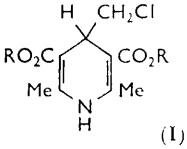
443. *Preparation and Reactions of Some Derivatives of Azepine*

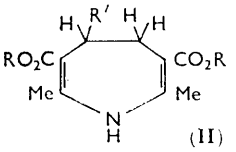
By M. Anderson and A. W. Johnson

The solvolysis of the esters of 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylic acid with sodium ethoxide causes ring expansion with the formation of the 4-ethoxy-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylic esters (II; R′ = OEt). These compounds lose ethanol readily and form derivatives of the 4*H*-azepine ring system (V) which, on heating, tautomerise to the 3*H*-azepine esters (VIII). Several reactions of these compounds are described including their reconversion to the original dihydropyridines, and base-catalysed ring opening reactions to give pyrrolic derivatives. Hydrogenation of the 4*H*-azepines yields the 4,5-dihydro-1*H*-azepines in the first place and then the perhydroazepines. The dihydroazepines also undergo ring-opening reactions to give a series of open-chain compounds and finally, by cyclisation, 1-acetyl-2-methylcyclopent-1-ene.

In a previous Paper,[1] we described the ring expansion of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) to the dihydroazepine (II; R = Et, R′ = CN) by the action of cyanide. It was observed that the dihydroazepine was smoothly degraded by ethanolic potassium hydroxide to ethyl acrylate as well as the pyrrole (III), and that by the action of nitrous acid [2] it could be rearranged to the furo-[2,3,*b*]pyridine (IV; X = O). This rearrangement of compound (II; R = Et, R′ = CN) was also accomplished by the action of silver nitrate except that in this case the product was accompanied by the 3,7-azaindene (IV; X = NH). The reactivity of the dihydropyridine (I; R = Et) has led us to examine the reaction of it, as well as the corresponding dimethyl ester, with other bases. The cyanodihydroazepine (II; R = Me, R′ = CN) has also been prepared from the dihydropyridine (I; R = Me) with cyanide.



(I)



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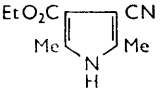
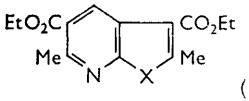


(III)

When the dihydropyridines (I; R = Me or Et) were treated with sodium ethoxide under various experimental conditions, three types of product could be obtained and the formation

[1] P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams, *J.*, 1963, 4819.
[2] E. Bullock, B. Gregory, and A. W. Johnson, *J.*, 1964, 1632.

of all three involved rearrangement of the dihydropyridine ring system. In cold ethanolic solution the products were the ethoxydihydroazepines (II; R = Me or Et, R′ = OEt) which exhibited NH absorption in the infrared spectrum as well as characteristic ultraviolet light absorption similar to that of the cyanodihydroazepines (II; R = Me or Et, R′ = CN). Although the diethyl ester (II; R = Et, R′ = OEt) was an oil, the dimethyl ester (II; R = Me, R′ = OEt) was crystalline.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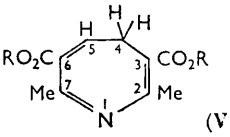
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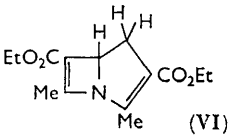
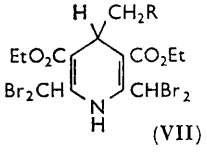

(VI)

The ethoxydihydroazepines were relatively unstable and readily eliminated ethanol, *e.g.*, by gentle warming or even by keeping solutions in carbon tetrachloride at room temperature, to form compounds which could also be obtained directly from the dihydropyridines (I; R = Me or Et) by reaction with sodium ethoxide in boiling ether. These products have been formulated as the 4*H*-azepines (V; R = Me or Et) although valency tautomeric bicyclic formulations such as (VI) may make a contribution to the overall structure. The 4*H*-azepine diethyl ester was a golden-coloured oil and was also obtained both from compound (I; R = Et) by the action of potassium cyanate in boiling ethanol when ethyl allophanate, $NH_2{\cdot}CO{\cdot}NH{\cdot}CO_2Et$, was formed as a by-product, and from the cyanodihydroazepine (II; R = Et, R′ = CN) by pyrolysis at 265° when hydrogen cyanide was liberated. A similar series of rearrangement reactions has been carried out with the dihydropyridine methyl ester (I; R = Me), when the 4*H*-azepine dimethyl ester (V; R = Me), a colourless crystalline solid, was obtained. The 4*H*-azepine structure for these esters (V; R = Et or Me) is proposed, partly as a consequence of the observed chemical reactions, *e.g.*, hydrogenation and alkaline fission (see below), and partly because of the interpretation of the nuclear magnetic resonance (n.m.r.) spectra. Thus, the spectrum of the ethyl ester (determined on an AEI MS 2 instrument operating at 60 Mc./sec.) contained poorly resolved multiplets at τ 7·0—6·4 and 8·3—7·9 which were ascribed to the two hydrogen atoms of the nuclear methylene group. Each of these C_4 protons coupled with the other and also with the adjacent C_5 proton which itself was associated with a triplet centred at τ 2·94. The nuclear methyl groups appeared as singlets at τ 7·75 and 7·59 and the ester ethyl groups as a triplet at τ 8·66 (J 7·2 c./sec.; CH_3) and a quartet at τ 5·78 (J 7·2 c./sec.; CH_2). A better spectrum (determined on a Varian 100 Mc./sec. instrument) was obtained for the dimethyl ester (V; R = Me) when the multiplets associated with the two C_4 methylenic protons were clearly revealed at τ 8·20 and 6·80. The C_5 proton appeared as a triplet at τ 2·97 (J 8·1 c./sec.) and the nuclear methyl groups as singlets at τ 7·82 and 7·65. The ester methyl groups also were revealed as singlets at τ 6·32 and 6·30.

The rearrangement of the 4-chloromethyl-1,4-dihydropyridines (I) to 4*H*-azepines (V) with loss of hydrogen chloride, brought about by a variety of nucleophilic reagents,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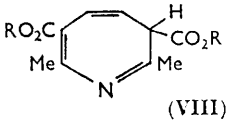
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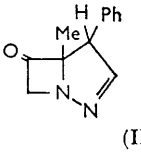

(IX)

has been found to be reversible. When the 4*H*-azepine esters were treated with hydrochloric acid, the original dihydropyridine esters (I; R = Me or Et) were re-formed and a similar reaction was obtained with hydrobromic acid to give the 4-bromomethyl-1,4-dihydropyridine ester. Similar rearrangements of the 4-ethoxy-4,5-dihydroazepine esters

under these conditions merely involved an initial loss of alcohol to give the 4*H*-azepine which then rearranged as before. When the 4*H*-azepine ethyl ester (V; R = Et) was treated with bromine in carbon tetrachloride solution, the nuclear methyl groups were converted to dibromomethyls and the hydrogen bromide formed in the reaction caused rearrangement of the ring to yield the yellow pentabromo-derivative (VII; R = Br).

Bromination of the original dihydropyridine (I; R = Et) with excess of bromine in carbon tetrachloride gave the tetrabromochloro-derivative (VII; R = Cl).

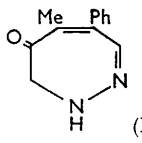
When the dihydropyridine (I; R = Et) or the 4*H*-azepine (V; R = Et) was treated with sodium ethoxide in boiling ethanol, the 3*H*-azepine ester (VIII; R = Et) was obtained. The same compound could also be prepared by pyrolysis of the cyanodihydroazepine (II; R = Et, R′ = CN) at 315—320° or by heating the 4*H*-azepine (V; R = Et) at this temperature for a few minutes. The corresponding dimethyl ester of the 3*H*-azepine was obtained by similar pyrolytic reactions, as well as by treatment of the dihydropyridine (I; R = Me) with sodium acetate in hot dimethyl sulphoxide. The formulation of compound (VIII) as a 3*H*-azepine rests largely on the interpretation of its infrared (saturated and unsaturated ester carbonyl groups) and n.m.r. spectra (see Experimental section).

