825. cis- *and* trans-3 : 4-cyclo*Pentanopiperidine.*

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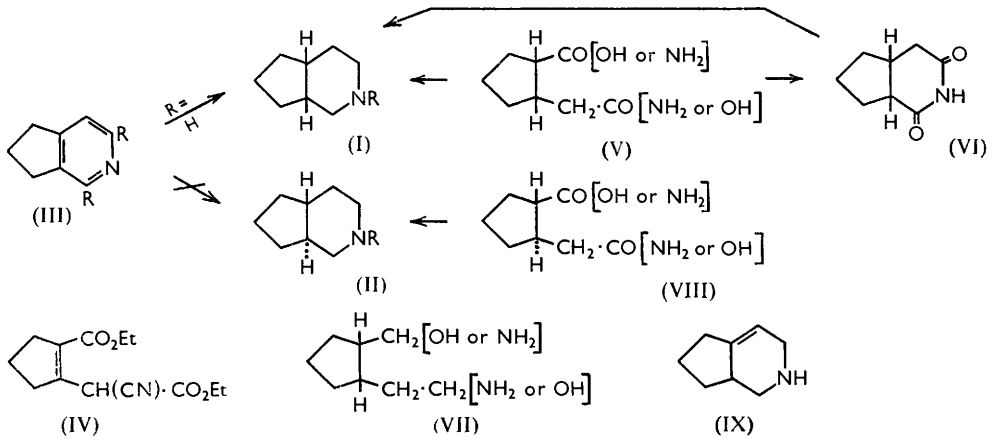
The compounds named above have been synthesised from *cis*- and *trans*-2-carboxy*cyclo*pentylacetic acid. The *cis*-base was identical with a compound previously obtained [1] by catalytic hydrogenation of 3 : 4-*cyclo*pentenopyridine. It provided an *N*-methyl derivative, which gave two isomeric *N*-oxides and a methiodide which underwent a normal Hofmann degradation. The *trans*-base was different from the product of sodium–ethanol reduction of 3 : 4-*cyclo*pentenopyridine, which has been shown to be unsaturated.

For a study of the possible influence of stereochemical factors on the pyrolysis of the *N*-oxides of cyclic tertiary bases, we needed the *cis*- (I; R = H) and the *trans*-isomer (II; R = H) of 3 : 4-*cyclo*pentanopiperidine, and of 3 : 4-*cyclo*heptanopiperidine, the lower and the higher homologue of decahydro*iso*quinoline. This paper describes some experiments in the first of these two series.

By catalytic hydrogenation of 3 : 4-*cyclo*pentenopyridine (III; R = H) Prelog and Metzler [1] obtained *cis*-3 : 4-*cyclo*pentanopiperidine. On the other hand, reduction with sodium and ethanol gave a base (picrate, m. p. 158°) which was taken to be the *trans*-isomer (II; R = H). Probably because of lack of material, physical constants for those bases were not given, and they were characterised only as picrates.

[1] Prelog and Metzler, *Helv. Chim. Acta*, 1946, **29**, 1170.

Prelog and Metzler [1] obtained 3 : 4-*cyclo*pentenopyridine (III; R = H) from the dihydroxy-compound (III; R = OH), through the dichloro-derivative. The dihydroxy-compound was prepared by cyclising ethyl α-cyano-α-(2-ethoxycarbonyl*cyclo*pent-1-enyl)-acetate (IV) with alkali, a method due to Kon and Nanji.[2] Re-examination of this route to the dihydroxy-compound (III; R = OH) proved it to be inconvenient. Like other



recent workers [3] we found the yield (53%) of ester (IV) obtainable from ethyl 2-oxo-*cyclo*pentanecarboxylate by Prelog and Metzler's method to be lower than that claimed, but a very minor modification greatly improved the process. The conditions described for the reaction by Kon and Nanji [2] were much less efficient, and an application of Cope's method [4] gave only 21% of ester (IV). However, the least satisfactory step in the sequence was the conversion (IV) ⟶ (III; R = OH). The yield of crude product was high, but of recrystallised material only 10—30%. Since the yield of the dichloro-compound (III; R = Cl) depended sharply on the purity of the dihydroxy-compound, considerable labour was needed to obtain any substantial quantity. Catalytic dechlorination proceeded smoothly. Reduction of the product (III; R = H) with sodium and alcohol gave what was clearly a mixture of bases. From this about 50% of a homogeneous picrate, m. p. 153—154°, was isolated, which seems to be the compound taken by Prelog and Metzler [1] to be the picrate of *trans*-3 : 4-*cyclo*pentanopiperidine.

