Monatshefte für Chemie 125, 565–570 (1994)

Monatshefte für Chemie
Chemical Monthly

New Synthetic Approach to 8-Allyltheophylline

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Summary. The synthesis of 8-allyltheophylline (**8**) from 5,6-diamino-1,3-dimethyluracil (**1**) and 3-butenoic acid by *Traube's* method *via* 6-amino-5-(3-butenoylamino)-1,3-dimethyluracil (**2**) failed because an attempted alkaline cyclization of the intermediate **2** afforded (*E*)-8-(1-propenyl)-theophylline (**3**) under rearrangement of the terminal C=C bond. Therefore, the cyclodehydratation of 6-(3-butenylamino)-5-nitroso-1,3-dimethyluracil (**7**), available from 6-chloro-1,3-dimethyluracil (**5**) *via* 6-(3-butenylamino) derivative **6** has to be used for obtaining the required product **8**.

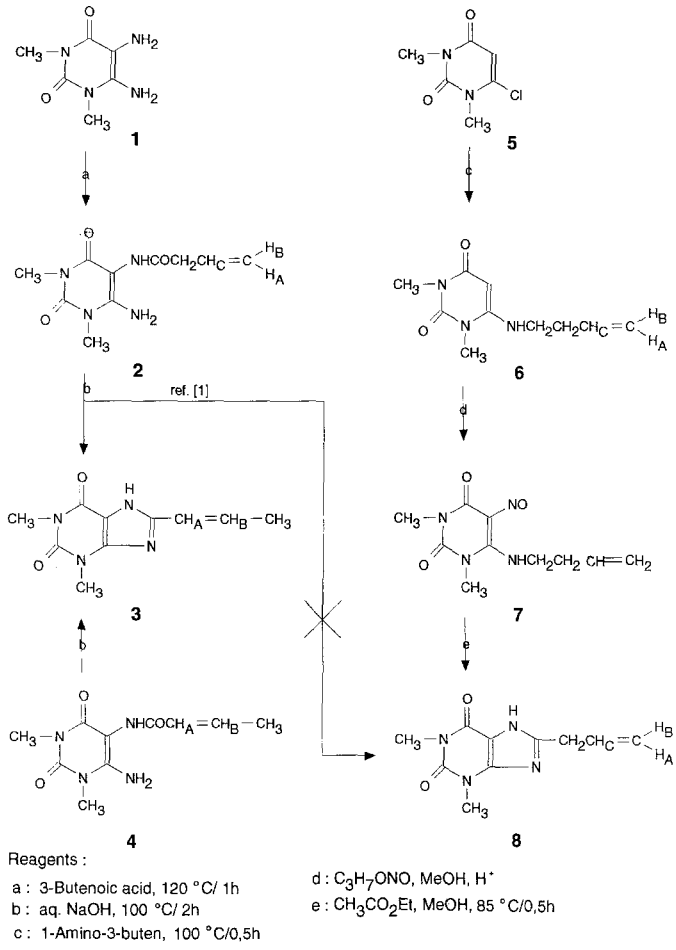
Keywords. 8-Allyltheophylline; 8-(1-Propenyl)-theophylline; Rearrangement of the terminal C=C bond.

Ein neuer synthetischer Zugang zu 8-Allyltheophyllin

Zusammenfassung. 8-Allyltheophyllin (**8**) kann nicht mittels der *Traube*-Synthese aus 5,6-Diamino-1,3-dimethyluracil und 3-Butensäure *via* 6-Amino-5-(3-butenoylamino)-1,3-dimethyluracil (**2**) hergestellt werden, weil bei der alkalischen Cyclisierung des Zwischenproduktes **2** Umlagerung der terminalen C=C-Doppelbindung unter Bildung von (*E*)-8-(1-Propenyl)theophyllin (**3**) erfolgt. Zur Darstellung der Verbindung **8** muss man daher die Dehydratationscyclisierung von 6-(3-Butenylamino)-5-nitroso-1,3-dimethyluracil (**7**) anwenden. Letzteres ist aus 6-Chloro-1,3-dimethyluracil über das 6-(3-Butenylamino)-Derivat **6** zugänglich.