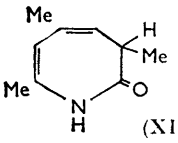
Simple azepine derivatives have been recognised only recently. Thus Huisgen and Appl [3] showed that the so-called " dibenzamil," prepared [4] by thermal decomposition of phenyl azide in presence of aniline, was a 2-anilino-2(?)*H*-azepine, although the precise location of the " extra " hydrogen atom was not determined. Paquette [5] has described the 2-ethoxy-, 2-ethylthio-, and 2-piperidino-derivatives of 3,5,7-trimethyl-3*H*-azepine, the position of the extra hydrogen atom being assigned by interpretation of the n.m.r. spectra. Benzene has been converted into 1-ethoxycarbonyl-1*H*-azepine by reaction with ethyl azidoformate, $N_3 \cdot CO_2Et$, under photolytic conditions,[6] and this azepine ester has been converted into 3*H*-azepine itself by hydrolysis and decarboxylation.[7]

It is evident that the 3*H*-azepine ring contains the most stable arrangement of bonds within the azepine ring and the rearrangement of 4*H*- to 3*H*-azepines probably involves transannular interactions which are well recognised in related seven-membered ring systems, *e.g.*, the 1,5-hydrogen shifts in 7-deuterocycloheptatriene [8] and other substituted cycloheptatrienes.[9] The formation of derivatives of bicyclo[3,2,0]heptanes by irradiation of cycloheptadienes,[10,11] including eucarvone,[12] or by solvolysis reactions, involving Wagner shifts, of certain terpene derivatives and related homocyclic compounds [13] is well known as is the formation of derivatives of bicyclo[3,2,0]heptadienes by irradiation of cycloheptatrienes [10] including tropolones [14] and colchicines.[15] Moore and his colleagues [16] have described the formation of 5-methyl-4-phenyl-1,2-diazabicyclo[3,2,0]hepten-6-one (IX), which was easily isomerised to the diazepinone (X). More recently the photoisomerisations

[3] R. Huisgen and M. Appl, *Chem. Ber.*, 1958, **91**, 1, 12; 1959, **92**, 2961.
[4] L. Wolff, *Annalen*, 1912, **394**, 59.
[5] L. A. Paquette, *J. Amer. Chem. Soc.*, 1962, **84**, 4987; 1963, **85**, 4053.
[6] K. Hafner and C. König, *Angew. Chem., Internat. Edn*, 1963, **2**, 96; W. Lwowski, T. J. Maricich, and T. W. Mattingley, *J. Amer. Chem. Soc.*, 1963, **85**, 1200.
[7] K. Hafner, *Angew. Chem., Internat. Edn*, 1964, **3**, 165.
[8] A. P. Ter Borg, H. Kloosterziel, and N. Van Meurs, *Rec. Trav. chim.*, 1963, **82**, 717.
[9] A. P. Ter Borg and H. Kloosterziel, *Rec. Trav. chim.*, 1963, **82**, 741; O. L. Chapman and G. W. Borden, *Proc. Chem. Soc.*, 1963, 221; E. Weth and A. S. Dreiding, *ibid.*, 1964, 59.
[10] W. G. Dauben and R. L. Cargill, *Tetrahedron*, 1961, **12**, 186.
[11] O. L. Chapman, D. J. Pasto, *et al.*, *J. Amer. Chem. Soc.*, 1962, **84**, 1213, 1220.
[12] G. Büchi and E. M. Burgess, *J. Amer. Chem. Soc.*, 1960, **82**, 4333; J. J. Hurst and G. H. Whitham, *J.*, 1963, 710.
[13] S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 505; E. E. van Tamelen and C. I. Judd, *ibid.*, 1958, **80**, 6305; K. B. Wiberg and G. W. Klein, *Tetrahedron Letters*, 1963, 1043.
[14] W. G. Dauben, K. Koch, and W. E. Thiessen, *J. Amer. Chem. Soc.*, 1959, **81**, 6087; O. L. Chapman *et al.*, *ibid.*, 1960, **82**, 3642; 1961, **83**, 1768; E. J. Forbes, *J.*, 1955, 3864; P. D. Gardner, R. L. Brandon, and G. R. Haynes, *J. Amer. Chem. Soc.*, 1957, **79**, 6334.
[15] O. L. Chapman, H. G. Smith, and R. W. King, *J. Amer. Chem. Soc.*, 1963, **85**, 803, 806; W. G. Dauben and D. A. Cox, *ibid.*, p. 2130.
[16] J. A. Moore *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 6026, 6029; 1962, **84**, 3022.

of 1,3-dihydro-3,5,7-trimethyl-2*H*-azepin-2-one (XI) and its *N*-methyl derivative to the bicyclic compounds (XII; R = H, Me) have been reported from two laboratories.[17]


(X)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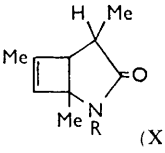
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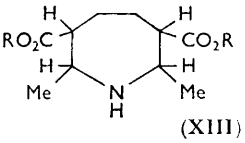
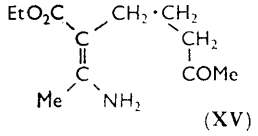
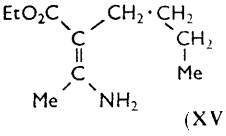
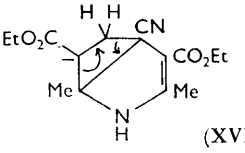

(XIII)


(XIV)

Both the 4*H*-azepines (V; R = Me or Et) and the 3*H*-azepines (VIII; R = Me or Et) on complete hydrogenation in ethanolic solution in presence of platinum gave the saturated products (XIII; R = Me or Et). However, when the dimethyl ester (V; R = Me) was hydrogenated in cyclohexane solution, a crystalline monocyclic dihydroazepine derivative (II; R = Me, R′ = H) was obtained, the structure of which was suggested by spectral measurements (*e.g.*, presence of NH group and ultraviolet absorption similar to that of the cyanodihydroazepine, II; R = Me, R′ = CN), and confirmed by hydrogenation to the saturated perhydroazepine (XIII; R = Me). When the dihydroazepine (II; R = Me, R′ = H) was heated with aqueous potassium hydroxide, ammonia was evolved and an oil with a strong peppermint odour was formed. This was identified as 1-acetyl-2-methylcyclopentene [18] (XIV) by its spectra and by the formation of derivatives. The formation


(XV)


(XVI)


(XVII)

of compound (XIV) from (II; R = Me, R′ = H) is visualised as a double nucleophilic displacement of the imino-group by two hydroxyl groups in the iminobis-(β-crotonic ester) system with subsequent hydrolysis and decarboxylation of the β-keto-ester groups and a final internal cyclisation of the 1,5-diketone. In support of this mechanistic view, it was found that the acyclic monoamino-intermediate (XV), together with (XIV), could be isolated from compound (II; R = Me, R′ = H) by treatment with ethanolic potassium hydroxide. The amine (XV) could be converted into compound (XIV) by treatment with aqueous potassium hydroxide and its ultraviolet absorption spectrum was similar to that of ethyl 2-(1′-aminoethylidene)hexanoate (XVI), prepared by treatment of ethyl 2-acetylhexanoate with ammonia.

