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Reactions of Ethyl 3-Ethoxymethylene-2,4-dioxovalerate and Ethyl Ethoxymethyleneoxaloacetate with Indole Analogs[1]

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The reactions of ethyl 3-ethoxymethylene-2,4-dioxovalerate (**1a**) and ethyl ethoxymethyleneoxaloacetate (**1b**) with indole analogs (**2**, **14**, **17**—**19**) are described. Treatment of **1a**, **b** with **2** in ethanol followed by refluxing in acetic anhydride afforded 3,4,10-trisubstituted pyrimido[1,2-*a*]indoles (**4a**, **b**). Hydrogenation or nucleophilic addition of **4a**, **b** was found to occur on the pyrimidine ring in a 1,4-fashion. Compounds **1a**, **b** were also reacted with **14** in ethanol under ice cooling to give the 3,4-disubstituted 9H-pyrimido-[2,3-*b*]indoles (**15a**, **b**) directly. Indole (**17**) or 2-methylindole (**18**) reacted with **1a** (or **1b**) to give a mixture of 3-indolylmethylene derivatives (**20a**, **b** and **21a**, **b**) and tris-(3-indolyl)-methanes (**23** and **24**).

Keywords——ethyl 3-ethoxymethylene-2,4-dioxovalerate; ethyl ethoxymethylene-oxaloacetate; 2-aminoindole; indole; cyclopropane; aziridine; pyrimido[1,2-*a*]indole; 9H-pyrido[2,3-*b*]indole; tris-(3-indolyl)methane

In the course of our studies on the reactivity of ethyl 3-ethoxymethylene-2,4-dioxovalerate (**1a**) and ethyl ethoxymethyleneoxaloacetate (**1b**),[3] we have reported that **1a** is a good reagent for the preparation of certain heterocyclic compounds.[4] We now present some reactions of **1a** and **1b** with indole analogs to give pyrimido[1,2-*a*]indole, 9H-pyrido[2,3-*b*]indole, and tris-(3-indolyl)methane derivatives.

When 2-amino-3-ethoxycarbonylindole (**2**)[5] was treated with an equimolar amount of **1a** in ethanol under ice cooling, ethyl 3-(3-ethoxycarbonyl-2-indolylamino)methylene-2,4-dioxovalerate (**3a**) was isolated in 95% yield. The proton magnetic resonance (PMR) spectrum of **3a** exhibited a vinyl proton at δ 8.72 as a doublet (J=14 Hz) coupled with the NH group. Compound **3a** was readily cyclized by refluxing in acetic anhydride for 30 minutes to provide diethyl 3-acetylpyrimido[1,2-*a*]indole-4,10-dicarboxylate (**4a**) as orange-yellow needles, which showed a pyrimidine ring proton at δ 9.14 as a singlet. On the other hand, cyclization of **3a** in refluxing toluene gave a colorless compound (**5a**) with an empirical formula of $C_{19}H_{20}N_2O_6$. Compound **5a** showed carbonyl absorption bands at 1750 and 1680 cm^{-1}, and a strong absorption band at 3340 cm^{-1} in its infrared (IR) spectrum (KBr), and a signal due to a vinyl proton at δ 7.65 as a doublet (J=6 Hz) coupled with the NH group in its PMR spectrum. The ultraviolet (UV) spectrum of **5a** showed absorption maxima at 256 (log ε 4.05) and 360 (log ε 4.36) nm, which are similar to those of compound **3a**. The structure of **5a** was deduced from these spectral data and finally confirmed by leading **5a** to **4a** by refluxing in acetic anhydride. It is interesting that **4a** reacted with water in dioxane at 50° to give **5a**, and also with methanol or ethanol to give the corresponding 1,4-adduct (**6a** or **7a**). The corresponding diester derivatives (**3b**, **4b**, **5b**, **6b**, and **7b**) were similarly obtained from **1b** by reaction with **2**.

1) A part of this work was reported at the 7th International Congress of Heterocyclic Chemistry, Tampa, Florida, August 1979.
2) Location: *2-10-65, Kawai, Matsubara, Osaka, 580, Japan.*
3) R.G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951).
4) T. Kurihara, H. Shin, and Y. Sakamoto, *Chem. Pharm. Bull.*, **27**, 1792 (1979); T. Kurihara, T. Uno, and Y. Sakamoto, *J. Heterocyclic Chem.*, **17**, 231 (1980).
5) K.L. Munshi, H. Kohl, and H.J. de Souza, *J. Heterocyclic Chem.*, **14**, 1145 (1977).

