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Synthesis of Imidazo[4,5-*e*]-*as*-triazine(6-Azapurine)Derivatives

Synthesis of some derivatives in the novel ring system, imidazo[4,5-*e*-*as*]-triazine(6-azapurine) (Va–f), has been described. 2-Benzyl-6-bromo-*as*-triazine-3,5(2*H*, 4*H*)-dione (1-benzyl-5-bromo-6-azauracil)(I) reacted smoothly with ammonia and benzylamine, to give 6-amino-(IIa) and 6-benzylamino-2-benzyl-*as*-triazine-3,5(2*H*, 4*H*)-dione(IIb) respectively. Selective thionation of these amino derivatives(IIa,b), by heating with phosphorus pentasulphide in pyridine, to lead to 6-amino-(IIIa) and 6-benzylamino-2-benzyl-*as*-triazin-3(2*H*)-one-5(4H)-thione(IIIb), effectively proceeded, and subsequent aminodethiolation of the latter (IIIa,b) also readily went on to afford 5,6-diamino-(IVa), 5-amino-6-benzylamino-(IVb), 5-benzylamino-6-amino-(IVc), and 5,6-dibenzylamino-2-benzyl-*as*-triazin-3(2*H*)-one (IVd).

An oxidative mode of cyclisation, by heating with ethyl orthoformate or benzaldehyde in nitrobenzene under reflux for a few hours, furnished a successful procedure for the preparation of 2-benzyl-5*H*-(Va) and 2,5-dibenzyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one(Vb), or 2-benzyl-5*H*-(Vc), 2,5-dibenzyl-(Vd), and 2,7-dibenzyl-6-phenyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (Ve), respectively. An attempted benzylation of Vc yielded a mixture of the products which consisted of Vd, as a minor component, and the alternative isomer assigned tentatively to 2,4-dibenzyl-6-phenyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one(Vf), as a major one, however, it was not contaminated with any isolable amount of Ve.

Studies on 2-aza- and 8-azapurine derivatives,[1] for potential antimetabolites or the chemistry *per se*, have recently attracted the attention of very numerous laboratories, but to our best knowledge, any report concerned with 6-aza analogue of purine has not yet been found. Notable biological activities of some compounds in the aza analogues of purine[2] and pteridine,[3] further, isolation of a naturally occurring pigment, a compound belonging to the pyrazolo[4,3-*e*]-*as*-triazine,[4] prompted us to report the synthesis of some derivatives in the novel ring system of imidazo[4,5-*e*]-*as*-triazine(6-azapurine) (Va—f).[5]

2-Benzyl-5,6-diamino-*as*-triazin-3(2*H*)-one (IVa: R=$C_6H_5CH_2$, R′=R″=H) was heated with an excess of ethyl orthoformate in nitrobenzene under reflux for 5 hours, to afford 2-benzyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (Va) (R=$C_6H_5CH_2$, R′=R″=H: mp 263—264°, colourless needles, IR ν_{max}^{KBr} cm^{-1}: 1640 (>N–CO), 3200 (NH), NMR (in CF_3CO_2D) τ: 0.72 (1H, s, C^6–H), 2.52 (5H, s, C_6H_5), 4.32 (2H, s, >N–CH_2–C_6H_5), 72% yield, *Anal.* Calcd. for $C_{11}H_9ON_5$: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.18; H, 4.00; N, 30.54). The amine IVa also reacted smoothly with benzaldehyde, in a similar reaction condition, to give 2-benzyl-6-phenyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (Vc) (R=$C_6H_5CH_2$, R′=H, R″=C_6H_5:mp>300°, colourless needles, IR ν_{max}^{KBr} cm^{-1}: 1640 (>N–CO), 3380 (NH), UV λ_{EtOH}^{max} nm (log ε): 256 (4.11),

