(lit.[6] mp 153.9—154.4°). *Anal.* Calcd. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.65; H, 4.29; N, 15.23.

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# Conversion of 6-Benzylidenehydrazino-1,3-dimethyluracils into $N^4$-Benzylideneamino-1,3-dimethylcytosines

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The reaction of 6-benzylidenehydrazino-1,3-dimethyluracils with phosphorus oxychloride gave $N^4$-benzylideneamino-6-chloro-1,3-dimethylcytosines, which serve as useful substrates for several nucleophilic displacements.

**Keywords**——6-benzylidenehydrazino-1,3-dimethyluracils; phosphorus oxychloride; $N^4$-benzylideneamino-6-chloro-1,3-dimethylcytosines; nucleophilic displacements; $N^4$-benzylideneamino-1,3-dimethylcytosines; 6-substituted $N^4$-benzylideneamino-1,3-dimethylcytosines

We have previously described that the reaction of 6-amino-1,3-dialkyluracils with phosphorus oxychloride or phosphorus oxybromide offers a new and general synthetic route to 1,3-dialkyl-6-halogenocytosines, which are useful starting materials for the preparation of various 1,3-dialkylcytosine derivatives.[2] The present paper describes the reaction of 6-benzylidenehydrazino-1,3-dimethyluracils with phosphorus oxychloride leading to $N^4$-benzylideneamino-6-chloro-1,3-dimethylcytosines, which serve as useful substrates for several nucleophilic displacements.

Refluxing of 6-benzylidenehydrazino-1,3-dimethyluracil (Ia)[3] with excess phosphorus oxychloride for 1 hr gave an excellent yield of $N^4$-benzylideneamino-6-chloro-1,3-dimethylcytosine (IIa), which was readily isolated by concentration of the reaction mixture and addition of aqueous ammonia. The structure of IIa was assigned by the elemental analysis and the following spectral data. The mass spectrum revealed a parent ion at *m/e* 276 and $M^+$+2 ion, indicating that one chlorine atom is contained in the molecule. The characteristic secondary amino absorption band at 3140 $cm^{-1}$ of Ia was disappeared and a new carbonyl band came out at 1685 $cm^{-1}$ in the infrared (IR) spectrum. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) showed four singlets [$\delta$ 3.48 (3H, N-Me), 3.52 (3H, N-Me), 6.98 (1H, =CH-), 8.43 (1H, $C^5$ H)] and a multiplet [$\delta$ 7.30—7.90 (5H, $C_6H_5$)]. This reaction was equally applicable to other 6-benzylidenehydrazino-1,3-dimethyluracils (Ib—e) to give the

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3) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 1484 (1975).

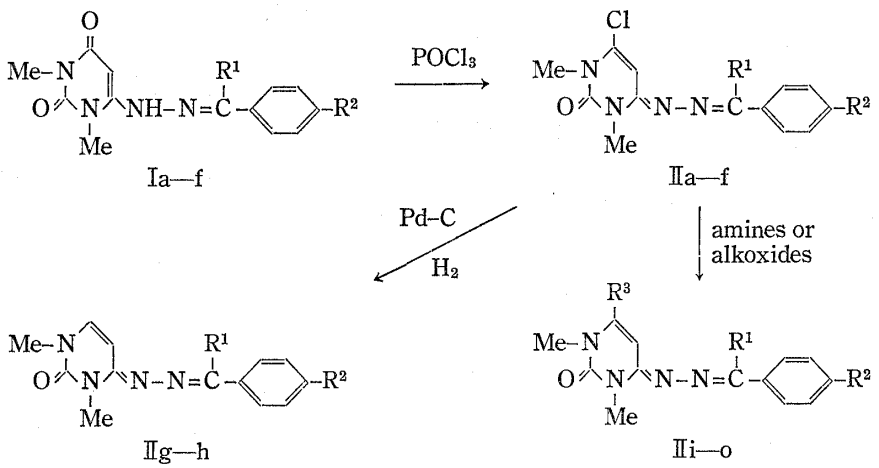
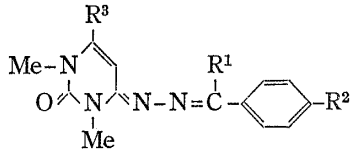



