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# Some 3-Amino and 3-Substituted-amino Derivatives of $\alpha^4$-Norpyridoxol†

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Some analogs of $\alpha^4$-norpyridoxol in which 3-hydroxyl group is replaced by amino and substituted-amino groups have been prepared and evaluated for anticoccidal activity. 3-Aroylamino analogs of $\alpha^4$-norpyridoxol have some coccidiostatic effect towards *Eimeria tenella*.

As a part of our investigations on the structural modifications of $\alpha^4$-norpyridoxol (**1**)[1] and 4-deoxypyridoxol (**2**, 4–DOP),[2] a new type of anticoccidial drugs, we have prepared 3-amino derivatives of $\alpha^4$-norpyridoxol and 4–DOP.

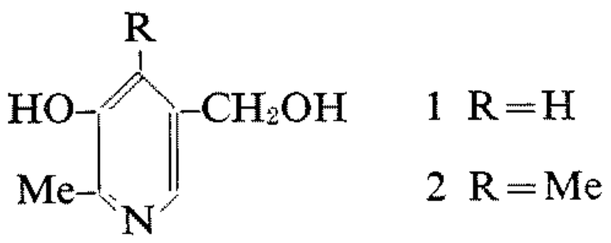
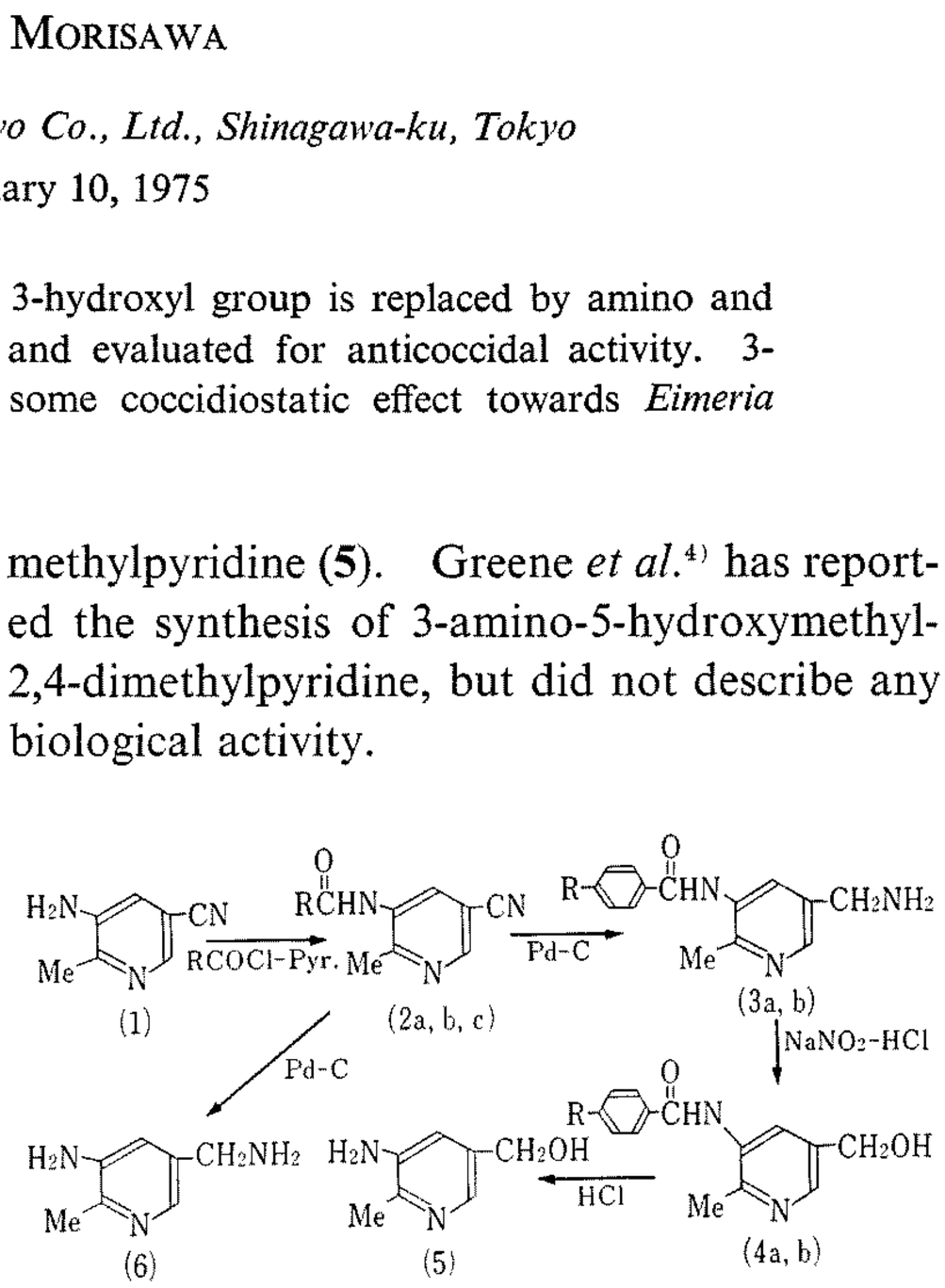



FIG. 1.