For our purposes, routes to *cis*- and *trans*-3 : 4-*cyclo*pentanopiperidine more convenient than those described above were necessary. These seemed to be offered by the anhydrides of *cis*- and *trans*-2-carboxy*cyclo*pentylacetic acid, which were accordingly examined.

cis-2-Carboxy*cyclo*pentylacetic acid and its anhydride were readily obtained by the methods of Linstead and Meade [5] and Cook and Linstead.[6] The anhydride was converted by ammonia into a mixture of the ammonium salts of the amidic acids (V). Pyrolysis of the mixture gave a high yield of the crystalline *cis*-imide (VI), with a smaller amount of the diamide. In preparing the imide it was thus unnecessary to isolate the pure amidic acids. Work on these compounds will be described later. The imide (VI) was reduced smoothly by lithium aluminium hydride to give a moderately good yield of *cis*-3 : 4-*cyclo*pentanopiperidine (I; R = H), the picrate of which proved to be identical with the picrate of the base prepared by Prelog and Metzler's method. With formaldehyde–formic acid, *cis*-3 : 4-*cyclo*pentanopiperidine gave the tertiary base (I; R = Me) which was characterised as its picrate, methiodide, and methopicrate.

[2] Kon and Nanji, *J.*, 1932, 2426.
[3] Protiva, Mychajlyszyn, and Jflek, *Chem. Listy*, 1955, **49**, 1045.
[4] Cope, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.
[5] Linstead and Meade, *J.*, 1934, 935.
[6] Cook and Linstead, *J.*, 1934, 956.

The crude mixture of amidic acids (V), obtained by acidifying the mixed ammonium salts described above, was also reduced with lithium aluminium hydride. The oily product consisted of a small yield of *cis*-3 : 4-*cyclo*pentanopiperidine and what was probably a mixture of amino-alcohols (VII). Examples of cyclisation of this kind occurring during reduction with lithium aluminium hydride have been encountered before,[7,8] notably by Segre and Viterbo [8] in the reduction of methyl β-(6-oxo-2-piperidyl)propionate and related compounds.

Efforts to apply a similar sequence of reactions to the preparation of *trans*-3 : 4-*cyclo*pentanopiperidine were only partly successful. *trans*-2-Carboxy*cyclo*pentylacetic acid and its anhydride were obtained by the methods of Cook and Linstead.[5] Comments on, and minor modifications to, these syntheses will be found below. All attempts to prepare the *trans*-imide have so far failed: heating the dicarboxylic acid with urea [9] gave only the diamide; treating the dicarboxylic anhydride with ammonia gave a mixture of ammonium salts of amidic acids, which on pyrolysis also produced the diamide; acidification of the mixed ammonium salts gave a mixture of the free amidic acids (to be described later). Like the mixture of *cis*-isomers, this mixture (VIII) was reduced with lithium aluminium hydride, giving some *trans*-3 : 4-*cyclo*pentanopiperidine (picrate, m. p. 144—145°) and a mixture of amino-alcohols. The latter could be converted into the cyclic base by treatment with hydrobromic acid followed by alkali, but conditions could not be found which made this cyclisation of practical value. *trans*-3 : 4-*cyclo*Pentanopiperidine (II; R = H) was converted into the *N*-methyl base (II; R = Me), characterised as its picrate and methiodide.

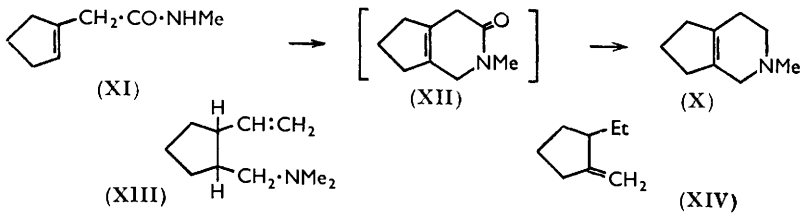
This preparation of *trans*-3 : 4-*cyclo*pentanopiperidine, though unsatisfactory as a source of the base in quantity, is unambiguous and raised the problem of the nature of the base (picrate, m. p. 158°) which Prelog and Metzler [1] regarded as the *trans*-saturated compound. The free base obtained from this picrate (our m. p. 153—154°) exhibited a higher refractive index than either *cis*- or *trans*-3 : 4-*cyclo*pentanopiperidine, and catalytic hydrogenation demonstrated the presence in it of one double bond. Furthermore, this saturation of the double bond produced *cis*-3 : 4-*cyclo*pentanopiperidine. Assuming that the double bond in the unsaturated base is in the heterocyclic ring, there are, of course, six possible structures for the compound. Four of these (two with the double bond terminating on nitrogen, and two with it situated αβ with respect to the –NH– group) seem to be eliminated by the observation that treatment of the unsaturated base with formaldehyde–formic acid gave an *N*-methylated base which was still unsaturated; with the double bond in the position mentioned, enamine reduction [10] to a saturated base would presumably have occurred. Of the two remaining structures (X; H for Me) seems to be rather more likely than (IX) both because of the resistance to reduction shown by the double bond and from the synthetic experiments described below.