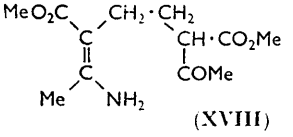
The course of the alkaline fission of the dihydroazepine ring (II) is profoundly affected by the presence of the 4-cyano-group, *i.e.*, (II; R = Et, R′ = CN). The formation of the pyrrole (III) from the cyanodihydroazepine by the action of alkali involves transannular interaction [*e.g.*, to (XVII)], prompted by carbanion formation at C_4, which takes precedence over nucleophilic displacement at the C_7 position as observed with compound (II; R = Me, R′ = H).

The 4,5-dihydro-3*H*-azepine esters are also hydrolysed easily by acids at room temperature; the dimethyl ester with hydrochloric acid initially yields compound (XVIII) which is rapidly hydrolysed to the keto-ester (XIX).

Reaction of the dihydropyridine (I; R = Et) with dilute ethanolic sodium hydroxide gave a crystalline acid, $C_{12}H_{15}NO_4$, which has been identified as β-(3′-ethoxycarbonyl-2′-methyl-1′-pyrrolyl)crotonic acid (XX; R = Et; R′ = H). The formation of the acid probably involves the 4*H*-azepine esters (V; R = Me or Et) as intermediates for the same acid (XX; R = Et, R′ = H) was obtained by treatment of (V; R = Et) with ethanolic

[17] O. L. Chapman and E. D. Hoganson, *J. Amer. Chem. Soc.*, 1964, **86**, 498; L. A. Paquette, *ibid.*, p. 500.
[18] T. R. Marshall and W. H. Perkin, *J.*, 1890, **57**, 241.

sodium hydroxide under similar conditions. The corresponding diethyl ester (XX; R = R′ = Et) was hydrogenated to ethyl β-(3′-ethoxycarbonyl-2′-methyl-1′-pyrrolyl)-butyrate, which was also synthesised by condensation of 1,2-dichloroethyl ethyl ether, ethyl acetoacetate, and ethyl 3-aminobutyrate.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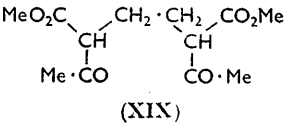
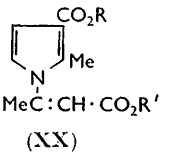
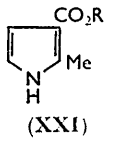

(XIX)


(XX)


(XXI)

Treatment of the dihydropyridine (I; R = Et) with hot aqueous ethanolic sodium acetate or with ammonium hydroxide at room temperature caused a similar rearrangement but in this case the crotonic ester side chain was eliminated giving the pyrroles (XXI) and ethyl acetoacetate. Once again the same products were obtained from the 4*H*-azepine ester (V; R = Et) by treatment with ammonium hydroxide, thus emphasising the ease of rearrangement of the 4*H*-azepine ring system (V) to pyrrolic derivatives of types (XX) and (XXI).

Experimental

Ultraviolet spectra were determined on ethanolic solutions with a Unicam S.P. 700 instrument and infrared spectra were measured for carbon tetrachloride solutions (except where otherwise stated) with a Unicam S.P. 100 instrument (corrected values given). Nuclear magnetic resonance spectra were measured for carbon tetrachloride solutions on an AEI RS2 instrument operating at 60 Mc./sec. M. p.s are uncorrected (Kofler block).

Dimethyl 4-Chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate [19] (I; R = Me).—1,2-Dichloroethyl ethyl ether [20] (50 ml.) was added to methyl 2-aminocrotonate [1] (50 g.) and the mixture shaken until a slurry of crystals had been produced. The mixture was then treated with ammonium hydroxide solution (300 ml. of 10%) and after a short time the lower layer became yellow as the exothermic reaction commenced. As soon as the vigorous reaction had subsided the flask was cooled in ice–water, and kept for 1 hr. at 0°. The yellow *product* was separated and washed with water and then small amounts cold ethanol and ether, affording yellow crystals (32·6 g.), m. p. 152—154°, raised to 158—159° after crystallisation from ethanol (Found: C, 53·0; H, 5·85; N, 5·4; Cl, 12·4. $C_{12}H_{16}ClNO_4$ requires C, 53·0; H, 5·85; N, 5·1; Cl, 13·0%). Light absorption: max. at 232 and 349 mμ; ε, 18,000 and 7360, respectively. The infrared spectrum ($CHCl_3$ solution) contained bands at 3441 and 3339 (NH) and 1701 (CO_2Me) cm.$^{-1}$. The n.m.r. spectrum ($CHCl_3$ solution) contained peaks at τ 3·32 (s; NH); 5·68 (t; J = 4·22 c./sec.; 4-CH); 6·25 (s; CO_2CH_3); 6·48 (d; J = 4·51 c./sec.; CH_2Cl) and 7·64 (s; C–CH_3).

Dimethyl 4-Cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (II; R = Me, R′ = CN).—Potassium cyanide (3·6 g.) was added to a stirred solution of the foregoing chloro-compound (3 g.) in dimethyl sulphoxide (40 ml.). After being stirred at room temperature for 18 hr., the light brown solution was diluted slowly with water when a colourless, granular precipitate was obtained. This was separated and dried (2·67 g.) and then crystallised from methanol when the *product* was obtained as colourless prisms, m. p. 187—188° (Found: C, 59·2; H, 6·0; N, 10·6%. $C_{13}H_{16}N_2O_4$ requires C, 59·1; H, 6·1; N, 10·6%). Light absorption max. at 229 and 326 mμ; ε, 13,870 and 14,140, respectively. The infrared spectrum ($CHCl_3$ solution) contained bands at 3419, 3347 (NH), 2240 (CN), and 1709 (CO_2Me) cm.$^{-1}$. The n.m.r. spectrum ($CHCl_3$ solution) contained peaks at 4·41 (s; NH); 5·44 (q; J_{AX} = 6·2 c./sec., J_{BX} = 1·5 c./sec.; CH·CN); 6·20 (s; CO_2CH_3); 6·43 (q; J_{AB} = 15·1 c./sec., J_{AX} = 6·2 c./sec.; H^A of CH_2); 7·52 (d; J_{AB} = 15 c./sec.; H^B of CH_2); 7·56 and 7·59 τ (both s; C–CH_3 groups). The $CH{\cdot}CH_2$ appears as an ABX system.[19]

Dimethyl 4-Ethoxy-2,7-dimethyl-4,5-dihydroazepine-3,6-dicarboxylate (II; R = Me, R′ = OEt).—A solution of sodium ethoxide (2·55 g.) in anhydrous ethanol (60 ml.) was added dropwise over 20 min. to a stirred solution of dimethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Me) (10·2 g.) in anhydrous ethanol (150 ml.) at room

[19] Cf. ref. 1.
[20] A. W. Johnson, *J.*, 1946, 895.

temperature. A transient yellow colour was produced after the addition of each drop of the sodium ethoxide solution and the colour persisted towards the end of the reaction. After the mixture had been stirred for a further hour at room temperature the precipitated sodium chloride was separated and the filtrate evaporated to dryness at room temperature *in vacuo*. The resulting oil contained some sodium chloride which was removed by extraction of the oil into ether several times and removal of the salt by filtration. After removal of the solvent at room temperature the resulting oil was kept overnight *in vacuo* and slowly crystallised. The crude product (10·05 g.) was crystallised from ether–light petroleum to give the *product* as needles (8·2 g.), m. p. 78—81°, raised to 86—88° by repeated recrystallisation (Found: C, 59·0; H, 7·4; N, 4·95. $C_{14}H_{21}NO_5$ requires C, 59·35; H, 7·45; N, 4·95%). Light absorption (n-hexane): max. at 223, 247, and 310 mμ; ε 13,400, 4770, and 11,700, respectively.

