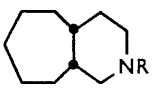
693. cis- *and* trans-3,4-*Cycloheptanopiperidine and Related Compounds.*

By G. G. Ayerst and K. Schofield.

trans-2-Carboxycycloheptylacetic anhydride gave, with ammonia, *trans*-2-carboxycycloheptylacetamide and *trans*-2-carbamoylcycloheptylacetic acid, the former predominating. Pyrolysis of these acids gave an equilibrium mixture of the imides of *cis*- and *trans*-2-carboxycycloheptylacetic acid. The equilibrium mixture was also formed, though more slowly, when either of the imides was heated.

Reduction of the imides gave *cis*- and *trans*-3,4-cycloheptanopiperidine. The methiodides of the derived *cis*- and *trans*-1-methyl-3,4-cycloheptanopiperidine were submitted to Hofmann degradation. *cis*-1-Methyl-3,4-cycloheptanopiperidine was best prepared by hydrogenation of 3,4-cycloheptenopyridine methiodide. Reduction of 3,4-cycloheptenopyridine with sodium and ethanol gave a mono-unsaturated base, whose *N*-methyl derivative was also synthesised from *N*-methylcyclohept-1-enylacetamide.

Recently we described the synthesis of *cis*- and *trans*-3,4-cyclopentanopiperidines, their 1-methyl derivatives, and the *N*-oxides of the latter.[1] This paper describes the extension of this work to the 3,4-cycloheptanopiperidine series (I and II; R = H).



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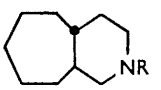

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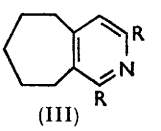

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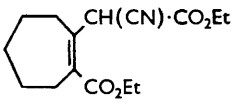
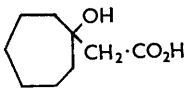


(IV)

We first examined the utility of 3,4-cycloheptenopyridine (III; R = H) as a source of the saturated compounds. Ethyl 2-oxocycloheptanecarboxylate was readily obtained from cycloheptanone and diethyl carbonate in presence of sodium hydride, a method superior to those described earlier.[2] The keto-ester, with ethyl cyanoacetate under the conditions used by Grewe and Mondon [3] in the cyclohexane series, gave ethyl α-cyano-α-(2-ethoxycarbonylcycloheptenyl)acetate (IV) (the position of the double bond was not determined). For hydrolysis of the nitrile (IV) with hydrochloric acid the reaction time proved to be critical. If hydrolysis was carried on too long no 2-carboxycycloheptenylacetic acid could be isolated, and cycloheptanone was formed. The first steps in this reaction are probably hydration and decarboxylation of 2-carboxycycloheptenylacetic acid to give an acid [4] (V), which by a reverse aldol reaction generates cycloheptanone. It is



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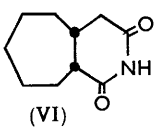

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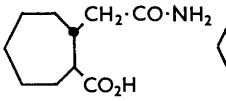

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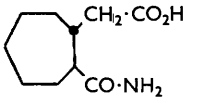

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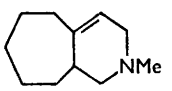


(IX)

noteworthy that in this hydrolysis a dihydroxypyridine derivative (III; R = OH) analogous to those produced in the cyclopentene [5] and cyclohexene [3] series was not formed.

2-Carboxycycloheptenylacetic acid gave 2,6-dihydroxy-3,4-cycloheptenopyridine (III;

[1] Ayerst and Schofield, *J.*, 1958, 4097.
[2] Manske and Leitch, *Canad. J. Res.*, 1936, **14**, *B*, 1; Prelog and Hinden, *Helv. Chim. Acta*, 1944, **27**, 1854.
[3] Grewe and Mondon, *Chem. Ber.*, 1948, **81**, 279.
[4] Reformatsky and Plesconasgoff, *Ber.*, 1895, **28**, 2838; Giljarow, *J. Russ. Phys. Chem. Soc.*, 1896, **28**, 501; Harding and Haworth, *J.*, 1910, **97**, 486; Pressman and Lucas, *J. Amer. Chem. Soc.*, 1940, **62**, 2069; Hauser and Breslow, *ibid.*, p. 2389.
[5] Kon and Nanji, *J.*, 1932, 2426.

R = OH) when heated with ammonium carbonate. The derived dichloro-compound (III; R = Cl) was then catalytically dechlorinated to 3,4-cycloheptenopyridine (III; R = H).

Unlike 3,4-cyclopentenopyridine,[1] 3,4-cycloheptenopyridine could not be hydrogenated in ethanol or acetic acid over Adams catalyst, either at room temperature or at 50°/110 atm. The results of Hamilton and Adams [6] prompted us to attempt to hydrogenate 3,4-cycloheptenopyridine methiodide; with a relatively large weight of Adams catalyst the methiodide was reduced quantitatively to *cis*-1-methyl-3,4-cycloheptanopiperidine (I; R = Me). This is the best method for preparing the tertiary base.

We also considered the use of *cis*-2-carboxycycloheptylacetic acid as a source of the base (I; R = H). Hydrogenation of the nitrile (IV), followed by acid hydrolysis, gave *cis*-2-carboxycycloheptylacetic acid. However, all attempts to prepare the anhydride of this acid gave the *trans*-anhydride, as was shown by conversion into the " *trans*-amidic " acids (see below) with no trace of the *cis*-isomers.

Despite these difficulties it proved possible to prepare the *cis*-imide (VI), for when the mixed amidic acids, prepared from either *cis*- or *trans*-2-carboxycycloheptylacetic acid, were pyrolysed, both the *trans*- and the *cis*-imide were formed, the latter, more soluble isomer being the minor product. Reduction of the *cis*-imide (VI) with lithium aluminium hydride gave *cis*-3,4-cycloheptanopiperidine (I; R = H), distinguished from the *trans*-isomer (see below) by the much greater solubility of its picrate. The secondary *cis*-base was readily methylated to give *cis*-1-methyl-3,4-cycloheptanopiperidine (I; R = Me).

trans-2-Carboxycycloheptylacetic acid proved to be the only practicable source of *trans*-3,4-cycloheptanopiperidine. The essential intermediate, ethyl cyclohept-1-ene-carboxylate, has been described,[7] but was prepared more conveniently by ethanolysis of 1-cyanocycloheptene. Michael addition of diethyl malonate to ethyl cyclohept-1-ene-carboxylate gave a good yield of diethyl *trans*-2-ethoxycarbonylcycloheptylmalonate, which on acid hydrolysis provided *trans*-2-carboxycycloheptylacetic acid. The derived anhydride reacted with ammonia to give a mixture of ammonium salts of amidic acids, which upon pyrolysis at 160° produced high yields of the *trans*-imide; at higher temperatures some of the *cis*-imide was also formed (see above). Lithium aluminium hydride reduced the *trans*-imide to *trans*-3,4-cycloheptanopiperidine (II; R = H) which upon methylation gave the *trans*-product (II; R = Me). Like their analogues in the cyclopentane series,[1] the mixed amidic acids (VII + VIII) from *trans*-2-carboxycycloheptylacetic anhydride were reduced by lithium aluminium hydride to a mixture of *trans*-3,4-cycloheptanopiperidine and amino-alcohols.