With regard to the other product(s) of sodium–ethanol reduction of compound (III; R = H), the infrared spectrum of the crude reduction mixture strongly suggested the presence of *cis*-3 : 4-*cyclo*pentanopiperidine. In fact, it proved possible to isolate *cis*-*N*-methyl-3 : 4-*cyclo*pentanopiperidine when the crude base remaining after removal of the unsaturated component was methylated.

The work of Belleau [11] suggested an alternative approach to derivatives of 3 : 4-*cyclo*pentanopiperidine. The essential intermediate was *N*-methyl*cyclo*pent-1-enylacetamide (XI). The acetic acid is easily available (see p. 4103) and was readily converted through its acid chloride into the methylamide. This, with trioxymethylene in trifluoroacetic acid gave a mixture from which could be isolated what was probably reasonably pure lactam (XII) (not analysed). Reduction with lithium aluminium hydride gave a

[7] Barry, Belton, Kelly, and Twomey, *Nature*, 1950, **166**, 303.
[8] Segre and Viterbo, *Experientia*, 1958, **14**, 54.
[9] Ficken, France, and Linstead, *J.*, 1954, 3730.
[10] Leonard and Sauers, *J. Amer. Chem. Soc.*, 1957, **79**, 6210.
[11] Belleau, *Canad. J. Chem.*, 1957, **35**, 673.

relatively unstable unsaturated base, of which the picrate (m. p. 155—157°) showed no mixed m. p. depression with the picrate (m. p. 150—151°) formed from the *N*-methylated



derivative of the unsaturated base resulting from sodium–ethanol reduction of 3 : 4-*cyclo*pentenopyridine. The significance of the difference in m. p.s is uncertain, for when the unsaturated base from reduction of the lactam was treated with sodium in boiling ethanol, lithium–liquid ammonia, or sodium–*tert.*-butyl alcohol–liquid ammonia, it appeared to be unchanged, but the m. p. of its picrate could in no case then be raised above 151—152°. The unstable base from the lactam gave *N*-methyl-*cis*-3 : 4-*cyclo*pentanopiperidine on hydrogenation. This work does not fix unambiguously the position of the double bonds in the unsaturated derivatives, but seems to favour the inter-ring position.

cis-*N*-Methyl-3 : 4-*cyclo*pentanopiperidine readily gave a mixture of the two possible isomeric *N*-oxides (as picrates) when treated with hydrogen peroxide in methanol. We hope to study the pyrolysis of these isomers. Some of the expected products might be characterised by comparison with the products of the standard Hofmann degradation of *cis*-*N*-methyl-3 : 4-*cyclo*pentanopiperidine methiodide. This latter degradation proceeded normally,[12] giving at the first stage the methine (XIII). Hydrogenation, and continued Hofmann degradation to (XIV), followed by oxidation to 2-ethyl*cyclo*pentanone demonstrated the direction of the initial opening. Besides (XIV), the second step of the Hofmann degradation provided a base (characterised as its methiodide) which was apparently isomeric with *cis*-1-dimethylaminomethyl-2-ethyl*cyclo*pentane. It seems likely that this product was the *trans*-isomer of the latter.

Experimental

Ethyl α-Cyano-α-(2-ethoxycarbonylcyclopent-1-enyl)acetate.—(*a*) Ethyl 2-oxo*cyclo*pentanecarboxylate (20 g.), ethyl cyanoacetate (14·2 g.), ammonium acetate (2 g.), acetic acid (6 ml.), and benzene (25 ml.) were heated under reflux in a flask attached to a Dean and Stark water-separator, until no more water separated. The mixture was washed with water (3 × 40 ml.), and the aqueous layer was extracted with benzene. The benzene was removed under reduced pressure. Distillation of the residual oil gave ethyl α-cyano-α-(2-ethoxycarbonyl*cyclo*pent-1-enyl)acetate (6·9 g., 21·5%), b. p. 130—136°/0·05 mm.

