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Pyrimidines. Part III.[1] The Reduction of Pyrimidines with Complex Metal Hydrides to give 1,6-Dihydropyrimidines

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A number of ethyl 4-substituted-2-methylthiopyrimidine-5-carboxylates in which the 4-substituent is CH:NOH (II), CN (V), Me (VI), Cl (VII), or OH (VIII), and also ethyl 4-acetamido-2-hydroxypyrimidine-5-carboxylate (XLI), were found to be reduced by complex metal hydrides to give 1,6-dihydropyrimidines. The structure of these products was established by ^{1}H n.m.r. spectoscopy. However, when ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate (VI) was treated with lithium aluminium hydride at a lower temperature (−70°), preferential reduction of the ester group occurred to give the 5-hydroxymethyl derivative (XVII) together with a small amount of 4,5-dimethyl-2-methylthiopyrimidine (XX). Treatment of ethyl 4-hydrazino-2-methylthiopyrimidine-5-carboxylate (IV) and of ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate (III) with lithium aluminium hydride readily gave the corresponding 5-hydroxymethyl derivatives.

In connection with other studies on the biological activity of 5-hydroxymethylpyrimidines,[2] 4-aminomethyl-5-hydroxymethyl-2-methylthiopyrimidine (I) and related compounds were required, and the reduction of ethyl 4-hydroxyiminomethyl-2-methylthiopyrimidine-5-carboxylate [1] (II) was therefore studied. This reduction was not expected to be difficult, as we were able

[1] Part II, R. S. Shadbolt and T. L. V. Ulbricht, *J. Chem. Soc.* (*C*), 1967, 1172.

[2] See T. L. V. Ulbricht in 'Progress in Nucleic Acid Research and Molecular Biology,' ed. J. N. Davidson and W. E. Cohn, Academic Press, New York, 1965, vol. 4.

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to reduce ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate [3] (III) and ethyl 4-hydrazino-2-methylthiopyrimidine-5-carboxylate [4] (IV) with lithium aluminium hydride to give the corresponding 5-hydroxymethyl derivatives (XVIII) and (XIX), and many successful reductions of ethyl pyrimidine-5-carboxylates to hydroxymethyl pyrimidines [2,5] and of oximes to amines [6] have been reported.

However on treatment of the oxime (II) with lithium aluminium hydride in pyridine, or lithium borohydride in tetrahydrofuran, or sodium borohydride in ethanol, the only compound that could be isolated had the composition $C_9H_{13}N_3O_3S$; that is, it contained two hydrogen atoms more than the starting material (II). The ^{1}H n.m.r. spectrum in deuteriated dimethyl sulphoxide, after accounting for the ester protons and the methylthio-protons, showed a methylene group (τ 5·8) superimposed as a singlet on the quartet of the ester methylene group, an aromatic proton (τ 1·3) as a singlet, and a singlet (τ −1·85). This spectrum could be accounted for by the structures ethyl 4-hydroxyiminomethyl-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XII) or by ethyl 4-hydroxyaminomethyl-2-methylthiopyrimidine-5-carboxylate (X). Although it was originally thought that the hydroxylamine (X) was the more likely structure, the reduction product was later shown to be the dihydropyrimidine (XII) (see below). This compound (XII) was almost completely resistant to further reduction, apparently due to the formation of an insoluble complex when treated with a metal hydride. Treatment of the oxime (II) with aluminium amalgam led to complete reduction of the hydroximinomethyl group and a 12% yield of ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate (VI) was obtained.

The reduction of the corresponding nitrile, ethyl 4-cyano-2-methylthiopyrimidine-5-carboxylate [1] (V), was next investigated. When the nitrile (V) was treated with lithium borohydride in tetrahydrofuran at 20°, or lithium aluminium hydride in tetrahydrofuran at −70°, a compound having the composition $C_9H_{11}N_3O_2S$ was isolated. This still had nitrile and ester bands in the i.r. spectrum, and was therefore ethyl 4-cyano-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XIII). Takamizawa and Hiria [7] showed that dihydropyrimidines could be dehydrogenated by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). When the reduction product of the nitrile (V) was treated with DDQ in toluene the nitrile (V) was reformed in 90% yield.

Treatment of the oxime reduction product (XII) and the cyanodihydropyrimidine (XIII) with acetic anhydride gave the same cyano-pyrimidine, having the composition $C_{11}H_{13}N_3O_2S$, which was ethyl 1(or 3)-acetyl-4-cyano-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XXIV). Hence the oxime reduction product was ethyl 4-hydroxyiminomethyl-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XII) and not ethyl 4-hydroxyaminomethyl-2-methylthiopyrimidine-5-carboxylate (X). The acetylation of this reduction product (XII) also gave a diacetyl derivative, which appeared to be ethyl 4-acetoxyiminomethyl-1(or 3)-acetyl-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XXV).

Takamizawa and Hiria [7] compared the ^{1}H n.m.r. spectra of 2-oxo(and thioxo)-1,2,3,4-tetrahydropyrimidines and the corresponding 1-alkyl, 3-alkyl, 1,3-dialkyl, 1-alkyl-3-acetyl, 1-acetyl-3-alkyl, and 1,3-diacetyl derivatives. They showed that the position of 6-H in the spectrum of the 1-acetyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidines was τ 0·5 downfield compared with the corresponding unacetylated compounds (the position of the 4-methylene hydrogens remaining unchanged), and similarly that the position of the 4-methylene hydrogens in the spectrum of the 3-acetyl-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidines was τ 0·5 downfield compared with the unacetylated compounds (whereas the position of 6-H was unchanged). From this they concluded that if one acetylated a 1,6- or 3,6-dihydropyrimidine the hydrogen(s) attached to the carbon atom next to the *N*-acetyl group would appear at a lower field than in the unacetylated material. It was also shown that the NH of a 3,6-dihydropyrimidine appeared at a lower field in the ^{1}H n.m.r. spectrum than the NH of a 1,6-dihydropyrimidine.