King and Booth [8] showed that catalytic hydrogenation of isoquinoline in methanol was accompanied by *N*-methylation. Similar reduction of 3,4-cycloheptenopyridine gave a mixture of *N*-methylated bases, but we were unable to separate a pure component from the mixture. Like 3,4-cyclopentenopyridine, 3,4-cycloheptenopyridine gave, on reduction with sodium and ethanol, a mono-unsaturated base which was not further reduced by hydrogen and Adams catalyst in neutral conditions. Treatment of the unsaturated base with formic acid and formaldehyde gave an *N*-methylated base which was still unsaturated. Thus, the double bond in the original compound could not start from the nitrogen atom or be αβ-situated with respect to it.[1] This conclusion is strengthened by the absence from the ultraviolet absorption spectrum of the compound (in cyclohexane) of any maximal absorption above 213 mμ.[9] Of the two possible structures for the unsaturated tertiary base, (IX) is tentatively preferred from the evidence of the infrared spectrum (moderately strong peak at 795 cm.$^{-1}$).[10]

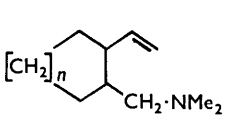
The unsaturated *N*-methylated base was synthesised by a method already used in the

[6] Hamilton and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2260.
[7] Buchner and Scheda, *Ber.*, 1904, **37**, 931.
[8] King and Booth, *J.*, 1954, 3798.
[9] Leonard and Locke, *J. Amer. Chem. Soc.*, 1955, **77**, 437.
[10] Jewers and McKenna, *J.*, 1960, 1575.

cyclopentane series.[1] For this synthesis a convenient source of cyclohept-1-enylacetic acid was needed. This acid had been prepared [11] by applying the Reformatsky reaction to cycloheptanone and dehydrating and hydrolysing the product. The acid so obtained contained 25% of the isomeric cycloheptylideneacetic acid. We used cyclohept-1-enylacetonitrile as a source of the desired acid. Cycloheptanone reacted with ethyl cyanoacetate in the presence of ammonium acetate to give ethyl α-cyano-α-(cyclohept-1-enyl)-acetate, which was slowly hydrolysed by acid to α-cyano-α-(cyclohept-1-enyl)acetic acid. Heated above its m. p. the latter gave cyclohept-1-enylacetonitrile, which was also readily obtained by the method of McCarthy and Brown.[12] Alkaline hydrolysis of cyclohept-1-enylacetonitrile gave a mixture of cyclohept-1-enyl- and cycloheptylidene-acetic acid, together with 23% of cycloheptanone. The ketone is probably formed through the hydroxy-acid (V), produced by hydration of cycloheptylideneacetic acid. The procedure of Hugh, Kon, and Mitchell [13] for separating cyclohept-1-enyl- and cycloheptylidene-acetic acid was wasteful, and it was preferable to separate the mixed acid chlorides by distillation. Cyclohept-1-enylacetyl chloride reacted quantitatively with methylamine. When heated with trioxymethylene and trifluoroacetic acid the resulting *N*-methylcyclohept-1-enylacetamide gave tetrahydro-1-methyl-3,4-cycloheptenopyrid-6-one, which was not purified but was reduced with lithium aluminium hydride to tetrahydro-1-methyl-3,4-cycloheptenopyridine. The picrate of this base was identical with that of the compound formed by *N*-methylating the sodium–ethanol reduction product of 3,4-cycloheptenopyridine as described above. The *N*-methyl base was converted by hydrogen and Adams catalyst in acetic acid into *cis*-1-methyl-3,4-cycloheptanopiperidine. Hydrogenation in ethanol was not complete, but the properties of the mixture of picrates obtained from the product suggested the presence of some of the *trans*-isomer.

With hydrogen peroxide *cis*- and *trans*-1-methyl-3,4-cycloheptanopiperidine each gave only one of the two possible *N*-oxides.

The methiodides of *cis*- and *trans*-1-methyl-3,4-cycloheptanopiperidine, when submitted to Hofmann degradation, gave *cis*- and *trans-NN*-dimethylaminomethyl-2-vinylcycloheptane (as X; $n = 3$), respectively. The structures of these products were proved by hydrogenation, further Hofmann degradation, and ozonolysis to 2-ethylcycloheptanone. It is clear, therefore, that *cis*-1-methyl-3,4-cyclopentano-,[1,10] -3,4-cyclohexano-,[8] and -3,4-cycloheptano-piperidine all undergo Hofmann degradation in the same sense. The conformation (XI) could formally permit the production of either (X) or (XII), whilst meeting the requirement of coplanarity of the participating atoms N–C–C–H; [14] in contrast, conformation (XIII) could lead only to (X). In both cases equatorial approach [14] of the attacking base (*E*2 mechanism) would lead us to expect products of type (X), and, in



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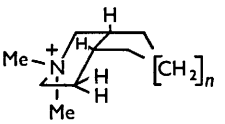

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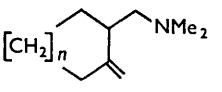

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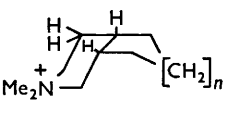


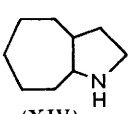
(XIII)

addition, the conformation (XIII) should be more stable than (XI) since it avoids axial oppositions between one of the *N*-methyl groups and hydrogen atoms in the carbocyclic ring, which are present in the latter. Conformational requirements in the *trans*-fused structures permit the formation only of *trans-NN*-dimethylaminomethyl-2-vinylcycloalkanes, as is observed with *trans*-3,4-cyclohexano- [8] and -3,4-cycloheptano-piperidine.

The product (see above) obtained by treating *trans*-2-carboxycycloheptylacetic anhydride with ammonia was separated, after acidification, into two isomeric amidic

[11] Wallach and Beeck-Vollenhoven, *Annalen*, 1901, **314**, 156; Kon and May, *J.*, 1927, 1549.
[12] McCarthy and Brown, *J. Amer. Pharm. Assoc.*, 1954, **43**, 661; Sugasawa and Saito, *Pharm. Bull. (Japan)*, 1956, **4**, 237.
[13] Hugh, Kon, and Mitchell, *J.*, 1929, 1435.
[14] McKenna, *Chem. and Ind.*, 1954, 406.

acids, m. p.s 203·5—204° and 156·5—158°, the former predominating. The related *cis*-compounds could not be prepared (see above). Application of the Hofmann bromination reaction to the lower melting "*trans*-amidic" acid gave a bicyclic lactam, m. p. 136—136·5°. In contrast, the higher-melting acid gave an amino-acid, which on pyrolysis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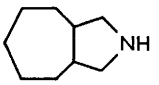
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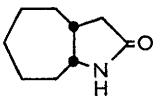
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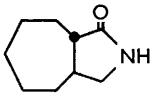
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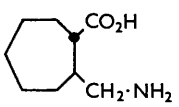
(XVIII)

provided two lactams, the major one having m. p. 165—167°, and the minor one m. p. 80—83°. Lithium aluminium hydride reduced these last two lactams to bicyclic bases giving picrates, m. p.s 186·5—188° and 122·5—124° respectively. These bases could be the *cis*- and *trans*-forms of either (XIV) or (XV). Prelog and Geyer [15] prepared both stereoisomers (XIV) but did not establish their configurations conclusively. Accordingly we submitted 2-oxocycloheptylacetic acid to the Leuckart reaction. Rather than a formamido-compound, the reaction produced a lactam. This lactam (XVI) could, from the results of Noyce and Bachelor,[16] be safely regarded as the *cis*-isomer, and on reduction it gave the *cis*-base. The m. p. of the picrate (122·5—124°) agreed with that reported by Prelog and Geyer [15] for their presumed *cis*-base. We failed to complete an independent synthesis of *trans*-2,3-cycloheptanopyrrolidine (as XIV), for on hydrogenation over Raney nickel, ethyl 2-oxocycloheptylacetate oxime gave the *cis*-lactam (XVI). With lithium aluminium hydride the oxime gave what was probably the (*trans*?-)amino-alcohol, but this could not be cyclised.

Our own preparation of *cis*-2,3-cycloheptanopyrrolidine picrate, and Prelog and Geyer's description of the "*trans*-picrate" prove that the bicyclic bases obtained by Hofmann bromination of the amidic acid, m. p. 203·5—204°, followed by reduction, are 3,4-cycloheptanopyrrolidines (XV); the base (picrate, m. p. 186·5—188°) is probably the *trans*-form, and the base (picrate, m. p. 122·5—124°), the *cis*-form. Correspondingly, the lactams, m. p.s 165—167° and 80—83°, are most probably (XVII) and its *cis*-isomer, respectively, whilst the amino-acid, m. p. 174—176°, and the amidic acid, m. p. 203·5—204°, are represented by (XVIII) and (VII). The amidic acid, m. p. 156·5—158°, must have the structure (VIII), and the derived lactam, m. p. 136—136·5°, must be *trans*-2,3-cycloheptanopyrrolid-5-one (XVI).

In our earlier paper [1] we described the action of ammonia upon *cis*- and *trans*-2-carboxycyclopentylacetic anhydride. We now show that in each of these reactions two isomeric amidic acids are formed, in poor yields in the *cis*-series. We have not so far been able to determine the structures of these compounds.

It is clear from the work described above that ammonia attacks *trans*-2-carboxycycloheptylacetic anhydride mainly at the acetic acid carbonyl group. Most probably the predominant acids formed from related anhydrides of the cyclopentane and cyclohexane [17] series arise in the same way, that is, by amidation of the strongest (least alkylated) acid group.

The isomeric amidic acids (VII and VIII), when heated at 220°, rapidly gave an equilibrium mixture of *cis*- and *trans*-imides (see below). In contrast the amidic acids derived from *trans*-2-carboxycyclopentylacetic anhydride gave only the *cis*-imide, none of the *trans*-imide being detectable.