(*b*) Ethyl 2-oxo*cyclo*pentanecarboxylate (20 g.), ethyl cyanoacetate (14 g.), and two drops of piperidine, allowed to react under the conditions of Kon and Nanji,[2] gave the same product (5·76 g., 20·8%), b. p. 117°/0·02 mm.

(*c*) Ethyl 2-oxo*cyclo*pentanecarboxylate (158·3 g.), ethyl cyanoacetate (115 g.), and piperidine (26·2 ml.) reacted under the conditions of Prelog and Metzler,[1] to give the product (126·8 g., 50%), b. p. 130—140°/0·05 mm.

A mixture of ethyl 2-oxo*cyclo*pentanecarboxylate (206·3 g.), ethyl cyanoacetate (151 g.), and piperidine (34·5 ml.) was set aside for 48 hr. Ether was added and the mixture was washed with dilute hydrochloric acid. Distillation of the dried ethereal layer gave the product (226 g., 68%), b. p. 130—136°/0·15 mm.

3 : 4-cyclo*Pentenopyridine* (III; R = H).—By the method of Prelog and Metzler [1] ethyl α-cyano-α-(2-ethoxycarbonyl*cyclo*pent-1-enyl)acetate gave 10—30% of pure 2 : 6-dihydroxy-3 : 4-*cyclo*pentenopyridine. This gave the 2 : 6-dichloro-compound in 76% yield, but use of the crude dihydroxy-compound gave only 14% of the dichloro-derivative. Dechlorination of 2 : 6-dichloro-3 : 4-*cyclo*pentenopyridine gave 3 : 4-*cyclo*pentenopyridine in 80% yield (as

[12] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953, p. 429.

picrate). Decomposition of the picrate (18·9 g.) with 10% sodium hydroxide solution (150 ml.), followed by steam-distillation and extraction of the distillate with ether, gave 3 : 4-*cyclo*pentenopyridine (5·6 g.), b. p. 78—80°/10 mm., n_D^{18} 1·5380.

Reduction of 3 : 4-cyclo*Pentenopyridine with Sodium and Ethanol.*—3 : 4-*cyclo*Pentenopyridine (4·05 g.) in boiling ethanol (300 ml.) was treated with sodium (25 g.) during 2 hr. The cooled mixture was acidified with concentrated hydrochloric acid. The residue left after removal of ethanol was basified with sodium hydroxide solution and extracted with ether. Distillation of the dried (K_2CO_3) extracts gave a mixture of bases (3·0 g.), b. p. 77—78°/16 mm., n_D^{18} 1·5000. This (2·5 g.) was treated with picric acid (4·5 g.) in ethanol. Fractional crystallisation of the product from ethanol gave yellow rhombs of a fairly insoluble picrate " A " (2·05 g.), m. p. 153—154° (Found: C, 47·8; H, 4·9. Calc. for $C_{14}H_{16}O_7N_4$: C, 47·7; H, 4·6%). From the mother-liquors an inseparable mixture of picrates " B " (1·94 g.) was recovered.

Picrate " A " (1·65 g.) was decomposed with sodium hydroxide solution, and the free base (0·43 g.; b. p. 72—73·5°/11 mm., n_D^{18} 1·5110) isolated in the usual way by steam-distillation and ether-extraction. The base (0·22 g.), 40% aqueous formaldehyde (0·4 ml.), and 98% formic acid (0·6 ml.) were heated for 4 hr. on the steam-bath. The solution was basified with potassium carbonate and extracted with ether. Treatment of the base recovered from the dried (K_2CO_3) extract with picric acid in ethanol gave a *picrate* which formed yellow needles, m. p. 150—151° (Found: C, 49·6; H, 5·5; N, 15·5. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 5·0; N, 15·3%), from the same solvent.

When the unsaturated base (0·169 g.) from picrate " A," reduced Adams's catalyst (0·1 g.), and ethanol (10 ml.) were shaken with hydrogen, uptake (29·6 ml.; theor., 30·9 ml.) was complete in 3 hr. Removal of the catalyst, concentration, treatment with picric acid, and recrystallisation from ethanol gave *cis*-3 : 4-*cyclo*pentanopiperidine (0·35 g.), m. p. and mixed m. p. with authentic material (see below), 138—140°.