Diethyl and Dimethyl 2,7-Dimethyl-4H-azepine-3,6-dicarboxylate (V; R = Et or Me).—(*a*) Finely divided sodium (0·77 g.) was prepared in xylene (30 ml.), cooled, and the xylene removed by decantation. The sodium was washed with anhydrous ether (3 × 50 ml.) and then anhydrous ethanol (2 ml.) was added to a suspension of the sodium in dry ether (90 ml.). The mixture was heated under gentle reflux overnight with stirring. The suspension of sodium ethoxide was added to a solution of dry diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate [1] (10 g.) in dry ether (600 ml.), a fine precipitate immediately appeared. The reaction mixture was heated under gentle reflux with stirring for 18 hr. and then cooled. The sodium chloride was separated and the ether removed under reduced pressure until the volume was *ca.* 100 ml. This solution was washed with water, dried, and the remainder of the solvent removed under reduced pressure to give the *product* as a golden oil (7·3 g., 83%), which was distilled. The main fraction had b. p. 142—145°/0·1 mm., n_D^{22} 1·5198 (Found: C, 62·9; H, 7·05; N, 5·85. $C_{14}H_{19}NO_4$ requires C, 63·3; H, 7·15; N, 5·3%); $\lambda_{max.}$ (hexane solution) 216, 269, and 326 mμ; ε 26,800, 3945, and 2555, respectively. The infrared spectrum contained an ester band at 1722 (broad) and another band at 1628 cm.$^{-1}$.

(*b*) A solution of the chloromethyl-1,4-dihydropyridine (I; R = Et) (5 g.) in ethanol (150 ml.) was treated with potassium cyanate (2·7 g.) and the mixture heated under reflux for 3 hr. on the water-bath. The inorganic material was separated and the volume of the filtrate reduced to *ca.* 30 ml. by distillation. After the liquid had been cooled, ether (50 ml.) was added, a colourless solid being precipitated. Water (50 ml.) was added and the ethereal layer separated, dried, and the solvent removed under reduced pressure to yield a golden-coloured oil (3·47 g., 79%) which from its ultraviolet and infrared spectra was shown to be identical with the product of the previous experiment.

The colourless solid was separated from the aqueous layer and dried over phosphorus pentoxide; it was then obtained as microcrystals, (0·3 g.), m. p. 185—190°, raised to 194—195° (lit.,[21] 195°) after sublimation (Found: C, 36·4; H, 5·85; N, 21·7. Calc. for $C_4H_8N_2O_3$: C, 36·35; H, 6·1; N, 21·2%). The ultraviolet absorption showed no max. above 220 mμ. The infrared spectrum (KBr disc) showed bands at 1705 (amide) and 1735 cm.$^{-1}$ (ester) in the carbonyl region and also showed evidence (band at 3440 and 3200 (broad) cm.$^{-1}$) of a bonded NH group. The sample was shown to be ethyl allophanate by direct comparison with an authentic specimen.

Dimethyl Ester.—(*a*) A suspension of sodium ethoxide in ether (90 ml.) was prepared as above (preparation (*a*)) from sodium (0·85 g.) and added to a solution of dimethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (10 g.) in anhydrous ether (600 ml.). The mixture was treated and worked up as above (preparation (*a*)) and yielded the *product* as a pale yellow oil which rapidly crystallised (7·97 g., 92%), m. p. 68—73°. This was crystallised from ether, or from aqueous ethanol, when it formed broad, colourless laths, m. p. 76·5—77·5° (Found: C, 60·7; H, 6·35; N, 6·05. $C_{12}H_{15}NO_4$ requires C, 60·75; H, 6·35; N, 5·9%). Light absorption: max. at 216, 275, and 328 mμ; ε 20,700, 3600, and 2900, respectively. The infrared spectrum contained bands at 1728 and 1719 (ester groups) and 1629 cm.$^{-1}$.

(*b*) A solution of dimethyl 4-ethoxy-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (II; R = Me, R′ = OEt) (197 mg.) in carbon tetrachloride (10 ml.) was kept at room temperature for 4 hr., the infrared spectrum then indicating the presence of ethanol and the 4*H*-azepine ester. Removal of the solvent *in vacuo* gave an oil which was chromatographed on silica gel (7 × 0·9 cm.), ether being used as eluant. The fraction showing absorption at 218 mμ (ether

[21] J. Bougault and J. Leboucq, *Bull. Soc. chim. France*, 1930, **47**, 594.

solution) was collected and the solvent removed, the resulting oil then crystallised on cooling and trituration. After crystallisation from ether the product formed short, colourless needles, m. p. 76—77°, identical with the ester obtained from the previous experiment.

(*c*) A solution of dimethyl 4-ethoxy-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (II; R = Me, R′ = OEt) (205 mg.) in dry ether was heated under reflux overnight. The ultraviolet absorption showed no change after this time showing that no elimination of ethanol had occurred. An excess of sodium ethoxide (50 mg.) was added and the mixture heated under reflux for a further 30 min.; the ultraviolet absorption then indicated that complete conversion into the 4*H*-azepine ester had taken place (max. at 216, 275, and 323 mμ). The sodium ethoxide was separated, more ether (40 ml.) added to the filtrate which was washed and dried, and the solvent removed *in vacuo*. The oily residue (132 mg.) solidified on cooling, and crystallisation from ether gave the 4*H*-azepine dimethyl ester as colourless prisms, m. p. 76—77°, identical with the previous two preparations.

Diethyl 2,7-Dimethyl-3H-azepine-3,6-dicarboxylate (VIII; R = Et).—A solution of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) (2 g.) in dry ethanol (20 ml.) was added to a solution of sodium ethoxide (0·59 g.) in ethanol and the turbid solution was heated under reflux for 1½ hr. The product was cooled, the precipitated sodium chloride separated off, and the volume of the filtrate reduced to one-half by evaporation under reduced pressure. Ether (30 ml.) was added to the remainder and the solution washed with water (30 ml.). The aqueous layer was extracted with ether (2 × 30 ml.) and the combined ethereal extracts washed and the solvent removed leaving a reddish oil (0·8 g.) which was purified by distillation from a bulb tube to give the *azepine* as an orange-yellow oil, b. p. (bath temp.) 122—123°/0·2 mm., n_D^{24} 1·5094 (Found: C, 63·3; H, 7·7; N, 5·2. $C_{14}H_{19}NO_4$ requires C, 63·3; H, 7·2; N, 5·3%). Light absorption: max. at 282 mμ; ε 6150 with an inflection at 235 mμ, ε 4980. The infrared spectrum contained bands at 1757 (saturated ester), 1720 (unsaturated ester) and 1633 cm.$^{-1}$. The n.m.r. spectrum contained signals at τ 7·85 (d; $J_{3,4}$ 5·6 c./sec.; 3-H), a pair of doublets centred at 4·35 ($J_{4,3}$ 5·6 c./sec.; $J_{4,5}$ 9·3 c./sec.; 4-H), 3·24 (d; $J_{5,4}$ 9·3 c./sec.; 5-H), 7·97 (s) and 7·54 (s) corresponding to 2- and 7-methyl groups, 8·64 (t; J 7·2 c./sec.; methyl of 3-ester), 8·61 (t; J 7·1 c./sec.; methyl of 6-ester), 5·72 (q; J 7·2 c./sec.; methylene of 3-ester) and 5·64 (q; J 7·1 c./sec.; methylene of 6-ester).

