Bicyclic Heterocycles with Nitrogen at the Ring Junction 1. Synthesis and Chemistry of Imidazo[5,1-*f*]-1,2,4-triazines

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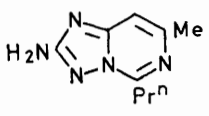
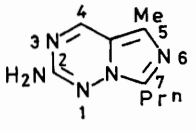
The synthesis of the potential bronchodilators 2-amino-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (12) and the corresponding triazine (2) is described and some chemical reactions of this novel ring system are discussed. Although *X*-ray analysis of the methanesulphonate salt of (12) indicated that protonation occurred on the nitrogen atom at position 6, acylation of the primary amino-group could still be achieved using a carboxylic acid in the presence of methanesulphonyl chloride.

THE triazolo[2,3-*c*]pyrimidine (1) is reported to be a potent inhibitor of histamine-induced bronchospasm in guinea-pigs and is of potential use as a bronchodilator drug.[1,2] Examination of CPK space-filling models showed that an imidazo[5,1-*f*][1,2,4]triazine could be constructed which was so remarkably related, with regard to its hetero-aromatic character and the superimposable arrangement of nitrogen atoms and alkyl groups, that it was considered likely that it would have similar biological activity. The synthesis of this novel compound (2) is the subject of this paper.



(1)



(2)

The preparations of some representative 2,7-diaminoimidazo[5,1-*f*][1,2,4]triazines have recently been reported [3-8] but at the outset of our work no compound based on this ring system had been described.

For the synthesis of (2), we directed our efforts towards the preparation of the triazinone (5) as a key intermediate. The ester (3), which was readily prepared in 50—65% yield by the condensation of diethyl oxalopropionate with aminoguanidine, formed the hydrazide (4) in quantitative yield on treatment with hydrazine but all attempts at transformation into the amine (5) using nitrous acid failed. Instead, the product of the attempted Curtius rearrangement was the highly insoluble bicyclic compound (7), presumably formed by the spontaneous cyclisation of the intermediate isocyanate (6). We found that cyclisation could be prevented by first benzylating the ester (3) with benzyl chloride–potassium carbonate prior to conversion into the hydrazide (9) and subsequent rearrangement to the amine (10). The overall yield from the ester (3) was 30—35%. The structure of the *N*-benzyl compound (8) was unequivocally established by an alternative synthesis from diethyl oxalopropionate and 1-amino-1-benzylguanidine.[9]

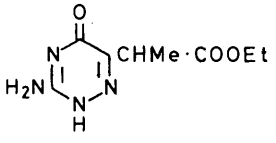
The amine (10) was readily acylated with butyryl chloride in pyridine and the product (11) converted directly into the imidazotriazinone (12) in low yield by heating with phosphorus oxychloride followed by chromatographic purification. In an alternative process the butyramide (11) was catalytically debenzylated with hydrogen over palladium–charcoal and the product cyclised with polyphosphoric acid to give the imidazotriazinone (12) in 76% overall yield. Reduction with lithium aluminium hydride in tetrahydrofuran followed by dehydrogenation of the product (13) by heating under reflux in *p*-cymene over 10% palladium oxide–charcoal gave the required imidazo[5,1-*f*][1,2,4]triazine (2). The overall yield from diethyl oxalopropionate was 15—25%.

The imidazotriazine (2) and the imidazotriazinone (12) were shown to be potent bronchodilators and this activity promoted further investigations of the chemistry of these compounds. The biological results will be described in detail elsewhere.

The pK_a values of the two bases (12) and (2), determined by ultraviolet spectrophotometry, were 5.2 and 5.13, respectively. In addition *X*-ray analysis of the methanesulphonate salt of the imidazotriazinone (12) and ^{13}C n.m.r. spectroscopy of the hydrochloride salt of the imidazotriazine (2) showed that protonation in both species had occurred at the nitrogen atom in the 6-position. Nevertheless the protonated species is acylated on the primary amino-group with acetic anhydride in acetic acid. The structure of the product (14) was confirmed by reduction with lithium aluminium hydride followed by dehydrogenation with Pd–C in *p*-cymene to give the imidazotriazine (15).

