

# N-(8-PURINYL)-CARBAMATES\*

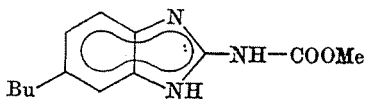
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Received June 6, 1975

The preparation of 4-butyl-1,2-phenylenediamine, the starting compound for the synthesis of the anthelmintic Parabendazole (1) is rather cumbersome.



Therefore, and in order to study the effect of replacing the benzimidazole ring of 1 by the purine ring on the biological properties, (8-purinylyl) analogues of 1 were synthesised as shown in Scheme 1. Compounds 2, 4, 5 and 7 of Scheme 1 are potentially tautomeric; for the tautomeric structures of type 2, 4 and 5 compounds see [1], [2a] and [2b], respectively. The tautomeric structure of the compounds 7 has not been investigated.

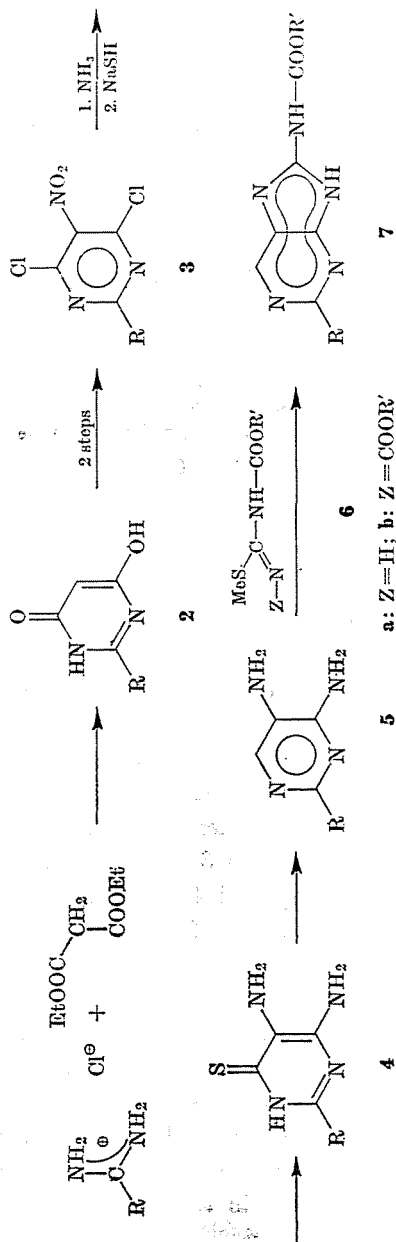
The first three steps of the synthesis sequence (leading ultimately to the 4,6-dichloro-5-nitropyrimidines 3) were performed essentially according to [3]. Ammonolysis of the compounds 3 led, depending on the molar ratio of the reactants, either to the required 4-amino-6-chloro-5-nitro- or to 4,6-diamino-5-nitropyrimidines. Treatment of the former with NaSH, and subsequent Raney nickel desulfuration furnished the diamino derivatives 5 via the thiones 4.

Conversion of the diamines 5 into the purinylcarbamates 7 was brought about by condensation with *N*-[(methylthio)formimidoyl]carbamates (6a) or [(methylthio)methylidyne]dicarbamates\*\*\* (6b). The yields achieved with type 6a compounds as reagents were very low; moreover, the condensation with type 6a reagents is not a structure proving synthesis. The amino group of the ammonia molecule eliminated in the course of the condensation may

\* Dedicated to Prof. G. Schay on the occasion of his 75th birthday.

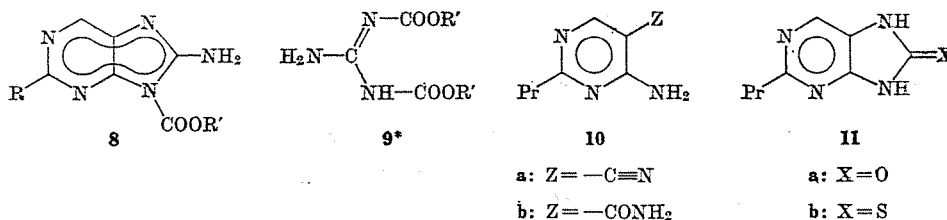
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\*\*\* The authors are indebted to Dr. Kurt L. Loening of Chemical Abstract Service for suggesting this name.