Dimethyl 2,7-Dimethyl-3H-azepine-3,6-dicarboxylate (VIII; R = Me).—Dimethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Me) (30 g., 1 mole) was added to a solution of anhydrous sodium acetate (18 g., 2 moles) in dimethyl sulphoxide (600 ml.). The mixture was then heated on the water-bath for 3 hr. with shaking initially to dissolve the dihydropyridine. The dark red solution was distilled *in vacuo* until most of the solvent had been removed and the semi-solid residue was extracted with ether several times (total vol., 500 ml.). After removal of the solvent from the extract, the residue was distilled under reduced pressure and the main fraction, b. p. 130—132°/1·5 mm., (13·6 g.) collected. A portion was redistilled in order to provide an analytical sample, n_D^{23} 1·5268 (Found: C, 60·75; H, 6·45; N, 5·9. $C_{12}H_{15}NO_4$ requires C, 60·75; H, 6·35; N, 5·9%). Light absorption (hexane): max. at 243 and 280 mμ; ε 4550 and 6300, respectively. The infrared spectrum contained bands at 1751 (saturated ester carbonyl), 1724 (unsaturated ester carbonyl) and 1634 cm.$^{-1}$. The n.m.r. spectrum contained signals at τ 7·87 (d; $J_{3,4}$ 5·5 c./sec.; 3-H), a pair of doublets centred at 4·37 ($J_{4,3}$ 5·5 c./sec.; $J_{4,5}$ 9·3 c./sec.; 4-H), 3·25 (d; $J_{5,4}$ 9·3 c./sec.; 5-H), 7·95 (s) and 7·52 (s) corresponding to 2- and 7-methyl groups, 6·67 (s) and 6·09 (s) corresponding to 3- and 6-ester methyl groups, respectively.

Pyrolyses of 4-Cyano-2,7-dimethyl-4,5-dihydroazepine-3,6-dicarboxylic Esters (II; R′ = CN).—The ester, either alone or mixed with washed copper powder, was introduced into a soda-glass tube (5—6 mm. internal diam.) and heated in a sublimation block (12 cm. long). The pressure was reduced to 0·02—0·05 mm. and fractionation of the volatile products was achieved by use of a copper tube protruding 15 cm. from the heating block and surrounding the glass tube.

(*a*) *Diethyl ester.* (i) An intimate mixture of the cyano-compound (20 mg.) and copper powder (2 g.) was heated at 265°. A colourless oil rapidly appeared in the cooler part of the tube and the pyrolysis was stopped as soon as the distillate contained any coloured material. Three zones of sublimed material were present; the first was unchanged starting material, the second was a mixture of starting material and pyrolysis product, and the most volatile product was a colourless oil, the ultraviolet and infrared spectra of which showed it to be diethyl

2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Et) (above); $\lambda_{max.}$ (hexane), 216, 269, and 326 mμ; $\nu_{max.}$ 1722 cm.$^{-1}$ (ester carbonyl).

(ii) The cyano-ester (20 mg.) was introduced into a sublimation tube followed by a column of pure quartz sand (*ca.* 10 cm.). The sand was heated in the block at 315—320° (15 min.) and then the tube gradually moved through the block so that the sample was distilled slowly through the preheated sand (15—20 min.). A colourless oil was thus obtained at the end of the copper tube. The oil was collected and shown to have $\lambda_{max.}$ 282 mμ, λ_{infl} 235 mμ. The infrared spectrum contained bands at 1720 and 1757 cm.$^{-1}$ (αβ-unsaturated and saturated ester groups, respectively). These spectra were identical with those of diethyl 2,7-dimethyl-3*H*-azepine-3,6-dicarboxylate (VIII) (above).

(*b*) *Dimethyl ester.* Similar pyrolytic experiments were carried out with the dimethyl ester. At 262°, the product showed spectra identical with those of dimethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate: $\lambda_{max.}$ 216, 275, and 323 mμ; $\nu_{max.}$ 1728 (ester carbonyl) cm.$^{-1}$.

At 364°, the volatile product showed spectra identical with those of dimethyl 2,7-dimethyl-3*H*-azepine-3,6-dicarboxylate: $\lambda_{max.}$ 243 and 280 mμ; $\nu_{max.}$ 1724 (αβ-unsaturated ester carbonyl) and 1751 (saturated ester carbonyl) cm.$^{-1}$.

*Pyrolysis of 2,7-Dimethyl-4*H*-azepine-3,6-dicarboxylic esters.*—These were pyrolysed at *ca.* 320° using the technique of sublimation through hot sand as detailed above. Both the diethyl and dimethyl esters gave volatile products, the spectra of which indicated that they were 2,7-dimethyl-3*H*-azepine-3,6-dicarboxylic esters (VIII).

*Dimethyl 2,7-Dimethyl-4,5-dihydro-1*H*-azepine-3,6-dicarboxylate* (II; R = Me, R′ = H).—A solution of dimethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Me) (3·092 g.) in purified cyclohexane (100 ml.) was hydrogenated at room temperature and pressure in presence of Adams platinum catalyst. The crystalline product tended to separate out during the reaction and the addition of fresh catalyst was necessary. The solution was warmed to dissolve the product after the absorption of one mole of hydrogen, and the catalyst was removed. The solvent was distilled off under reduced pressure leaving an oily residue which was dissolved in a small quantity of ether and chromatographed on a column of alumina (Spence type H) using ether as the eluant. The *product* was obtained from the early fractions of the chromatogram as a colourless oil which crystallised on cooling. It was recrystallised from light petroleum and was then obtained as large colourless prisms (1·52 g.), m. p. 90—92°. It could also be recrystallised from cyclohexane as long needles which sublimed at 80—85°/0·01 mm. to give colourless prisms, m. p. 91—92° (Found: C, 59·9; H, 7·15; N, 5·55. $C_{12}H_{17}NO_4$ requires C, 60·25; H, 7·15; N, 5·85%). Light absorption (n-hexane): max. at 226 and 321 mμ; ε 13,780 and 13,360 respectively with an inflection at 252 mμ, ε 3830. The infrared spectrum contained bands at 3426 and 3377 (NH), 1710 (ester carbonyl), and 1642 (C=C) cm.$^{-1}$. The n.m.r. spectrum ($CHCl_3$ solution) contained bands at τ 4·40 (s; NH), 6·24 (s; ester CH_3), 7·26 (nuclear CH_2), and 7·68 τ (nuclear CH_3).

Diethyl and Dimethyl Perhydro-2,7-dimethylazepine-3,6-dicarboxylate (XIII; R = Et or Me).—(*a*) A solution of diethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Et) (3·85 g.) in dry ethanol (100 ml.) was hydrogenated at atmospheric pressure in presence of Adams catalyst. Absorption of hydrogen continued for 3 days although absorption of the first molar equivalent occurred rapidly. After removal of the catalyst the solvent was evaporated leaving a pale yellow oil which was taken up in ether, washed, and then the solvent removed and the residue distilled. The main fraction (0·67 g.) had b. p. 138—140°/1 mm. and was redistilled, b. p. 109—110° (bath temp.) /0·3 mm., n_D^{25} 1·4716 (Found: C, 61·9; H, 9·0; N, 5·4. $C_{14}H_{25}NO_4$ requires C, 61·95; H, 9·3; N, 5·15%). The infrared spectrum contained bands at 1732 (not sharp; saturated ester carbonyls) and 3357 (NH) cm.$^{-1}$. The n.m.r. spectrum contained signals at τ 8·95 (d; *J* 7·1 c./sec.; 2- and 7-*C*-methyl groups), 8·67 (t; *J* 7·2 c./sec.; ester methyls) and 5·77 (q; *J* 7·2 c./sec.; ester methylenes). Shoulders to lower field on the absorptions associated with the ester ethyl groups are ascribed to non-equivalent conformations of the esters (cf. infrared ester carbonyl band).