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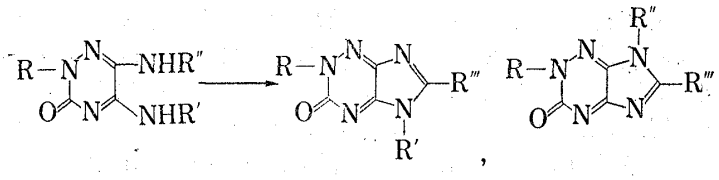
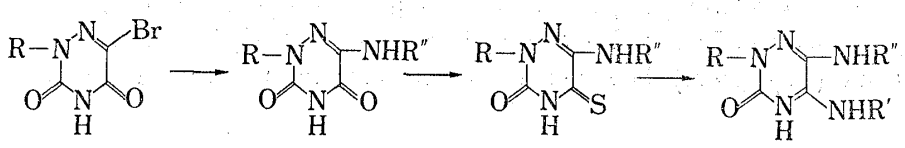
316 (4.42), NMR (in CF_3CO_2D) τ: 1.46—2.25 (5H, m, C_6H_5), 2.51 (5H, s, C_6H_5), 4.36 (2H, s, >N–CH_2–C_6H_5), 77% yield, *Anal.* Calcd. for $C_{17}H_{13}ON_5$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.08; H, 4.22; N, 23.11). This type of ring closure, an oxidative mode of cyclisation, was applied to the benzylamines, IVb (R=R′=$C_6H_5CH_2$, R″=H) and IVc (R=R″=$C_6H_5CH_2$, R′=H), to embody the formation of 2,5-dibenzyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (Vb) (R=R′=$C_6H_5CH_2$, R‴=H: mp 162°, colourless needles, IR ν_{max}^{KBr} cm^{-1}: 1660 (>N–CO), NMR (in $CDCl_3$) τ: 1.89 (1H, s, C^6–H), 2.25—2.75 (10H, m, $C_6H_5\times2$), 4.53 (2H, s, >N–CH_2–C_6H_5), 4.84 (2H, s, >N–CH_2–C_6H_5), 38% yield, *Anal.* Calcd. for $C_{18}H_{15}ON_5$: C, 68.13; H, 4.76; N, 22.07. Found: C, 67.95; H, 4.65; N, 21.94), 2,5-dibenzyl-6-phenyl-imidazo[4,5-e]-*as*-triazin-3(2H)-one (Vd) (R=R′=$C_6H_5CH_2$, R‴=C_6H_5: mp 186—187°, colourless needles, IR ν_{max}^{KBr} cm^{-1}: 1670 (>N–CO), UV λ_{max}^{EtOH} nm (log ε): 262 (4.26), 290 (4.18), 369 (3.98), NMR (in $CDCl_3$) τ: 2.08—3.00 (15H, m, $C_6H_5\times3$), 4.49 (2H, s, >N–CH_2–C_6H_5), 4.65 (2H, s, >N–CH_2–C_6H_5), 41% yield, *Anal.* Calcd. for $C_{24}H_{19}ON_5$: C, 73.27; H, 4.87; N, 17.80. Found: C, 73.07; H, 4.80; N, 17.73), and 2,7-dibenzyl-6-phenyl-imidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one (Ve) (R=R″=$C_6H_5CH_2$, R‴=C_6H_5: mp 223°, pale yellow needles, IR ν_{max}^{KBr} cm^{-1}: 1628 (>N–CO), UV λ_{max}^{KBr} nm (log ε): 257 sh (3.66), 315 (4.27), NMR (in CF_3CO_2D) τ: 1.58—2.92 (15H, m, $C_6H_5\times3$), 4.20 (2H, s, >N–CH_2–C_6H_5), 4.36 (2H, s, >N–CH_2–C_6H_5), 51% yield, *Anal.* Calcd. for $C_{24}H_{19}ON_5$: C, 73.27; H, 4.87; N, 17.80. Found: C, 73.34; H, 4.92; N, 17.94), respectively.