Chart 1

TABLE I. $N^4$-Benzylideneamino-1,3-dimethylcytosines



| Compd. No. | $R^1$ | $R^2$ | $R^3$ | mp (°C) | Yield (%) | Recrystn. solvent | Formula | Analysis (%) Calcd. (Found) C | H | N | IR (Nujol) $cm^{-1}$ (CO) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | H | H | Cl | 146—147 | 97 | EtOH | $C_{13}H_{13}ClN_4O$ | 56.42 (56.36 | 4.74 4.73 | 20.25 20.49) | 1685 |
| IIb | H | Cl | Cl | 160—161 | 91 | EtOH | $C_{13}H_{12}Cl_2N_4O$ | 50.17 (49.96 | 3.89 3.89 | 18.01 18.13) | 1683 |
| IIc | H | Me | Cl | 169—170 | 90 | EtOH | $C_{14}H_{15}ClN_4O$ | 57.83 (57.67 | 5.20 5.20 | 19.27 19.32) | 1685 |
| IId | H | OMe | Cl | 167—168 | 89 | EtOH | $C_{14}H_{15}ClN_4O_2$ | 54.81 (54.75 | 4.93 4.93 | 18.27 18.42) | 1685 |
| IIe | H | $NMe_2$ | Cl | 215—216 | 90 | EtOH–DMF | $C_{15}H_{18}ClN_5O$ | 56.32 (56.11 | 5.67 5.65 | 21.90 22.01) | 1685 |
| IIf | Me | H | Cl | 125—126 | 82 | EtOH | $C_{14}H_{15}ClN_4O$ | 57.83 (57.67 | 5.20 5.17 | 19.27 19.31) | 1685 |
| IIg | H | H | H | 145—147 | 37 | MeOH–$H_2O$ | $C_{13}H_{14}N_4O$ | 64.44 (64.15 | 5.82 5.78 | 23.13 23.23) | 1680 |
| IIh | Me | H | H | 123—124 | 31 | EtOH | $C_{14}H_{16}N_4O$ | 65.60 (65.45 | 6.29 6.23 | 21.86 21.73) | 1670 |
| IIi | H | H | $C_6H_5NH$ | 230—232 | 60 | EtOH–DMF | $C_{19}H_{19}N_5O$ | 68.45 (68.29 | 5.74 5.70 | 21.01 21.02) | 1658 |
| IIj | H | H | $C_6H_5CH_2NH$ | 184—186 | 81 | EtOAc | $C_{20}H_{21}N_5O$ | 69.14 (68.88 | 6.09 6.13 | 20.16 20.20) | 1659 |
| IIk | H | H | OMe | 178—180 | 90 | EtOH | $C_{14}H_{16}N_4O_2$ | 61.75 (61.83 | 5.92 5.91 | 20.58 20.74) | 1687 |
| IIl | H | H | OEt | 115—116 | 89 | EtOH | $C_{15}H_{18}N_4O_2$ | 62.92 (62.81 | 6.34 6.40 | 19.57 19.58) | 1689 |
| IIm | Me | H | $C_6H_5NH$ | 204—205 | 87 | EtOH | $C_{20}H_{21}N_5O$ | 69.12 (68.94 | 6.09 6.05 | 20.17 20.28) | 1663 |
| IIn | Me | H | OMe | 172—173 | 94 | EtOH | $C_{15}H_{18}N_4O_2$ | 62.92 (62.87 | 6.34 6.26 | 19.57 19.80) | 1689 |
| IIo | Me | H | OEt | 144—146 | 97 | EtOH | $C_{16}H_{20}N_4O_2$ | 63.98 (63.96 | 6.71 6.73 | 18.65 18.90) | 1686 |

corresponding $N^4$-benzylideneamino-6-chloro-1,3-dimethylcytosines (IIb—e) in high yields. Analogous treatment of 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)-uracils (If)[4] with phosphorus oxychloride furnished 6-chloro-1,3-dimethyl-$N^4$-(α-methylbenzylideneamino)-cytosine (IIf) as expected. Satisfactory analytical and spectral data were obtained for IIf: The mass spectrum exhibited a parent ion at *m/e* 290 and $M^+$+2 ion. The IR spectrum was quite similar to that of IIa and the NMR spectrum ($CDCl_3$) showed four singlets [δ 2.45 (3H, =C-Me), 3.50 (3H, N-Me), 3.52 (3H, N-Me), 6.88 (1H, $C^5$ H)] and a multiplet [δ 7.33—8.00 (5H, $C_6H_5$)].