Both the *cis*- and the *trans*-imide of the cycloheptane series, when kept at 195° for 72 hr., gave an equilibrium mixture containing approximately 63% of the *trans*-isomer. At higher temperatures this proportion fell, though our method of analysis was too

[15] Prelog and Geyer, *Helv. Chim. Acta*, 1945, **28**, 576.
[16] Noyce and Bachelor, *J. Amer. Chem. Soc.*, 1952, **74**, 4577.
[17] Bachmann, Ross, Dreiding, and Smith, *J. Org. Chem.*, 1954, **19**, 222.

insensitive to allow the calculation of the heat of isomerisation. The equilibrium proportions of the *cis*- and *trans*-imide do not differ significantly from those found for *cis*- and *trans*-2-carboxycyclohexylacetic imides,[17] but the cycloheptane derivatives seem to reach (uncatalysed) equilibrium much more slowly than do the cyclohexane derivatives.

Experimental

Ethyl 2-Oxocycloheptanecarboxylate.—Cycloheptanone (50 g.) and ethanol (2 ml.) were added, with stirring during ¼ hr., to freshly ground sodium hydride (21·4 g.), ether (200 ml.), and diethyl carbonate (108 g.). The mixture was boiled and stirred until a white solid started to separate (3 hr.); then the heating was stopped. Stirring was continued for a further 3 hr. The unchanged sodium hydride was decomposed with acetic acid (20 ml.), and the mixture diluted with ice. The product was extracted with ether, and the ethereal layer was washed with sodium hydrogen carbonate solution and then with water. The dried (Na_2SO_4) extract was distilled to give the β-keto-ester (53·7 g., 65%), b. p. 128—136°/14 mm.

Ethyl α-Cyano-α-(2-ethoxycarbonylcyclohept-1-enyl)acetate (IV).—Ethyl 2-oxocycloheptanecarboxylate (44·7 g.), ethyl cyanoacetate (28·6 g.), acetic acid (12 ml.), ammonium acetate (5·86 g.), and dry benzene (50 ml.) were heated under reflux in a flask attached to a water separator until no more water separated (9½ hr.). The mixture, on cooling, was diluted with ether and washed with sodium carbonate solution and then with water. The residue was distilled, to give *ethyl α-cyano-α-(2-ethoxycarbonylcyclohept-1-enyl)acetate* (42·7 g., 63%), b. p. 150—152°/0·2 mm., n_D^{17} 1·4930 (Found: C, 64·2; H, 7·9; N, 5·3. $C_{15}H_{21}NO_4$ requires C, 64·5; H, 7·6; N, 5·0%).

2-Carboxycyclohept-1-enylacetic Acid.—Ethyl α-cyano-α-(2-ethoxycarbonylcyclohept-1-enyl)-acetate (40 g.) and concentrated hydrochloric acid (350 ml.) were heated under reflux for 16 hr. When cooled and kept overnight the acid crystallised. It (13·5 g., 48%) was filtered off and washed with ether to remove adhering oil. A portion was crystallised from ether–light petroleum (b. p. 60—80°), giving needles of *2-carboxycyclohept-1-enylacetic acid*, m. p. 139—140° (Found: C, 60·4; H, 7·0. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

If refluxing was continued for 54 hr. no acid could be isolated. Instead, a neutral fraction was obtained which on distillation gave cycloheptanone (32%), b. p. 64—68°/20 mm., n_D^{20} 1·4600. The semicarbazone crystallised from aqueous ethanol as needles, m. p. 160—161° (reported b. p. 179—180°, n_D^{20} 1·4608; semicarbazone, m. p. 163—164°).

2,6-Dihydroxy-3,4-cycloheptenopyridine (III; R = OH).—2-Carboxycyclohept-1-enylacetic acid (19·9 g.) and dry ammonium carbonate (34·5 g.) were well mixed in a 250 ml. flask connected to an air-condenser arranged for distillation, and heated rapidly to 180° and then during 1 hr. to 235°. The mixture began to melt and froth at 180° but resolidified at 200°. At 230—235° the mixture began to melt again with evolution of water and also with the formation of a blue compound which sublimed into the condenser. On cooling, the residue solidified. It was crystallised from glacial acetic acid to give *2,6-dihydroxy-3,4-cycloheptenopyridine* (14·5 g., 81%) as buff needles, m. p. 217—219° (Found: C, 66·6; H, 7·6; N, 8·0. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%).

2,6-Dichloro-3,4-cycloheptenopyridine (III; R = Cl).—2,6-Dihydroxy-3,4-cyclohepteno-pyridine (10·1 g.) and phosphorus oxychloride (30 ml.) were divided equally between 3 Carius tubes which were sealed at a pressure of 100 mm. and heated at 200° for 3½ hr. On cooling, the contents were poured on ice and basified with potassium carbonate. The product was extracted thoroughly with ether. The dried (K_2CO_3) ethereal extract was distilled, to give *2,6-dichloro-3,4-cycloheptenopyridine* (11·3 g., 93%), b. p. 107—110°/0·1 mm., as a colourless oil which crystallised. From methanol it formed needles, m. p. 64·5—65·5° (Found: C, 55·8; H, 4·8; N, 6·7. $C_{10}H_{11}Cl_2N$ requires C, 55·6; H, 5·1; N, 6·5%).

3,4-Cycloheptenopyridine (III; R = H).—2,6-Dichloro-3,4-cycloheptenopyridine (14·5 g.), sodium methoxide solution [prepared from sodium (16·3 g.) and methanol (330 ml.)] and settled Raney nickel (45 g.) were shaken with hydrogen until uptake ceased (2350 ml. in 9 hr.). The nickel was removed and the filtrate was diluted with water (300 ml.). The base was extracted with ether. The combined ethereal extracts were then acidified with concentrated hydrochloric acid and evaporated to 50 ml. The residue was strongly basified with sodium hydroxide and extracted with ether. The dried (K_2CO_3) ethereal extract was distilled to give *3,4-cycloheptenopyridine* (7·3 g., 74%), b. p. 128—130°/20 mm., n_D^{21} 1·5390 (Found: C, 81·4; H, 8·9; N, 9·7.

$C_{10}H_{13}N$ requires C, 81·6; H, 8·9; N, 9·5%). The *picrate* crystallised as bright yellow plates, m. p. 141—142° (Found: C, 50·6; H, 4·5. $C_{16}H_{16}N_4O_7$ requires C, 51·0; H, 4·3%), from ethanol.

The base (3·4 g.), when heated under reflux in dry ether (25 ml.) with methyl iodide (17 g.) for ½ hr., gave the *methiodide* (6·6 g., 99%), which crystallised as white needles, m. p. 136—137° (Found: C, 45·7; H, 5·6. $C_{11}H_{16}IN$ requires C, 45·7; H, 5·6%). The *methopicrate* formed yellow plates, m. p. 123—124° (Found: C, 52·0; H, 4·8. $C_{17}H_{18}N_4O_7$ requires C, 52·3; H, 4·7%), from ethanol.

cis-1-*Methyl*-3,4-*cycloheptanopiperidine* (I; R = Me).—(*a*) 3,4-Cycloheptenopyridine methiodide (6·6 g.), prehydrogenated Adams catalyst (2·5 g.), and ethanol (10 ml.) were shaken with hydrogen. Hydrogenation ended in about 10 hr. The catalyst was filtered off and the filtrate, after the addition of concentrated hydrochloric acid (1 ml.), was concentrated to 10 ml. The residue was basified with sodium hydroxide and the product was extracted with ether. The dried (K_2CO_3) ethereal extract was distilled, to give cis-1-*methyl*-3,4-*cycloheptanopiperidine* (3·36 g., 88%), b. p. 114—115°/22 mm., n_D^{19} 1·4860 (Found: C, 78·9; H, 12·6; N, 7·8. $C_{11}H_{21}N$ requires C, 79·0; H, 12·6; N, 8·3%).

The picrate crystallised from ethanol as yellow needles, m. p. 201—202°, alone and mixed with *cis*-1-methyl-3,4-cycloheptanopiperidine picrate (m. p. 201—202°) described below.