The bases liberated in the same way from the mixture of picrates " B " (1·6 g.) were methylated similarly. The methylated product was converted into a mixture of picrates. Fractional crystallisation from ethanol gave, as the only homogeneous material which could be isolated, *cis*-1-methyl-3 : 4-*cyclo*pentanopiperidine picrate (0·6 g.) as long yellow needles, m. p. and mixed m. p. with authentic material, 210—211°. A mixture with *trans*-1-methyl-3 : 4-*cyclo*pentanopiperidine picrate (m. p. 213·5—214°) had m. p. 205—206°.

Imide (VI) *of* cis-2-*Carboxy*cyclo*pentylacetic Acid.*—*cis*-2-Carboxy*cyclo*pentylacetic anhydride [6] (85·3 g.) was heated under reflux with aqueous ammonia (1350 ml.; *d* 0·880) for 1 hr. Water was removed under reduced pressure and the residue was pyrolysed at 160° for 3 hr. The crystalline product was extracted with ether and recrystallised from ether–light petroleum (b. p. 60—80°). The *imide* formed platelets (70·8 g.), m. p. 89·5—91° (Found: C, 63·0; H, 7·2; N, 8·9. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1%).

cis-3 : 4-cyclo*Pentanopiperidine* (I; R = H).—(i) The imide (59·4 g.) was extracted (Soxhlet) into a boiling mixture of ether (250 ml.) and lithium aluminium hydride (59 g.). Boiling was continued for 1 hr. after all the imide had been extracted. The mixture was decomposed with wet ether, and the product liberated by addition of solid sodium hydroxide. It was isolated by continuous extraction (24 hr.) with ether. Processing of the dry (Na_2SO_4) extract gave the base (23·2 g.), b. p. 71—73°/14 mm., n_D^{18} 1·4892 (Found: C, 76·7; H, 11·8; N, 11·4. Calc. for $C_8H_{15}N$: C, 76·7; H, 12·1; N, 11·2%). The picrate separated as pale yellow needles, m. p. 142—143° (Found: C, 47·8; H, 5·0. Calc. for $C_{14}H_8O_7N_4$: C, 47·5; H, 5·1%), which did not depress the m. p. of a specimen prepared by the method of Prelog and Metzler.[1]

(ii) *cis*-2-Carboxy*cyclo*pentylacetic anhydride (78 g.) in benzene (500 ml.) was treated with dry ammonia for 2 hr. The very deliquescent mixture of ammonium salts was collected and freed from solvent in a desiccator. The white powder was acidified with hydrochloric acid, and the resulting amidic acid extracted from ammonium chloride by boiling tetrahydrofuran in a Soxhlet apparatus. Removal of the tetrahydrofuran under reduced pressure left a sticky solid. A portion of this mixture (15 g.) was extracted (Soxhlet) into a boiling mixture of tetrahydrofuran (250 ml.) and lithium aluminium hydride (12 g.), and then boiled for 4 hr. The product, isolated in the usual way, gave on distillation *cis*-3 : 4-*cyclo*pentanopiperidine (1·53 g.), b. p. 76—80°/16 mm., n_D^{15} 1·4908 (identified as the picrate, m. p. 138—140°), and a heavy colourless oil, b. p. 152—160°/16 mm., $n_D^{16\cdot5}$ 1·4974. The latter was probably a mixture of amino-alcohols.

cis-1-*Methyl*-3 : 4-cyclo*pentanopiperidene* (I; R = Me).—*cis*-3 : 4-*cyclo*Pentanopiperidine

(23·2 g.), 40% formaldehyde (25 ml.), and 98% formic acid (36 ml.) were heated under reflux for 4 hr. The usual processing gave the 1-*methyl base* (22·88 g., 88·7%), b. p. 64—66°/12 mm., n_D^{19} 1·4745 (Found: C, 77·5; H, 12·4; N, 9·8. $C_9H_{17}N$ requires C, 77·6; H, 12·3; N, 10·0%). The *picrate* formed yellow needles, m. p. 210·5—211·5° (Found: C, 48·9; H, 5·2. $C_{15}H_{20}O_7N_4$ requires C, 48·9; H, 5·5%), from ethanol. The *methiodide* (44·76 g., 96·8%) was prepared by addition, with cooling, of methyl iodide (115 g.) to the *N*-methyl base (22·88 g.); it crystallised from ethanol in colourless needles, m. p. 254—255° (Found: C, 42·4; H, 6·9. $C_{10}H_{20}NI$ requires C, 42·7; H, 7·2%). The *methopicrate* prepared from the methiodide crystallised from ethanol as feathery yellow plates, m. p. 167·5—168·5° (Found: C, 50·4; H, 5·7. $C_{16}H_{22}O_7N_4$ requires C, 50·3; H, 5·8%).