The chlorocytosine derivatives prepared above served as useful starting materials for several transformation reactions. For example, catalytic dechlorination of IIa and IIf over palladium-carbon in ethanol yielded $N^4$-benzylideneamino-1,3-dimethylcytosine (IIg) and 1,3-dimethyl-$N^4$-(α-methylbenzylideneamino)cytosine (IIh), respectively. Treatment of the chlorocytosines, IIa and IIf, with amines or alkoxides gave the desired 6-substituted $N^4$-benzylideneamino-1,3-dimethyl-cytosines (IIi—o) (Chart 1 and Table I).

## Experimental[5]

**$N^4$-Benzylideneamino-6-chloro-1,3-dimethylcytosines (IIa—e) and 6-Chloro-1,3-dimethyl-$N^4$-(α-methylbenzylideneamino)cytosine (IIf). General Procedure**——A mixture of the appropriate 6-benzylidenehydrazino-1,3-dimethyluracils (**Ia**—e) (0.01 mol) or 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracil(If) (0.01 mol) and phosphorus oxychloride (50 ml) was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo* and the residue was triturated with 5% aqueous ammonia. The insoluble crystals were filtered and recrystallized to give the corresponding pure products IIa—f.

**$N^4$-Benzylideneamino-1,3-dimethylcytosine (IIg) and 1,3-Dimethyl-$N^4$-(α-methylbenzylideneamino)-cytosine (IIh). General Procedure**——A solution of IIa or IIf (0.001 mol) in ethanol (200 ml) containing 10% palladium-carbon (0.2 g) was hydrogenated at room temperature under atmospheric pressure. Hydrogenation was stopped when the theoretical volume (22.4 ml) of hydrogen was consumed. The solution was filtered and concentrated *in vacuo* to dryness. The residue was triturated with 5% aqueous ammonia and the insoluble crystals were recrystallized to give the corresponding pure products IIg—h.

Compound IIg, MS *m/e*: 242 ($M^+$). NMR δ: 3.32 (s, 3H, N-Me), 3.47 (s, 3H, N-Me), 6.73 (s, 2H, $C^5$ H and $C^6$ H),[6] 7.27—7.90 (m, 5H, $C_6H_5$), 8.42 (s, 1H, =CH–).

Compound IIh, MS *m/e*: 256 ($M^+$). NMR δ: 2.45 (s, 3H, =C–Me), 3.32 (s, 3H, N-Me), 3.49 (s, 3H, N-Me), 6.68 (s, 2H, $C^5$ H and $C^6$ H),[6] 7.30—8.00, (m, 5H, $C_6H_5$).

**6-Substituted Amino-$N^4$-benzylideneamino-1,3-dimethylcytosines (IIi—j and IIm). General Procedure**——A mixture of IIa or IIf (0.001 mol) and the appropriate amines (aniline or benzylamine) (0.002 mol) in ethanol (20 ml) was refluxed for 2 hr. The reaction mixture was concentrated *in vacuo* and the residue was triturated with 5% aqueous ammonia. The insoluble crystals were filtered and recrystallized to give the corresponding pure products IIi—j and IIm.

**6-Alkoxy-$N^4$-benzylideneamino-1,3-dimethylcytosines (IIk—l and IIn—o). General Procedure**——A suspension of IIa or IIf (0.001 mol) in the appropriate absolute alcohols (methanol or ethanol) (20 ml) dissolving metallic sodium (0.002 g atom) was refluxed for 2 hr. The reaction mixture was concentrated *in vacuo* and the residue was covered with water. The insoluble crystals were filtered and recrystallized to give the corresponding pure products IIk—l and IIn—o.

4) K. Senga, Y. Kanamori, S. Nishigaki, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1917 (1976).
5) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co, Ltd. spectrophotometer, Model IR-E from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 70 eV.
6) Two protons at position 5 and 6 appeared as a sharp singlet, however, the expected coupling with this signal could not be observed under the concentration employed.