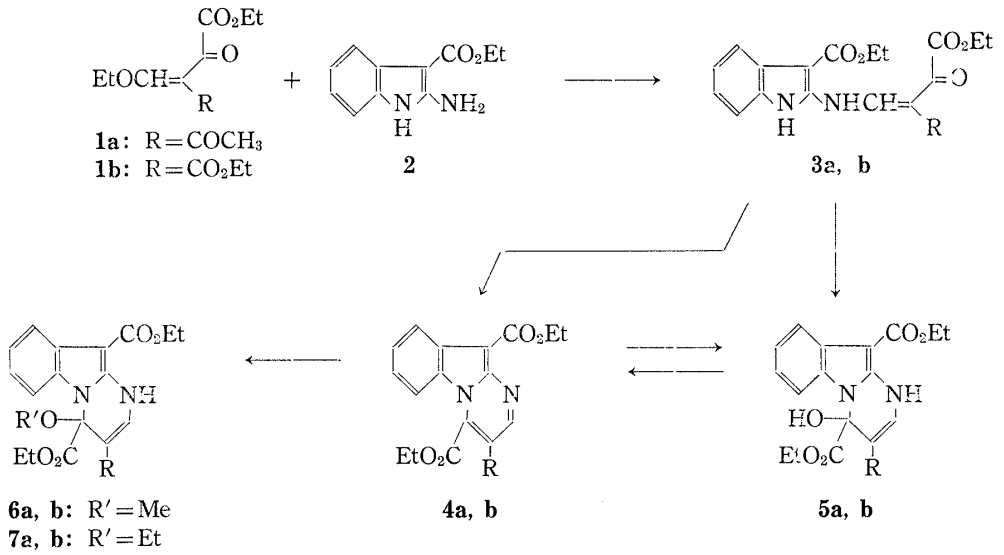


Chart 1

Catalytic hydrogenation of **4a, b** in the presence of 5% palladium on charcoal in dioxane afforded the 1,4-dihydro derivatives (**8a, b**), which were hydrolyzed with potassium hydroxide to give the corresponding carboxylic acids (**9a, b**); these were subsequently oxidized with manganese dioxide to yield 3,10-disubstituted pyrimido[1,2-*a*]indoles (**10a, b**). These compounds were unreactive as regards catalytic hydrogenation or nucleophilic addition.

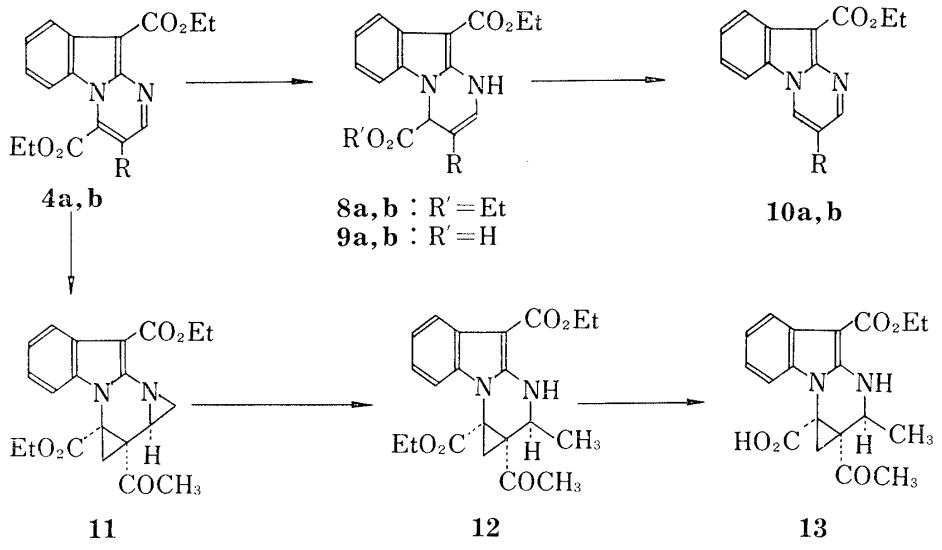


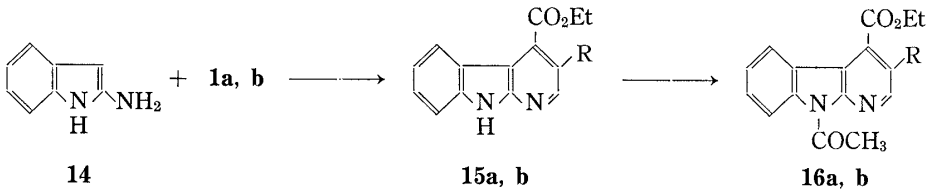
Chart 2

Previously, we reported the reaction of 6-acetyl-7-carbethoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamide with diazomethane in ether under ice cooling to yield 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa[5*a*,6*a*]pyrazolo[1,5-*a*]pyrimidine-3-carboxamide in 89% yield.[6] In contrast to the result obtained for pyrazolopyrimidine **4a** reacted with diazomethane under ice cooling to give a colorless crystalline substance (**11**) whose analytical and PMR data indicated the presence of cyclopropane and aziridine rings; namely signals due to cyclopropane

6) T. Kurihara and Y. Sakamoto, *Heterocycles*, **12**, 397 (1979).

ring protons appeared at δ 0.76 and 2.74 as a doublet with a coupling constant (J) of 7.5 Hz, aziridine ring methylene protons at δ 1.48 and 2.91 as a doublet with $J=6$ Hz and aziridine ring methine proton at δ 3.50 as a triplet with $J=6$ Hz. The irradiation technique has shown that the methylene protons on the aziridine ring do not couple.[7] To confirm this structure, catalytic hydrogenation was carried out under usual conditions to give **12** as a sole product; this showed a new PMR signal due to methyl protons as a doublet resulting from hydrogenolysis of the aziridine ring, and one C_2-proton multiplet at δ 4.50 which collapsed into a quartet on deuterium exchange. Thus, compound **11** was confirmed to be diethyl 2b-acetyl-1,2a,2b,3a-tetrahydro-2H-aziridino[1,2*a*]-3H-cyclopropa[2*b*,3*a*]pyrimido[1,2-*a*]indole-3a,9-dicarboxylate.[8] Reaction of **4b** with diazomethane, however, resulted in the formation of a complex mixture from which no products could be isolated. Hydrolysis of **12** with ethanolic potassium hydroxide gave only the corresponding carboxylic acid (**13**).