In an attempt to form an *N*-sulphonyl derivative of (12) using methanesulphonyl chloride in acetic acid the product was unexpectedly shown to be the *N*-acyl derivative (14). This was presumably formed *via* a mechanism involving formation of the mixed anhydride $Me{\cdot}SO_2{\cdot}O{\cdot}CO{\cdot}Me$. Adaptation of this observation led to a general method for acylating the primary amino-group. This involved heating the imidazotriazinone (12) with a carboxylic acid and at least 1 mol of methanesulphonyl chloride at 130—150 °C for 3—5 h to give amides that generally crystallized out as the methanesulphonate salts on diluting the cooled reaction mixture with ether.

On heating with 5N-HCl the imidazotriazinone (12) is degraded to water-soluble fragments. Under similar hydrolytic conditions the imidazotriazine (2) is comparatively stable but this compound is degraded to the



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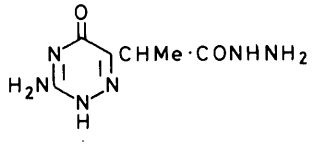

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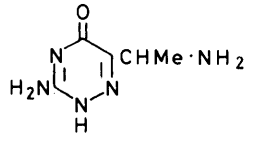

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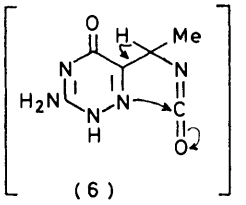

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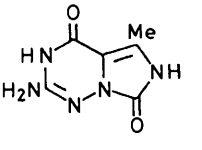

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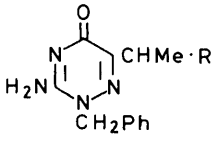
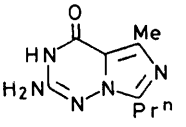


(8) R = CO_2Et
(9) R = $CONHNH_2$
(10) R = NH_2
(11) R = $NH{\cdot}CO{\cdot}Pr^n$



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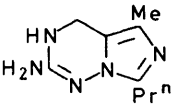
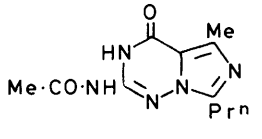


(13)

ketone (16) on reaction with bromine in the presence of mineral acid at room temperature. In addition the imidazotriazine (2) is also susceptible to nucleophilic addition at the 3,4-azomethine bond. Thus with



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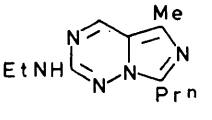
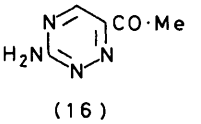


(15)

methylmagnesium bromide, it gives the stable product (17), whereas with dimedone and with sodium hydrogensulphite or sulphur dioxide in the presence of water it gives the adducts (18) and (19), respectively, that revert to the parent compound on treatment with base. The adduct (19) is insoluble in water and probably exists as a zwitterion. Acylation of the imidazotriazine (2) occurred in a similar fashion to that observed with the imidazotriazinone (12) but, whereas the latter was unreactive towards nitrous acid, the imidazotriazine (2) formed the secondary amine (20) (identified by mass spectrometry).



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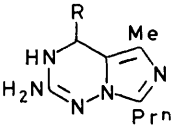
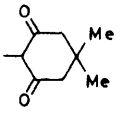
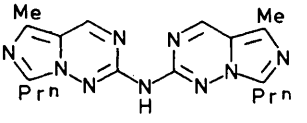


(17) R = Me

(18) R =



(19) R = SO_3H



(20)

EXPERIMENTAL

The ^1H n.m.r. (tetramethylsilane as internal standard), i.r., and u.v. spectra were measured (by Dr. J. H. Hunt and

his staff) on Varian A60, Perkin-Elmer 357, and Perkin-Elmer 402 spectrometers, respectively, and the mass spectrum was recorded (by Dr. R. Tanner) on an A.E.I. MS 30 spectrometer. The elemental analyses were determined (by Dr. L. R. Rowe and his staff) on a Hewlett–Packard 185B C, H, and N analyser. The pK_a measurements were determined in water according to the method of Albert and Serjeant.[10]

3-*Amino*-2,5-*dihydro*-α-*methyl*-5-*oxo*-1,2,4-*triazine*-6-*acetic Acid Ethyl Ester* (3).—Aminoguanidine hydrogen carbonate (177 g) and diethyl oxalopropionate (229 g) in ethanol (3.4 l) were heated under reflux with stirring for 2 h. Removal of the solvent and treatment of the residue with water afforded the *triazinone* (3) (154 g, 64%), m.p. 256.5—257.5° (from ethanol) (Found: C, 45.0; H, 5.7; N, 26.95. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%).