Results and Discussion

The attempt to prepare 8-allyltheophylline (*i.e.* 8-allyl-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) (**8**) employing *Traube*'s synthesis from 5,6-diamino-1,3-dimethyluracil (**1**) *via* 6-amino-5-(3-butenoylamino)-1,3-dimethyluracil (**2**) according to ref. [1] afforded on cyclization of the intermediate **2** in aqueous alkaline medium (*E*)-8-(1-propenyl)-theophylline (**3**) and not the reported 8-allyl derivative **8** (Scheme 1), as evidenced by the ^{1}H NMR spectrum. This was deduced from the presence of the signal of terminal methyl group at 1.95 ppm ($J_{Me,H_B} = 6.7$ Hz) arising from the hydrocarbon chain attached to position 8 of the purine skeleton. Presence of the characteristic signals of the allyl group of compound **2** used for cyclization in the ^{1}H NMR spectrum at 5.32 ppm (CH_A, $J_{H_A,H_C} = 10.5$ Hz), 5.37 ppm (CH_B, $J_{H_B,H_C} = 17.4$ Hz, $J_{H_A,H_B} = 1.5$ Hz), 6.05 ppm (CH_C) and 3.25 ppm (CH_2CO) proves the reported structure of the 5-(3-butenoylamino) derivative. Consequently, the cyclization had to be accompanied by a rearrangement of the terminal double bond in conjugation with the purine ring system to furnish the final compound **3**.



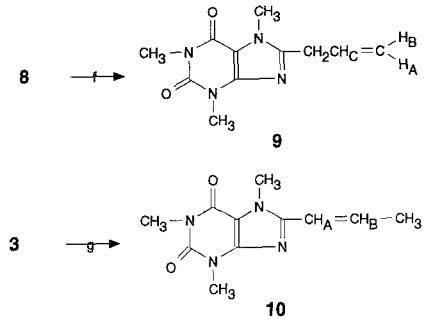
As anticipated and later proved by HPLC, rearrangement of the terminal double bond takes place even on heating compound **8** in aqueous alkaline-metal hydroxide; the position 8 of the allyl group at the xanthine skeleton of compound **8**, prepared by the method mentioned below, is definite. A one-hour reflux of the allyl derivative **8** with one equivalent of 0.1 *M* NaOH yielded a mixture consisting of 88.8 and 11.2% of compounds **3** and **8**, respectively. Because cyclization of the acylamino derivative **2** furnishes compound **3**, it is impossible to decide unequivocally whether rearrangement of the terminal double bond occurs with compound **2**, or after its conversion to **8**, or simultaneously. This rearrangement appears also on cyclization of the intermediate **2** with phosphorus oxychloride; it is worth noting that the allyl derivative **8** was not determined in the product by HPLC. Similar rearrangements of the double bond from the more remote position of the alkenyl chain in conjugation with the carboxyl groups carbonyl were reported with *e.g.* 3-, 4- and 10-alkenoic acids and 3-cyclohexenecarboxylic acid under both basic and acid catalysis [2–4].

To ascertain unambiguously the structure of the rearranged product, i.e. the (*E*)-8-(1-propenyl) derivative **3**, the latter was synthesized by *Traube*'s method [5] from the 5,6-diamino derivative **1** and (*E*)-2-butenoic chloride *via* 6-amino-5-((*E*)-2-butenoylamino)-1,3-dimethyluracil (**4**). Its cyclization in aqueous alkaline

medium gave a product identical (m.p., HPLC, mass spectrum, elemental analysis, ^{1}H NMR spectrum) with compound **3**, obtained from the intermediate **2**. The intermediate **4** can also be cyclized into (*E*)-8-(1-propenyl) derivative **3** with phosphorus oxychloride in dimethylformamide. Nevertheless, the reaction product contains only 79% of compound **3**.

The attempted preparation of compound **8** by *Traube*'s method was successful for a cyclodehydratation of 5-nitroso-6-alkylaminouracils according to ref. [6]. This reaction has already been employed for obtaining 8-vinyl-[7] and 8-ethinyl-theophyllines [8].

We now aminolyzed 6-chloro-1,3-dimethyluracil (**5**) with an excess of an aqueous solution of 1-amino-3-butene to 6-(3-butenylamino)-1,3-dimethyluracil (**6**). Acid catalyzed nitrosation of the latter with propyl nitrite afforded the corresponding 5-nitroso derivative **7**, which on reflux in ethyl acetate yielded the required 8-allyltheophylline (**8**). Presence of the allyl group in the side chain was corroborated by the presence of a doublet of a CH_2 group at 3.69 ppm and doublets of terminal protons CH_A at 5.22 ($J_{H_A,H_C} = 10.5$ Hz) and CH_B at 5.29 ppm ($J_{H_B,H_C} = 16.7$ Hz, $J_{H_A,H_B} = 1.4$ Hz).