When 2-aminoindole (**14**)[9] was treated with **1a, b** in ethanol under ice cooling, a complicated reaction occurred and 9H-pyrido[2,3-*b*]indole derivatives (**15a, b**), which showed a PMR signal at δ 8.30 (1H, doublet of doublets) in the case of **15a**, were isolated in only about 25% yield. Acetylation of **15a, b** with acetic anhydride and acetic acid afforded monoacetates (**16a, b**), which exhibited PMR signals at δ 8.30 and 8.50 (each 1H, each a doublet of doublets) due to C_5- and C_8-protons in the case of **16a**. Thus, compounds **15a, b** were confirmed to be 3,4-disubstituted 9H-pyrido[2,3-*b*]indoles.



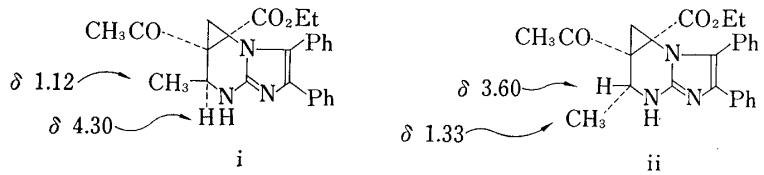
14 **15a, b** **16a, b**

Chart 3

The reactions of **1a, b** with indoles (**17**, **18**, and **19**) were also investigated. Heating of **1a** with an equimolar amount of **17** in ethanol gave a mixture of **20a** and **23** in yields of 12 and 19%, respectively. When **20a** was treated with hydrochloric acid in ethanol, indole-3-carboxaldehyde (**25**) was isolated. Thus, the structure of **20a** was confirmed to be ethyl 3-(3-indolylmethylene)-2,4-dioxovalerate. Product **23** had an empirical formula of $C_{25}H_{19}N_3$, indicating that this compound contains three indole moieties. Its PMR spectrum, which showed signals at δ 6.40 (1H, singlet), δ 6.7—7.5 (15H, multiplet) and δ 10.77 (3H, broad singlet), and its UV spectrum, which is closely related to that of indole itself, are consistent with the structure 23. Finally, **23** was confirmed to be tris-(3-indolyl)methane by direct

7) F.P. Woener, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2786 (1971).

8) The stereochemistry of compound **11** and **12** is proposed to be as follows. We obtained two configurational isomers (i and ii) with respect to the C_6-methyl group; this is an unreported result. In the PMR spectra (DMSO-d_6) of these isomers, the C_6-methine proton of (i) (multiplet which collapsed into a quartet on deuterium exchange) and the C_6-methyl protons of (ii) appeared at lower field than that of (ii) (quartet) and those of (i), respectively, due to the anisotropic effect of the acetyl group located on the same side. Comparing the data for (i) and (ii) with those for **12**, it is proposed that **12** has the same stereostructure as (i). On the basis of this conclusion, the stereostructure of **11** was determined as shown in Chart 2.



i ii

9) R. Pshorr and G. Hoppe, *Chem. Ber.*, **43**, 2543 (1910).

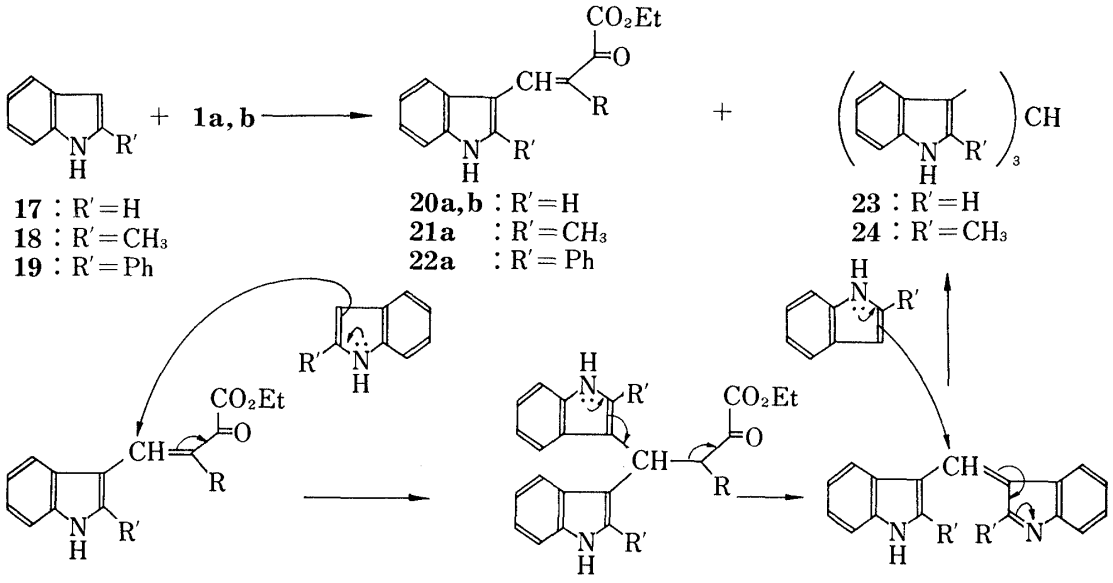


Chart 4

comparison with an authentic sample prepared by the method of Bergman.[10] The yield of **23**, which was also obtained by the reaction of **20a** with indole, was increased to 42% by using two equivalents of indole. Based on these data, a plausible mechanism for the formation of **23** was considered to be as shown in Chart 4.

Similar reactions of **17** with **1b** and of 2-methylindole (**18**) with **1a** were observed. The reaction of 2-phenylindole (**19**) with **1a**, however, was very slow, and only ethyl 3-(2-phenyl-3-indolyl)methylene-2,4-dioxovalerate (**22a**) was isolated in a low yield.