3-*Amino*-2,5-*dihydro*-α-*methyl*-5-*oxo*-1,2,4-*triazine*-6-*acetohydrazide* (4).—A solution of the ester (4) (0.5 g) in hydrazine hydrate (15 ml) was allowed to stand for 3 days. Removal of the solvent under reduced pressure afforded the *hydrazide* (4) (0.47 g, 100%), m.p. 266—268° (from water) (Found: C, 36.2; H, 5.2; N, 42.8. $C_6H_{10}N_6O_2$ requires C, 36.4; H, 5.1; N, 42.4%); $\lambda_{max.}$ (EtOH–NaOH) 253 nm (ε 5 070).

2-*Amino*-5-*methylimidazo*[5,1-f][1,2,4]*triazine*-4,7(3H,-6H)-*dione* (7).—A solution of the hydrazide (5) (5.0 g) in 5N-hydrochloric acid (1.4 g) and t-butanol (30 ml) was cooled to 3 °C and amyl nitrite (5 ml) added dropwise with stirring. The mixture was heated at 50 °C for 0.5 h and the product (7) precipitated as a buff *solid* (3.0 g, 62%), m.p. >400° (Found: C, 37.1; H, 4.2; N, 36.45. $C_6H_7N_5O_2 \cdot 0.5H_2O$ requires C, 38.0; H, 4.2; N, 36.8%); $\nu_{max.}$ (Nujol) 3 350, 3 320, 3 190, 1 695, and 1 645 cm^{-1}; τ(D_2O–DCl) 7.49 (3 H, s, CH_3); $\lambda_{max.}$ (0.1N-NaOH–EtOH) 223 (ε 14 900), 242 (14 900), and 317 nm (4 200) (Found: M^+, 181. $C_6H_7N_5O_2$ requires M, 181).

3-*Amino*-2-*benzyl*-2,5-*dihydro*-α-*methyl*-5-*oxo*-1,2,4-*triazine*-6-*acetic Acid Ethyl Ester* (8).—*Method* (A). A mixture of the ester (2.0 g), benzyl chloride (1.3 g), anhydrous potassium carbonate (1.6 g), and sodium iodide (0.5 g) in butanone (100 ml) was heated under reflux with stirring for 2 days. The mixture was filtered to remove inorganic material and the filtrate was concentrated to provide a yellow oil. This was dissolved in ethyl acetate, washed with water, and dried. Removal of the solvent and trituration of the oily residue with ether–light petroleum–ethyl acetate furnished the N-*benzyltriazinone* (8) (1.8 g, 65%), m.p. 151—152° (from ethyl acetate) (Found: C, 58.2; H, 6.2; N, 18.0. $C_{15}H_{18}N_4O_3 \cdot 0.5H_2O$ requires C, 58.0; H, 6.1; N, 18.0%); $\nu_{max.}$ ($CHBr_3$) 3 460, 3 365, and 1 722 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 and 263 nm (ε 7 320); τ($CDCl_3$–[$^2H_6$]-DMSO) 8.84 (3 H, t, CH_2CH_3), 8.59 (3 H, d, CH_3), 5.93 (2 H, q, CH_2CH_3), 6.0—6.48 (1 H, m, CH_3CH), 4.87 (2 H, s, CH_2Ph), 2.99 (2 H, br s, NH_2), and 2.75 (5 H, s, aromatic).

Method (*B*). 1-Amino-1-benzylguanidine sulphate [9] (565 mg) and anhydrous sodium acetate (220 mg) were suspended in ethanol (50 ml) containing diethyl oxalopropionate (594 mg) and the mixture was heated under reflux with stirring for 6 h. Removal of the solvent gave an oil which was chromatographed on silica gel to give the *triazinone* (8) (84 mg, 10%), m.p. 153—155° (from ethyl acetate). A mixed m.p. 152—155° with a sample prepared by method (A) showed no depression.