Reagents :
f : CH_2N_2, Et_2O, THF, r.t./ 1h
g: Me_2SO_4, MeOH, aq. NaOH, pH 8-9, r.t./ 3h

Compound **8** was methylated (Scheme 2) to the 7-methyl derivative **9** (allylcaffeine) by diazomethane in diethyl ether-tetrahydrofuran.

Methylation with diazomethane was preferred over the common alkylation of the alkali metal salt of compound 8 with methyl iodide or dimethyl sulfate to avoid migration of the double bond in the unsaturated side chain in alkaline medium. Presence of the third methyl and the allyl groups in the product was ascertained by analysis of the ^{1}H NMR spectrum.

In analogy (*E*)-8-(1-propenyl)caffeine (**10**) was obtained by methylation of compound **3** with dimethyl sulfate at *pH* 8–9 in aqueous methanol.

Experimental Part

The melting points are uncorrected. Samples for analyses were dried over phosphorus pentoxide at 100 °C/65 Pa for 8 h. The UV spectra were measured with a Specord M-40 spectrophotometer, the

mass spectra with a Jeol 100 D apparatus at 70 eV ionization energy. The ^{1}H NMR spectra were recorded with a Bruker AM-300 instrument operating at 300 MHz; tetramethylsilane served as internal reference. Signals of compound **6** were assigned by means of a 2D COSY experiment [9]. Composition and purity of the reaction products were monitored by HPLC (see Table 1) employing the Hewlett-Packard model 1050 column 0.4 × 25.0 cm packed with Separon SGX C18 (5 μm); mobile phase: acetonitrile-water 3:7 (by volume), flow rate 0.5 ml/min, detection by UV (300 nm). The HPLC data are given in weight per cent.

6-Amino-5-(3-butenoylamino)-1,3-dimethyluracil (**2**)

A mixture of 5,6-diamino-1,3-dimethyluracil (ref. [10]) (**1**; 12.0 g, 70.7 mmol) and 3-butenoic acid (25.2 g, 0.29 mmol) was heated at 120 °C (bath temperature) with stirring for 1 h. 2-Propanol (200 ml) was added to the hot melt and the solution thus obtained was left to stand overnight at 0 °C. The crystalline product was filtered off, washed with 2-propanol (20 ml) and dried under diminished pressure at 110 °C. Yield 11.2 g, m.p. 225–227 °C; the second portion (1.2 g, m.p. 224–226 °C, totally 74%) was obtained by concentrating the mother liquor to one third of the original volume. Crystallization of both portions from ethanol gave 10.7 g (64%), m.p. 226–227 °C of the title product; HPLC purity: 100%. Ref. [1] reports m.p. 219–220 °C. Anal.: calcd. for $C_{10}H_{14}N_4O_3$ (238.2): C 50.41, H 5.92, N 23.52; found: C 50.69, H 6.00, N 23.61. UV (methanol): 272 nm (log $\varepsilon = 4.28$). ^{1}H NMR ($CDCl_3$): $\delta = 3.25$ (d, CH_2–CO), 3.28 (s, N-3–CH_3), 3.45 (s, N-1–CH_3), 5.32 (dd, $J_{H_A,H_C} = 10.5$ Hz, CH_A), 5.37 (dd, $J_{H_B,H_C} = 17.4$ Hz, $J_{H_A,H_B} = 1.5$ Hz, CH_B), 6.05 (m, CH_C). MS, m/z: 238 (M^+).

6-Amino-5-((E)-2-butenoylamino)-1,3-dimethyluracil (**4**)

(*E*)-2-Butenoic chloride (ref. [11]) (25.1 g, 23.0 ml, 0.24 mol) was added at 70 °C to the 5,6-diamino derivative **1** (34.0 g, 0.20 mol) dissolved in dry pyridine (500 ml) at 90 °C with stirring during 15 min. The mixture was refluxed for 15 min and allowed to cool with stirring to room temperature. After c. 3 h the separated product was filtered off, suspended in ethanol (50 ml), filtered off again and recrystallized from water (600 ml). Yield 28.6 g (60%), m.p. 274–277 °C. The analytical sample recrystallized from ethanol had m.p. 279–281 °C, HPLC purity: 100%. Anal.: calcd. for $C_{10}H_{14}N_4O_3$ (238.2): C 50.41, H 5. 92, N 23.52; found C 50.60, H 6.03, N 23.66. UV (methanol): 271 nm (log $\varepsilon = 4.30$). ^{1}H NMR ($CDCl_3$): $\delta = 1.95$ (d, $J_{Me,H_B} = 6.8$ Hz, C–CH_3), 3.25 (s, N-3–CH_3), 3.45 (s, N-1–CH_3), 6.20 (d, $J_{H_A,H_B} = 16.2$ Hz, CH_A), 6.98 (m, CH_B). MS, m/z: 238 (M^+).