Scheme 1

namely, in principle, come either from position 4 of the diamine **5** or from the reagents **6a**. While in the latter case type **7** compounds are necessarily



\* Potentially tautomeric compound. Tautomeric structure arbitrarily drawn

formed, in the former isomers of type **8** could equally be obtained. Condensation of the diamines **5** with type **6b** reagents, on the other hand, can lead only to products of type **7** (or their 1-alkoxycarbonyl derivatives which could easily be recognized on the basis of the microanalysis results), but not to their type **8** isomers; moreover, the yields achieved with type **6b** compounds as the reagents were much better.

Condensation of **5** (R=Pr) with urea and thiourea furnished 2-propyl-7H-purin-8(9H)-one (**11a**) and -thione (**11b**), respectively. The former was obtained also by NaOCl treatment of 4-amino-2-propyl-5-pyrimidinecarboxamide (**10b**), itself prepared by partial hydrolysis of the corresponding carbonyl nitrile (**10a**). Attempts to convert **11a** or **11b** into **7** (R=Pr) failed.

*Biological screening:* **5** (R=Pr, R'=Me) was tested for trichostrongylostatic activity on sheep (per os administration) and was found inactive.

## Experimental

### 6-Hydroxy-4(3H)-pyrimidinones (**2**)

a) Diethyl malonate (122 ml; 0.8 mole) was added at 40 °C to an anhydrous methanolic soln (800 ml) of sodium (56 g; 2.4 mole). Butanamidinium chloride [**4**] (98 g; 0.8 mole) was added, and the mixture was allowed to stand overnight and subsequently refluxed for 6 hrs. The solvent was distilled off, and the residue was dissolved in water (800 ml). Conc. HCl (190 ml) was added (pH 3) to precipitate 109 g (88%) of **2** (R=Pr), m.p. 302 °C, which proved sufficiently pure for being used in the following step.

Recryst. from water raised the m.p. to 309–310 °C, lit. m.p. 296 °C (dec.) [**3**]

C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> (154.17), calc. C 54.54, H 6.54, N 18.12; found C 54.54, H 6.62, N 18.33%.

The compound has been obtained earlier by condensation of ethyl butyrate with malondiamide [3]

b) 2 (R = Bu) was similarly obtained in 60% yield starting with pentanamidinium chloride [5]. M.p. 299–300 °C (dec.) lit. [3] 300 °C (dec.).

#### 6-Hydroxy-5-nitro-4(3H)-pyrimidinones

Nitration of the compounds 2 was performed essentially as described in [3] to yield 78% of 6-hydroxy-5-nitro-2-propyl-4(3H)-pyrimidinone, m.p. 301–302 °C (dec.; from aq. EtOH),

$C_7H_9N_3O_4$  (199.17), calc. C 42.21, H 4.55, N 21.10; found C 42.89, H 4.81, N 20.81%;

and 66% 2-butyl-6-hydroxy-5-nitro-4(3H)-pyrimidinone, respectively, m.p. 295 °C (dec.; from aq. EtOH), lit. m.p. 265 °C [3].

$C_8H_{11}N_3O_4$  (213.19), calc 45.07, H 5.20, N 19.71; found C 45.31, H 5.64, N 19.95%.

#### 4,6-Dichloro-5-nitropyrimidinones (3)

a) The 2-butyl derivative has been obtained essentially as described in [3]. B.p. 125–130 °C/3 torr, lit. 142–143 °C/17 torr.

b) The 2-propyl derivative was similarly obtained in 78% yield. M.p.: 39 °C; b.p. 107 °C/4 torr, 125 °C/10 torr. (The bath temperature during distillation must not exceed 150 °C since vigorous decomposition may take place at elevated temperatures.) The compound may be conveniently purified by sublimation in vacuum.

$C_7H_7Cl_2N_3O_2$  (236.07), calc Cl 30.09, N 17.79; found Cl 29.89, N 17.25%

#### 4-Amino-6-chloro-5-nitropyrimidines

a) The 2-butyl derivative has been obtained in 88% yield as described in [3], m. p. 125–126 °C, lit. m.p. 132 °C.

b) The 2-propyl derivative was similarly obtained in 76% yield, m.p. 143 °C.

$C_7H_9ClN_4O_2$  (216.63), calc C 38.81, H 4.20, Cl 16.36, N 25.86; found C 39.45, H 4.50, Cl 15.75, N 26.08%.

The crude product was contaminated with unchanged starting material. Purification was effected by extraction with light petroleum. By evaporating the solvent 19% of the starting compound was recovered.