cis-1-*Methyl*-3 : 4-cyclo*pentanopiperidine* 1-*Oxides*.—35% Hydrogen peroxide (1·5 ml.) was added slowly with stirring to ice-cold *cis*-1-methyl-3 : 4-*cyclo*pentanopiperidine (0·48 g.) in methanol (1 ml.). The mixture became homogeneous after 1 hr. and was left at room temperature for 24 hr. Platinum black prepared from Adams's catalyst (0·03 g.) in methanol (5 ml.) was added and the whole stirred for 1 hr. more. The catalyst was filtered off and the filtrate was treated with picric acid (0·83 g.) in boiling water (15 ml.). The immediate bright yellow precipitate (1·26 g.) was fractionally crystallised from ethanol to give two picrates. The more insoluble *picrate* crystallised as yellow needles, m. p. 185—186° (Found: C, 46·7; H, 5·7. $C_{15}H_{20}O_8N_4$ requires C, 46·9; H, 5·3%). The isomeric *picrate* crystallised as small pale yellow needles, m. p. 164—165° (Found: C, 47·2; H, 5·2%).

trans-2-*Carboxy*cyclo*pentylacetic Anhydride*.—*cyclo*Pentanone (100 g.), potassium cyanide (60·6 g.), and water (200 ml.) were stirred together below 10° and treated with 40% sulphuric acid (200 ml.) during 3 hr.[13] The mixture was stirred overnight at 0°. Distillation of the dried (Na_2SO_4) ether extract of the resulting oil gave *cyclo*pentanone cyanohydrin (90 g.), b. p. 118—119°/14 mm. This was converted into 1-cyano*cyclo*pentene. The nitrile (63·5 g.), ethanol (124 ml.), and concentrated sulphuric acid (78 ml.) were boiled for 48 hr. Processing gave ethyl *cyclo*pent-1-enecarboxylate (51·3 g.), b. p. 90—92°/23 mm., and a residue of *cyclo*pent-1-enecarboxyamide (17 g.), m. p. 205—210° (reported,[14] m. p. 210°). Addition of diethyl sodiomalonate to the ester under Cook and Linstead's [6] conditions gave only 40% of diethyl *trans*-2-ethoxycarbonyl*cyclo*pentylmalonate. Use of a half-molar excess of diethyl malonate raised the yield to 66%. The remaining steps to the anhydride went as reported.[6]

trans-2-*Carboxy*cyclo*pentylacetic Diamide*.—(i) The anhydride (1 g.) was heated under reflux for 1 hr. with aqueous ammonia (15 ml.; *d* 0·880). After evaporation to dryness under reduced pressure a residue remained which was pyrolysed at 120—160° for 3 hr. The resulting oil solidified when triturated with methanol, and crystallisation from this solvent gave needles of the *diamide*, m. p. 180—183° (Found: C, 56·3; H, 8·0. $C_8H_{14}O_2N_2$ requires C, 56·4; H, 8·3%).

(ii) The anhydride (1 g.) was heated for 1 hr. at 135° with urea (0·22 g.). After cooling, it was treated with methanol to give a product (0·6 g.) which after two recrystallisations from methanol had m. p. 178—180°.

trans-3 : 4-cyclo*Pentanopiperidine* (II; R = H).—*trans*-2-Carboxy*cyclo*pentylacetic anhydride (38·5 g.) in dry benzene (400 ml.) was treated with dry ammonia for 2 hr. Working up as before gave the mixed amidic acids (28·7 g.; m. p. 152—156°). This mixture (10 g.) was reduced as in the case of the mixed *cis*-acids with tetrahydrofuran (250 ml.) and lithium aluminium hydride (10·9 g.). Distillation of the product gave *trans*-3 : 4-*cyclo*pentanopiperidine (0·66 g.), b. p. 76—78°/20 mm., n_D^{19} 1·4830 [the *picrate* formed prisms, m. p. 144—145° (Found: C, 47·3; H, 5·1; N, 15·6. $C_{14}H_{18}O_7N_4$ requires C, 47·4; H, 5·1; N, 15·8%), from ethanol], and a mixture of amino-alcohols (5·43 g.), b. p. 130—132°/7 mm., n_D^{21} 1·4885 (Found: C, 67·3; H, 11·8. $C_8H_{17}ON$ requires C, 67·1; H, 11·9%).