(*b*) A similar hydrogenation of the corresponding 4*H*-azepine dimethyl ester gave *dimethyl-perhydro-2,7-dimethylazepine-3,6-dicarboxylate*, b. p. 92—94° (bath temp.)/0·05 mm., $n_D^{21.5}$ 1·4792 (Found: C, 59·3; H, 8·85; N, 5·55. $C_{12}H_{21}NO_4$ requires C, 59·7; H, 7·95; N, 5·8%). The infrared spectrum contained bands at 1741 and 1732 (saturated ester carbonyls) and 3357 (NH) cm.$^{-1}$.

(*c*) Hydrogenation of dimethyl 2,7-dimethyl-3*H*-azepine-3,6-dicarboxylate (VIII; R = Me) (2·16 g.) in methanol (50 ml.) in presence of Adams platinum catalyst gave an oil (2·21 g.)

which distilled at 96—98° (bath temp.)/0·2 mm. to give a colourless distillate (1·48 g.), the infrared spectrum of which was identical with that of the previous preparation. A sample distilled from a bulb-tube had n_D^{25} 1·4695. The n.m.r. spectrum contained signals at τ 9·02 (d; J 6·9 c./sec.; 2- and 7-*C*-methyl groups) and 6·39 (s; ester methyl groups). The latter signal showed a shoulder to lower field, again indicating non-equivalence of the ester groups.

(*d*) A solution of dimethyl 4,5-dihydro-2,7-dimethyl-1*H*-azepine-3,6-dicarboxylate (II; R = Me, R′ = H) (0·954 g.) in methanol (50 ml.) was hydrogenated at atmospheric pressure over Adams catalyst (0·10 g.). The absorption of hydrogen was slow and ceased after 5 days. Removal of catalyst and solvent gave a residue, the spectra of which indicated that a little unsaturated material still remained. This was separated by chromatography on alumina when the first fractions contained only saturated material (no infrared band at 1710 cm.$^{-1}$ associated with unsaturated ester carbonyl). Removal of the solvent gave a colourless oil (XIII; R = Me) (0·422 g.) which was distilled from a bulb-tube and had b. p. (bath temp.) 97—98°/0·07 mm., n_D^{25} 1·4698, and an infrared spectrum identical with those of the preceding two preparations.

β-(3-*Ethoxycarbonyl*-2-*methyl*-1-*pyrrolyl*)*crotonic Acid* (XX; R = Et, R′ = H).—(*a*) A solution of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) (5 g.) in ethanol (150 ml.) was treated with a solution of sodium hydroxide (1·84 g.) in water (500 ml.), and the mixture stirred for 24 hr. at room temperature. After being cooled to 5—10°, the solution was extracted with ether (200 ml.) and then made acid to Congo Red with hydrochloric acid. The acid solution was then extracted with ether and the extract was dried and the solvent removed. The oily residue was dissolved in the minimum amount of warm ethanol and then water was added until the solution just became turbid. After this mixture had been cooled and scratched, the acidic *product* (2·36 g., 60%) crystallised, m. p. 107—109°, raised to 109—110° after crystallisation from ethanol when it formed colourless hexagonal plates (Found, on a sample sublimed at 95—100°/0·01 mm.: C, 60·7; H, 6·5; N, 5·8. $C_{12}H_{15}NO_4$ requires C, 60·75; H, 6·35; N, 5·9%). Light absorption: max. at 248 mμ, ε 10,230. The ester carbonyl band in the infrared spectrum (chloroform solution) was at 1700 cm.$^{-1}$ and carboxylic acid bands at 1683 and 1672 cm.$^{-1}$. The n.m.r. spectrum contained bands at τ −0·05 (s; CO_2H), 3·46 (d; J 2·90 c./sec.; nuclear 2-CH), 3·61 (d; J 2·90 c./sec.; 3-CH), 3·96 (q; J 1·36 c./sec.; side-chain =CH), 5·58 (q; J 7·5 c./sec.; ester CH_2), 7·44 (s; 5-C–CH_3), 7·66 (d; J 1·18 c./sec.; side-chain =C–CH_3), 8·54 (t; J 7·51 c./sec.; ester CH_3).

(*b*) An aqueous solution of sodium hydroxide (12 ml. of 1%) was added to a solution of diethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Et) (250 mg.) in ethanol (5 ml.) and the mixture was stirred for 15 hr. at room temperature during which it became slightly yellow. The product was acidified with 50% hydrochloric acid, cooled (ice) and extracted with ether (2 × 30 ml.). The ethereal extract was dried and the solvent removed under reduced pressure to give a light brown oil which rapidly solidified on cooling (163 mg.), m. p. 95—105°. This was crystallised from aqueous ethanol and sublimed *in vacuo*; it then had m. p. 109—110° and was identical in all respects with the product (XX; R = Et, R′ = H) obtained in the previous experiment.

The corresponding *ethyl ester* was obtained from the acid by heating an ethanolic solution containing a small quantity of sulphuric acid under reflux on the steam-bath for 4 hr. After distillation it was obtained as a colourless oil (82%), b. p. 136—138° (bath temp.)/0·2 mm.; $n_D^{24.5}$ 1·5102 (Found: C, 63·0; H, 7·35; N, 5·35. $C_{14}H_{19}NO_4$ requires C, 63·4; H, 7·2; N, 5·3%). Light absorption: max. at 248 mμ, ε 9340. The infrared spectrum contained bands at 1728 and 1712 (ester carbonyls) cm.$^{-1}$. The n.m.r. spectrum ($CHCl_3$ solution) contained bands at τ 3·52 (d; J 3·28 c./sec.; 2-CH), 3·66 (d; J 3·20 c./sec.; 3-CH); 4·07 (q; J 1·51 c./sec.; =CH·CO_2Et), 5·84 (q; J 7·28 c./sec.; nuclear ester CH_2), 6·08 (q; J 7·55 c./sec.; side-chain ester CH_2), 7·68 (s; nuclear =C·CH_3), 7·87 (s; side-chain =C·CH_3), 8·70 (t; J 7·06 c./sec.; nuclear ester CH_3), 8·96 (t; J 7·15 c./sec.; side-chain ester CH_3).

Ethyl-β-(3′-*Ethoxycarbonyl*-2′-*methyl*-1′-*pyrrolyl*)*butyrate*.—(*a*) A redistilled sample of the above crotonic ester (XVIII; R = R′ = Et) (1·21 g.) in dry ethanol (30 ml.) was hydrogenated in presence of Adams platinum catalyst. The absorption of hydrogen corresponded to one equivalent. The catalyst was separated, and the solution poured into a stirred mixture of ice and saturated sodium hydrogen carbonate solution. A colourless oil separated which eventually crystallised. This was separated and a further quantity obtained by extraction of the mother-liquors with ether. The combined *product* (0·995 g., 82%) formed colourless prisms, m. p. 39—40° (from light petroleum) (Found: C, 62·9; H, 7·65; N, 5·75. $C_{14}H_{14}NO_4$ requires

C, 62·9; H, 7·9; N, 5·25%). Light absorption: max. at 230 and 253 mμ; ε 9390 and 7620 respectively. The infrared spectrum contained bands at 1743 (saturated ester) and 1709 (unsaturated ester) cm.$^{-1}$. The n.m.r. spectrum showed bands at τ 3·58 (s; 2-CH and 3-CH), 5·32 (sextet; *J* 7·02 c./sec.; side-chain CH), 5·84 (q; *J* 7·11 c./sec.; nuclear ester CH_2), 5·96 (q; *J* 7·49 c./sec.; side-chain ester CH_2), 7·36 (d; *J* 7·11 c./sec.; side-chain CH_2), 7·48 (s; 5-C–CH_3), 8·57 (d; *J* 6·75 c./sec.; side-chain CH_3), 8·70 (t; nuclear ester CH_3), 8·83 (t; *J* 7·39 c./sec.; side-chain-ester CH_3).