3-Amino-6-chloro-5-cyano-2-methylpyridine, obtained from 5-cyano-2-methylpyridine by the procedure of Perez-Median *et al.*[3] was acylated with acyl chlorides in pyridine. The resultant 3-aroylamino derivatives (**2a**, **b**) were hydrogenated in the presence of palladium on carbon to give 5-aminomethyl-3-aroylamino-2-methylpyridines (**3a**, **b**), while a similar attempt to convert the 3-acetylamino-5-cyano-derivative (**2c**) to the corresponding 5-aminomethyl compound (**3**) yielded only 3-amino-5-aminomethyl-2-methylpyridine (**6**). Diazotization of the primary amine (**3a**, **b**), followed by hydrolysis of the diazonium salt gave 3-aroylamino-5-hydroxymethyl-2-methylpyridines (**4a**, **b**). Treatment of benzoylamino derivative (**4a**) with hydrochloric acid gave a good yield of 3-amino-5-hydroxymethyl-2-methylpyridine (**5**). Greene *et al.*[4] has reported the synthesis of 3-amino-5-hydroxymethyl-2,4-dimethylpyridine, but did not describe any biological activity.




a; R=Ph, b; R=*p*-Methoxyphenyl, c; R=Ac

FIG. 2.

3-Amino-5-hydroxymethyl-2, 4-dimethylpyridine and 3-amino-5-hydroxymethyl-2-methylpyridine (**5**) as well as the intermediates (**3**, **4**) leading to (**5**) have been tested against *Eimeria acervulina* and *E. tenella*. The 3-amino analog of 4–DOP exhibited moderate anticoccidial activity against *E. acervulina* at 200 ppm in feed but was less active than $\alpha^4$-norpyridoxol. 3-Aroylamino compounds (**3**, **4**) have some coccidiostatic effect towards *E. tenella*.

## EXPERIMENTAL

Melting points were uncorrected. IR spectra were obtained with Perkin-Elmer 221 and JASCO IRA–2 spectrometers and NMR spectra were recorded with a Varian A–60 spectrometer using TMS as an internal standard. Typical experimental procedures are de-

† Studies on Anticoccidial Agents. Part V. For paper Part IV of this series see Y. Morisawa, M. Kataoka, T. Watanabe, N. Kitano and T. Matsuzawa, *Agr. Biol. Chem.*, **39**, 1275 (1975).

scribed for the preparation of compounds (**2**, **3** and **4**).

*3-Benzoylamino-6-chloro-5-cyano-2-methylpyridine* (**2a**)

Benzoyl chloride (5.6 g) was added dropwise to a solution of 3-amino-6-chloro-5-cyano-2-methylpyridine (**1**, 5.6 g) in pyridine (70 ml). The mixture was stirred at room temperature for 16 hr, poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$) and the solvent was removed to leave a crystalline product. Recrystallization from EtOAc-*n*-hexane gave 7.95 g of (**2a**), mp 205~206°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3360, 2250, 1680. *Anal.* Found: C, 62.00; H, 3.67; N, 15.51; Cl, 13.23. *Calcd.* for $C_{14}H_{10}N_3OCl$: C, 61.80; H, 3.68; N, 15.35; Cl, 13.08.

*3-p-Methoxybenzoylamino-6-chloro-5-cyano-2-methylpyridine* (**2a**)

Mp 238~240°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3350, 2230, 1670. *Anal.* Found: C, 59.79; H, 3.91; N, 13.83; Cl, 11.58. *Calcd.* for $C_{15}H_{12}N_3O_2Cl$: C, 59.71; H, 4.01; N, 13.93; Cl, 11.75.

*3-Acetylamino-6-chloro-5-cyano-2-methylpyridine* (**2c**)

Mp 184~185°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3250, 2240, 1665. *Anal.*Found: C, 51.65; H, 3.84; N, 20.25; Cl, 16.69. *Calcd.* for $C_9H_8N_3OCl$: C, 51.56; H, 3.85; N, 20.05; Cl, 16.91.

*5-Aminomethyl-3-benzoylamino-2-methylpyridine 2HCl* (**3a**)

To a suspension of preactivated 10% Pd–C catalyst (2.8 g) in MeOH (60 ml) containing conc. HCl (5 ml) was added a solution of 3-benzoylaminopyridine (**2a**, 2.8 g) in MeOH (200 ml). The mixture was shaken in $H_2$ atmosphere for 8 hr. After separation of the catalyst, the filtrate was evaporated into dryness to leave a colorless crystalline product (2.9 g), which was recrystallized from MeOH to give (**3a**), mp 230~250°C (indefinite). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3025, 1680. NMR $\delta_{TMS}^{DMSO\text{-}D_6}$: 2.78 (3H, s, $C_2$–Me), 4.25 (2H, broad, $C_5$–$CH_2$), 7.41~7.74 (3H, aromatic H), 8.01~8.26 (2H, aromatic H), 8.63 (1H, d, $J$=1.5 Hz), 8.76 (1H, d, $J$=1.5 Hz). *Anal.* Found: C, 53.41; H, 5.40; N, 13.28; Cl, 22.36. Calcd. for $C_{14}H_{17}N_3OCl_2$:C, 53.52; H, 5.45; N, 13.37; Cl, 22.56.