The mixed amino-alcohols (1 g.) were heated under reflux with 50% hydrobromic acid (25 ml.) for 8 hr. The hydrobromic acid was removed under reduced pressure and the sticky residue was dissolved in water (50 ml.) and added slowly to 0·1N-sodium hydroxide (153 ml.). The mixture was kept at 45—50° for 3½ hr., then subjected to steam-distillation. From the distillate ether recovered a base (0·35 g.). Conversion into the picrate and recrystallisation from ethanol gave *trans*-3 : 4-*cyclo*pentanopiperidine picrate (0·4 g.), m. p. 143—144°. The use of 60% hydrobromic acid did not improve the cyclisation.

[13] *Org. Synth.*, Collected Vol. II, p. 7.
[14] Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1945, **12**, 978.

trans-1-*Methyl*-3 : 4-cyclo*pentanopiperidine* (II; R = Me).—Methylation of the *trans*-base (0·2 g.) in the usual way, with 40% aqueous formaldehyde (0·3 ml.) and 98% formic acid (0·4 ml.), gave the 1-methyl base, the *picrate* of which formed yellow needles, m. p. 213·5—214° (Found: C, 48·3; H, 5·5. $C_{15}H_{20}O_7N_4$ requires C, 48·9; H, 5·5%), from ethanol. The *methiodide* separated from ethanol as needles, m. p. 219—220° (Found: C, 43·0; H, 7·3. $C_{10}H_{10}NI$ requires C, 42·7; H, 7·2%).

N-*Methyl*cyclo*pent*-1-*enylacetamide* (XI).—*cyclo*Pentanone (25 g.), ethyl cyanoacetate (42 g.), ammonium acetate (5·9 g.), and acetic acid (11·8 ml.) in dry benzene (250 ml.) gave, by the general procedure of Cope,[4] ethyl α-cyano-α-*cyclo*pent-1-enylacetate (51 g.), b. p. 156—158°/18 mm., m. p. 52—54°. Hydrolysis of the ester (10·3 g.) with boiling concentrated hydrochloric acid for 3½ hr., followed by concentration to 40 ml., gave the acid [6·5 g.; m. p. 126—128°, after crystallisation from ether–light petroleum (b. p. 60—80°)]. Pyrolysis of the acid (8·66 g.) at 210—230° for 10 min. and distillation of the residue gave *cyclo*pent-1-enylacetonitrile (4·76 g.), b. p. 80—82°/18 mm. The method of Sugasawa and Saito [15] was slightly more convenient, and gave 53·1 g. of the nitrile from 50 g. of *cyclo*pentanone. The nitrile (53·1 g.) was boiled overnight with aqueous potassium hydroxide (106 g. in 750 ml. of water). Acidification, ether-extraction, and distillation gave *cyclo*pent-1-enylacetic acid [16] (46 g.), b. p. 134—136°/18 mm.

Pure thionyl chloride (63 ml.) was added to a stirred solution of *cyclo*pent-1-enylacetic acid (52 g.) in dry benzene (170 ml.), and the solution was then heated under reflux for 1 hr. Benzene and excess of thionyl chloride were removed under reduced pressure, and the process was repeated three times with dry benzene (3 × 150 ml.). A solution of the residue in benzene (200 ml.) was stirred in an ice-bath and treated slowly with 25% aqueous methylamine (96 ml.) so that the temperature did not rise above 10°. After 1½ hr. the organic layer was separated, and the aqueous layer extracted with benzene (100 ml.). Distillation of the combined benzene solutions gave, after drying, N-*methyl*cyclo*pent*-1-*enylacetamide* (37 g.), b. p. 158—160°/20 mm., n_D^{17} 1·4945 (Found: C, 69·1; H, 9·2. $C_8H_{13}ON$ requires C, 69·0; H, 9·4%), which solidified (m. p. < 30°).

Tetrahydro-1-*methyl*-3 : 4-cyclo*pentenopyridine* (X).—The amide (37 g.), trifluoroacetic acid (116 g.), and trioxymethylene (9·6 g.) were heated on the water-bath for 6 hr. The solvent was removed under slightly reduced pressure, and the residue was then distilled. The product (33 g., b. p. 142—152°/10 mm.) was distilled through a column packed with helices, giving an oil (11·9 g.), b. p. 84—86°/1 mm., n_D^{21} 1·4730 (evidently the pyridone), and unchanged methylamide (16 g.; b. p. 158—164°/16 mm., n_D^{21} 1·4960).