Experimental[11]

Ethyl 3-(3-Ethoxycarbonyl-2-indolylamino)methylene-2,4-dioxovalerate (3a) and Ethyl 3-Ethoxycarbonyl-2-indolylaminomethyleneoxaloacetate (3b)——A solution of 0.01 mol of **1a** (or **1b**) in 10 ml of EtOH was added to a stirred solution of 2.04 g (0.01 mol) of 2-amino-3-ethoxycarbonylindole (**2**) in 60 ml of EtOH with cooling in ice-water. After stirring for 2 hr, the yellow precipitate was collected by filtration, washed with cold EtOH and dried.

3a; Yellow needles of mp 103—104° (from EtOH). Yield: 95%. IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1740 and 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 258 (4.06), 367 (4.25). PMR (DMSO-d_6) δ: 1.30 and 1.37 (each 3H, each t, J=6 Hz, 2×$CH_2\underline{CH_3}$), 2.40 (3H, s, $COCH_3$), 4.25 and 4.36 (each 3H, each q, J=6 Hz, 2×$C\underline{H_2}CH_3$), 7.13—7.96 (4H, m, Ar–H), 8.72 (1H, d, J=14 Hz, CH), 12.66 (1H, bs, NH) and 13.17 (1H, bd, J=14 Hz, NH). *Anal.* Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.42; H, 5.47; N, 7.69.

3b; Yellow needles of mp 191—193° (from EtOH). Yield : 95%. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1755 and 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε): 260 (4.00), 365 (4.33). PMR (DMSO-d_6) δ: 1.0—1.6 (9H, m, 3×$CH_2\underline{CH_3}$), 4.0—4.7 (6H, m, 3×$C\underline{H_2}CH_3$), 7.1—8.05 (4H, m, Ar–H), 9.05 (1H, d, J=23 Hz, CH) and 13.0 (1H, bd, J=23 Hz, NH). *Anal.* Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.90; H, 5.77; N, 6.94.

Diethyl 3-Acetylpyrimido[1,2-*a*]indole-4,10-dicarboxylate (4a) and Triethyl Pyrimido[1,2-*a*]indole-3,4,10-tricarboxylate (4b)——A solution of 0.005 mol of **3a** (or **3b**) in 50 ml of acetic anhydride was refluxed for 30 min. After concentration *in vacuo*, the residue was extracted with anhydrous hot ligroin. The extract was cooled to yield orange-yellow needles of **4a** or **4b**, which were recrystallized from ligroin.

4a; mp 105—106°. Yield: 27%. IR λ_{max}^{KBr} cm^{-1}: 1740 and 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε): 238 (4.32), 244 (4.32), 300 (4.38), 307 (4.44), 350 (4.08) and 360 (4.06). PMR ($CDCl_3$) δ: 1.50 (6H, t, J=6 Hz, 2×$CH_2\underline{CH_3}$), 2.70 (3H, s, $COCH_3$), 4.56 and 4.75 (each 2H, each q, J=6 Hz, 2×$C\underline{H_2}CH_3$), 7.3—7.83 (3H, m, Ar–H), 8.57 (1H, dd, J=8 and 3 Hz, C_9–H) and 9.14 (1H, s, C_2–H). *Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.46; H, 5.00; N, 7.70.

10) J. Bergman, *J. Heterocyclic Chem.*, **8**, 329 (1971).

11) All melting points are uncorrected. IR spectra were measured on a JASCO IRA-1 machine, UV spectra on a Shimadzu UV-200 spectrophotometer, PMR spectra on a Hitachi R-24A spectrometer, using tetramethylsilane as an internal standard, and mass spectra (MS) on a Hitachi RMU-7L spectrometer.

4b; mp 110—112°. Yield: 24%. IR ν_{max}^{KBr} cm^{-1}: 1750, 1720 and 1680 (C=O). PMR ($CDCl_3$) δ: 1.34—2.67 (9H, m, $3\times CH_2C\underline{H}_3$), 4.31—4.90 (6H, m, $3\times C\underline{H}_2CH_3$), 8.60 (1H, dd, $J=8$ and 3 Hz, C_9–H) and 9.20 (1H, s, C_2–H). *Anal.* Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.41; H, 5.04; N, 7.51.

Diethyl 3-Acetyl-1,4-dihydro-4-hydroxypyrimido[1,2-*a*]indole-4,10-dicarboxylate (5a) and Triethyl 1,4-Dihydro-4-hydroxypyrimido[1,2-*a*]indole-3,4,10-tricarboxylate (5b)——Method a: A solution of 1 mmol of **3a** (or **3b**) in 100 ml of dry toluene was refluxed for 5 hr. After concentration *in vacuo*, the crystalline residue was recrystallized from benzene to afford **5a** (or **5b**).

5a; Colorless crystals of mp 175—177°. Yield: 84%. IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1750 and 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε): 256 (4.05), 360 (4.36). PMR ($CDCl_3$) δ: 1.08 and 1.45 (each 3H, each t, $J=6$ Hz, $2\times CH_2C\underline{H}_3$), 2.32 (3H, s, $COCH_3$), 4.05—4.56 (4H, m, $2\times C\underline{H}_2CH_3$), 5.63 (1H, s, OH), 7.65 (1H, d, $J=6$ Hz, C_2–H) and 9.76 (1H, bd, $J=6$ Hz, NH). *Anal.* Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.39; H, 5.14; N, 7.61.

5b; Colorless crystals of mp 182—184°. Yield: 87%. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1760, 1690 and 1655 (C=O). PMR ($CDCl_3$) δ: 1.10, 1.31 and 1.45 (each 3H, each t, $J=6$ Hz, $3\times CH_2C\underline{H}_3$), 4.10—4.60 (6H, m, $3\times C\underline{H}_2CH_3$), 5.46 (1H, s, OH), 7.80 (1H, d, $J=6$ Hz, C_2–H) and 9.63 (1H, bd, $J=6$ Hz, NH). *Anal.* Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.78; H, 5.40; N, 6.97.