(*b*) Methylation of *cis*-3,4-cycloheptanopiperidine (3·2 g.) (see below) in the way described below for the *trans*-isomer gave *cis*-1-methyl-3,4-cycloheptanopiperidine (2·8 g.), b. p. 114—116°/22 mm., n_D^{19} 1·4840, that gave a *picrate*, yellow needles, m. p. 201—202° (Found: C, 51·4; H, 6·1; N, 14·3. $C_{17}H_{24}N_4O_7$ requires C, 51·5; H, 6·1; N, 14·1%) (from ethanol), and *methiodide* (formed in ether), needles, m. p. 270·5—271·5° (Found: C, 46·2; H, 7·6. $C_{12}H_{24}IN$ requires C, 46·6; H, 7·8%) (from ethanol).

(*c*) Tetrahydro-1-methyl-3,4-cycloheptanopyridine (0·5 g.) (see below) in glacial acetic acid (10 ml.) was shaken in contact with hydrogen over Adams catalyst (0·2 g.). Uptake of hydrogen (108 ml.) ceased after 1 hr. The filtrate, on removal of the catalyst, was evaporated to dryness and the residue was basified with 10% sodium hydroxide solution. The dried (K_2CO_3) ethereal extract was concentrated and treated with picric acid (0·7 g.) in ethanol (5 ml.). There was an immediate yellow precipitate of the picrate (0·9 g.), m. p. 199—200°. This crystallised from ethanol as long yellow needles and had m. p. and mixed m. p. 202—202·5° with *cis*-1-methyl-3,4-cycloheptanopiperidine picrate (m. p. 202—202·5°).

Ethyl α-*Cyano*-α-(cis-2-*ethoxycarbonylcycloheptyl*)*acetate*.—Ethyl α-cyano-α-(2-ethoxycarbonylcyclohept-1-enyl)acetate (96 g.) was hydrogenated in ethanol (100 ml.) over Adams catalyst (1·8 g.). The theoretical amount of hydrogen was taken up in 11 hr. The catalyst was filtered off and the residue distilled, to give *ethyl* α-*cyano*-α-(cis-2-*ethoxycarbonylcycloheptyl*)*acetate* (79 g., 83%), b. p. 142—144°/0·3 mm., n_D^{20} 1·4695 (Found: C, 64·0; H, 8·6. $C_{15}H_{23}NO_4$ requires C, 64·0; H, 8·3%).

cis-2-*Carboxycycloheptylacetic Acid*.—Ethyl α-cyano-α-(*cis*-2-ethoxycarbonylcycloheptyl)-acetate (40 g.) and concentrated hydrochloric acid (300 ml.) were heated under reflux for 6 hr. The water was removed under reduced pressure and the residue was extracted with ether. The filtered extract was shaken with saturated sodium hydrogen carbonate solution. The carbonate extract was acidified with concentrated hydrochloric acid and extracted with ether. The dried (Na_2SO_4) ethereal solution was evaporated to give the acid as an oil which crystallised. Crystallisation from ether–light petroleum (b. p. 60—80°) gave cis-2-*carboxycycloheptylacetic acid*, m. p. 108—111° (Found: C, 60·0; H, 7·7. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%). When this acid was heated under reflux with acetic anhydride, *trans*-2-carboxycycloheptylacetic anhydride, b. p. 148—150°/0·3 mm., n_D^{16} 1·5003 (see below), was formed, as shown by its conversion into the *trans*-imide.

1-*Cyanocycloheptene*.—A stirred, ice-cooled mixture of cycloheptanone (100 g.), potassium cyanide (62 g.), and water (120 ml.) was treated with 40% sulphuric acid (200 ml.) dropwise for 3 hr. The stirring was continued with ice-cooling overnight. Distillation of the dried (Na_2SO_4) ethereal extract of the resulting oil gave the cyanohydrin (101 g., 81%), b. p. 136—140°/12 mm.

Freshly distilled thionyl chloride (180 ml.) was added dropwise during 1½ hr. to a stirred ice-cooled mixture of the cyanohydrin (101 g.) and dry benzene (200 ml.). The solution was then gently warmed on a water-bath for 1½ hr. It was then cooled in ice and treated with water. The aqueous layer was extracted once with benzene (50 ml.), and the combined benzene layers were treated with anhydrous sodium carbonate. Distillation gave 1-cyanocycloheptene

(63·5 g., 72%), b. p. 95—96°/12 mm., $n_D^{16·5}$ 1·4880 (Found: C, 79·5; H, 9·3; N, 11·3. Calc. for $C_8H_{11}N$: C, 79·3; H, 9·2; N, 11·5%).

Ethyl Cyclohept-1-enecarboxylate.—(*a*) 1-Cyanocycloheptene (63·5 g.), ethanol (290 ml.), and concentrated sulphuric acid (85 ml.) were heated under reflux for 60 hr. After cooling, the solution was diluted with a large volume of water, extracted with ether, and washed with 5% sodium hydrogen carbonate solution. The dried (Na_2SO_4) ethereal extract was distilled, to give ethyl cyclohept-1-enecarboxylate (63 g., 71%), b. p. 106—112°/14 mm. The residue from the distillation crystallised from methanol–ether as colourless needles of cyclohept-1-enecarboxamide (4·1 g.), m. p. 125—127°.

(*b*) Cyclohept-1-enecarboxamide (25 g.), ethanol (140 ml.), and concentrated sulphuric acid (40 ml.) were heated under reflux for 72 hr. The mixture was diluted with water (750 ml.), and the oil which separated was extracted thoroughly with ether. The dried (Na_2SO_4) combined ethereal extracts were distilled, to give ethyl cyclohept-1-enecarboxylate (22 g., 73%), b. p. 116—119°/22 mm., n_D^{19} 1·4750.

Diethyl trans-2-*Ethoxycarbonylcycloheptylmalonate.*—Ethyl cyclohept-1-enecarboxylate (53 g.) and a solution prepared from sodium (7·6 g.), ethanol (88 ml.), and diethyl malonate (75·8 g.) were heated under reflux for 3 hr., then kept overnight. The usual processing gave the ester (76 g., 73%), b. p. 160—166°/0·2 mm., n_D^{17} 1·4630 (Found: C, 61·9; H, 8·0. $C_{17}H_{28}O_6$ requires C, 62·2; H, 8·6%).

trans-2-*Carboxycycloheptylacetic Acid.*—Diethyl *trans*-2-ethoxycarbonylcycloheptylmalonate (76 g.) and concentrated hydrochloric acid (300 ml.) were heated under reflux for 72 hr. The hydrochloric acid was removed under reduced pressure, leaving the acid (45·5 g., 98·4%) as a sticky syrup. A portion crystallised from ether–light petroleum (b. p. 60—80°) as clusters of very small needles of trans-2-*carboxycycloheptylacetic acid*, m. p. 136—138° (Found: C, 60·0; H, 8·0. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

trans-2-*Carboxycycloheptylacetic Anhydride.*—*trans*-2-Carboxycycloheptylacetic acid (45·5 g.) and acetic anhydride (450 ml.) were heated under reflux for 1 hr. Removal of acetic anhydride under reduced pressure, and distillation, gave trans-2-*carboxycycloheptylacetic anhydride* (37·7 g., 91%), b. p. 134—136°/0·1 mm., n_D^{16} 1·5005 (Found: C, 66·4; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

trans-NN′-*Dimethyl*-2-*carbamoylcycloheptylacetamide.*—*trans*-2-Carboxycycloheptylacetic anhydride (1 g.) and 30% aqueous methylamine (4 ml.) were heated under reflux for 1 hr. The residue from evaporation under reduced pressure was pyrolysed for 4 hr. at 160°. The *product* crystallised, with difficulty, as a white powder, m. p. 138—140° (Found: C, 63·2; H, 9·2; N, 11·9. $C_{12}H_{22}N_2O_2$ requires C, 63·7; H, 9·8; N, 12·4%), from ethyl acetate.

trans-3,4-*Cycloheptanopiperidine*-2,6-*dione.*—(*a*) *trans*-2-Carboxycycloheptylacetic anhydride (37·7 g.) and aqueous ammonia (400 ml.; *d* 0·880) were heated under reflux for 1 hr. The ammonia was removed under reduced pressure and the residue was pyrolysed at 165° for 6 hr. On cooling, the residue solidified. Crystallisation from ethanol gave the trans-*imide* (27 g., 80%) as colourless plates, m. p. 162—164° (Found: C, 66·7; H, 8·3; N, 7·6. $C_{10}H_{15}NO_2$ requires C, 66·3; H, 8·3; N, 7·7%).