3-*Amino*-2-*benzyl*-2,5-*dihydro*-α-*methyl*-5-*oxo*-1,2,4-*triazine*-6-*acetohydrazide* (9).—The ester (8) (7.5 g) in methanol (100 ml) and hydrazine hydrate (100 ml) was allowed to stand for 3 days at room temperature. Removal of the solvent under reduced pressure gave the *hydrazide* (9) as needles (5.0 g, 70%), m.p. 246—247° (from methanol) (Found: C, 54.4; H, 5.9; N, 29.6. $C_{13}H_{16}N_6O_2$ requires C, 54.2; H, 5.95; N, 29.15%); $\nu_{max.}$ (Nujol) 3 325, 3 270, 3 100, 1 655, and 1 670 cm^{-1}; $\lambda_{max.}$ (EtOH–HCl) 213 (ε 25 000) and 263 nm (7 550); τ($CDCl_3$–[$^2H_6$]-DMSO) 0.97 (1 H, br s, $NHNH_2$), 2.3—3.0 (7 H, 2 × br s, $NHNH_2$ and aromatic), 4.75 (2 H, s, CH_2Ph), 5.9 (2 H, br s, NH_2), 5.5—6.35 (1 H, q, CH_3CH), and 8.72 (3 H, d, $CHCH_3$).

3-*Amino*-6-(1-*aminoethyl*)-2-*benzyl*-1,2,4-*triazin*-5(2H)-*one* (10).—The hydrazide (9) (6.0 g) in 2N-hydrochloric acid (21.6 ml) was cooled to 5 °C and sodium nitrite (1.44 g) in water (10 ml) was added dropwise with stirring while keeping the temperature below 10 °C. The mixture was allowed to warm to room temperature over 2 h; 2N-hydrochloric acid (10 ml) was added and the mixture warmed on a steam-bath until all the solids dissolved. The solution was basified with sodium hydrogen carbonate and concentrated under reduced pressure. The residual solid was extracted with boiling isopropanol and concentrated to give the *amine* (10) (3.3 g, 65%), m.p. 246—248° (from water) (Found: C, 58.8; H, 6.3; N, 28.3. $C_{12}H_{15}N_5O$ requires C, 58.8; H, 6.3; N, 28.6%); $\nu_{max.}$ (Nujol) 1 650 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 23 000) and 263 nm (7 150); τ(D_2O–DCl) 8.35 (3 H, d, CH_3CH), 5.15 (1 H, q, CH_3CH), 4.55 (2 H, s, CH_2Ph), and 2.5 (5 H, s, aromatic).

N-[1-(3-*Amino*-2-*benzyl*-2,5-*dihydro*-5-*oxo*-1,2,4-*triazin*-6-*yl*)*ethyl*]*butyramide* (11).—Butyric anhydride (288 ml) was added to a stirred suspension of the amine (10) (400 g) in dioxan (4 l). The suspension was stirred at room temperature for 2 h to give a viscous mixture which was diluted with ether (2.4 l). The solid was filtered off, washed with ether (2.6 l), dried, and then dissolved in hot methanol (2.44 l) and hot water (4.85 l) added. The *amide* (11) crystallized on cooling (418 g, 81%), m.p. 192—194° (Found: C, 61.35; H, 7.0; N, 22.4. $C_{16}H_{21}N_5O_2$ requires C, 61.0; H, 6.75; N, 22.2%); $\lambda_{max.}$ (EtOH) 259 nm (ε 7 200).