(E)-8-(1-Propenyl)theophylline (**3**)

A) Cyclization of the acyl derivative **2** according to ref. [1] afforded after acidification with acetic acid, washing with water and drying at 70 °C at reduced pressure the crude product; its HPLC analysis showed following composition: 98.6% of compound **3**, 1.0% of compound **8** and 0.4% of the unreacted acyl derivative **2**. Compound **3** was obtained by crystallization from ethanol in 99.0% purity, m.p. 284–285 °C (cf. ref. [1]: m.p. 284–285 °C).

B) Acyl derivative **4** (2.38 g, 10 mmol) was heated in a stirred solution of 1*M* NaOH (11 ml, 11 mmol) and water (5 ml) at 100 °C for 2 h. Water (16 ml) was added to the cooled mixture to which carbon dioxide was introduced at an ambient temperature. The separated compound **3** was filtered off, washed with water (2 × 5 ml) and dried at 70 °C under reduced pressure. Yield 1.73 g (79%), m.p. 286–288 °C. HPLC purity: 99.0%. Anal.: calcd. for $C_{10}H_{12}N_4O_2$ (220.2): C 54.53, H 5.49, N 25.44; found: C 54.75, H 5.65, N 25.59. UV (methanol): 231 (4.38), 306 nm (log $\varepsilon = 4.29$). ^{1}H NMR ($CDCl_3$): $\delta = 1.95$ (d, $J_{Me,H_B} = 6.7$ Hz, C–CH_3), 3.45 (s, N-3–CH_3), 3.62 (s, N-1–CH_3), 6.40 (d, $J_{H_A,H_B} = 16.4$ Hz, CH_A), 7.05 (m, CH_B). MS, m/z: 220 (M^+).

6-(3-Butenylamino)-1,3-dimethyluracil (**6**)

4-Chloro-1,3-dimethyluracil (**5**; 3.49 g, 20 mmol) and 1-amino-3-butene (ref. [12]) (7.11 g, 100 mmol) were stirred and heated at 100 °C in water (7 ml) for 30 min. The sirup obtained by evaporation of water under reduced pressure was dissolved in ethyl acetate (120 ml) and left to stand at 5 °C for 2 days. The separated 1-amino-3-butene hydrochloride was filtered off. The filtrate was concentrated under diminished pressure to 40% of its original volume and left standing at 0 °C for 20 h. The separated product (3.56 g, 85%), had m.p. 106–111 °C. The analytical sample recrystallized from ethyl acetate had m.p. 110–113 °C. Anal.: calcd. for $C_{10}H_{15}N_3O_3$ (209.2): C 57.40, H 7.23, N 20.08; found: C 57.03, H 7.50, N 19.82. UV (methanol): 272 nm ($\log \varepsilon = 4.34$). ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (q, CH_2–CH=), 3.1 (q, NH–CH_2–), 3.20, (s, N-3–CH_3), 3.32 (s, N-1–CH_3), 4.75 (s, =C–H), 5.08 (dd, $J_{H_A,H_C} = 11.2$ Hz, CH_A), 5.09 (dd, $J_{H_B,H_C} = 16.5$ Hz, $J_{H_A,H_B} = 1.6$ Hz, CH_B), 5.15 (bt, NH), 5.71 (m, CH_C=); MS, m/z: 209 (M^+).

8-Allyltheophylline (**8**)