IVa–c Va–d Ve

Fig. 1

An appropriate synthetic approach to the amines (IVa—c), promising to build up the imidazo[4,5-*e*]-*as*-triazine ring, or the like, has been presumably sought but remained as yet unsettled for these several years. The synthetic scheme presented here consists of three steps: (i) Aminodebromination of 2-benzyl-6-bromo-*as*-triazine-3,5(2*H*, 4*H*)-dione (I); (ii) Selective thionation of 6-amino-(IIa) and 6-benzylamino-2-benzyl-*as*-triazine-3,5(2*H*, 4*H*)-dione (IIb) to 6-amino-(IIIa) and 6-benzylamino-2-benzyl-*as*-triazin-3(2*H*)-one-5(4*H*)-thione (IIIb), respectively; (iii) Aminodethiolation of the thiones (IIIa, b) to the 5,6-diamino-2-benzyl-*as*-triazin-3(2*H*)-ones (IVa—d). I (mp 187°)[6] was converted, by heating with aqueous



I IIa,b IIIa,b IVa–d

Fig. 2

ammonia, in the presence of catalytic amount of copper, under pressure, to IIa (R=$C_6H_5CH_2$, R″=H: mp 291—292°, colourless crystals, IR ν_{max}^{KBr} cm^{-1}: 1670 (>N–CO), 1705 (>N–CO), 3280, 3430 (NH_2), NMR (in DMSO-d_6) τ: 2.61 (5H, s, C_6H_5), 3.77 (2H, s, NH_2), 5.09 (2H, s, >N–CH_2–C_6H_5), 91% yield) and with benzylamine to IIb (R=R″=C_6H_5–CH_2: mp 224—225°, colourless needles, IR ν_{max}^{KBr} cm^{-1}: 1660 (>N–CO), 1705 (>N–CO), 3360 (NH), NMR (in DMSO-