Method b: A solution of 1 mmol of **3a** (or **3b**) in 20 ml of acetic anhydride was refluxed for 30 min. After concentration *in vacuo*, the residue was dissolved in 20 ml of 85% aqueous dioxane and this solution was refluxed for 10 min. Removal of the solvent gave crystals of **5a** (0.253 g, 68%) and **5b** (0.29 g, 72%). Their IR spectra were identical with those of the samples obtained by Method a.

Reaction of 4a, b with Alcohols——A solution of 0.1 mmol of **4a** (or **4b**) in 20 ml of alcohol (MeOH or EtOH) was refluxed for 30 min. After removal of the solvent by evaporation, the residue was recrystallized from an appropriate solvent to afford **6a, b** or **7a, b** in 75—80% yields (Table I).

Diethyl 3-Acetyl-1,4-dihydro-4-methoxypyrimido[1,2-*a*]indole-4,10-dicarboxylate (6a)——IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1760 and 1670 (C=O). UV λ_{max}^{EtOH} nm (log ε): 255 (3.78), 358 (4.15). PMR ($CDCl_3$) δ: 1.16 and 1.45 (each 3H, each t, $J=6$ Hz, $2\times CH_2C\underline{H}_3$), 2.40 (3H, s, $COCH_3$), 3.00 (3H, s, OCH_3), 4.06—4.57 (4H, m, $2\times C\underline{H}_2CH_3$), 7.95 (1H, d, $J=6$ Hz, C_2–H) and 9.70 (1H, bd, $J=6$ Hz, NH).

Triethyl 1,4-Dihydro-4-methoxypyrimido[1,2-*a*]indole-3,4,10-tricarboxylate (6b)——IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1770 and 1690 (C=O). PMR ($CDCl_3$) δ: 1.15, 1.32 and 1.46 (each 3H, each t, $J=6$ Hz, $3\times CH_2C\underline{H}_3$), 3.03 (3H, s, OCH_3), 4.03—4.56 (6H, m, $3\times C\underline{H}_2CH_3$) and 9.48 (1H, bd, $J=6$ Hz, NH).

Diethyl 3-Acetyl-1,4-dihydro-4-ethoxypyrimido[1,2-*a*]indole-4,10-dicarboxylate (7a)——IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1760 and 1670 (C=O). PMR ($CDCl_3$) δ: 1.03, 1.10 and 1.45 (each 3H, each t, $J=6$ Hz, $3\times CH_2C\underline{H}_3$), 3.00 (2H, q, $J=6$ Hz, $C\underline{H}_2CH_3$), 4.02—4.55 (4H, m, $2\times C\underline{H}_2CH_3$), 7.93 (1H, d, $J=6$ Hz, C_2–H) and 9.70 (1H, bd, $J=6$ Hz, NH).

Triethyl 1,4-Dihydro-4-ethoxypyrimido[1,2-*a*]indole-3,4,10-tricarboxylate (7b)——IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1760 and 1680 (C=O). PMR ($CDCl_3$) δ: 1.0—1.56 (12H, m, $4\times CH_2C\underline{H}_3$), 2.75—3.60 (4H, m, $2\times C\underline{H}_2CH_3$), 4.10—4.56 (4H, m, $2\times C\underline{H}_2CH_3$) and 9.50 (1H, bd, $J=6$ Hz, NH).

Catalytic Hydrogenation of 4a, b——A solution of 0.1 mol of **4a** (or **4b**) in 30 ml of dioxane was shaken with H_2 over 0.2 g of 5% Pd-C for 3 hr using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo* to afford **8a** (or **8b**) as colorless crystals, which were recrystallized from an appropriate solvent in 65% (or 68%) yield (Table I).

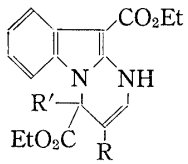
Diethyl 3-Acetyl-1,4-dihydropyrimido[1,2-*a*]indole-4,10-dicarboxylate (8a)——IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1715 and 1690 (C=O). UV λ_{max}^{EtOH} nm (log ε): 260 (3.85), 365 (4.21). PMR ($CDCl_3$) δ: 1.20 and 1.43 (each 3H, each t, $J=6$ Hz, $2\times CH_2C\underline{H}_3$), 2.35 (3H, s, $COCH_3$), 4.17 and 4.42 (each 2H, each q, $J=6$ Hz, $2\times C\underline{H}_2CH_3$), 6.05 (1H, s, C_4–H), 7.66 (1H, d, $J=6$ Hz, C_2–H) and 9.33 (1H, bd, $J=6$ Hz, NH).

Triethyl 1,4-Dihydropyrimido[1,2-*a*]indole-3,4,10-tricarboxylate (8b)——IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1730 and 1690 (C=O). PMR (DMSO-d_6) δ: 1.09, 1.26 and 1.38 (each 3H, each t, $J=6$ Hz, $3\times CH_2C\underline{H}_3$), 4.05, 4.18 and 4.35 (each 2H, each q, $J=6$ Hz, $3\times C\underline{H}_2CH_3$), 5.92 (1H, s, C_4–H), 7.63 (1H, d, $J=6$ Hz, C_2–H) and 10.20 (1H, bd, $J=6$ Hz, NH).