When we compared the ^{1}H n.m.r. spectra of ethyl 4-cyano-2-methylthio-1,6(or 3,6)-dihydropyrimidine (XIII) and its *N*-acetyl derivative (XXIV) in deuteriated dimethyl sulphoxide, it was found that the 6-methylene hydrogens appeared as a singlet at τ 5·9 (superimposed on the ester methylene quartet) in the former, and as a singlet at τ 5·43 in the latter. In the former, the NH proton appeared as a broad singlet at τ 1·4, which disappeared on adding deuterium oxide.

Reduction of the nitrile (V) had therefore given ethyl 4-cyano-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XIII) which had been acetylated to the 1-acetyl derivative (XXIV), and the reduction product of the oxime (II) was ethyl 4-hydroxyiminomethyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XII), acetylation of which had given the 1-acetyl cyanodihydropyrimidine (XXIV) together with ethyl 4-acetoxyiminomethyl-1-acetyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XXV).

When the reduction of the cyano-pyrimidine (V) with lithium aluminium hydride was carried out at −70° and the temperature then allowed to rise to 20°, a compound with the composition $C_7H_9N_3OS$ was isolated, whose i.r. spectrum showed no ester band, but which showed an OH band and an NH band; acetylation gave a diacetyl

[3] E. Peters, H. J. Minnemeyer, A. W. Spears, and H. Tieckelmann, *J. Org. Chem.*, 1960, **25**, 2137.
[4] M. Hauser, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, 1960, **25**, 1570.
[5] See D. J. Brown, 'The Pyrimidines,' ed. A. Weissberger, Interscience, New York, 1962.
[6] See M. Gaylord, 'Reduction with Complex Metal Hydrides,' Interscience, New York, 1955.
[7] A. Takamizawa and K. Hiria, *Chem. Pharm. Bull.*, 1964, **12**, 804, 1418; 1965, **13**, 681; *J. Org. Chem.*, 1965, **30**, 2290; A. Takamizawa, K. Hiria, and Y. Sato, *ibid.*, 1964, **29**, 1740.

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derivative, and the i.r. spectrum now showed ester and amide bands. Thus the reduction product was 4-cyano-5-hydroxymethyl-2-methylthio-1,6(or 3,6)-dihydropyrimidine (XXII) and its diacetyl derivative 5-acetoxymethyl-1(or 3)-acetyl-4-cyano-2-methylthio-1,6(or 3,6)-dihydropyrimidine (XXIII). The ^{1}H n.m.r. spectrum of the reduction product in deuteriated dimethyl sulphoxide showed two singlets, each having an area corresponding to two protons (τ 5·87 and 6·23), assigned to the side-chain methylene hydrogens and to the ring methylene hydrogens; these appeared at τ 5·42 and 5·72 in the diacetyl derivative. These shifts indicate that the reduction product and its diacetyl derivative were 1,6-dihydropyrimidines, as would be expected, since the initial reduction product of the nitrile (V) was a 1,6-dihydropyrimidine (XIII).

There have been several reports of complex metal hydrides reducing the pyrimidine ring to give dihydropyrimidines [5,8] of unproven configuration (apart from those giving 5,6-dihydropyrimidines). We found that 1,6-dihydropyrimidines were formed in a number of other reductions of this type.

Treatment of ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate (VI) with lithium borohydride or lithium aluminium hydride in tetrahydrofuran at 20° gave a small quantity of the 5-hydroxymethyl derivative (XVII) but the major product was shown to be 4-methyl-2-methylthio-1,6(or 3,6)-dihydropyrimidine-5-carboxylate (XIV). The ^{1}H n.m.r. spectrum in deuteriochloroform showed a singlet, corresponding to two protons, at τ 5·73 (superimposed on the ester methylene quartet), and a singlet corresponding to a single proton at τ 3·94. The former singlet was assigned to the 6-methylene hydrogens, and the latter to the NH proton (it disappeared on the addition of deuterium oxide). The position of the NH proton is in agreement with a 1,6-dihydro-structure (Takamizawa and Hiria [7]

[8] C. D. May and P. Sykes, *J. Chem. Soc.* (*C*), 1966, 649.

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found that in deuteriochloroform the NH proton of 1,6-dihydropyrimidines occurred at τ 3·6—4·0, and in 3,6-dihydropyrimidines at τ 1·1—1·4). Comparison of the ^{1}H n.m.r. spectrum of this dihydropyrimidine (XIV) with its 1-acetyl derivative (XXVI) showed only a small shift for the 6-methylene hydrogens in this case (τ 0·13).

Previously it had been shown that reduction of heterocyclic ring systems is temperature-dependent, low temperatures favouring reduction of functional groups in side chains and high temperatures favouring ring reduction, and that heterocyclic esters may be reduced to the corresponding methyl derivatives by use of excess of lithium aluminium hydride.[6] When the reduction of the 4-methyl pyrimidine (VI) was carried out at —70° the required alcohol (XVII) was formed in over 50% yield, together with a small amount of 4,5-dimethyl-2-methylthiopyrimidine (XX). Excess of lithium aluminium hydride favoured the formation of the dimethyl pyrimidine (XX). The alcohol (XVII), although formed, was difficult to isolate as such, and was converted into the benzoate or *p*-nitrobenzoate, which could readily be crystallised.

The reduction of ethyl 2,4-bismethylthiopyrimidine-5-carboxylate with lithium aluminium hydride at 20° gave a complex mixture, and the only compound which could be isolated proved to be 2,4-bismethylthio-5-methylpyrimidine (XXI).

Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate (VII) gave with lithium aluminium hydride at —70° an unstable product (as indicated by t.l.c.), and neither a dihydropyrimidine nor a 5-hydroxymethyl derivative could be isolated, in contrast to the results of Schellenberger and Winter[9] who successfully reduced the corresponding 2-methyl compound in this manner. The chloro-pyrimidine (VII) with lithium borohydride in tetrahydrofuran at 20° gave a high yield of ethyl 4-chloro-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XV) (as indicated by the ^{1}H n.m.r. spectra of the reduction product and of the *N*-acetyl derivative.) The chlorodihydropyrimidine (XV) rapidly decomposed on standing in dimethyl sulphoxide solution, and the main product formed had the composition $C_8H_{12}N_2O_3S$, indicating that hydrolysis had taken place. Since the same compound could be obtained in low yield by treating ethyl 4-hydroxy-2-methylthiopyrimidine-5-carboxylate (VIII) with lithium aluminium hydride, the probable structure was ethyl 4-hydroxy-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XVI). However, the ^{1}H n.m.r. spectrum suggested that the tautomeric structure, ethyl-6-oxo-2-methylthio-1,4,5,6-tetrahydropyrimidine-5-carboxylate (XI) predominated. The ^{1}H n.m.r. spectrum in chloroform at 60 Mc./sec. showed a quartet at τ 6·55 and a triplet at τ 6·1 (after the methylthio, ester, and NH protons had been accounted for), whose area corresponded to one and two protons respectively; in the ^{1}H n.m.r. spectra at 100 Mc./sec. the quartet remained, but the triplet became a multiplet. If structure (XI) is correct the quartet at τ 6·55 could be assigned to the 5-proton, and the multiplet at τ 6·1 could be assigned to the 6-methylene protons.

The chlorodihydropyrimidine (XV) was converted into the thiocyanatodihydropyrimidine (XXVIII) with potassium thiocyanate.

Ethyl 4-amino-2-hydroxypyrimidine-5-carboxylate[10] (XXIX) was acetylated to give the *N*-acetyl derivative (XXX), and this on treatment with lithium borohydride in dimethylformamide gave two products, namely ethyl 4-acetamido-2-hydroxy-3,6-dihydropyrimidine-5-carboxylate (XXXI) and ethyl 4-amino-2-hydroxy-3,6-dihydropyrimidine-5-carboxylate (XXXII). The latter compound (XXXII) was probably formed by hydrolysis of the former (XXXI) during the working up of the reaction. The ^{1}H n.m.r. spectra of these products suggests that in solution they exist largely as 2-oxo-1,2,3,6-tetrahydropyrimidines rather than 2-hydroxy-1,6-dihydropyrimidines.

Although the reduction products we have isolated have been shown to be 1,6-dihydropyrimidines, many of the reductions gave as many as ten products as indicated by t.l.c. and consequently it is possible that 3,6-dihydropyrimidines are formed as minor products.

The 1,6-dihydropyrimidines were not very stable, and decomposed at room temperature over several months. The u.v. spectra of the 1,6-dihydropyrimidines (excluding those containing tautomeric groups) exhibited two maxima, the difference between the two maxima being 90—100 mμ.

Takamizawa and Hiria[7] were able to differentiate between the 1,6- and 3,6-dihydropyrimidines from the appearance of the NH bands in the i.r. spectra in Nujol. Although the dihydropyrimidines we prepared were characterised by an NH band in Nujol at 3120—3315 cm.$^{-1}$ which appeared at 3340—3415 cm.$^{-1}$ in solution, the bands were not sufficiently well defined to establish the compounds as 1,6-dihydropyrimidines on the basis of i.r. spectra alone.

The ^{1}H n.m.r. spectra of the 1,6-dihydropyrimidines were interpreted by comparison with the ^{1}H n.m.r. of the starting materials. In the 1,6-dihydropyrimidines the ring methylene protons appeared at τ 5·9—6·4 and were often superimposed on the ester methylene quartet (τ 5·6—6·0). The NH protons appeared at τ 3·3—5·1 in deuteriochloroform and at τ 1·1—3·3 in deuteriated dimethyl sulphoxide (with the exception of the 4-oxo-1,4,5,6-tetrahydropyrimidine (XX) in which the NH proton appeared at τ 0·71 in deuteriochloroform). Coupling was not observed between the NH protons and the 6-methylene protons.

May and Sykes[8] reduced a number of ethyl pyrimidine-5-carboxylates and 5-cyano- and 5-carbamoyl-pyrimidines with lithium aluminium hydride and obtained dihydropyrimidines of unknown configuration. They suggested that only pyrimidines not having sub-

[9] A. Schellenberger and K. Winter, *Z. physiol. Chem.*, 1966, **344**, 16.

[10] T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, 1956, **21**, 567.

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stituents in the 4- or 6-position were liable to ring reduction, but this is obviously not so. However, it would seem probable that the presence of one unsubstituted position facilitates ring reduction, and that since steric factors affect the reduction of nitrogen heterocycles and the mechanism involves attack by a hydride ion at positions adjacent to ring nitrogens,[11] 2,4,5-trisubstituted pyrimidines should give 1,6-dihydropyrimidines. It would also appear that some 1,6-dihydropyrimidines are resistant to further ring reduction by complex metal hydrides in view of the fact that reduction of ethyl 4-cyano-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XIII) yielded the alcohol (XXII). In contrast, Takamizawa, Hayashi, and Tori[12] were able to reduce catalytically ethyl 2-methyl-1,6-dihydropyrimidine-5-carboxylate to the tetrahydro-derivative, and this could also be obtained by the catalytic reduction of ethyl 4-chloro-2-methyl pyrimidine-5-carboxylate.

The influence of the groups occupying the 2-, 4-, and 5-positions on the reduction is less clear, although an electron-withdrawing group (CO_2Et, CN) in the 5-position appears to facilitate ring reduction. The same seems to apply to position 4, since the formation of a dihydropyrimidine from ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate (VI) or ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate (VII) can be prevented by lowering the reaction temperature, whereas the tendency of the corresponding 4-cyano-compound (V) to be reduced to the dihydropyrimidine (XIII) is unaffected. Schwan, Tieckelmann, Holland, and Bryant[13] were able to isolate 5-hydroxymethyl-2,4-dimethylpyrimidine by treatment of the appropriate ester with lithium aluminium hydride at −70°, whereas at room temperature a product tentatively identified as a tetrahydropyrimidine was obtained. In view of our results it would seem more likely to have been a 1,6-dihydropyrimidine.