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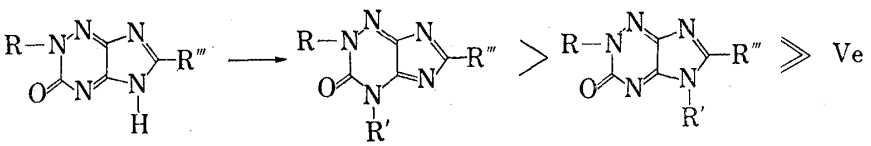
d_6) τ: 2.68 (10H, s, $C_6H_5\times2$), 5.18 (2H, s, >N–CH_2–C_6H_5), 5.70 (2H, d, –NH–CH_2–C_6H_5, J=6 Hz), 45% yield), respectively. Selective thionation[6-9] of IIa was effected by heating with phosphorus pentasulphide in dry pyridine for 1.5 hours, followed by a proper working up, to give IIIa (R=$C_6H_5CH_2$, R″=H: mp 216°, yellow needles, IR ν_{max}^{KBr} cm^{-1}: 1665 (>N–CO), 3280, 3380 (NH_2), UV λ_{EtOH}^{max} nm (log ε): 249 (3.79), 316 (3.89), 358 (3.90), NMR (in DMSO-d_6) τ: 2.59 (5H, s, C_6H_5), 3.73 (2H, s, NH_2), 5.03 (2H, s, >N–CH_2–C_6H_5), 64% yield, *Anal.* Calcd. for $C_{10}H_{10}ON_4S$: C, 51.27; H, 4.30; N, 23.91. Found: C, 51.03; H, 4.27; N, 23.79). IIb afforded similarly IIIb (R=R″=$C_6H_5CH_2$: mp 186—187°, yellow needles, IR ν_{max}^{KBr} cm^{-1}: 1660 (>N–CO), 3340 (NH), UV λ_{EtOH}^{max} nm (log ε): 249 (3.96), 309 (3.93), 384 (3.75), NMR (in $CDCl_3$) τ: 2.67 (10H, s, $C_6H_5\times2$), 5.01 (2H, s, >N–CH_2–C_6H_5), 5.58 (2H, d, –NH–CH_2–C_6H_5, J=6 Hz), 75% yield, *Anal.* Calcd. for $C_{17}H_{16}ON_4S$: C, 62.94; H, 4.97; N, 17.27. Found: C, 62.80; H, 4.94; N, 17.24). Aminodethiolation of each of the thiones, IIIa, b, with ammonia and benzylamine proceeded smoothly, to afford the corresponding 5,6-diamines, IVa (R=$C_6H_5CH_2$, R′=R″=H: mp 253° (decomp.), colourless crystals, IR ν_{max}^{KBr} cm^{-1}: 1680 (>N–CO), 3260, 3420 (NH_2), NMR (in DMSO-d_6), τ: 2.69 (5H, s, C_6H_5), 4.20 (2H, s, NH_2), 5.10 (2H, s, >N–CH_2–C_6H_5), 90% yield, *Anal.* Calcd. for $C_{10}H_{11}ON_5$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.11; H, 5.08; N, 32.29), IVb (R=R′=$C_6H_5CH_2$, R″=H; mp 262°, colourless crystals, IR ν_{max}^{KBr} cm^{-1}: 1620 (>N–CO), 3170, 3300 (NH), NMR (in DMSO-d_6) τ: 2.61 (5H, s, C_6H_5), 2.67 (5H, s, C_6H_5), 4.13 (2H, s, NH_2), 5.07 (2H, s, >N–CH_2–C_6H_5), 5.40 (2H, d, –NH–CH_2–C_6H_5, J=6 Hz), 90% yield, *Anal.* Calcd. for $C_{17}H_{17}ON_5$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.26; H, 5.47; N, 22.75), IVc (R=R″=$C_6H_5CH_2$, R′=H: mp 283° (decomp.), colourless crystals, IR ν_{max}^{KBr} cm^{-1}: 1670 (>N–CO), 3280 (NH), NMR (in DMSO-d_6) τ: 2.65 (5H, s, C_6H_5), 2.74 (5H, s, C_6H_5), 5.12 (2H, s, >N–CH_2–C_6H_5), 5.70 (2H, d,–NH–CH_2–C_6H_5, J=6 Hz), 83% yield, *Anal.* Calcd. for $C_{17}H_{17}ON_5$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.38; H, 5.54; N, 22.97), and IVd (R=R′=R″=$C_6H_5CH_2$: mp 190—192°, colourless crystals, IR ν_{max}^{KBr} cm^{-1}: 1630 (>N–CO), 3310 (NH), NMR (in DMSO-d_6) τ: 2.63 (10H, s, $C_6H_5\times2$), 2.72 (5H, s, C_6H_5), 5.10 (2H, s, >N–CH_2–C_6H_5), 5.43 (2H, d, –NH–CH_2–C_6H_5, J=6 Hz), 5.70 (2H, d, –NH–CH_2–C_6H_5, J=6 Hz), 89% yield, *Anal.* Calcd. for $C_{24}H_{23}ON_5$: C, 72.52; H, 5.83; N, 17.62. Found: C, 72.35; H, 5.80; N, 17.55), respectively.

An attempted benzylation of Vc afforded a mixture of the products, which consisted of Vd, as a rather minor component (5% yield), and the alternative isomer whose precise structure was not yet determined, but tentatively formulated as 2,4-dibenzyl-6-phenyl-imidazo[4,5-*e*]-*as*-triazin-3(2H)-one (Vf) (R=R′=$C_6H_5CH_2$, R‴=C_6H_5: mp 206—207°, pale yellow needles, IR ν_{max}^{KBr} cm^{-1}: 1680 (>N–CO), NMR (in CF_3CO_2D), τ: 1.20—2.80 (15H, m, $C_6H_5\times3$), 4.22, 4.39 (each 2H, s, >N–CH_2–C_6H_5), UV λ_{EtOH}^{max} nm (log ε): 248 (3.93), 333 (4.17), 346 (4.16), *Anal.* Calcd. for $C_{24}H_{19}ON_5$: C, 73.27; H, 4.87; N, 17.80. Found: C, 73.30; H, 4.98; N, 17.68), as a rather major one (74% yield), however, it was not contaminated with any isolable amount of Ve.



Vc Vf Vd

Fig. 3

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