), 29.5 (1-CH_3), 44.6 (3'-C), 57.5 (1'-C), 106.7 (C-5), 117.7 (2'-C), 139.7 (C-8), 149.8 (C-4), 152.2 (C-2), 154.5 (C-6); EI-MS: *m/z* (%): 249 (2.2) [$M^+ + 1$], 248 (12), [M^+], 180 (100), [$M^+ - C_5H_8$], 151 (5), 123 (24), 95 (38), 83 (12), 69 (55); HRMS: Calcd. for $C_{12}H_{16}N_4O_2$ 248.12732; found 248.12729.

1,5,5a,8-Tetrahydro-1,3,8,8-tetramethyl-2H-pyrrolo[1,2-e]purine-2,4(3H)-dione (**5**)

Obtained from the mixture of the reaction product, as described above for **4**, m.p. 116–119 °C [methylene chloride:petroleum ether (40–60 °C) (5:5)] in 8% overall yield (0.035 g). IR (KBR): 3580 (NH), 2925 (C–H), 1703 (C=O), 1658 (C=O), 1020 (C=C) cm^{-1}; ^{1}H-NMR: $\delta = 1.56$ [s, 6H, 8-(2 × CH_3)], 3.45 (s, 3H, 1-CH_3), 3.63 (s, 3H, 3-CH_3), 5.12 (dd, $J = 5.5$ Hz, 0.8 Hz, 1H, 5a-H), 5.19 (d, $J = 0.8$ Hz, 1H, 7-H), 6.15 (dd, $J = 10.3$Hz, 7.3 Hz, 1H, 6-H), 11.32 (b, 1 H, NH); ^{13}C-NMR: $\delta = 27.4$ [8-(2 × CH_3)], 28.6

(1-CH_3), 29.7 (3-CH_3), 60.8 (C-5a), 106.2 (C-4a), 114.9 (C-8), 138.9 (C-6), 142.0 (C-7), 149.5 (9a-C), 151.3 (C-2), 153.8 (C-4); EI-MS: *m/z* (%): 249 (0.5) [$M^+ + 1$], 248 (18) [M^+], 233 (10) [$M^+ - CH_3$], 181 (20) [249 – C_5H_8], 180 (100) [$M^+ - C_5H_8$], 179 (22) [180-H], 149 (34), 123 (54), 95 (46), 83 (23), 69 (56), 57 (69); HRMS: Calcd. for $C_{12}H_{16}N_4O_2$ 248.12732; found 248.12694.

8a,9-Dihydro-1,3,6,6-tetramethyl-1H-pyrrolo-[2,1-f]purine-2,4(3H,6H)-dione (**7**)

Obtained from the mixture of the reaction product, as described above for **4**, [methylene chloride: petroleum ether (40–60 °C) (1:9)] in 10% yield (0.042 g), m.p. 123–125 °C. IR (KBr): 3480 (NH), 2960 (C–H), 2130 (C=C), 1715 (C=O), 1680 (C=O) cm^{-1}; ^{1}H-NMR: $\delta = 1.85$ [s, 6H, 6-(2 × CH_3)], 3.43 (s, 3H, 1-CH_3), 3.61 (s, 3H, 3-CH_3), 5.24 (d, $J = 7.2$ Hz, 1H, 8a-H), 5.31 (d, $J = 1.7$ Hz, 7-H), 6.32 (dd, $J = 7.2$ Hz, 1.7 Hz, 1H, 8-H), 7.71 (s, 1H, NH); ^{13}C-NMR $\delta = 27.7$ [6-(2 × CH_3)], 28.6 (1-CH_3), 29.8 (3-CH_3), 61.3 (6-C), 106.2 (C-4a), 115.2 (C-8a), 139.4 (C-7), 141.8 (C-8), 149.7 (C-9a), 150.9 (C-2), 154.4 (C-4); EI-MS: *m/z* (%): 249 (1.5) [$M^+ + 1$], 248 (15) [M^+], 181 (22) [249-C_5H_8], 180 (100) [$M^+ - C_5H_8$], 179 (18) [180-H], 151 (12), 123 (23), 95 (15), 83 (45), 69 (50); HRMS: Calcd. for $C_{12}H_{16}N_4O_2$ 248.12732; found 248.12673.

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References

[1] Acetylene Chemistry, Part 31: Reisch J., Usifoh C. O. (1993) J. Heterocyl. Chem. **30**: 659
[2] Mitsunobu O. (1981) Synthesis: 1
[3] Reisch J., Voerste A. A. W., Top M., Dziemba P. (1992) Monatsh. Chem. **123**: 473
[4] Reisch J., Rao A. R. R., Usifoh C. O. (1993) Monatsh. Chem. **124**: 1217
[5] Daly J. W., Padgett W., Shamin M. T., Butts-Lamp P., Waters J. (1985) J. Med. Chem. **28**: 487
[6] Peet N. P., Lentz N. L., Meng E. C., Dudley M. W., Ogden A. M. L., Demeter D. A., Weintraub H. J. R., Bey P. (1990) J. Med. Chem. **33**: 3127
[7] Abou-Gharbia M., Nielsen S. T., Webb M. B. (1987) U.S. Patent 4,716,166
[8] Abou-Gharbia M., Nielsen S. T., Andree T. H., Tasse R., Leventer S. (1990) Drug Dev. Res. **21**: 63
[9] Reisch J. (1968) Arzneim. Forsch./Drug Res. **18**: 1485
[10] Reisch J., Seeger U. (1977) Arch. Pharm. (Weinheim) **310**: 851
[11] Garst J. E., Kramer G. L., Wu Y. J., Wells J. N. (1976) J. Med. Chem. **19**: 499
[12] Powloski M., Buschauer A., Schunack W. (1989) Arch. Pharm. (Weinheim) **322**: 447
[13] Fisher P., Lösch G., Schmidt R. R. (1978) Tetrahedron Lett.: 1505
[14] Parkin A., Harnden M. R. (1982) J. Heterocycl. Chem. **19**: 33
[15] Wright G. E., Dudycz L. W., Kazimierczuk Z., Brown N. C., Khan N. N. (1987) J. Med. Chem. **30**: 109
[16] Toyota A., Katagiri N., Kaneko C. (1992) Chem. Pharm. Bull. **40**: 1039
[17] Jenny T. F., Horlacher J., Previsani N., Benner S. A. (1992) Helv. Chim. Acta **75**: 1944

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