EXPERIMENTAL

Column chromatography was carried out on Merck silica for chromatography (0·05—0·2 mm.). Ascending t.l.c. and preparative t.l.c. were carried out on Merck silica GF_{254} in 3 : 2 ethyl acetate–benzene (A), 9 : 1 ethyl acetate–benzene (B), benzene (C), chloroform containing 1% ethanol (D), ethyl acetate (E), methylene chloride (F), ether (G), 4 : 1 ethyl acetate–ethanol (H), and acetone (J). Compounds were detected on chromatograms by observation under a short-wave u.v. lamp. The $\lambda_{max.}$ values were determined on a Hilger Uvispek in 95% ethanol ($C \sim 1$ mg./100 ml.) and are followed by ($10^{-4}\,\varepsilon$). ^{1}H N.m.r. spectra were determined at 20° on a Varian A 60 unless stated otherwise in approximately 10% solutions in deuteriated chloroform ($CDCl_3$) or deuteriated dimethyl sulphoxide (DMSO) using tetramethylsilane as an internal standard. I.r. spectra were determined on a Perkin-Elmer 237 instrument.

The preparation of intermediates is described in Part II,[1] with the exception of ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate (III),[3] ethyl 4-hydrazino-2-methylthiopyrimidine-5-carboxylate (IV),[4] and ethyl 4-amino-2-hydroxypyrimidine-5-carboxylate (XXIX)[10] which we prepared by literature methods.

The *N*-acetyl derivatives of the 1,6-dihydropyrimidines were prepared by heating under reflux with acetic anhydride for 4 hr. The solution was evaporated and the residue purified by preparative t.l.c.

5-Hydroxymethyl-4-methylamino-2-methylthiopyrimidine (XVIII).—Ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate (III) (3·65 g.) in ether (100 ml.) was added over 2 hr. with stirring to a suspension of lithium aluminium hydride (950 mg.) in ether (50 ml.). The reaction was heated under reflux for 3 hr., cooled, and water (4 ml.) added. The mixture was filtered, the residue was extracted with hot acetone, and the combined filtrates were evaporated. The residue, recrystallised from ethanol, gave the *5-hydroxymethylpyrimidine* (XVIII) as prisms (2·0 g., 67%), m. p. 157—158° (Found: C, 45·3; H, 6·0; N, 23·2. $C_7H_{11}N_3OS$ requires C, 45·3; H, 6·0; N, 22·7%), $\lambda_{max.}$ 234 and 288·5 mμ (1·94 and 0·66).

4-Hydrazino-5-hydroxymethyl-2-methylthiopyrimidine (XIX).—Ethyl 4-hydrazino-2-methylthiopyrimidine-5-carboxylate (IV) (14·3 g.) in tetrahydrofuran (100 ml.) was added with stirring over 35 min. to a suspension of lithium aluminium hydride (5·0 g.) in tetrahydrofuran (250 ml.) at −70°. The reaction was stirred for 1 hr. at −70°, and then the temperature was allowed to rise to 20° over 2 hr. Water (5 ml.) and acetic acid (7·5 ml.) were then added dropwise and the mixture filtered. The filtrate was evaporated, the residue dissolved in chloroform (1·5 l.), and the resulting solution used to extract (Soxhlet) the solid residue from the filtration for several hours. The chloroform was filtered hot, the filtrate evaporated to a volume of 50 ml., and the solid filtered off, m. p. 144—145° (7·88 g., 67%). Recrystallisation from ethyl acetate (450 ml.) gave the *hydrazinohydroxymethylpyrimidine* (XIX) as needles (5·53 g.), m. p. 145—146° (Found: C, 38·8; H, 5·6; N, 29·8; S, 17·2. $C_6H_{10}N_4OS$ requires C, 38·7; H, 5·4; N, 30·1; S, 17·2%), $\lambda_{max.}$ 236 and 287 mμ (1·80 and 0·70).

Ethyl 4-Hydroxyiminomethyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XII).—(*a*) Ethyl 4-hydroxyiminomethyl-2-methylthiopyrimidine-5-carboxylate (II) (480 mg.) was suspended in ethanol (10 ml.) and sodium borohydride (80 mg.) added, and the solution stirred for 90 min. and evaporated. The residue was dissolved in ethyl acetate (20 ml.), and the solution washed with water (2 × 10 ml.). The ethyl acetate was evaporated and the residue recrystallised from benzene gave the *dihydropyrimidine* (XII) as yellow prisms (350 mg., 72%), m. p. 140—141° (decomp.) (Found: C, 44·7; H, 5·3; N, 16·9; S, 13·4. $C_9H_{13}N_3O_3S$ requires C, 44·4; H, 5·4; N, 17·2; S, 13·2%), $\nu_{max.}$ (Nujol) 3400 and 3150 cm.$^{-1}$ (OH, NH) and 1690 cm.$^{-1}$ (CO), $\lambda_{max.}$ 236 and 334 mμ (1·59 and 0·43), $\lambda_{max.}$ at pH 2 243 and 320 mμ (2·06 and 0·57). The n.m.r. spectrum (DMSO) showed peaks at τ −1·85 (s, 1H,OH), 1·3 (s, 1H, CH), 5·8 (s, 2H, ring CH_2), 5·85 (q, 2H, ester CH_2), 7·63 (s, 3H, CH_3S), and 8·75 (t, 3H, CH_3 ester).

(*b*) The hydroxyiminomethylpyrimidine (II) was treated with lithium borohydride in tetrahydrofuran for 2 hr. at 20°, and the reaction subject to preparative t.l.c. in (A) to

[11] See R. E. Lyle and P. S. Anderson, *Adv. Heterocyclic Chem.*, 1966, **6**, 46.

[12] A. Takamizawa, S. Hayashi, and K. Tori, *J. Chem. Soc. Japan*, 1958, **78**, 1166.

[13] T. J. Schwan, H. Tieckelmann, J. F. Holland, and B. Bryant, *J. Medecin. Chem.*, 1965, **8**, 750.

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give one major band (R_F 0·46) which when extracted gave the dihydropyrimidine (XII) (25%).

(*c*) The hydroxyiminomethylpyrimidine (II) in pyridine was added to a solution of lithium aluminium hydride in pyridine, and the reaction stirred and heated for 2 hr. at 45°. The reaction was worked up, and the product when purified by preparative t.l.c. in (A) gave the dihydropyrimidine (XII) (21%).