3-Acetyl-1,4-dihydro-10-ethoxycarbonylpyrimido[1,2-*a*]indole-4-carboxylic Acid (9a)——A solution of 1.5 g of **8a** and 0.47 g of KOH in 150 ml of absolute EtOH was refluxed for 7 hr. After cooling, the resulting precipitate was collected and dissolved in 5 ml of H_2O. Acidification of the aqueous solution by the addition of 5% HCl precipitated 0.98 g (71%) of **9a**, mp 223—226° (dec.) (from H_2O). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1740 and 1670 (C=O). PMR (DMSO-d_6) δ: 1.39 (3H, t, $J=6$ Hz, $CH_2C\underline{H}_3$), 2.33 (3H, s, $COCH_3$), 4.37 (2H, q, $J=6$ Hz, $C\underline{H}_2CH_3$), 5.93 (1H, s, C_4–H), 7.78 (1H, d, $J=6$ Hz, C_2–H) and 10.30 (1H, bd, $J=6$ Hz, NH). *Anal.* Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.95; H, 4.92; N, 8.55.

1,4-Dihydro-3,10-diethoxycarbonylpyrimido[1,2-*a*]indole-4-carboxylic Acid (9b)——A solution of 2.60 g of **8b** and 0.768 g of KOH in 200 ml of absolute EtOH was treated as described for the preparation of **9a** to afford 1.824 g (77%) of **9b**, mp 160—162° (dec.) (from DMF–H_2O). IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1740 and 1640 (C=O). PMR (DMSO-d_6) δ: 1.26 and 1.47 (each 3H, each t, $J=6$ Hz, $2\times CH_2C\underline{H}_3$), 4.20 and 4.35 (each 2H, each q, $J=6$ Hz, $2\times C\underline{H}_2CH_3$), 5.85 (1H, s, C_4–H), 7.63 (1H, d, $J=6$ Hz, C_2–H) and 10.23 (1H, bd, $J=6$ Hz, NH). *Anal.* Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.27; H, 4.98; N, 8.10.

Table I. 1,4-Dihydropyrimido[1,2-*a*]indole Derivatives



Compd. No.	R	R′	mp (°C) Recryst. solv.	Formula	Analyses (%) Calcd (Found) C	H	N
6a	$COCH_3$	OCH_3	190—192 (EtOH)	$C_{20}H_{22}N_2O_6$	62.16 (61.70	5.74 5.78	7.25 7.25)
6b	$CO_2C_2H_5$	OCH_3	150—151 (MeOH)	$C_{21}H_{24}N_2O_7$	60.56 (60.54	5.81 5.67	6.73 6.55)
7a	$COCH_3$	OC_2H_5	196—198 (EtOH)	$C_{21}H_{24}N_2O_6$	62.99 (62.93	6.04 6.03	7.00 7.11)
7b	$CO_2C_2H_5$	OC_2H_5	138—139 (EtOH)	$C_{22}H_{26}N_2O_7$	61.38 (61.48	6.09 6.30	6.57 6.33)
8a	$COCH_3$	H	195—197 (benzene)	$C_{19}H_{20}N_2O_5$	64.03 (64.26	5.66 5.40	7.86 7.99)
8b	$CO_2C_2H_5$	H	154—155 (ligroin)	$C_{20}H_{22}N_2O_6$	62.16 (62.43	5.74 5.49	7.25 7.51)

Ethyl 3-Acetylpyrimido[1,2-*a*]indole-10-carboxylate (10a)——A suspension of 0.98 g of **9a** and 1.30 g of manganese dioxide (MnO_2) in 20 ml of DMF was stirred overnight at room temperature. MnO_2 was filtered off and the filtrate was concentrated *in vacuo*. The crystalline residue was recrystallized from EtOH to give 0.53 g (63%) of **10a**, mp 203—205°, as orange-yellow needles. IR ν_{max}^{KBr} cm^{-1}: 1695 and 1680 (C=O). PMR (DMSO-d_6) δ: 1.40 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.67 (3H, s, $COCH_3$), 4.38 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 9.50 (1H, d, C_2–H) and 10.50 (1H, d, J=3 Hz, C_4–H). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.87; H, 4.92; N, 9.71.

Diethyl Pyrimido[1,2-*a*]indole-3,10-dicarboxylate (10b)——A solution of 1 g of **9b** and 1.2 g of MnO_2 in 30 ml of DMF was treated as described for the preparation of **10a** to afford 0.677 g (78%) of **10b**, mp 147—148° (from EtOH), as orange-yellow needles. IR ν_{max}^{KBr} cm^{-1}: 1700 and 1670 (C=O). PMR ($CDCl_3$) δ: 1.46 and 1.51 (each 3H, each t, J=6 Hz, 2×$CH_2C\underline{H}_3$), 4.45 and 4.53 (each 2H, each q, J=6 Hz, 2×$C\underline{H}_2CH_3$), 9.10 (1H, d, J=3 Hz, C_2–H) and 9.32 (1H, d, J=3 Hz, C_4–H). *Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.98. Found: C, 65.33; H, 5.10; N, 8.74.

Diethyl 2b-Acetyl-1,2a,2b,3a-tetrahydro-2H-aziridino[1,2*a*]-3H-cyclopropa[2*b*,3*a*]pyrimido[1,2-*a*]indole-3a,9-dicarboxylate (11)——Compound **4a** (1.27 g) was added to 50 ml of an ethereal solution containing excess diazomethane with cooling in ice-water, and the suspension was stirred overnight. The precipitate was collected and recrystallized from EtOH to give 0.573 g (30%) of **11**, mp 180—181°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1720 and 1700 (C=O). PMR ($CDCl_3$) δ: 0.76 and 2.74 (each 1H, each d, J=7.5 Hz, NCH_2), 1.16 and 1.43 (each 3H, each t, J=6 Hz, 2×$CH_2C\underline{H}_3$), 1.48 and 2.91 (each 1H, each d, J=6 Hz, CH_2), 2.43 (3H, s, $COCH_3$), 3.50 (1H, t, J=6 Hz, CH) and 4.06—4.60 (4H, m, 2×$C\underline{H}_2CH_3$). *Anal.* Calcd for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 65.70; H, 5.75; N, 7.46.