(*b*) *trans*-2-Carboxycycloheptylacetic anhydride (12·2 g.) was treated as in (*a*) but the residue, after removal of the aqueous ammonia, was pyrolysed at 190° for 6 hr. The crystalline residue gave, after two recrystallisations from ethanol, white plates, m. p. 162—164°, of *trans*-imide (6·65 g., 55%). The residue remaining after concentration of the mother-liquor was extracted with light petroleum (b. p. 60—80°), to give the cis-*imide* (3·0 g., 25%) which formed white needles, m. p. 105—106° (Found: C, 66·5; H, 8·4; N, 7·9. $C_{10}H_{15}NO_2$ requires C, 66·3; H, 8·3; N, 7·7%), from that solvent.

trans-3,4-*Cycloheptanopiperidine* (II; R = H).—The *trans*-imide (17·6 g.) was extracted (Soxhlet) into a solution of lithium aluminium hydride (17·5 g.) in ether (700 ml.). The excess of lithium aluminium hydride was decomposed with wet ether, and the base was liberated with sodium hydroxide solution and isolated by continuous extraction for 24 hr. with ether. Distillation of the dried (Na_2SO_4) ethereal extract gave trans-3,4-*cycloheptanopiperidine* (10·35 g., 70%), b. p. 118—119°/14 mm., n_D^{21} 1·4940 (Found: C, 78·4; H, 12·5; N, 9·0. $C_{10}H_{19}N$ requires C, 78·4; H, 12·5; N, 9·1%). The *picrate* formed orange rhombs, m. p. 147—149° (Found: C, 50·7: H, 5·6. $C_{16}H_{22}N_4O_7$ requires C, 50·3; H, 5·8%), from ethanol.

trans-1-*Methyl*-3,4-*cycloheptanopiperidine* (II; R = Me).—*trans*-3,4-Cycloheptanopiperidine (10·35 g.), 40% aqueous formaldehyde (12·5 ml.), and 98% formic acid (16·8 ml.) were heated

on a water-bath for 4 hr. After cooling, the mixture was basified with potassium carbonate. The dried (K_2CO_3) ethereal extract gave, on distillation, trans-1-*methyl*-3,4-*cycloheptanopiperidine* (10·3 g., 91%), b. p. 112—114°/20 mm., n_D^{18} 1·4830 (Found: C, 78·9; H, 12·6; N, 8·5. $C_{11}H_{21}N$ requires C, 79·0; H, 12·6; N, 8·4%). The *picrate* formed yellow needles, m. p. 227—228° (Found: C, 51·4; H, 5·8. $C_{17}H_{24}N_4O_7$ requires C, 51·5; H, 6·1%), from ethanol. The *methiodide* crystallised from ethanol in long white needles, m. p. 267—268° (Found: C, 46·8; H, 7·9. $C_{12}H_{24}IN$ requires C, 46·6; H, 7·8%). The *methopicrate* crystallised from ethanol as yellow platelets, m. p. 115—116° (Found: C, 52·6; H, 6·3. $C_{18}H_{26}N_4O_7$ requires C, 52·8; H, 6·4%).

cis-3,4-*Cycloheptanopiperidine* (I; R = H).—The *cis*-imide (5·87 g.), reduced in the way described for the *trans*-isomer, gave cis-3,4-*cycloheptanopiperidine* (3·5 g., 71%), b. p. 118—119°/21 mm., $n_D^{20·5}$ 1·4965 (Found: C, 78·3; H, 12·5; N, 9·1%). The *picrate* gave pale yellow needles, m. p. 146—147·5° (Found: C, 50·2; H, 6·2; N, 14·3%), from benzene.

Reduction of the Amidic Acids from trans-2-*Carboxycycloheptylacetic Anhydride.*—The mixed amidic acids (2 g.) (see below) were extracted (Soxhlet) into a boiling mixture of tetrahydrofuran (120 ml.) and lithium aluminium hydride (5 g.), and the mixture was boiled for 8 hr. After cooling, the excess of lithium aluminium hydride was decomposed with aqueous tetrahydrofuran. The mixture was then acidified with concentrated hydrochloric acid, and the tetrahydrofuran was removed on the water-bath. The aqueous extract, after ether-extraction, was strongly basified with aqueous sodium hydroxide and extracted continuously with ether (24 hr.). The dried (K_2CO_3) extract was distilled, giving *trans*-3,4-cycloheptanopiperidine (0·35 g., 23%), b. p. 108—110°/10 mm., and a mixture of amino-alcohols (0·33 g., 19%), b. p. 154—156°/8 mm. (Found: C, 70·8; H, 12·4; N, 7·7. Calc. for $C_{10}H_{21}NO$: C, 70·2; H, 12·4; N, 8·2%).

The lower-boiling fraction formed from ethanol a picrate, m. p. 146—148°, alone and mixed with *trans*-3,4-cycloheptanopiperidine picrate (m. p. 147—149°).

Reduction of 3,4-*Cycloheptenopyridine with Sodium and Ethanol.*—3,4-Cycloheptenopyridine (1·13 g.) in ethanol (125 ml.) was heated under reflux on a water-bath, and sodium (15 g.) was added during 1½ hr. After cooling, the mixture was acidified with hydrochloric acid, and the alcohol was removed. The mixture was basified with potassium carbonate, and the base isolated with ether. The dried (K_2CO_3) ethereal extract was concentrated and treated with a solution of picric acid (2·2 g.) in ethanol. *Tetrahydro*-3,4-*cycloheptenopyridine picrate* (0·67 g.) crystallised from ethanol as yellow plates, m. p. 181—183° (Found: C, 50·4; H, 5·0; N, 14·6. $C_{16}H_{20}N_4O_7$ requires C, 50·5; H, 5·3; N, 14·7%).

Ethyl α-*Cyano*-α-(*cyclohept*-1-*enyl*)*acetate.*—Cycloheptanone (25 g.), ethyl cyanoacetate (27·5 g.), ammonium acetate (6 g.), and acetic acid (12 ml.) in dry benzene (125 ml.) were refluxed under a water-separator. The theoretical amount of water separated in 1 hr. The benzene solution was washed twice with water and twice with 10% sodium carbonate solution. The benzene was removed under reduced pressure and the residue was distilled, to give the *product* (41·4 g., 90%), b. p. 116—118°/0·25 mm., $n_D^{17·5}$ 1·5020 (Found: C, 70·2; H, 8·4. $C_{12}H_{17}NO_2$ requires C, 69·6; H, 8·3%).

Cyclohept-1-*enylacetonitrile.*—(*a*) Ethyl α-cyano-α-(cyclohept-1-enyl)acetate (16·8 g.) and concentrated hydrochloric acid (100 ml.) were boiled together for 24 hr. The ethereal extract of the mixture was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and distilled, to give unchanged starting material (3·0 g.), b. p. 115—116°/0·15 mm. The sodium carbonate washings were acidified with concentrated hydrochloric acid, and a dried (Na_2SO_4) ethereal extract therefrom was evaporated to dryness, leaving α-cyano-α-(cyclohept-1-enyl)acetic acid (6·65 g., 46%), m. p. 89—90°. Pyrolysis gave cyclohept-1-enylacetonitrile (3·5 g., 70%), b. p. 110—114°/14 mm., n_D^{20} 1·4810.

(*b*) Cycloheptanone (150 g.), cyanoacetic acid (113 g.), ammonium acetate (10·3 g.), and benzene (200 ml.) were heated under a water-separator. The required amount of water was collected after 17 hr. The benzene was removed under reduced pressure and the residue was pyrolysed at 200—230° for 45 min. The residue was diluted with ether and was washed with water. The dried (Na_2SO_4) solution was distilled, to give the product (149 g., 83%), b. p. 116—120°/18 mm.

Hydrolysis of Cyclohept-1-*enylacetonitrile.*—Cyclohept-1-enylacetonitrile (149 g.) and potassium hydroxide (300 g.) in water (750 ml.) were heated under reflux for 48 hr. The cooled mixture was poured into water and acidified with concentrated hydrochloric acid. The products

were extracted with ether. The ether was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled, to give cycloheptanone (28·5 g., 23%), b. p. 62—66°/18 mm., n_D^{18} 1·4618. The carbonate extract was acidified with concentrated hydrochloric acid, and a dried (Na_2SO_4) ethereal extract therefrom was distilled to give a mixture of cyclohept-1-enylacetic and cycloheptylideneacetic acid (104 g., 61%), b. p. 158—160°/18 mm.