Reduction of Ethyl 4-Hydroxyiminomethyl-2-methylthiopyrimidine-5-carboxylate (II) *with Aluminium Amalgam.*—Aluminium foil (750 mg.) was stirred with a 5% mercuric chloride solution (100 ml.) for 2 min., filtered, and washed with water and methanol. The foil was added to a suspension of the hydroxyiminomethylpyrimidine (II) in ether (50 ml.) and methanol (5 ml.). After standing for 1 hr., ether (45 ml.), methanol (5 ml.), and water (0·5 ml.) were added, and after a further 3 hr. the reaction mixture was filtered. The residue was washed with ether (3 × 100 ml.), the combined filtrates were evaporated, and the residue was subjected to preparative t.l.c. in (B). The band having R_F 0·7 was extracted and gave a solid (52 mg., 12%) which was shown to be ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate (VI) (i.r. and u.v.).

Ethyl 4-Cyano-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XIII).—(*a*) Ethyl 4-cyano-2-methylthiopyrimidine-5-carboxylate (V) (20 g.) in tetrahydrofuran (60 ml.) was added over 20 min. with stirring to a suspension of lithium aluminium hydride (8·6 g.) in tetrahydrofuran (250 ml.) at −70°. The reaction was stirred for 90 min. at −70°, and then water (8·6 ml.), acetic acid (10 ml.), and ethyl acetate (250 ml.) were added. The reaction mixture was filtered and the residue extracted with hot ethyl acetate (6 × 200 ml.). The combined filtrates were evaporated and the residue recrystallised from ethyl acetate (500 ml.) to give the *cyanodihydropyrimidine* (XIII) as yellow needles (14·8 g., 73%), m. p. 190—191° (decomp.) (Found: C, 48·1; H, 5·0; N, 18·2. $C_9H_{11}N_3O_2S$ requires C, 48·0; H, 4·9; N, 18·6%), $\nu_{max.}$ (Nujol) 3310 (NH) and 2240 cm.$^{-1}$ (CN), $\lambda_{max.}$ 277 and 375 mμ (0·49 and 0·53), $\lambda_{max.}$ at pH 2 275 and 375 mμ (0·46 and 0·34). The n.m.r. spectrum (DMSO) showed peaks at τ 5·73 (s, 2H, ring CH_2), 5·84 (q, 2H, ester CH_2), 7·62 (s, 3H, CH_3S), and 9·78 (t, 3H, CH_3 ester).

(*b*) The cyano-pyrimidine (V) was stirred with a solution of lithium borohydride in tetrahydrofuran for 2 hr., the solution passed down a silica column, and the column eluted with ethyl acetate. The ethyl acetate on concentration to a small volume gave the cyanodihydropyrimidine (XIII) in 23% yield, m. p. 190—191° (decomp.).

Dehydrogenation of Ethyl 4-Cyano-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XIII).—The dihydropyrimidine (XIII) (223 mg.), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (227 gm.), and toluene (10 ml.) were heated under reflux for 1 hr. The reaction was cooled and filtered, and the filtrate evaporated. The residue was subjected to preparative t.l.c. in (C), the plates being eluted three times, and the major band extracted to give ethyl 4-cyano-2-methylthiopyrimidine-5-carboxylate (V), m. p. 46—47° (204 mg., 92%).

Ethyl 1-Acetyl-4-cyano-2-methylthio-1,6-dihydropyrimidine 5-carboxylate (XXIV).—The residue from the acetylation of the cyanodihydropyrimidine (XIII) was subjected to preparative t.l.c. in (D), the plates being eluted three times, which gave one major band. This was extracted to give a solid (54%), which gave on recrystallisation from light petroleum (b. p. 100—120°) the N-*acetyl derivative* as yellow needles (30%), m. p. 115—116° (Found: C, 49·7; H, 5·1; N, 15·8. $C_{11}H_{13}N_3O_3S$ requires C, 49·4; H, 4·9; N, 15·7%), $\nu_{max.}$ (CH_2Cl_2) 2240 (CN) and 1700 cm.$^{-1}$ (CO), $\lambda_{max.}$ 219, 290, and 357 mμ (0·88, 0·32, and 0·60). The n.m.r. spectrum (DMSO) showed peaks at τ 5·43 (s, 2H, ring CH_2), 5·74 (q, 2H, ester CH_2), 2·35 and 2·43 (both s, 3H, CH_3S and CH_3CO), and 8·72 (t, 3H, ester CH_3).

Ethyl 5-Acetoxyiminomethyl-1-acetyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XXV).—The residue from the acetylation of the hydroxyiminomethyldihydropyrimidine (XII) was subjected to preparative t.l.c. in (D) to give two major yellow bands. The faster band (R_F 0·52) was extracted and rechromatographed in (D) to give the *N*-acetylcyanodihydropyrimidine (XXIV) (30%), identical with the product obtained previously. The slower band (R_F 0·25) was extracted and rechromatographed in (D) to give a solid (16%), which when recrystallised from di-isopropyl ether gave the NO-*diacetyl derivative* (XXV) as yellow needles (10%), m. p. 87—88° (Found: C, 47·5; H, 5·3; N, 12·8. $C_{13}H_{17}N_3O_5S$ requires C, 47·7; H, 5·2; N, 12·8%), $\lambda_{max.}$ 247 and 347 mμ (1·82 and 0·75).