#### 4,6-Diamino-5-nitro-2-propylpyrimidine

The dichloro compound 3 (R = Pr) was dissolved in ether (10 ml/g 3). Excess (15 mole/mole 3) ethanolic  $NH_3$  was added at 5 °C, and the mixture was kept overnight in a refrigerator to furnish the title compound in essentially

theoretical yield, m.p. 198 °C (from water). The product may be purified by sublimation at 190 °C (bath temperature), 3 torr.

$C_7H_{11}N_5O_2$  (197.20), calc C 42.63, H 5.62; found C 42.65, H 5.48%.

#### 5,6-Diamino-4(3H)-pyrimidinethiones (4)

a) The 2-butyl derivative was obtained in 85% yield as described in [3] by allowing to react 4-amino-2-butyl-6-chloro-5-nitropyrimidine with aqueous-ethanolic NaSH soln. M.p. and lit. m.p.: 187—188 °C

b) The 2-propyl derivative was similarly obtained in 82% yield, m.p. 184 — 185 °C (from  $H_2O$ ). 4 (R = Pr) tends to form a crystalline monohydrate. The water of crystallization is lost during drying over  $P_2O_5$  at 78 °C, 1 torr.

$C_7H_{12}N_4S_2$  (184.28), calc S 17.37; found S 17.00%.

#### 4,5-Diaminopyrimidines (5)

a) The 2-butyl derivative was obtained in 87% yield by Raney-Ni desulfuration of the corresponding thione (4, R = Bu) as described in [3]. M.p. 122 — 123 °C, lit. 121 — 122 °C.

b) The 2-propyl derivative was similarly obtained in essentially theoretical yield, m.p. 148—150 °C (purified by sublimation at 160 °C [bath temperature], 1 torr).

$C_7H_{12}N_4$  (152.20), calc C 55.24, H 7.95, N 36.81; found C 55.04, H 7.92, N 36.88%

#### [(Methylthio)methylidyne]dicarbamates (6b)

a) The dimethyl ester **6b** (R' = Me) was obtained in 66% yield as described in [6], m.p. 101 — 102 °C, lit. 100 — 102 °C. IR (KBr):  $\nu_{C=O}$  1750  $cm^{-1}$

b) The diethyl ester **6b** (R' = Et) was obtained similarly in 64% yield. The product was an oil which turned crystalline below 0 °C. It proved sufficiently pure for the subsequent condensation without further purification. Lit. m.p. 50 — 51 °C [7]. IR (KBr):  $\nu_{C=O}$  1750  $cm^{-1}$ . Further characterization of our product has been performed by ammonolysis to the guanidine derivative **9** (R' = Et) [7].

#### Dimethyl (aminomethylidyne)dicarbamate (9, R' = Me)

This compound has been obtained — in analogy to the preparation of the diethyl ester (**9**, R' = Et) [7] — in 73% yield by ammonolysis of **6b** (R' = Me) in methanolic soln at 0 °C, m.p. 211 °C (dec.; from aq. MeOH).

$C_5H_9N_3O_4$  (175.15), calc C 34.29, H 5.18, N 23.99; found C 34.37, H 5.12, N 24.06%.

*N*-(8-Purinyl)-carbamates (7)

a) A mixture of **5** (R = Bu) (7.80 g; 47 mmole), **6b** (R' = Me) (20 g; 97 mmole), MeOH (50 ml), water (100 ml), and AcOH (8 ml) was stirred for 1 hr each, at room temperature and 80 °C, and for 10 hrs at 100 °C (bath temperatures), respectively, to yield 7.0 g (60%) of **7** (R = Bu, R' = Me) as a crystalline product, m.p. 220 °C (dec.; from MeOH).

$C_{11}H_{15}N_5O_2$  (249.27), calc C 53.00, H 6.07; found C 52.91, H 6.27%. IR (KBr):  $\nu_{NH}$  3300,  $\nu_{C=O}$  1720  $cm^{-1}$

b) A mixture of **5** (R = Pr) (4.0 g; 26 mmole), **6b** (R' = Et) (8.0 g; 34 mmole), EtOH (50 ml) and conc HCl (3 drops) was refluxed for 16 hrs. AcOH (3 ml) was added, and refluxing was continued for another 12 hrs to yield 3.2 g (49%) of **7** (R = Pr, R' = Et), m.p. 245 – 250 °C (from EtOH).

$C_{11}H_{15}N_5O_2$  (249.27), calc C 53.00, H 6.07, N 28.09; found C 52.74, H 6.24, N 27.70%.