This mixture (104 g.) was heated with pure thionyl chloride (135 ml.) in benzene (400 ml.) on a water-bath for 1½ hr. The benzene and excess of thionyl chloride were removed under reduced pressure and the process was repeated with benzene (3 × 200 ml.). The residue was distilled, giving as the major product cyclohept-1-enylacetyl chloride (77·6 g., 68%), b. p. 98—103°/13 mm. (reported b. p. 100—104°/13 mm.), and a mixture of cyclohept-1-enylacetyl and cycloheptylideneacetyl chloride (23·2 g., 20%), b. p. 104—120°/13 mm. (reported b. p. of cycloheptylideneacetyl chloride, 120—121°/13 mm.). The major part of the mixture had b. p. 104—110°/13 mm.

N-*Methylcyclohept*-1-*enylacetamide*.—40% Aqueous methylamine (250 ml.) was added during 30 min. to an ice-cooled solution of cyclohept-1-enylacetyl chloride (84·6 g.) in dry benzene (300 ml.). The mixture was stirred for 1½ hr. The benzene layer was removed and the aqueous layer was extracted twice with benzene. The combined dried (Na_2SO_4) benzene layers were distilled, to give the *amide* (75·4 g., 92%), m. p. 34—38°, b. p. 130—131°/1·5 mm., n_D^{21} 1·4980 (Found: C, 71·8; H, 10·3; N, 8·0. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·3; N, 8·4%).

Tetrahydro-1-*methyl*-3,4-*cycloheptenopyridine* (IX?).—(i) *N*-Methylcyclohept-1-enylacetamide (75·4 g.), trioxymethylene (20 g.), and trifluoroacetic acid (270 g.) were heated on the water-bath for 6 hr. Trifluoroacetic acid and the excess of trioxymethylene were removed under slightly reduced pressure. The residue was distilled and the fraction (70 g.), b. p. 135—160°/0·5 mm., was collected. This fraction was redistilled, to give a fore-run (5·0 g.), b. p. <121°/0·2 mm., n_D^{21} 1·4000, and a main fraction (43·8 g.), b. p. 121—126°/0·15 mm., n_D^{21} 1·4980.

The main fraction of tetrahydro-1-methyl-3,4-cycloheptenopyrid-6-one (42 g.) in dry ether (100 ml.) was added dropwise to lithium aluminium hydride (19 g.) in ether (100 ml.) at such a rate as to maintain refluxing. Heating was continued for a further 3 hr. and the excess of lithium aluminium hydride was decomposed with water. Distillation of the dried (K_2CO_3) ethereal extract gave the *product* (23·4 g., 61%), b. p. 112°/16 mm., n_D^{20} 1·5000 (Found: C, 79·8; H, 11·6. $C_{11}H_{19}N$ requires C, 79·9; H, 11·6%) [*picrate*, yellow needles, m. p. 165—167° (Found: C, 52·1; H, 5·6; N, 14·1. $C_{17}H_{22}N_4O_7$ requires C, 51·8; H, 5·6; N, 14·2%), from ethanol].

(ii) Tetrahydro-3,4-cycloheptenopyridine [from the picrate (0·3 g.)], 98% formic acid (0·6 ml.), and 40% aqueous formaldehyde (0·4 ml.) were heated for 4 hr. on the water-bath. The mixture was processed in the usual way and the product was treated with picric acid (0·2 g.) in ethanol (2 ml.), to give a picrate (0·2 g.), m. p. 124—128°, which formed yellow needles from ethanol. Two recrystallisations raised the m. p. to 164—166°, and a mixture with tetrahydro-1-methyl-3,4-cycloheptenopyridine picrate (m. p. 165—167°) (see above) had m. p. 164—166°.

trans-1-*Methyl*-3,4-*cycloheptanopiperidine* 1-*Oxide*.—35% Hydrogen peroxide (6·3 ml.) was added slowly, with stirring, to ice-cold *trans*-1-methyl-3,4-cycloheptanopiperidine (2·1 g.) in methanol (2 ml.). The mixture became homogeneous after about 3 hr., but it was kept for 24 hr. Platinum black, prepared from Adams catalyst (0·1 g.) in methanol (5 ml.), was added and the mixture was stirred for ½ hr. The catalyst was filtered off and the filtrate was treated with picric acid (3 g.) in boiling water. The immediate bright yellow precipitate (4·1 g.) of trans-1-*methyl*-3,4-*cycloheptanopiperidine* 1-*oxide picrate* crystallised as bright yellow needles, m. p. 177—178° (Found: C, 48·9; H, 5·7. $C_{17}H_{24}N_4O_8$ requires C, 49·5; H, 5·9%), from ethanol.

cis-1-*Methyl*-3,4-*cycloheptanopiperidine* 1-*Oxide*.—In the same way *cis*-1-methyl-3,4-cycloheptanopiperidine (1 g.) gave cis-1-*methyl*-3,4-*cycloheptanopiperidine* 1-*oxide picrate* (2 g.), yellow needles (from ethanol), m. p. 177—179° (Found: C, 49·7; H, 6·1; N, 13·5%).

Hofmann Degradation of cis-1-*Methyl*-3,4-*cycloheptanopiperidine Methiodide*.—*cis*-1-Methyl-3,4-cycloheptanopiperidine methiodide (5·9 g.) in water (70 ml.) was shaken with silver oxide prepared from silver nitrate (6·6 g.) and 10% sodium hydroxide solution (20 ml.). A filtered portion gave a negative iodide test after 4 hr. The filtrate was then concentrated at 45—50°/22 mm. The syrupy hydroxide was pyrolysed at 120—140° and the pyrolysate was

collected in a receiver cooled in dry carbon dioxide–acetone. The product was extracted with ether, and the dried (K_2CO_3) ethereal extract was distilled, to give *cis*-dimethylaminomethyl-2-vinylcycloheptane (X) (3·1 g., 89%), b. p. 112—114°/23 mm., n_D^{19} 1·4730 [*picrate*, yellow plates, m. p. 129—131° (Found: C, 52·5; H, 7·0. $C_{18}H_{26}N_4O_7$ requires C, 52·7; H, 6·4%), from ethanol].

cis-*Dimethylaminomethyl*-2-*ethylcycloheptane*.—*cis*-Dimethylaminomethyl-2-vinylcycloheptane (2·8 g.), prehydrogenated Adams catalyst (0·4 g.), and ethanol (15 ml.) were shaken with hydrogen. Hydrogenation was complete in 1 hr. (uptake, 350 ml.). Filtration and distillation gave *cis*-dimethylaminomethyl-2-ethylcycloheptane (2·61 g., 92%), b. p. 118—121°/34 mm., $n_D^{20·5}$ 1·4652. This gave a *picrate*, yellow needles, m. p. 130—131° (Found: C, 52·5; H, 7·1. $C_{18}H_{28}N_4O_7$ requires C, 52·4; H, 6·8%), from ethanol, and a *methiodide*, needles, m. p. 257—258° (Found: C, 48·6; H, 8·6. $C_{13}H_{28}IN$ requires C, 48·0; H, 8·5%), from acetone–ether.

Hofmann Degradation of cis-*Dimethylaminomethyl*-2-*ethylcycloheptane Methiodide*.—This methiodide (3·8 g.), treated in the way described above, gave a crude product which was extracted with ether. The basic material was extracted with 2N-hydrochloric acid, and the extract was treated with aqueous sodium hydroxide and extracted with ether. The dried (K_2CO_3) ethereal extract was evaporated to dryness and treated with methyl iodide (4 g.). The methiodide (0·22 g., 6%) crystallised as white needles, m. p. 255·5—256·5°, from acetone–ether and gave no depression of m. p. on admixture with starting material (m. p. 257—258°).

The ethereal extract, after the washing with 2N-hydrochloric acid, was dried (Na_2SO_4) and distilled in the presence of crystals of quinol, to give 2-ethylcycloheptanemethine (0·85 g., 53%), b. p. 168—170°. The methine (0·4 g.), in dry ethyl acetate, was treated with a stream of ozone for 6 hr. Adams catalyst (0·2 g.) was added and the mixture was cooled and shaken with hydrogen. Hydrogen uptake (95 ml.) was completed in 5 min. Filtration and evaporation gave a residue which was converted into the 2,4-dinitrophenylhydrazone. This formed from ethanol red needles, m. p. 115—116°. A mixture with 2-ethylcycloheptanone 2,4-dinitrophenylhydrazone (m. p. 117—118°) had m. p. 117—118°.