2-*Amino*-5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]*triazin*-4(3H)-*one* (12).—*Method A*. A solution of the amide (11) (411 g) in 2N-hydrochloric acid (2.05 l) and ethanol (2.11 l) was hydrogenated over 10% palladium–carbon until uptake of hydrogen had ceased (4 h). The mixture was filtered through Hyflo and the filtrate was concentrated to approximately half the volume by evaporation under reduced pressure and then basified to pH 8 by the addition of solid sodium carbonate. The precipitate was filtered off and washed with water to give N-[1-(3-*amino*-4,5-*dihydro*-5-*oxo*-1,2,4-*triazin*-6-*yl*)*ethyl*]*butyramide* (256 g, 88%) m.p. 309—311° (Found: C, 48.3; H, 6.7; N, 31.3. $C_9H_{15}N_5O_2$ requires C, 48.0; H, 6.7; N, 31.1%); $\lambda_{max.}$ (0.1N-HCl) 259 nm (ε 5 600); $\lambda_{max.}$ (0.1 N-NaOH) 290 nm (ε 6 100). This amide (250 g) was added with stirring to polyphosphoric acid (1.7 kg) at 90 °C (bath temperature) over 0.5 h. The temperature was raised to 150 °C and stirring continued for 2 h. The cooled solution was poured into iced water (4.5 l) and the pH adjusted to 6 by the careful addition of 70% sodium hydroxide solution while maintaining the temperature at 15—30 °C. The precipitate was filtered off, washed with water (2 l), and suspended in warm ethanol (525 ml). A solution of 10% ethanol–hydrogen chloride (570 ml) was added over 15 min to give a precipitate of 2-*amino*-5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]*triazin*-4(3H)-*onium chloride* (249 g, 93%), m.p. 284° (Found: C, 44.4;

H, 5.9; N, 28.6. $C_9H_{13}N_5O$·HCl requires C, 44.4; H, 5.8; N, 28.7%). A portion was converted into the free *base* (12), m.p. 264—268° (Found: C, 52.1; H, 6.4; N, 34.0. $C_9H_{13}N_5O$ requires C, 52.2; H, 6.3; N, 33.8%); $\lambda_{max.}$ (EtOH) 265 (ε 5 650) and 227 nm (32 300); $\lambda_{max.}$ (0.1N-HCl) 221 (ε 33 300) and 252 nm (5 650); $\nu_{max.}$ (Nujol) 3 405, 3 335, 3 220, 3 070, and 1 700 cm^{-1}; τ(D_2O–DCl) 8.97 (3 H, t, $CH_2CH_2CH_3$), 8.13 (2 H, m, $CH_2CH_2CH_3$), 7.32 (3 H, s, CH_3), and 6.9 (2 H, t, $CH_2CH_2CH_3$).

The base formed a methanesulphonate that crystallized with one molecule of water as *prisms*, m.p. 176—178° (from ethanol–ethyl acetate) (Found: C, 37.3; H, 6.0; N, 22.0. $C_9H_{13}N_5O$·CH_3SO_3H·H_2O requires C, 37.4; H, 6.0; N, 21.8%).

Method (*B*). The butyramide (11) (2.2 g) was heated under reflux in phosphorus oxychloride (50 ml) for 0.5 h. The solution was cooled, poured onto ice and conc. hydrochloric acid, then brought to pH 7 and extracted continuously with ethyl acetate. Removal of the solvent left an oil which on trituration with ether afforded a brown solid (1.3 g) which was absorbed from ethyl acetate (15 ml) onto silica gel (50 g). The first fraction eluted with ethyl acetate (150 ml) was discarded. Further elution with ethyl acetate (700 ml) furnished the crude *imidazotriazinone* (12) as an off-white solid, (0.26 g, 17%) m.p. 258—260°. A mixed m.p. with a sample prepared by method (A) showed no depression.

2-*Amino*-3,4-*dihydro*-5-*methyl*-7-*propylimidazo*[5,1-f]-[1,2,4]*triazine* (13).—The imidazotriazinone hydrochloride (12) (5 g) and lithium aluminium hydride (2.9 g) in tetrahydrofuran (200 ml) were heated under reflux for 78 h. The excess of lithium aluminium hydride was decomposed by the sequential addition of water (2.9 ml), 15% sodium hydroxide (2.9 ml), and water (8.7 ml). The inorganic precipitate was removed by filtration and the filtrate was concentrated to afford the *dihydro-compound* (3.4 g, 86%), m.p. 242—246° (from ethyl acetate) (Found: C, 55.8; H, 7.8; N, 36.7. $C_9H_{15}N_5$ requires C, 55.9; H, 7.8; N, 36.2%); $\nu_{max.}$ (Nujol) 1 640, 1 610, and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 250 nm (ε 10 800); τ(D_2O–DCl) 8.98 (3 H, t, $CH_2CH_2CH_3$), 8.16 (2 H, m, $CH_2CH_2CH_3$), 7.68 (3 H, s, 5-CH_3), 6.98 (2 H, t, $CH_2CH_2CH_3$), and 5.34 (2 H, s, $HNCH_2$). The *hydrochloride* had m.p. 263° (decomp.) (from ethanol–ether) (Found: C, 46.7; H, 6.85; N, 30.7. $C_9H_{15}N_5$·HCl requires C, 47.05; H, 7.0; N, 30.5%).