*5-Aminomethyl-3-p-methoxybenzoylamino-2-methylpyridine 2HCl* (**3b**)

Mp 250°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1680. NMR $\delta_{TMS}^{DMSO\text{-}d_6}$: 2.78 (3H, s, $C_2$–Me), 3.85 (3H, s, OMe), 4.26 (2H, broad, $C_5$–$CH_2$), 7.07 (2H, d, $J$=8.5 Hz, aromatic H), 8.13 (2H, d, $J$=8.5 Hz, aromatic H), 8.73 (1H, d, $J$=1.5 Hz), 8.85 (1H, d, $J$=1.5 Hz). *Anal.* Found: C, 52.19; H, 5.72; N, 12.06; Cl, 20.61; Calcd. for $C_{15}H_{19}N_3O_2Cl_2$: C, 52.34; H, 5.56; N, 12.21, Cl, 20.60.

*3-Amino-5-aminomethyl-2-methylpyridine 2HCl* (**6**)

A solution of 3-acetylamino-5-cyano-2-methylpyridine (**2c**, 3 g) in MeOH (160 ml) containing conc. HCl (9 ml) was hydrogenated in the presence of 10% Pd–C (4 g). After separation of the catalyst, the filtrate was concentrated to give a pale brown crystalline product. Recrystallization from MeOH afforded 1.99 g of the diamino derivative (**6**), mp 295~296°C (dec.) (lit.[3] dec. 295~297°C). *Anal.* Found: C, 39.87; H, 6.34; N, 19.96; Cl, 33.70. *Calcd.* for $C_7H_{13}N_3Cl_2$: C, 39.99; H, 6.24; N, 20.01; Cl, 33.76.

*3-Benzoylamino-5-hydroxymethyl-2-methylpyridine HCl* (**4a**)

An aqueous solution (16 ml) of $NaNO_2$ (1.0 g) was added at 80°C in 20 min to a solution of 5-aminomethyl compound (**3a**, 3.2 g) in 0.5 N HCl solution (20 ml). The mixture was stirred at 80°C for 1 hr, the solvent was removed to leave a crystalline residue, which was extracted with absolute EtOH several times. The extract was concentrated into a small volume and addition of EtOAc afforded a crystalline product. Recrystallization from the same solvent mixture gave 1.85 g of (**4a**), mp 175~200°C (indefinite). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3325, 1685. NMR $\delta_{TMS}^{D_2O}$: 2.72 (3H, s, $C_2$–Me), 4.87 (2H, s, $C_5$–$CH_2$), 7.55~7.80 (3H, m, aromatic H), 7.80~8.10 (2H, m, aromatic H), 8.55 (2H, broad s, $C_4$ and $C_6$–H). *Anal.* Found: C, 60.31; H, 5.47; N, 10.25; Cl, 12.77. *Calcd.* for $C_{14}H_{15}N_2O_2Cl$: C, 60.33; H, 5.42; N, 10.05; Cl, 12.72.

*3-p-Methoxybenzoylamino-5-hydroxymethyl-2-methylpyridine HCl* (**4b**)

Mp 200~212°C (indefinite) on recrystallization from EtOH-ether. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3350, 3225, 1670. NMR $\delta_{TMS}^{DMSO\text{-}d_6}$: 2.75 (3H, s, $C_2$–Me), 3.85 (3H, s, OMe), 4.70 (2H, s, $C_5$–$CH_2$), 7.06 (2H, d, $J$=8.5 Hz, aromatic H), 8.10 (2H, d, $J$=8.5 Hz, aromatic H), 8.53 (2H, $C_4$ and $C_6$–H). *Anal.* Found: C, 58.60; H, 5.48; N, 9.07; Cl, 11.66. *Calcd.* for $C_{15}H_{17}N_2O_3Cl$: C, 58.35, H, 5.55; N, 9.07; Cl, 11.48.

*3-Amino-5-hydroxymethyl-2-methylpyridine HCl* (**5**)

A solution of 3-benzoylamino compound (**4a**, 1.3 g) in 5 N HCl (60 ml) was refluxed for 5 hr, cooled and shaken with ether. The aqueous layer separated was concentrated into dryness to give a colorless product, which was recrystallized from MeOH to afford 0.63 g of **5**, mp 232~236°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400, 3325, 3210. NMR $\delta_{TMS}^{DMSO\text{-}d_6}$: 2.53 (3H, s, $C_2$–Me), 4.55 (2H, s, $C_5$–$CH_2$), 7.60 (1H, d, $J$=1.5 Hz), 7.77 (1H, d, $J$=1.5 Hz). *Anal.* Found: C, 47.99; H, 6.51; N, 15.94; Cl, 20.47. *Calcd.* for $C_7H_{11}N_2OCl$: C, 48.14; H, 6.35; N, 16.04; Cl, 20.30.

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