Hofmann Degradation of trans-1-*Methyl*-3,4-*cycloheptanopiperidine Methiodide*.—The methiodide (10·05 g.), degraded in the same way as the *cis*-isomer, gave an unsaturated base, b. p. 110°/35 mm. The *picrate* crystallised from ethanol as yellow platelets, m. p. 101—102° (Found: C, 52·5; H, 5·95. $C_{18}H_{26}N_4O_7$ requires C, 52·7; H, 6·4%).

trans-*Dimethylaminomethyl*-2-*ethylcycloheptane*.—The product of the preceding degradation (5 g.) was hydrogenated in the presence of 30% palladium–charcoal (0·26 g.) and ethanol (25 ml.). Hydrogen uptake was complete in 10 min. The ethanol was removed. trans-*Dimethylaminomethyl*-2-*ethylcycloheptane picrate* gave yellow needles, m. p. 96—98° (Found: C, 52·3; H, 6·7%), from ethanol. The *methiodide* formed plates, m. p. 254° (Found: C, 48·2; H, 8·6%), from ethanol.

Hofmann Degradation of trans-*Dimethylaminomethyl*-2-*ethylcycloheptane Methiodide*.—This *trans*-methiodide (5·4 g.) gave, in the usual way, a distillate, b. p. 70—80°/15 mm. The oil, isolated by ether-extraction of the distillate, was separated by 2N-hydrochloric acid into a basic and a neutral fraction (0·8 g.).

The basic fraction gave, with methyl iodide, starting material (0·8 g., 15%), m. p. and mixed m. p. 254°.

The neutral fraction was ozonised as above. Half of the product was converted into its semicarbazone which crystallised from aqueous alcohol as plates, m. p. 137—138° (Found: C, 61·4; H, 9·4. Calc. for $C_{10}H_{19}N_3O$: C, 60·9; H, 9·7%), mixed m. p. with 2-ethylcycloheptanone semicarbazone (m. p. 141—142°) 137·5—138·5°. The remainder of the product was converted into its 2,4-dinitrophenylhydrazone which crystallised from ethanol as red needles, m. p. 115—117° (Found: C, 56·4; H, 6·4. Calc. for $C_{15}H_{20}N_4O_4$: C, 56·25; H, 6·3%) alone and mixed with 2-ethylcycloheptanone 2,4-dinitrophenylhydrazone (m. p. 117—118°).

Ethyl 1-*Ethyl*-2-*oxocycloheptane*-1-*carboxylate*.—Ethyl 2-oxocycloheptanecarboxylate (30 g.), powdered sodium (3·75 g.), and dry toluene (300 ml.) were stirred overnight at room temperature. Ethyl iodide (27 g.) was added during ½ hr. and, after being stirred for a further 2 hr., the mixture was refluxed for 5 hr. The mixture was cooled and filtered. The filtrate was washed with water, the toluene removed under reduced pressure, and the product distilled, to give ethyl 1-ethyl-2-oxocycloheptane-1-carboxylate (20·5 g., 59%), b. p. 130—140°/13 mm.

[*semicarbazone*: needles, m. p. 146·5—147·5° (Found: C, 58·2; H, 8·4. $C_{13}H_{23}N_4O_4$ requires C, 58·0; H, 8·6%), from aqueous alcohol].

2-*Ethylcycloheptanone*.—Ethyl 1-ethyl-2-oxocycloheptane-1-carboxylate (20·5 g.), 48% hydrobromic acid (100 ml.), acetic acid (100 ml.), and water (50 ml.), were heated under reflux overnight. The ketone was removed with the acetic acid and water under reduced pressure. The distillate was neutralised with potassium hydroxide, and the ketone extracted with ether. Distillation of the dried (Na_2SO_4) extract gave 2-ethylcycloheptanone (9·3 g., 68·7%), b. p. 198—202°, n_D^{17} 1·4591 [semicarbazone: plates, m. p. 141—142° (Found: C, 61·2; H, 9·9. Calc. for $C_{10}H_{19}N_3O$: C, 60·9; H, 9·7%), from aqueous ethanol; 2,4-*dinitrophenylhydrazone*, red needles, m. p. 117—118° (Found: C, 56·6; H, 6·5. $C_{15}H_{20}N_4O_4$ requires C, 56·25; H, 6·3%), from ethanol].

Amidic Acids form trans-2-*Carboxycycloheptylacetic Anhydride*.—The anhydride (35·4 g.) in dry benzene (250 ml.) was treated with dry ammonia for 4 hr. The deliquescent mixture of ammonium salts was collected and freed from benzene in a desiccator. The white powder was acidified with 6N-hydrochloric acid, giving a mixture of amidic acids (37·9 g., 98%). Crystallisation of the mixture (20 g.) from tetrahydrofuran–light petroleum (b. p. 60—80°) gave, as the most soluble fraction, platelets (2·7 g.) of trans-2-*carbamoylcycloheptylacetic acid* (VIII), m. p. 156·5—158° (Found: C, 60·7; H, 8·6; N, 7·1. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%), fairly insoluble isomer, trans-2-*carboxycycloheptylacetamide* (VII), which crystallised from methanol as prisms (12·2 g.), m. p. 203·5—204° (decomp.) (Found: C, 60·1; H, 8·6; N, 7·0%), and a mixture (1·4 g.), m. p. 175—176°.

Hofmann Bromination of trans-2-*Carboxycycloheptylacetamide*.—The amidic acid (m. p. 201—203°) (2 g.), in 10% aqueous sodium hydroxide (10 ml.), was treated at 0° with sodium hypobromite solution (14 ml.) [from 10% aqueous sodium hydroxide (70 ml.) and bromine (2·55 ml.)], then heated for ½ hr. at 70°. After cooling, the whole was made faintly acidic with 6N-hydrochloric acid, and the product (1·09 g.) then separated (m. p. 174—176°). It gave a positive ninhydrin test.

The product (1·7 g.) was pyrolysed at 190—195° for 3 min. The residue solidified on cooling and recrystallised from light petroleum (b. p. 60—80°), giving platelets of a mixture of lactams, m. p. 107—108° (Found: C, 70·5; H, 9·75; N, 9·5. Calc. for $C_9H_{15}NO$: C, 70·5; H, 9·9; N, 9·15%). This was later shown to consist of two components, the more insoluble (0·15 g.), m. p. 165—167°, and the more soluble (0·37 g.), m. p. 81—85°.

The lactam, m. p. 165—167° (0·24 g.), in dry ether (40 ml.) was added to lithium aluminium hydride (0·36 g.) in ether (20 ml.), and the solution was refluxed for 2 hr. The usual processing and treatment of the residue with picric acid gave trans(?)-3,4-*cycloheptanopyrrolidine picrate* which formed yellow needles, m. p. 186·5—188° (Found: C, 48·2; H, 5·2. $C_{15}H_{20}N_4O_7$ requires C, 48·9; H, 5·45%), from ethanol.

Similar treatment of the lactam, m. p. 81—85° (0·5 g.), gave cis(?)-3,4-*cycloheptanopyrrolidine picrate* which crystallised from ethanol as yellow needles, m. p. 122·5—124° (Found: C, 48·2; H, 5·45%); a mixed m. p. with *cis*-2,3-cycloheptanopyrrolidine picrate (m. p. 121—122°) was 114—116°.

Hofmann Bromination of trans-2-*Carbamoylcycloheptylacetic Acid*.—The amidic acid (m. p. 156·5—158°) (2 g.) was treated as described for the isomer. A slight excess of 6N-hydrochloric acid was added to the cooled solution, which was then evaporated under reduced pressure. The organic material was dissolved in ethyl acetate, and the dried (Na_2SO_4) extract was concentrated, leaving a sticky solid which could not be crystallised. On treatment with 10% aqueous sodium hydroxide (2 ml.) a portion crystallised and was recrystallised from light petroleum (b. p. 60—80°), to give trans-2,3-*cycloheptanopyrrolid*-5-*one* (cf. XVI) as plates, m. p. 136—136·5° (Found: C, 70·9; H, 9·9; N, 8·8. $C_9H_{15}NO$ requires C, 70·5; H, 9·9; N, 9·1%).

Ethyl 2-*Oxocycloheptylacetate*.—Ethyl bromoacetate (15 g.) was added to 1-cycloheptenylpyrrolidine (15 g.) in dry dioxan (60 ml.) during ½ hr. White crystals were formed and were replaced by a heavy red oil during boiling (2 hr.). After cooling, water (30 ml.) was added and the mixture stirred in the cold for 2 hr. The product was extracted with benzene, and the dried (Na_2SO_4) extract was distilled, to give ethyl 2-oxocycloheptylacetate (3·3 g., 18%), b. p. 131—134°/9 mm., and cycloheptanone (2·2 g., 22%). The method of Plattner *et al.*,[18] starting from ethyl 2-oxocycloheptylcarboxylate, gave ethyl 2-oxocycloheptylacetate in 33% overall conversion.