2-*Amino*-5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]*triazine* (2).—A suspension of the dihydro-compound (13) (11 g) and 10% palladium oxide–charcoal (15 g) in *p*-cymene (500 ml) was heated under reflux with stirring for 5 h. The mixture was filtered hot through Hyflo and the filtrate extracted with 2N-hydrochloric acid. The acid extract was basified with solid sodium carbonate and extracted with ethyl acetate to give the *imidazotriazine* (2) as a yellow solid (9.55 g, 88%), m.p. 116—119° (from cyclohexane) (Found: C, 56.5; H, 6.85; N, 36.6. $C_9H_{13}N_5$ requires C, 56.6; H, 6.9; N, 36.7%). The *hydrochloride* had m.p. 146° (decomp.) (Found: C, 47.8; H, 6.3; N, 30.4; $C_9H_{13}N_5$·HCl requires C, 47.5; H, 6.2; N, 30.8%); $\lambda_{max.}$ (EtOH) 247 (ε 13 900), 315 (500), and 360sh nm (270); τ(D_2O–DCl) 9.02 (3 H, t, $CH_2CH_2CH_3$), 8.1 (2 H, m, $CH_2CH_2CH_3$), 7.48 (3 H, s, 5-CH_3), 7.06 (2 H, t, $CH_2CH_2CH_3$), *ca.* 4.95 (2 H, br s, NH_2), and 1.31 (1 H, s, N=CH).

N-(3,4-*Dihydro*-5-*methyl*-4-*oxo*-7-*propylimidazo*[5,1-f]-[1,2,4]*triazin*-2-*yl*)*acetamide* (14).—*Method* (*A*). The imidazotriazinone hydrochloride (12) (5 g) and methanesulphonyl chloride (3.5 ml) were heated under reflux in acetic acid (100 ml) for 24 h. The amber solution was evaporated to dryness and the residue was dissolved in water (100 ml). Addition of sodium carbonate afforded the *acetamide* (14) (4.64 g, 92%), m.p. 221—223° (Found: C, 52.35; H, 6.2; N, 28.15; $C_{11}H_{15}N_5O_2$ requires C, 53.0; H, 6.1; N, 28.1%); τ(DMSO) 9.06 (3 H, t, $CH_2CH_2CH_3$), 8.38 (2 H, m, $CH_2CH_2CH_3$), 7.85 (3 H, s, CH_3CO), 7.58 (3 H, s, 5-CH_3), 7.26 (3 H, t, $CH_2CH_2CH_3$), and 6.78 (2 H, br, HN × 2).

Method (*B*). The imidazotriazinone (14 g) was heated in glacial acetic acid (12 ml) and acetic anhydride (12 ml) at 100 °C for 4 h and the solution was then poured onto ice and neutralized with sodium carbonate. The *acetamide* was extracted with ethyl acetate and converted into the *hydrochloride* salt, m.p. 267—269° (from ethanol–ether) (Found: C, 46.1; H, 5.7; N, 24.6. $C_{11}H_{15}N_5O_2$·HCl requires C, 46.2; H, 5.7; N, 24.5%).