4-Cyano-5-hydroxymethyl-2-methylthio-1,6-dihydropyrimidine (XXII).—The cyanopyrimidine (V) (11·15 g.) in tetrahydrofuran (60 ml.) was added with stirring over 20 min. to a suspension of lithium aluminium hydride (4·75 g.) in tetrahydrofuran (250 ml.) at −70°. The solution was stirred for 2 hr. at −70°, and then the temperature was allowed to rise to 0° over 75 min. Water (4·75 ml.) and acetic acid (7·4 ml.) was added, and the mixture filtered. The residue was extracted (Soxhlet) for 10 hr. with chloroform, and the chloroform and the filtrate were combined and evaporated. The residue after recrystallisation from ethanol (50 ml.) and then from water (100 ml.) gave the *hydroxymethyldihydropyrimidine* (XXII) (2·14 g., 19%), m. p. 189—191° (decomp.) (Found: C, 45·4; H, 4·8; N, 22·8. $C_7H_9N_3OS$ requires C, 45·9; H, 4·9; N, 22·9%), $\nu_{max.}$ (Nujol) 3470, 3240, and 3200 cm.$^{-1}$ (OH, NH), $\lambda_{max.}$ 243 and 336 mμ (0·78 and 0·64). The n.m.r. spectrum (DMSO) showed peaks at τ 1·96 (s, 1H, NH), 2·58 (s, 1H, OH), 5·87 (s, 2H, ring CH_2), 6·23 (s, 2H, side chain CH_2), and 7·64 (s, 3H, MeS).

5-Acetoxymethyl-1-acetyl-4-cyano-2-methylthio-1,6-dihydropyrimidine (XXIII).—The solid residue from the acetylation of the hydroxymethyldihydropyrimidine (XXII) was purified by preparative t.l.c. in (D) using multiple elution to give a major yellow band. This was extracted and the solid obtained recrystallised from ethyl acetate gave the NO-*diacetyldihydropyrimidine* (36%) as yellow needles, m. p. 193—194° (Found: C, 49·1; H, 5·0; N, 15·4. $C_{11}H_{13}N_3O_3S$ requires C, 49·4; H, 4·9; N, 15·7%), $\nu_{max.}$ (Nujol) 1730 (CO) and 1690 cm.$^{-1}$ (CONH), $\lambda_{max.}$ 244·5 and 355 mμ (0·66 and 1·20). The n.m.r. spectrum (DMSO at 60°) showed peaks at τ 5·4 (s, 2H, ring CH_3), 5·72 (s, 2H, side chain CH_2), and 7·60, 7·56, and 7·5 (all s, 3H, CH_3S, *N*-acetyl, ester CH_3).

Ethyl 4-Methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XIV).—The methyl pyrimidine (VI) (520 mg.) was added to a 0·5M-solution of lithium borohydride in tetrahydrofuran (2·5 ml.). After 16 hr. the solution was directly applied to t.l.c. plates, which were eluted with (D) three times to give three major bands. The fastest moving band proved to be starting material (36 mg., 7%). The yellow band was extracted to give a solid (300 mg., 58%), which when recrystallised from carbon tetrachloride gave the *methyl dihydropyrimidine* (XIV) as yellow needles (159 mg.),

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m. p. 111—113° (Found: C, 50·8; H, 6·5; N, 12·6. $C_9H_{14}N_2O_2S$ requires C, 50·5; H, 6·6; N, 13·1%), $\nu_{max.}$ (CCl_4) 3340 (NH) and 1710 cm.$^{-1}$ (CO), $\lambda_{max.}$ 220 and 310 mμ (0·93 and 0·56), $\lambda_{max.}$ at pH 2 217, 246, and 306 mμ (0·75, 0·8, and 0·58). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 3·94 (s, 1H, NH), 5·73 (s, 2H, ring CH_2), 5·81 (q, 2H, ester CH_2), 7·57 (s, 3H, CH_3S), 7·75 (s, 3H, CH_3), and 8·74 (t, 3H, ester CH_3). The slowest moving band was extracted to give a gum (72 mg., 17%). This was rechromatographed in (D), and then recrystallised from light petroleum (b. p. 100—120°) to give *5-hydroxymethyl-4-methyl-2-methylthiopyrimidine* (XVII) as needles, m. p. 48·0—48·5° (Found: C, 49·7; H, 5·8; N, 16·0. $C_7H_{10}N_2OS$ requires C, 49·4; H, 5·9; N, 16·5%), $\lambda_{max.}$ 253 mμ (1·79).

Ethyl 1-Acetyl-4-methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XXVI).—The residue from the acetylation of the methyldihydropyrimidine (XIV) was subjected to preparative t.l.c. in (G), and after extraction of the major yellow band, in (F), using mutiple elutions. The major band was extracted to give a solid (61%), which when recrystallised from light petroleum (b. p. 80—100°) gave the N-*acetyl dihydropyrimidine* (XXVI) as yellow prisms (20%), m. p. 78—79° (Found: C, 52·0; H, 6·6; N, 11·0. $C_{11}H_{16}N_2O_3S$ requires C, 51·6; H, 6·3; N, 10·9%), $\lambda_{max.}$ 214 and 330 mμ (0·90 and 0·98). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 5·60 (s, 2H, ring CH_2), 5·77 (q, 2H, ester CH_2), 7·5 and 7·62 (both s, 3H, CH_3S and CH_3CO), 7·65 (s, 3H, CH_3), and 8·68 (t, 3H, ester CH_3).

5-Benzoyloxymethyl-4-methyl-2-methylthiopyrimidine.—The methyl pyrimidine (VI) (106 g.) in tetrahydrofuran (300 ml.) was added with stirring over 30 min. to a suspension of lithium aluminium hydride (10·45 g.) in tetrahydrofuran (300 ml.) at −75°. The reaction was stirred for 2 hr. at −75°, and then the temperature was allowed to rise to −20° over 1 hr. Water (10·5 ml.) and acetic acid (15·0 ml.) were added, the reaction mixture was filtered, and the residue was extracted with acetone (4 × 700 ml.). The combined filtrates were evaporated to give an oil (87·5 g.). The oil was dissolved in pyridine (400 ml.), and benzoyl chloride (59 ml.) was added to the solution over 1 hr. with stirring and ice-cooling. After standing for 16 hr., the solution was evaporated, and water (1 l.) and ether (1 l.) added to the residue. The ether was separated off, washed with N-hydrochloric acid (500 ml.), N-sodium hydrogen carbonate (500 ml.), and water (500 ml.), and evaporated. The residue was dissolved in benzene, and the solution poured into a silica column (40 × 5 cm.). The column was eluted with benzene (10 l.), and the eluate evaporated to give a solid (115·7 g.), which on recrystallisation from 95% ethanol (300 ml.) gave the *5-benzoyloxymethyl pyrimidine* (55·5 g.), m. p. 81—82°. The mother-liquor on concentration to a volume of 150 ml. gave a second crop (19·1 g., total yield 55%), m. p. 80—81° (Found: C, 61·3; H, 5·3; N, 10·3. $C_{14}H_{14}N_2O_2S$ requires C, 61·3; H, 5·2; N, 10·2%), $\nu_{max.}$ (Nujol) 1730 cm.$^{-1}$ (CO), $\lambda_{max.}$ 235 and 258 mμ (1·15 and 1·72). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 1·52 (s, 1H, CH), 1·8—3·4 (m, 5H, benzene ring), 4·7 (s, 2H, side chain CH_2), and 7·45 (s, 6H, CH_3S + CH_3).