[18] Plattner, Fürst, and Jirasek, *Helv. Chim. Acta*, 1946, **29**, 730.

cis-2,3-*Cycloheptanopyrrolid-5-one* (XVI).—2-Oxocycloheptylacetic acid (10 g.), ammonium formate (19 g.), and 98% formic acid (7·5 ml.) were heated under reflux for 8 hr. The oil precipitated by diluting the cooled mixture with water was collected in ether and distilled. cis-2,3-*Cycloheptanopyrrolid-5-one* (5·95 g., 66%), b. p. 125—127°/0·2 mm. (Found: C, 70·2; H, 9·7; N, 9·3%), crystallised as needles, m. p. 68—70°, from light petroleum (b. p. 60—80°).

cis-2-*Aminocycloheptylacetic Acid.*—*cis*-2,3-Cycloheptanopyrrolid-5-one (1 g.) was refluxed for 3 hr. with concentrated hydrochloric acid (10 ml.). The mixture was evaporated to dryness under reduced pressure, to yield a glass which crystallised when treated with 10% aqueous sodium hydroxide (5 ml.). The *amino-acid*, m. p. 173—174° (Found: C, 57·2; H, 10·2. $C_9H_{17}NO_2,H_2O$ requires C, 57·1; H, 10·1%), separated from ethanol.

cis-2,3-*Cycloheptanopyrrolidine* (XIV).—*cis*-2,3-Cycloheptanopyrrolid-5-one (2·3 g.) in dry ether (25 ml.) was added dropwise to lithium aluminium hydride (2·4 g.) in dry ether (100 ml.) at such a rate as to maintain refluxing. Then the mixture was refluxed for a further 3 hr. The usual processing gave *cis*-2,3-cycloheptanopyrrolidine (1·66 g., 79%), b. p. 100—104°/22 mm., n_D^{19} 1·4900 [picrate, orange needles, m. p. 121—122° (Found: C, 49·2; H, 5·7. Calc. for $C_{15}H_{20}N_4O_7$: C, 48·9; H, 5·5%), from aqueous ethanol].

cis-1-*Methyl*-2,3-*cycloheptanopyrrolidine.*—*cis*-2,3-Cycloheptanopyrrolidine (1·36 g.) was methylated in the usual way with formic acid and formaldehyde. *cis*-1-Methyl-2,3-cycloheptanopyrrolidine (1·1 g., 72%), b. p. 92—94°/22 mm., n_D^{19} 1·4730, gave a *picrate* which formed yellow needles, m. p. 201—202° (Found: C, 50·7; H, 5·5. $C_{16}H_{22}N_4O_7$ requires C, 50·3; H, 5·8%), from ethanol. The *methiodide* gave needles, m. p. 246·5—247° (Found: C, 45·5; H, 7·95. $C_{11}H_{22}IN$ requires C, 44·8; H, 7·5%), from ethanol–ether.

Ethyl 2-*Hydroxyiminocycloheptylacetate.*—Ethyl 2-oxocycloheptylacetate (11·5 g.), hydroxylamine hydrochloride (10·1 g.), pyridine (18·3 ml.), and ethanol (60 ml.) were refluxed together for 1 hr. The cooled mixture was treated with water and extracted with ether. The ethereal layer was washed with 2N-hydrochloric acid, dried (Na_2SO_4), and distilled, to give the *oxime*, b. p. 150—156°/0·5 mm., n_D^{16} 1·4912 (Found: C, 63·0; H, 9·1. $C_{11}H_{19}NO_3$ requires C, 62·0; H, 9·0%).

Hydrogenation of Ethyl 2-*Hydroxyiminocycloheptylacetate.*—The oxime (2·8 g.) in ethanol (100 ml.) was hydrogenated over a teaspoonful of Raney nickel at 60 atm. for 8 hr. The catalyst and ethanol were removed and an ethereal solution of the product was extracted with 2N-hydrochloric acid. The acid extract was basified with potassium carbonate, and ether then removed an oil which crystallised on cooling. The *lactam* (1·4 g., 70%) crystallised from light petroleum (b. p. 60—80°) as colourless plates, m. p. 73—75° (Found: C, 70·4; H, 9·8; N, 9·0. $C_9H_{15}NO$ requires C, 70·5; H, 9·8; N, 9·1%). Because of deterioration of the sample it could not be compared with the lactam obtained from the Leuckart reaction on 2-oxocycloheptylacetic acid.

Amidic Acids from trans-2-*Carboxycyclopentylacetic Anhydride.*—*trans*-2-Carboxycyclopentylacetic anhydride (38·5 g.) in dry benzene (400 ml.) was treated with dry ammonia for 2 hr. The deliquescent solid product was collected and dried *in vacuo*. Acidification of the solid with 6N-hydrochloric acid gave a mixture (28·7 g., 74%), which (11·68 g.) on crystallisation from tetrahydrofuran–light petroleum (b. p. 60—80°) gave needles (6·31 g.) of an *amidic acid*, m. p. 165·5—167° (Found: C, 56·3; H, 7·8; N, 7·7. $C_8H_{13}NO_3$ requires C, 56·1; H, 7·7; N, 8·2%), fine needles (3·4 g.) of an *isomer*, m. p. 123—124° (Found: C, 56·6; H, 7·9%), and a mixture (1·24 g.), m. p. 152—154°.

Amidic Acids from cis-2-*Carboxycyclopentylacetic Anhydride.*—Similar treatment of *cis*-2-carboxycyclopentylacetic anhydride (21 g.) gave a mixture of amidic acids (7 g.). Crystallisation from tetrahydrofuran–light petroleum (b. p. 60—80°) gave as the most soluble fraction an *amidic acid* which from benzene formed feathery plates, m. p. 115—117° (Found: C, 56·1; H, 7·8; N, 8·1%), and a less soluble *isomer*, m. p. 163—165° (Found: C, 56·3; H, 7·5%).

Pyrolysis of trans-2-*Carboxycycloheptylacetamide.*—The pure amidic acid (10 g.), m. p. 203·5—204°, was pyrolysed at 220° under nitrogen for 1¼ hr. Recrystallisation of the residue from ethanol gave *trans*-3,4-cycloheptanopiperidine-2,6-dione (5·1 g., 56%), m. p. 160—162°. Evaporation of the mother-liquors and extraction of the residue with light petroleum (b. p. 60—80°) gave the *cis*-imide (2·25 g., 25%), m. p. 105—106°. Equilibrium was reached in about 10 min.

Similar results were obtained by pyrolysing *trans*-2-carbamoylcycloheptylacetic acid.

Pyrolysis of Amidic Acids Obtained from trans-2-*Carboxycyclopentylacetic Anhydride.*—(*a*) The mixed amidic acids (0·2 g.) were heated at 200° for 1 hr. under nitrogen. The residue was

triturated with tetrahydrofuran which left some starting material undissolved. Addition of light petroleum (b. p. 60—80°) to the tetrahydrofuran gave the *cis*-imide (0·1 g.), m. p. 86—87°.

(*b*) Either of the pure amidic acids (0·6 g.) (see above) was heated at 210° for 1½ hr. under nitrogen. Recrystallisation of the product from ether–light petroleum (b. p. 60—80°) gave the *cis*-imide (0·4 g.), m. p. 88—90°.

Equilibration of cis- *and* trans-*Imides.*—A mixed m. p. curve for these imides was constructed, the temperatures at which the last trace of solid disappeared being recorded (see Table). The sample (0·1 g.) was sealed in a small bulb and suspended in the vapour of a boiling

Mixed m. p. of cis- *and* trans-*imide.*

trans (%)	100	83·6	68·7	41·1	31·6	0
M. p.	162°	153°	145°	133°	123°	106°

Epimerisations of 2-carboxycycloheptylacetic imide.

Starting isomer	Temp.	Duration (hr.)	Composition, *trans* (%)	Starting isomer	Temp.	Duration (hr.)	Composition, *trans* (%)
cis	195°	¾	0	*trans*	195°	50	68
cis	195	15¾	38	*trans*	195	72	63
cis	195	50	55	*cis*	244	72	61
cis	195	72	63	*trans*	244	72	61
trans	195	1	100				

liquid. In this way the temperature at which the sample was held could be maintained to an accuracy of ±0·5° for long periods. The solvents used were n-octyl alcohol (195°) and di-n-butyl phthalate (244°). After the heating the bulbs were plunged into solid carbon dioxide–acetone. The imides were unaffected at 195° during 1 hr. No appreciable darkening occurred even after 72 hr. at 244°.

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