3,4-*Dihydro*-2-*ethylamino*-5-*methyl*-7-*propylimidazo*-[5,1-f][1,2,4]*triazine*.—The hydrochloride of the acetamide (14) (1.42 g) was added to a stirred suspension of lithium aluminium hydride (1.3 g) in tetrahydrofuran (60 ml) and the mixture heated under reflux for 20 h. Water (1.3 ml), 15% aqueous sodium hydroxide (1.3 ml), and then water (3.9 ml) were added to decompose the excess of lithium aluminium hydride, and the inorganic precipitate was removed by filtration. The filtrate was concentrated and the *ethylamino-compound* isolated as the maleate salt (1.17 g, 70%) m.p. 129—130.5° (from ethyl acetate) (Found: C, 53.5; H, 6.4; N, 20.9. $C_{11}H_{19}N_5$·$C_4H_4O_4$ requires C, 53.4; H, 6.9; N, 20.8%); $\lambda_{max.}$ (EtOH) 256 nm (ε 11 800); τ($CDCl_3$) 8.6—9.2 (6 H, m, CH_3CH_2NH and $-CH_2CH_2-CH_3$), 7.9—8.6 (2 H, m, $CH_2CH_2CH_3$), 7.9 (3 H, s, 5-CH_3), 7.22 (2 H, t, $CH_2CH_2CH_3$), 6.7 (2 H, quintet collapses to a quartet on deuteriation, CH_3CH_2NH), 5.68 (2 H, s, $HNCH_2$), 4.91 (1 H, t, CH_3CH_2NH), and 3.46 (1 H, br s, $HNCH_2$).

2-*Ethylamino*-5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]-*triazine* (15).—A solution of 3,4-dihydro-2-ethylamino-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazine (1.83 g) in *p*-cymene (100 ml) was stirred and heated under reflux with 10% palladium oxide–charcoal (3 g) for 3 h. The catalyst was filtered off and the filtrate extracted with 2N-HCl (3 × 100 ml). The extracts were washed with ethyl acetate (2 × 50 ml), neutralised with solid potassium carbonate, and then extracted with ethyl acetate. The organic layers were washed with water and dried ($MgSO_4$). Evaporation left the product as bright yellow microcrystals (1.4 g, 77%) m.p. 98—100° (from aqueous ethanol) (Found: C, 59.8; H, 7.6; N, 31.5. $C_{11}H_{17}N_5$ requires C, 60.25; H, 7.8; N, 31.9%); $\lambda_{max.}$ 215 (ε 17 580), 244 (26 220), and 323 nm (5 190); τ(DMSO) 9.09 (3 H, t, $CH_3CH_2CH_2$), 8.81 (3 H, t, CH_3CH_2NH), 8.22 (2 H, m, $CH_2CH_2CH_3$), 7.6 (3 H, s, 5-CH_3), 7.12 (2 H, t, $CH_2CH_2CH_3$), 6.7 (2 H, m, CH_3CH_2NH), 2.96 (1 H, br −N=CH), and 1.07 (1H, s, NH).

Reaction of the Imidazotriazine (2) *with Bromine*.—A mixture of the imidazotriazine (2) (0.54 g), 2N-hydrochloric acid (12.5 ml), bromine (0.17 ml), and glacial acetic acid (5 ml) was stirred for 1 h at room temperature and then quenched with water (50 ml). The solution was neutralized with solid sodium carbonate and extracted with ethyl acetate (4 × 50 ml) and the extracts were dried ($MgSO_4$) and filtered through a column of silica gel (20 g). Evaporation gave 6-*acetyl*-3-*amino*-1,2,4-*triazine* (16) as a yellow solid (0.26 g, 75%), m.p. 179—180° (from cyclohexane) (Found: C, 43.4; H, 4.6; N, 40.6. $C_5H_6N_4O_4$ requires

C, 43.5; H, 4.4; N, 40.6%); $\nu_{max.}$ ($CHBr_3$) 3 520, 3 405, and 1 690 cm^{-1}, $\lambda_{max.}$ (EtOH) 274 (ε 17 400), 319 (4 200), and 380sh nm (600), τ($CDCl_3$) 1.30 (1 H, s, N=CH), 2.35 (2 H, br s, H_2N), and 7.3 (3 H, s, $COCH_3$).