4,5-Dimethyl-2-methylthiopyrimidine (XX).—Reduction of the methyl pyrimidine (VI) at −70° using 1·5 moles of lithium hydride per mole of ester gave two main products (by t.l.c.). These were purified by preparative t.l.c. in (E). The slower component (R_F 0·63) proved to be 5-hydroxymethyl-4-methyl-2-methylthiopyrimidine (XVII) (15%), and the faster component (R_F 0·92) proved to be *4,5-dimethyl-2-methylthiopyrimidine* (XX) (6%), b. p. 80°/0·2 mm. (Found: C, 54·5; H, 6·6; N, 18·1; S, 21·0. $C_7H_{10}N_2S$ requires C, 54·5; H, 6·5; N, 18·2; S, 20·8%), $\lambda_{max.}$ 250 and 292 mμ.

4-Methyl-2-methylthio-5-(4-nitrobenzoyloxymethyl)pyrimidine.—The crude alcohol (XVII) was acylated with 4-nitrobenzoyl chloride and pyridine and the reaction worked up in a similar manner to the benzoylation, and the product recrystallised from light petroleum (b. p. 100—120°) gave the *4-nitrobenzoate*, m. p. 148·5—149·5° (Found: C, 52·8; H, 4·2. $C_{14}H_{13}N_3O_2S$ requires C, 52·7; H, 4·1%), $\lambda_{max.}$ 259 mμ (3·01).

Ethyl 4-Chloro-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XV).—The chloro-pyrimidine (VII) (980 mg.) was added to a 0·5M-solution of lithium borohydride in tetrahydrofuran (8·4 ml.) at 0°. After 2 hr. silica (10 g.) was added, the slurry poured on to a silica column (20 × 2 cm.), and the column eluted with ether. The ether was evaporated to give a solid (910 mg., 92%), which when recrystallised from benzene (15 ml.) gave the *chlorodihydropyrimidine* (XV) as yellow prisms (640 mg.), m. p. 166—168° (decomp.) (Found: C, 40·4; H, 4·6; N, 11·8. $C_8H_{11}ClN_2O_2S$ requires C, 40·9; H, 4·7; N, 11·9%), $\nu_{max.}$ (Nujol) 3290 (NH) and 1700 cm.$^{-1}$ (CO), $\lambda_{max.}$ 257 and 350 mμ (0·71 and 0·74), $\lambda_{max.}$ at pH 2 253 and 323 mμ (0·74 and 0·43). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 3·96 (s, 1H, NH), 5·70 (s, 2H, ring CH_2), 5·77 (q, 2H, ester CH_2), 7·52 (s, 3H, CH_3S), and 8·70 (t, 3H, ester CH_3).

Ethyl 1-Acetyl-4-chloro-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (XXVII).—The residue from the acetylation of the chlorodihydropyrimidine (XV) was subjected to preparative t.l.c. in (C), using multiple elution, to give one major yellow band. This on extraction gave a solid (19%), which when recrystallised from light petroleum (b. p. 100—120°) gave the N-*acetyl dihydropyrimidine* (XXVII) as yellow needles (8%), m. p. 109—110°. When the time of the reaction was halved, the yield before recrystallisation was 40% (Found: C, 43·5; H, 4·7; N, 10·2. $C_{10}H_{13}ClN_2O_3S$ requires C, 43·4; H, 4·7; N, 10·1%), $\lambda_{max.}$ 233, 273, and 338 mμ (0·94, 0·47, and 1·00). The n.m.r. spectrum ($CDCl_3$), showed peaks at τ 5·45 (s, 2H, ring CH_2), 5·74 (q, 2H, ester CH_2), 7·50 and 7·60 (both s, 3H, CH_3CO and CH_3S), and 8·68 (t, 3H, ester CH_3).

Ethyl 2-Methylthio-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (XI).—(*a*) The chlorodihydropyrimidine (XV) (1·02 g.) and dimethyl sulphoxide (10 ml.) were put aside for 24 hr. Ethyl acetate (50 ml.) was added, and the solution was washed with N-sodium hydrogen carbonate solution and then water. The ethyl acetate was evaporated to give a residue (820 mg.), which was subjected to preparative t.l.c. in (G). The major band was extracted (384 mg., 41%), and on crystallisation from ethyl acetate–light petroleum gave the *oxo-pyrimidine* (XI) (212 mg.), m. p. 86—86·5° (Found: C, 44·4; H, 5·6; N, 12·9; S, 14·6. $C_8H_{12}N_2O_3S$ requires C, 44·4; H, 5·6; N, 13·0; S, 14·8%), $\lambda_{max.}$ 216 and 250 mμ (1·15 and 0·73). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 0·71 (s, 1H, NH), 5·76 (q, 2H, ester CH_2), 6·0—6·3 (m, 2H), 6·55 (q, 7·57 (s, 3H, CH_3S), and 8·88 (t, 3H, ester CH_3).

(*b*) Ethyl 4-hydroxy-2-methylthiopyrimidine-5-carboxylate (VIII) (530 mg.) was added over 15 min. to a solution of lithium aluminium hydride (200 mg.) in tetrahydrofuran (15 ml.). After 2 hr. water (0·2 ml.) and acetic acid (0·3 ml.) were added, and the reaction mixture was filtered.