Diethyl 2a-Acetyl-2-methyl-1,2a,2b,3a-tetrahydro-3H-cyclopropa[2*a*,3*a*]pyrimido[1,2-*a*]indole-3a,9-dicarboxylate (12)——A solution of 0.5 g of **11** in 200 ml of EtOH was shaken with H_2 over 0.2 g of 5% Pd-C for 6 hr using Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo* to afford **12** (0.448 g, 88%), mp 126—127° (from ligroin), as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3380 (NH), 1730 and 1660 (C=O). PMR (DMSO-d_6) δ: 0.95 and 1.32 (each 3H, each t, J=6 Hz, 2×$CH_2C\underline{H}_3$), 1.70 and 2.36 (each 1H, each d, J=7 Hz, CH_2), 2.30 (3H, s, $COCH_3$), 3.97 and 4.23 (each 2H, each q, J=6 Hz, 2×$C\underline{H}_2CH_3$) and 4.50 (1H, m, $C\underline{H}CH_3$). *Anal.* Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.74; H, 6.37; N, 7.41.

2a-Acetyl-9-ethoxycarbonyl-2-methyl-1,2a,2,3a-tetrahydro-3H-cyclopropa[2*a*,3*a*]pyrimido[1,2-*a*]indole-3a-carboxylic Acid (13)——A solution of 0.2 g of **12** and 0.035 g of KOH in 50 ml of 95% EtOH was stirred for 5 hr. Concentration *in vacuo* left a yellow solid, which was dissolved in 5 ml of H_2O. Acidification of the aqueous solution by the addition of 5% HCl precipitated 0.117 g (64%) of yellow crystals of **13**, mp 121—124° (dec.) (from H_2O). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1730 and 1640 (C=O). PMR (DMSO-d_6) δ: 1.08 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 1.33 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 1.62 and 2.33 (each 1H, each d, J=6 Hz, CH_2), 2.27 (3H,

s, $COCH_3$), 4.27 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$) and 4.50 (1H, m, $C\underline{H}CH_3$). *Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.34; H, 5.19; N, 8.18.

Ethyl 3-Acetyl-9H-pyrimido[2,3-*b*]indole-4-carboxylate (15a) and Diethyl 9H-Pyrimido[2,3-*b*]indole-3,4-dicarboxylate (15b)——A solution of 0.01 mol of **1a** (or **1b**) in 10 ml of EtOH was added to a stirred solution of 1.32 g (0.01 mol) of **14** in 40 ml of EtOH with cooling in ice-water. After stirring for 2 hr, the yellow precipitate was collected by filtration, washed with cold EtOH and dried.

15a; Yellow needles of mp 198—199° (from EtOH). Yield: 28%. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1740 and 1680 (C=O). PMR (DMSO-d_6) δ: 1.34 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.70 (3H, s, $COCH_3$), 4.36 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 7.20—7.68 (3H, m, Ar–H), 8.30 (1H, dd, J=8 and 3 Hz, C_5–H), 9.17 (1H, s, C_2–H) and 12.46 (1H, bs, NH). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.22; H, 4.86; N, 10.12.

15b; Yellow needles of mp 163—165° (from EtOH). Yield: 25%. IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 1730 and 1635 (C=O). PMR (DMSO-d_6) δ: 1.33 (6H, t, J=6 Hz, 2×$CH_2C\underline{H}_3$), 4.35 (4H, q, J=6 Hz, 2×$C\underline{H}_2CH_3$), 8.35 (1H, dd, J=8 and 3 Hz, C_5–H), 9.07 (1H, s, C_2–H) and 12.65 (1H, bs, NH). *Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.20; H, 5.19; N, 8.82.

Ethyl 3,9-Diacetyl-9H-pyrimido[2,3-*b*]indole-4-carboxylate (16a) and Diethyl 9-Acetyl-9H-pyrimido-[2,3-*b*]indole-3,4-dicarboxylate (16b)——A solution of 0.25 g of **15a** (or **15b**) in a mixture of 4.5 ml of acetic anhydride and 1 ml of acetic acid was refluxed for 1 hr. After concentration *in vacuo*, the residue was recrystallized from an appropriate solvent to afford **16a** (or **16b**).

16a; Colorless crystals of mp 203—204° (from MeOH). Yield: 59%. IR ν_{max}^{KBr} cm^{-1}: 1740 and 1700 (C=O). PMR (DMSO-d_6) δ: 1.32 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.68 (3H, s, $COCH_3$), 3.11 (3H, s, $NCOCH_3$), 4.35 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 7.35—7.75 (2H, m, Ar–H), 8.30 (1H, dd, J=8 and 3 Hz, C_5–H), 8.54 (1H, dd, J=8 and 3 Hz, C_8–H) and 9.12 (1H, s, C_2–H). *Anal.* Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.61; H, 4.80; N, 8.61.

16b; Colorless crystals of mp 96—98° (from EtOH). Yield: 91%. IR ν_{max}^{KBr} cm^{-1}: 1740 and 1705 (C=O). PMR (DMSO-d_6) δ: 1.35 (6H, t, J=6 Hz, 2×$CH_2C\underline{H}_3$), 2.97 (3H, s, $NCOCH_3$), 4.40 (4H, q, J=6 Hz, 2×$C\underline{H}_2CH_3$), 7.30—7.73 (2H, m, Ar–H), 8.30 (1H, dd, J=8 and 3 Hz, C_5–H), 8.50 (1H, dd, J=8 and 3 Hz, C_8–H) and 9.00 (1H, s, C_2–H). *Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.45; H, 4.86; N, 8.07.