One drop of saturated ethanolic hydrogen chloride as catalyst was added to the methanolic solution (17 ml) of the intermediate **6** (3.14 g, 15 mmol) at 40 °C. Propyl nitrite (5.88 g, 6.54 ml, 56 mmol) was poured into the stirred solution through the reflux condenser and the mixture was kept stirred at 40 °C for 30 min. The volatile components were distilled off under reduced pressure and the sirupy residue of the 5-nitroso derivative **7** turned into red crystals. These were dissolved in hot ethyl acetate (30 ml); methanol (3 ml) was added to this solution which was then heated (85 °C bath temperature) for 30 min. From the originally red solution turning its colour into brown-white crystals separated to afford a thick mass. The product was filtered off after cooling and crystallized from methanol (80 ml + charcoal). Yield 1.73 g (52%), m.p. 234–236 °C, HPLC purity: 99.9%. Anal.: calcd. for $C_{10}H_{12}N_4O_2$ (220.2): C 54.53, H 5.49, N 25.44; found C 54.37, H 5.59, N 25.43. UV (methanol): 278 nm ($\log \varepsilon = 4.16$). ^{1}H NMR ($CDCl_3$): $\delta = 3.48$ (s, N-3–CH_3), 3.62 (s, N-1–CH_3), 3.69 (d, CH_2–CH_C=), 5.22 (dd, $J_{H_A,H_C} = 10.5$ Hz, CH_A), 5.29 (dd, $J_{H_B,H_C} = 16.7$ Hz, $J_{H_A,H_B} = 1.4$ Hz, CH_B), 6.09 (sextet, CH_C), 9.72 (s, NH); MS, m/z: 220 (M^+).

8-Allylcaffeine (**9**)

Diazomethane in dry diethyl ether (20 ml, *ca.* 5 mmol) was dropped into the stirred solution of compound **8** (220 mg, 1.0 mmol) in diethyl ether-tetrahydrofuran (1:1, 100 ml). The mixture was then stirred at room temperature for 1 h, the solvents were evaporated under reduced pressure, the residue was dissolved in chloroform and trace amounts of the unreacted starting material were extracted with 2% sodium hydroxide (2 × 10 ml). The chloroform solution was dried with Na_2SO_4, the solvent was distilled off and the residue was crystallized from methanol (6 ml). Yield 135 mg (58%), m.p. 143–145 °C, HPLC purity: 99.9%. Anal.: calcd. for $C_{11}H_{14}N_4O_2$ (234.3): C 56.40, H 6.02, N 23.92; found: C 56.48, H 6.12, N 24.00. UV (methanol): 279 nm ($\log \varepsilon = 4.15$). ^{1}H NMR ($CDCl_3$): $\delta = 3.39$ (s, N-3–CH_3), 3.57 (s, N-1–CH_3), 3.90 (s, N-7–CH_3), 3.55 (d, CH_2–CH_C=), 5.11 (dd, $J_{H_A,H_C} = 10.5$ Hz, CH_A), 5.23 (dd, $J_{H_B,H_C} = 17.5$ Hz, $J_{H_A,H_B} = 1.4$ Hz, CH_B), 5.94 (sextet, CH_C); MS, m/z: 324 (M^+).

(E)-8-(1-Propenyl)caffeine (**10**)

1*M* KOH (c. 15 ml) was dropped into the suspension of compound **3** (2.20 g, 10 mmol), in methanol (20 ml) and dimethyl sulfate (1.89 g, 1.42 ml, 15 mmol) with stirring at 15 °C; the *pH* value of this solution has to be kept between 8 to 9 and the dropping time lasts *ca.* 3 h. The mixture was left standing overnight, the separated crystals were filtered off, dried under reduced pressure and crystallized from ethanol (50 ml). Yield 2.0 g (85%), m.p. 194–196 °C, HPLC purity: 99.9%. Anal.: calcd. for $C_{11}H_{14}N_4O_2$ (234.3): C 56.40, H 6.02, N 23.92; found: C 56.57, H 5.91, N 24.23. UV (methanol): 232 (4.45), 307 nm ($\log \varepsilon = 4.36$). ^{1}H NMR ($CDCl_3$): $\delta = 1.98$ (dd, $J_{Me,H_B} = 6.9$ Hz, $J_{Me,H_A} = 1.8$ Hz, C–CH_3), 3.37 (s,

N-3-CH_3), 3.55 (s, N-1-CH_3), 3.91 (s, N-7-CH_3), 6.30 (dd, $J_{AB} = 15.4$ Hz, CH_A), 6.98 (sextet, CH_B); MS, m/z: 220 (M^+).

Table 1. Retention time (t_R), capacity factor (c) and the resolution factor (R_{ji}) of compounds **2**, **3**, **4**, and **8**

Compound	t_R	c^a	R_{ji}
4	3.885	0.798	
			0.2033
2	3.946	0.829	
			6.2114
8	6.120	1.830	
			3.4675
3	7.507	2.475	

[a] $C = \frac{t_R - t_0}{t_0}$; dead time: $t_0 = 2.16$ min.

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Received June 17, 1993. Accepted July 16, 1993