(*b*) An intimate mixture of 1,2-dichloroethyl ethyl ether (0·4 ml.) and ethyl acetoacetate (0·3 ml.) was added to a stirred solution of ethyl β-aminobutyrate [22] (1·4 g. in 15 ml. water). Initially the mixture became turbid and eventually a yellow-brown oil separated. After being stirred for 2 hr., the reaction mixture was cooled to 0° and extracted with ether (50 ml.). After removal of the ether, the residue was chromatographed on alumina (9 × 2 cm.) and eluted with ether. The elution was followed by measurement of ultraviolet spectra and the early fractions showing max. at 230 and 253 mμ were collected and the solvent removed. The resulting oil (180 mg.) solidified after cooling and trituration. It was crystallised from light petroleum and formed colourless prisms, m. p. 39—40°, alone and mixed with the foregoing product.

Methyl (*and Ethyl*) *2-Methylpyrrole-3-carboxylate* (XXI; R = Me, Et).—(*a*) Ammonia solution (10 ml.; *d* 0·88) was mixed with dimethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Me) (332 mg.), and ethanol was added until the organic material had dissolved. The mixture was stirred at room temperature for 2 days. After neutralisation of the product with 50% hydrochloric acid, the solution was cooled in ice–water and then extracted with ether (2 × 50 ml.). The ethereal extract was dried and the solvent removed, leaving an oil which gave a cherry-red colour with ferric chloride, consistent with the presence of a β-keto-ester (ethyl acetoacetate). On cooling, the oil largely solidified and the product was crystallised from aqueous ethanol giving colourless plates of methyl 2-methylpyrrole-2-carboxylate, m. p. 54—58°, raised to 63—64° (lit.,[23] 67—68°; we find 63—64° for authentic specimen prepared following Benary [24]), after sublimation at 45—50°/0·01 mm. (Found: C, 60·0; H, 6·15; N, 10·15. Calc. for $C_7H_9NO_2$: C, 60·4; H, 6·45; N, 10·05%); $\lambda_{max.}$ 225 and 255 mμ; ε 8025 and 6970, respectively; $\nu_{max.}$ 3476, 3347 (NH), and 1715 (ester carbonyl) cm.$^{-1}$. The n.m.r. spectrum showed bands at τ 0·22 (s; NH), 3·46 and 3·49 (s; 2-CH and 3-CH), 6·13 (s; ester CH_3), and 7·46 (s; 5-C–CH_3).

(*b*) A similar experiment with diethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (1·014 g.) gave colourless prisms (600 mg.), m. p. 77—78°, of ethyl 2-methylpyrrole-3-carboxylate [24] (see below).

(*c*) A solution of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) (1 g.) in ethanol (25 ml.) was stirred with ammonia solution (60 ml.; *d* 0·88) for 3½ days at room temperature. The product was worked up as in the previous experiment, and it yielded an oil (50 mg.) which had a strong odour of ethyl acetoacetate and gave a positive ferric reaction. The oil rapidly solidified and the solid after filtration had m. p. 77—79° raised to 78—79° after sublimation at 50—60°/0·01 mm. and was identical with ethyl 2-methylpyrrole-3-carboxylate (see below).

(*d*) A solution of sodium acetate (3·1 g.) in aqueous ethanol (100 ml. of ethanol with 17 ml. of water) was added to a solution of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) (5 g.) in aqueous ethanol (150 ml. of ethanol with 25 ml. of water) and the mixture heated under reflux on the water-bath for 4½ hr. The ethanol was then removed by distillation, the residue cooled, diluted with water (200 ml.) and extracted with ether (100 ml.). The ethereal extract was separated, dried, and the solvent removed leaving an oil which largely crystallised when cooled (ice). The crystalline product (0·54 g.), m. p. 75—78°, was separated leaving a pleasant-smelling oil which gave a positive ferric reaction. The oil was distilled and the fraction of b. p. 175—185° collected and shown to be ethyl acetoacetate by comparison of the infrared spectrum with that of an authentic specimen and by preparation of the semicarbazone which formed needles, m. p. 128—129°, identical with an authentic specimen.

The crystalline ethyl 2-methylpyrrole-3-carboxylate, m. p. 75—78°, was purified by sublimation at 50—60°/0·01 mm., it then had m. p. 78—79° (lit.,[24] 78—79°) (Found: C, 62·7; H,

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[23] H. Rapoport and C. D. Willson, *J. Org. Chem.*, 1961, **26**, 1102.
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7·35; N, 9·3. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·2; N, 9·15%). Light absorption: max. at 225 and 257 mμ; ε 7270 and 6380, respectively. The n.m.r. spectrum ($CHCl_3$ solution) contained bands at τ 0·60—0·95 (s; NH), 3·45 and 3·49 (both s; 2-CH and 3-CH), 5·69 (q; *J* 7·09 c./sec.; ester CH_2), 7·48 (s; nuclear C–CH_3), 8·62 (t; *J* 7·09 c./sec.; ester CH_3).

Acid Rearrangement of Dimethyl 2,7-Dimethyl-4H-azepine-3,6-dicarboxylate.—(*a*) Concentrated hydrochloric acid (1·0 ml.) was added to a solution of the dimethyl ester (V; R = Me) (238 mg.) in ether (40 ml.) and the mixture shaken vigorously for 2 min. Water (10 ml.) was added with shaking, and the ethereal layer separated, washed, and dried. Evaporation of the solvent under reduced pressure gave an almost colourless crystalline residue (209 mg.) which was crystallised from methanol, forming short, pale yellow fluorescent needles, m. p. 157—159°, identical with authentic dimethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.[1]

A similar rearrangement of dimethyl 4-ethoxy-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (above, 115 mg.) gave the same product (88 mg.), m. p. 154—158° raised to 158—159° after crystallisation from methanol.

(*b*) An aqueous solution of hydrobromic acid (10 ml. of 48%) was shaken vigorously with a solution of dimethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Me) (737 mg.) in ether (200 ml.) for 2 min. Water (40 ml.) was then added and the shaking repeated. After separation of the aqueous layer, the ethereal solution was washed, dried, and the solvent removed *in vacuo*. The residual *dimethyl 4-bromomethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate* (896 mg.) rapidly crystallised and had m. p. 150—153° (decomp.), raised to 152—153° (decomp.) after crystallisation from methanol (Found: C, 44·95; H, 4·9; N, 4·25; Br, 25·05. $C_{12}H_{16}BrNO_4$ requires C, 45·3; H, 5·05; N, 4·4; Br, 25·1%). The product was unstable in warm methanolic solutions.

A similar rearrangement of dimethyl 4-ethoxy-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (169 mg.) gave the same bromomethyldihydropyridine ester (166 mg.), m. p. 152—153° (decomp.) after crystallisation from methanol. Light absorption: max. at 232 and 349 mμ; ε 17,950 and 6920.