Reaction of 1a with Indole (17)——A mixture of 5.49 g of **1a** and 3 g of **17** in 60 ml of EtOH was refluxed for 5 hr. The solid that formed upon cooling was collected by filtration and recrystallized from EtOH to afford 1.76 g (19%) of tris-(3-indolyl)methane (**23**) of mp 254—255° (lit.[12] 254—256°) as colorless needles. PMR (DMSO-d_6) δ: 6.40 (1H, s, CH), 6.70—7.45 (15H, m, Ar–H) and 10.77 (3H, s, 3×NH). MS *m/e*: 361 (M^+). *Anal.* Calcd for $C_{25}H_{19}N_3$: C, 83.07; H, 5.30; N, 11.63. Found: C, 83.35; H, 5.51; N, 11.62. The filtrate was concentrated *in vacuo* to give a semi-solid, which was agitated with benzene. The resulting precipitate was recrystallized from benzene to afford 0.91 g (12%) of ethyl 3-(3-indolylmethylene)-2,4-dioxovalerate (**20a**) of mp 78—80° as yellow needles. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1740 (C=O). UV λ_{max}^{EtOH} nm (log ε): 276 (4.10), 282 (4.07) and 410 (4.35). PMR (DMSO-d_6) δ: 1.25 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.60 (3H, s, $COCH_3$), 4.20 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 7.20—8.0 (4H, m, Ar–H), 8.37 (1H, s, CH) and 8.66 (1H, s, C_2–H). *Anal.* Calcd for $C_{16}H_{15}NO_4 \cdot 1/2$ benzene: C, 70.36; H, 5.59; N, 4.32. Found: C, 70.47; H, 5.37; N, 4.51.

Reaction of 1b with Indole (17)——A solution of 1.7 g of **1b** and 1 g of **17** was treated as described for **1a** to give a mixture of **23** (15%) and 0.44 g (16%) of diethyl 3-indolylmethyleneoxaloacetate (**20b**) of mp 124—125° (from benzene) as yellow needles. IR ν_{max}^{KBr} cm^{-1}: 3380 (NH), 1720 and 1700 (C=O). PMR (DMSO-d_6) δ: 1.10—1.44 (6H, m, 2×$CH_2C\underline{H}_3$), 4.06—4.46 (4H, m, 2×$C\underline{H}_2CH_3$), 7.20—7.80 (4H, m, Ar–H), 8.30 (1H, s, CH) and 8.50 (1H, s, C_2–H). *Anal.* Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.43. Found: C, 65.04; H, 5.19; N, 4.53.

Reaction of 1a with 2-Methylindole (18)——A mixture of 1.63 g of **1a** and 1 g of **18** in 30 ml of EtOH was refluxed for 18 hr. The solid that formed upon cooling to room temperature was collected by filtration and recrystallized from DMF–H_2O to afford 0.24 g (8%) of tris-3-(2-methylindolyl)methane (**24**) of mp 320—321° (lit.[10] 319—320°) as colorless needles. PMR (DMSO-d_6) δ: 1.93 (9H, s, 3×CH_3), 6.10 (1H, s, CH), 6.50—7.30 (12H, m, Ar–H) and 10.75 (3H, s, 3×NH). *Anal.* Calcd for $C_{28}H_{25}N_3$: C, 83.34; H, 6.25; N, 10.41. Found: C, 83.11; H, 6.30; N, 10.23. The filtrate was concentrated *in vacuo* to give a semi-solid, which was agitated with EtOH. The resulting solid was recrystallized from EtOH to give 1.74 g (46%) of ethyl 3-(2-methyl-3-indolylmethylene)-2,4-dioxovalerate (**21a**) of mp 185—187° as orange-red needles. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1740 (C=O). PMR (DMSO-d_6) δ: 1.25 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3), 2.55 (3H, s, $CO\text{-}CH_3$), 4.23 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 7.0—7.50 (4H, m, Ar–H) and 8.16 (1H, s, CH). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.14; H, 5.63; N, 4.96.

Reaction of 1a with 2-Phenylindole (19)——A mixture of 1.1 g of **1a** and 1 g of **19** in 30 ml of EtOH was refluxed for 13 hr. **19** formed upon cooling in ice-water was recovered by filtration, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with benzene, to afford 0.85 g (41%) of ethyl 3-(2-phenyl-3-indolylmethylene)-2,4-dioxovalerate (**22a**) of mp 124—125°

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(from benzene–ligroin) as orange-red needles. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1735 (C=O). PMR (DMSO-d_6) δ: 1.20 (3H, t, $J=6$ Hz, $CH_2C\underline{H}_3$), 2.33 (3H, s, $COCH_3$), 4.25 (2H, q, $J=6$ Hz, $C\underline{H}_2CH_3$), 7.20—7.50 (9H, m, Ar–H) and 7.95 (1H, s, CH). *Anal.* Calcd for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.88. Found: C, 73.28; H, 5.36; N, 4.04.

Reaction of 20a with Hydrochloric Acid in Ethanol——A solution of 0.5 g of **20a** in 30 ml of EtOH including a few drops of conc. HCl was refluxed for 1 hr. After concentration *in vacuo*, the dark brown residue was subjected silica gel column chromatography, eluting with $CHCl_3$. From the first eluate, indole-3-carboxaldehyde was obtained as colorless crystals (15 mg, mp 195—196°, lit., 195—198°).

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