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The residue was extracted with ethyl acetate (3 × 60 ml.), and the combined filtrates were evaporated. The residue (62 mg.) when subjected to preparative t.l.c. in (G) gave one major band (R_F 0·7) which was extracted to give a solid (25 mg., 5%) shown to be the oxotetrahydropyrimidine (XI) (u.v. and i.r. spectra).

Ethyl 2-Methylthio-4-thiocyanato-1,6-dihydropyrimidine-5-carboxylate (XXVIII).— The chlorodihydropyrimidine (XV) (1·17 g.), potassium thiocyanate (470 mg.), ethyl acetate (20 ml.), and acetone (5 ml.) were stirred at 20° for 2 hr., and the solution was filtered. The filtrate was evaporated and the residue subjected to preparative t.l.c. in (D), using multiple elution, to give one major yellow band. This was extracted and the solid obtained (660 mg.) when recrystallised from benzene–light petroleum gave the *thiocyanatodihydropyrimidine* (XXVIII) (480 mg., 37%) as yellow prisms, m. p. 195—196° (decomp.) (Found: C, 41·7; H, 4·4; N, 15·9; S, 25·0. $C_9H_{11}B_3O_2S_2$ requires C, 42·0; H, 4·3; N, 16·3; S, 24·9%), $\nu_{max.}$ (CH_2Cl_2) 3240 (NH), 2160 cm.$^{-1}$ (SCN), $\lambda_{max.}$ 257 and 360 mμ (1·22 and 0·77), $\lambda_{max.}$ at pH 2 255 and 363 mμ (1·14 and 0·77).

2,4-*Bismethylthio-5-methylpyrimidine* (XX).—Ethyl 2,4-bismethylthiopyrimidine-5-carboxylate (IX) (3·1 g.) in ether (100 ml.) was added with stirring over 1 hr. to a suspension of lithium aluminium hydride (760 mg.) in ether (100 ml.). After stirring for 1 hr., the reaction was heated under reflux for 3 hr., and then ethyl acetate (5 ml.), water (1 ml.), and acetic acid (2 ml.) were added, and the reaction mixture was filtered. The residue was extracted with acetone (200 ml.) and the combined filtrates evaporated to give a residue (1·88 g.). This was purified by preparative t.l.c. in (E) several times, the component having R_F 0·9 being extracted, to finally give an oil (250 mg., 11%), which when crystallised from light petroleum (b. p. 60—80°) gave the *5-methyl pyrimidine* (XX) as prisms (60 mg.), m. p. 35·5—36·5° (Found: C, 45·1; H. 5·4; N, 15·1; S, 34·4%), $\lambda_{max.}$ 254 and 305 mμ (2·18 and 0·63).

Ethyl 4-Acetamido-2-hydroxypyrimidine-5-carboxylate (XXX).—Ethyl 4-amino-2-hydroxypyrimidine-5-carboxylate (XXIX) (4·07 g.), pyridine (10 ml.), and acetic anhydride (10 ml.) were shaken for 4 hr., and the solution was filtered. The filtrate was evaporated almost to dryness under reduced pressure and ethyl acetate added to give the *acetamido-pyrimidine* (XXX) (3·1 g.). A sample was purified by dissolving in dimethyl formamide–ethyl acetate (2 : 1), filtering the solution, and precipitating the acetyl derivative with ethyl acetate, m. p. 217° (decomp.) (Found: C, 48·0; H, 4·8; N, 18·8. $C_9H_{11}N_3O_4$ requires C, 48·0; H, 4·9; N, 18·65%).

Ethyl 4-Acetamido-2-hydroxy-3,6-dihydropyrimidine-5-carboxylate (XXXI) *and Ethyl 4-Amino-2-hydroxy-3,6-dihydropyrimidine-5-carboxylate* (XXXII).—The acetamidopyrimidine (XXX) (500 mg.) was dissolved in warm dimethyl formamide (12 ml.), the solution cooled to 20°, and a solution of lithium borohydride (50 mg.) in dimethyl formamide (3 ml.) added. After 4 hr. the solution was adjusted to pH 4 (2NHCl), then to pH 7 (NH_4OH), and then evaporated under reduced pressure, initially at 45° and finally at 55°. Water (10 ml.) was added, and the solid filtered off (400 mg.), m. p. 180—182°. The solid was extracted with chloroform, and the filtrate was evaporated and the residue subjected to preparative t.l.c. in (H), the plates being eluted three times. The major band, after extraction gave a solid (280 mg., 55%) which when recrystallised from ethyl acetate (15 ml.) gave the *acetamido-dihydropyrimidine* (XXXI) (173 mg.) as needles, m. p. 190—190·5° (Found: C, 47·8; H, 6·0; N, 18·5. $C_9H_{23}N_3O_4$ requires C, 47·6; H, 5·8; N, 18·5%), $\lambda_{max.}$ 215 and 308 mμ (1·44 and 1·27). The n.m.r. spectrum ($CDCl_3$) showed peaks at τ −1·61, 0·02, and 3·62 (all s, 1H, 3NH), 5·80 (q, 2H, ester CH_2), 5·86 (s, 2H, ring CH_2), 7·8 (s, 3H, CH_3CO), and 8·7 (t, 3H, ester CH_3).

The solid insoluble in chloroform (97 mg.) was subjected to preparative t.l.c. in (J), and the major band (R_F 0·8) extracted to give a solid (39 mg., 10%), which when recrystallised from ethanol (5 ml.) gave the *aminodihydropyrimidine* (XXXII) (28 mg.), m. p. 254—258° (Found: C, 45·5; H, 6·0; N, 22·8. $C_7H_{11}N_3O_3$ requires C, 45·4; H, 6·0; N, 22·7%), $\lambda_{max.}$ 286 mμ (1·93). The n.m.r. spectrum (DMSO, figures corrected from those at 100 mc./sec.) showed peaks at τ 1·86 and 3·32 (both s, 1H, 2NH), 3·69 (s, 2H, NH_2), 6·03 (q, 2H, ester CH_2), 6·24 (s, 2H, ring CH_2), and 8·88 (t, 3H, ester CH_3).

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