Diethyl 4-Chloromethyl-2,6-bis(dibromomethyl)-1,4-dihydropyridine-3,5-dicarboxylate (VII; R = Cl).—A saturated solution of bromine in carbon tetrachloride was added dropwise to a stirred solution of diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = Et) (1 g.) in carbon tetrachloride (100 ml.) until the colour of the bromine persisted. The reaction mixture was kept at room temperature with occasional cooling. After the mixture had stood overnight, the carbon tetrachloride and excess of bromine were removed under vacuum with gentle heating, acetone (20 ml.) was added to the residue, and the solution heated under reflux for 10 min. The acetone was then removed by suction and the residue was dissolved in hot ethanol and then cooled. Yellow needles of the *product* (1·1 g., 25%) separated, which after recrystallisation from ethanol had m. p. 107·5—108·5° (Found: C, 27·1; H, 2·5; Br, Cl, 57·5. $C_{14}H_{16}Br_4ClNO_4$ requires C, 27·2; H, 2·6; Br, Cl, 57·5%). Light absorption: max. at 239 and 350 mμ; ε 16,900 and 4800, respectively. The infrared spectrum contained bands at 3387, 3207 (NH), and 1703 (ester carbonyl) cm.$^{-1}$. The n.m.r. spectrum showed max. at τ 2·00 (s; $CHBr_2$), 2·61 (s; NH), 5·74 (q; *J* 7·06 c./sec.; ester CH_2), 5·76 (t; *J* 4·23 c./sec.; 4-CH), 6·56 (d; *J* 4·23 c./sec.; CH_2Cl), and 8·62 (t; *J* 7·06 c./sec.; ester CH_3).

Diethyl 4-Bromomethyl-2,6-bis(dibromomethyl)-1,4-dihydropyridine-3,5-dicarboxylate (VII; R = Br).—A saturated solution of bromine in carbon tetrachloride was added dropwise to a stirred solution of diethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (V; R = Et) (1 g.) in carbon tetrachloride (50 ml.) until excess of bromine was present. After the mixture had been kept overnight, the solvent and excess of bromine were removed by distillation under reduced pressure, leaving a dark brown residue. This was boiled for a few minutes with acetone (20 ml.) in order to remove the last traces of bromine and then the acetone was removed by distillation. Ethanol (2 ml.) was added to the hot residue and, on cooling, the yellow *product* (1·22 g.; 49%) crystallised out and was recrystallised from ethanol; it formed pale yellow prisms, m. p. 94—95° (Found: C, 25·2; H, 2·4; Br, 59·6. $C_{14}H_{16}Br_5NO_4$ requires C, 25·4; H, 2·4; Br, 60·3%). Light absorption: max. at 238 and 348 mμ; ε 15,400 and 4300, respectively. The infrared spectrum contained bands at 3385, 3209 (NH), and 1703 (ester carbonyl) cm.$^{-1}$. The n.m.r. spectrum showed max. at τ 1·90 (s; C*H*Br_2), 2·50 (s; NH), 5·67 (t; *J* 4·9 c./sec.; 4-CH), 5·69 (q; *J* 7·12 c./sec.; ester CH_2), 6·66 (d; *J* 4·99 c./sec.; 4-CH_2Br), 8·62 (t; *J* 7·08 c./sec.; ester CH_3).

Reaction of Dimethyl 4,5-Dihydro-2,7-dimethyl-1H-azepine-3,6-dicarboxylate with Potassium Hydroxide.—(*a*) The dimethyl ester (II; R = Me, R′ = H) (349 mg.) was heated under reflux for 3 hr. with a solution of potassium hydroxide (1·5 g.) in water (5 ml.) containing sufficient ethanol to give a homogeneous solution. Ammonia was evolved from the reaction and the resulting solution was cooled, diluted with water (20 ml.), and extracted with ether (60 ml.). The ethereal extract was dried and the solvent removed to give a pale yellow oil with a strong peppermint odour. The oil was ketonic and was converted directly into the oxime (65 mg.) which formed colourless prisms, m. p. 83·5—84°, after crystallisation from light petroleum (Found: N, 10·05. Calc. for $C_8H_{13}NO$: N, 10·1%). The m. p. was not depressed on admixture with an authentic specimen [18] of the oxime of 1-acetyl-2-methylcyclopent-1-ene.

(*b*) The dimethyl ester (II; R = Me, R′ = H) (267 mg.) in ethanol (5 ml.) was added to a boiling solution of potassium hydroxide (186 mg.) in ethanol (15 ml.). The mixture immediately turned yellow and remained this colour throughout the reaction. The mixture was heated under reflux and the course of the reaction followed by periodically measuring the ultraviolet absorption. When all of the starting material appeared to have reacted (22½ hr.), the ethanol was distilled off, leaving a yellow brown residue which was extracted with ether. The ethereal extract was dried and evaporated leaving an almost colourless oil which was separated into three components by chromatography on alumina (Spence type H), ether being used as eluant. The first fraction was a colourless oil with a peppermint odour which absorbed at 246 mμ (in ether) and showed no NH or OH band in the infrared spectrum. It proved to be 1-acetyl-2-methylcyclopent-1-ene (XIV) identical with that described in the previous experiment, and gave an oxime, m. p. 83·5—84·5°, $\lambda_{max.}$ 242 mμ, and a semicarbazone, m. p. 219—221° (lit.,[25] 219°), $\lambda_{max.}$ 268 mμ. The second fraction from the chromatogram was unchanged starting material and the third fraction (XV) was a colourless oil absorbing at 287 mμ, ε 13,610. The infrared absorption showed max. at 1725 (ketone carbonyl), 1668 (bonded ester carbonyl), 3312, and 3507 (NH) cm.$^{-1}$.

Ethyl 2-(1-Aminoethylidene)hexanoate.—A brisk stream of dry ammonia was passed into a solution of ethyl 2-acetylhexanoate [26] (20 g.) in ethanol (20 ml.) for 10 hr. The reaction was followed by measurements of the ultraviolet absorption spectra, the absorption at 280 mμ indicating the formation of the product. The reaction mixture was distilled under reduced pressure and the larger fraction b. p. 102—104°/7 mm. shown to be starting material. The higher-boiling fraction, b. p. 130—135°/13 mm., (5·4 g.) tended to solidify in the condenser and was the required *product.* It was crystallised from aqueous ethanol and formed colourless feathery needles, m. p. 40—41° (Found: C, 64·6; H, 10·1; N, 7·6. $C_{10}H_{19}NO_2$ requires C. 64·85; H, 10·35; N, 7·55%); $\lambda_{max.}$ 288 mμ (ε 15,920); $\nu_{max.}$ 1666 (bonded ester carbonyl), 3314, and 3506 (NH) cm.$^{-1}$.

Dimethyl αα′-Diacetyladipate.—Aqueous hydrochloric acid (1 : 1; 20 ml.) was added to a solution of dimethyl 4,5-dihydro-2,7-dimethyl-1*H*-azepine-3,6-dicarboxylate (II; R = Me, R′ = H) in ether (50 ml.). The mixture was shaken vigorously for 3 hr., the ether layer being replaced after every 30 min. The combined ether extracts were dried and evaporated, leaving a yellow oil (544 mg.) which solidified after cooling and trituration. Crystallisation from aqueous methanol gave the product as short pale yellow laths (216 mg.), m. p. 70—74°, raised to 75—77° after repeated sublimation *in vacuo* (Found: C, 55·4; H, 7·05. $C_{12}H_{18}O_6$ requires C, 55·8; H, 7·1%). The product slowly gave a purple ferric reaction and the infrared spectrum indicated the presence of the β-keto-ester system: $\nu_{max.}$ 1724 (ketone carbonyl) and 1752 (ester carbonyl) cm.$^{-1}$. An authentic specimen, prepared and purified by the method used by Perkin [27] to obtain the diethyl ester, had m. p. 75—77° (from ether–light petroleum) and was identical with the foregoing ester. This ester has been prepared by Kon and Nandi,[28] but no physical data were recorded.

We are grateful to Professor E. Bullock for interpretations of some of the n.m.r. spectra, to Dr. J. H. Beynon, Imperial Chemical Industries Limited (Dyestuffs Division), for determination of a n.m.r. spectrum at high resolution, and to Boots Pure Drug Co., Ltd., for a maintenance grant to one of us (M. A.).

THE UNIVERSITY, NOTTINGHAM. [*Received, September 14th,* 1964.]

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