2-*Amino*-3,4-*dihydro*-4,5-*dimethyl*-7-*propylimidazo*-[5,1-f][1,2,4]*triazine* (17).—The imidazotriazine (2) (1.0 g) was added from a Soxhlet extraction apparatus to methylmagnesium iodide [prepared from magnesium turnings (0.72 g) and iodomethane (4.2 g)] and heated under reflux in ether (100 ml). The reaction was refluxed for 3 h and then cooled and treated with 20% ammonium chloride solution (30 ml) to precipitate the *dihydroimidazotriazine* (17) (0.81 g, 75%), m.p. 268—271° (from ethyl acetate–methanol). The hydrochloride had m.p. 252—254° (from ethanol–ether) (Found: C, 47.1; H, 7.4; N, 27.5. $C_{10}H_{17}N_5 \cdot HCl \cdot 0.5H_2O$ requires C, 47.5; H, 7.5; N, 27.7%); τ(DMSO) 9.12 (3 H, t, $CH_2CH_2CH_3$), 8.65 (3 H, d, 4-CH_3), 8.28 (2 H, m, $CH_2CH_2CH_3$), 7.78 (3 H, s, 5-CH_3), 7.19 (2 H, t, $CH_2CH_2CH_3$), 5.22 (1 H, q, 4-CH_3CH), 3.71 (3 H, br s, $\overset{+}{N}H$), and 2.28 (1 H, br s, NH or NH_2).

2-*Amino*-3,4-*dihydro*-4-(4,4-*dimethyl*-2,6-*dioxocyclohexyl*)-5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]*triazine* (18).—Dimedone (1 g) in 50% aqueous ethanol was added at room temperature to the imidazotriazine (2) (1 g) in 50% aqueous ethanol, and the solid *adduct* separated immediately (1.5 g, 87%), m.p. 243° (Found: C, 61.6; H, 7.5; N, 20.9. $C_{17}H_{25}N_5O_2$ requires C, 61.6; H, 7.6; H, 21.1%); τ($CDCl_3$) 8.88 (3 H, t, $CH_2CH_2CH_3$), 8.82 [6 H, s, $(CH_3)_2C<$], 7.8—8.4 (2 H, m, $CH_2CH_2CH_3$), 7.70 (3 H, s, 5-CH_3), 7.39 [4 H, br s, $CH_2C(CH_3)_2CH_2$], 6.90 (2 H, t, $CH_2CH_2CH_3$), 3.63 (1 H, s, HNC*H*), and 1.52 (br s, HN).

2-*Amino*-3,4-*dihydro*-5-*methyl*-7-*propylimidazo*-[5,1-f]-[1,2,4]*triazine*-4-*sulphonic Acid* (19).—Sulphur dioxide was passed into a solution of the imidazotriazine (2) (1.91 g) in ethanol (5 ml) and water (5 ml) until the yellow colour had disappeared. The precipitate was filtered off to give the *title compound* (19) as an amorphous powder (2.72 g, 100%), m.p. 232—234° (from aqueous ethanol) (Found: C, 39.5; H, 5.7; H, 25.4. $C_{19}H_{15}N_5O_3S$ requires C, 39.6; H, 5.5; N, 25.6%); $\nu_{max.}$ (Nujol) 1 200 and 1 035 cm^{-1}.

2,2′-*Iminobis*(5-*methyl*-7-*propylimidazo*[5,1-f][1,2,4]-*triazine*) (20).—Sodium nitrite (690 mg) in water (40 ml) was added dropwise with stirring over 30 min to the imidazotriazine (2) (1.9 g) in 2N-hydrochloric acid (40 ml). The reaction was kept at 0—2 °C throughout the addition and for a further 30 min, and was then allowed to return to 20 °C over 1 h. The solution was neutralised and the *bisimidazotriazine* separated as pale yellow needles (140 mg, 7.4%), m.p. 253—254° (Found: C, 58.8; H, 6.4; N, 34.4. $C_{18}H_{23}N_4$ requires: C, 59.2; H, 6.3; N, 34.5%); $\lambda_{max.}$ (EtOH) 243 (ε 24 090) and 261 nm (24 710); τ(TFA) 8.75 (3 H, t, $CH_2CH_2CH_3$), 7.78 (2 H, m, $CH_2CH_2CH_3$), 7.02 (3 H, s, 5-CH_3), 6.45 (2 H, t, $CH_2CH_2CH_3$), and 0.50 (<1 H, s, N=CH) (Found: M^+, 365. $C_{18}H_{23}N_9$ requires M, 365). The dihydrochloride had m.p. 244—248° (from chloroform–ether) (Found: C, 50.8; H, 5.6; N, 28.6. $C_{18}H_{23}N_9 \cdot 2HCl$ requires C, 49.3; H, 5.8; N, 28.8%).

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