IR (KBr):  $\nu_{NH}$  3300,  $\nu_{C=O}$  1715  $cm^{-1}$

c) Methyl chloroformate (11.5 ml; 150 mmole) was added under continuous stirring within 1 min to a soln of di(*S*-methylthiuronium) sulfate (10 g; 72 mmole) in water (30 ml). The temperature was kept between 15 to 20 °C throughout. (External ice-water cooling may be necessary.) Stirring and cooling were continued and, after 5 min, aqueous (20 ml) KOH (12.3 g; 0.22 mole) soln was added by drops within 5 min and, after another 90 min, a mixture of **5** (R = Pr) (5.0 g; 33 mmole), MeOH (30 ml) and AcOH (5 ml). The mixture was stirred for 10 hrs, and the temperature was gradually raised. (During the last 6 hrs the bath temperature was 100 °C). 4.65 g (60%) of practically pure **7** (R = Pr, R' = Me), m.p. 225 – 226 °C was obtained; reprecipitation with light petroleum from a soln in  $CHCl_3$ –MeOH did not change the m.p.

$C_{10}H_{13}N_5O_2$  (235.25), calc C 51.06, H 5.57, N 29.77; found C 50.96, H 5.63, N 29.52%.

IR (KBr):  $\nu_{NH}$  3300,  $\nu_{C=O}$  1720  $cm^{-1}$

4-Amino-2-propyl-5-pyrimidinecarboxamide (**10b**)

The nitrile **10a** [8] (20 g; 124 mmole) was added under stirring and cooling to conc  $H_2SO_4$  (60 ml). The resulting soln was kept for 36 hrs at room temperature and poured onto ice (250 g). 40% NaOH soln. (165 ml) was added to the mixture under cooling until it became slightly alkaline. The resulting product

was filtered off, thoroughly washed with water and recrystallized from very dil. aq. EtOH to yield 19.5 g (88%) of **10b**, m.p. 204–205 °C.

$C_8H_{12}N_4O$  (180.21), calc C 53.32, H 6.71; found C 53.40, H 6.73%. IR (KBr):  $\nu_{NH}$  broad, with local maxima at 3400, 3280, 3180;  $\nu_{C=O}$  1650  $cm^{-1}$

### 2-Propyl-7H-purine-8(9H)-one (**11a**)

a) An aqueous NaOCl soln, obtained by saturating an aqueous (125 ml) NaOH (20 g; 0.5 mole) soln with  $Cl_2$  (25 to 30 min) was added to the suspension of **10b** (12 g; 67 mmole) in an aqueous (180 ml) KOH (20 g; 0.36 mole) soln. The mixture was stirred, until a clear soln resulted (1 hr), and allowed to stand overnight. The reaction was completed by heating for 2 hrs on a steam-bath. AcOH (25 ml) was added at 50 °C to precipitate 10.6 g (89%) of **11a**, m.p. 245 – 246 °C.

$C_8H_{10}N_4O$  (178.20), calc C 53.92, H 5.66, N 31.44; found C 53.68, H 5.61, N 31.79%. IR (KBr):  $\nu_{NH}$  broad with local maxima at 3400, 3100, 2950 and 2650;  $\nu_{C=O}$ : 1730  $cm^{-1}$

b) **5** (R=Pr) (0.3 g; 2 mmole) and urea (0.7 g; 12 mmole) were thoroughly mixed and heated for 1 hr at 155–160 °C (bath temperature). The resolidified melt was pulverized and extracted with boiling water (4 ml) to yield 0.30 g (86%) of **11a**, m.p. and mixed m.p. with the product obtained according to (a) 246 °C.

### 2-Propyl-7H-purine-8(9H)-thione (**11b**)

**5** (R = Pr) (0.70 g; 4.6 mmole) and thiourea (2.0 g; 26 mmole) were thoroughly mixed and heated for 90 min at 180 to 200 °C (bath temperature). The resolidified melt was pulverized and extracted with boiling water (5 ml) to yield 0.75 g (84%) of **11b**, m.p. 286 – 290 °C (dec.). Recrystallization from  $H_2O$  raised the m.p. to 290 – 293 °C (dec.).

$C_8H_{10}N_4S$  (194.25), calc C 49.48, H 5.19, S 16.48; found C 49.90, H 5.20, N 16.33%.

### Acknowledgements

The authors are indebted to Mrs. S. Viszt-Simon and Mrs. Zauer-Csüllög for the micro-analyses and to Dr. P. Kolonits and staff for the IR spectra. The biological screening has been performed at the Department for Parasitology of the National Institute of Veterinary Surgery (Országos Állategészségügyi Intézet), Budapest.

### Summary

N-(8-Purinyl)-carbamates, diaza analogues of the anthelmintic Parabendazole have been synthesized.

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