The pyridone (15 g.) in dry ether (50 ml.) was added to lithium aluminium hydride (10·2 g.) in dry ether (75 ml.) fast enough to maintain boiling. After these had been heated for 3 hr. under reflux, working up by the usual methods gave the product (5·34 g.), b. p. 72—76°/18 mm., n_D^{17} 1·4840, which formed a *picrate*, m. p. 155—157° (Found: C, 48·7; H, 5·3. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 5·0%), as yellow needles from ethanol. Subsequent preparations of the picrate from the attempted reductions by dissolving metals gave homogeneous products, m. p. 151—153°, whose m. p.s could not be raised by further recrystallisation and which gave no depression with the above picrate (m. p. 155—157°). The *methiodide* crystallised from acetone–ether in needles, m. p. 146—147° (Found: C, 43·3; H, 6·7. $C_{10}H_{18}NI$ requires C, 43·0; H, 6·5%).

Hydrogenated in ethanol (5 ml.) in the way described above, the tetrahydropyridine (0·23 g.) took up 37·75 ml. of hydrogen (theor., 37·6 ml.) in 45 min. In the usual way the resulting solution provided *cis*-1-methyl-3 : 4-*cyclo*pentanopiperidine picrate (0·4 g.), m. p. and mixed m. p. 210·5—211°. A mixture with the *trans*-isomer (m. p. 213·5—214°) had m. p. 207—208°.

Hofmann Degradation of cis-1-*Methyl*-3 : 4-cyclo*pentanopiperidine Methiodide*.—The methiodide (4·2 g.) in water (60 ml.) was shaken in the dark with silver oxide (from 5·0 g. of silver nitrate) until an iodide test was negative. The filtered solution was evaporated under reduced pressure at 45—50°, and the temperature was then raised to 120—130°, providing a distillate of *cis*-1-dimethylaminomethyl-2-vinyl*cyclo*pentane, b. p. 65—70°/15 mm. This gave a *picrate* which crystallised from ethanol as yellow platelets, m. p. 123·5—124·5° (Found: C, 50·7; H, 5·7; N, 14·9. $C_{16}H_{22}O_7N_4$ requires C, 50·3; H, 5·8; N, 14·7%), and a *methiodide*, forming plates, m. p. 229—230° (Found: C, 45·2; H, 7·7. $C_{11}H_{22}NI$ requires C, 44·8; H, 7·5%), from acetone–ether.

The crude unsaturated base from the above decomposition was hydrogenated in ethanol

[15] Sugasawa and Saito, *Pharm. Bull.* (*Japan*), 1956, **4**, 237.
[16] Harding and Haworth, *J.*, 1910, 486.

with 30% palladised charcoal (0·2 g.), giving *cis*-1-dimethylaminomethyl-2-ethyl*cyclo*pentane (1·4 g.), b. p. 82—83°/22 mm., n_D^{16} 1·4540. The *picrate* formed yellow rhombs, m. p. 84—85° (Found: C, 49·8; H, 6·2. $C_{16}H_{24}O_7N_4$ requires C, 50·0; H, 6·3%), from ethanol. The *methiodide* gave platelets, m. p. 215—217° (Found: C, 44·7; H, 8·0. $C_{11}H_{24}NI$ requires C, 44·45; H, 8·1%), from acetone–ether. The oxide, prepared as described above, formed a yellow *picrate*, m. p. 104·5—106° (Found: C, 47·6; H, 5·8. $C_{16}H_{24}O_8N_4$ requires C, 48·0; H, 6·0%), which gave platelets from ethanol.

cis-1-Dimethylaminomethyl-2-ethyl*cyclo*pentane methiodide (9·53 g.) was submitted to Hofmann degradation as described above. The oily distillate was separated, after ether-extraction, by 2N-hydrochloric acid into a neutral (2·56 g.) and a small basic fraction. The basic fraction provided a *methiodide* which crystallised as platelets, m. p. 253—254° (Found: C, 44·7; H, 7·9. $C_{11}H_{24}NI$ requires C, 44·45; H, 8·1%), from acetone–ether.

The neutral product (0·43 g.) in dry ethyl acetate was treated with ozone for 8 hr. The solution was shaken with Adams's catalyst and hydrogen until reduction ceased, then filtered and distilled. The crude product (0·2 g., b. p. 160—200°) formed a semicarbazone which crystallised from aqueous alcohol in white plates, m. p. 179—180° (Found: C, 57·0; H, 9·1. Calc. for $C_8H_{15}ON_3$: C, 56·8; H, 8·95%), alone and mixed with 2-ethyl*cyclo*pentanone semicarbazone (m. p. 180—182°).

2-*Ethyl*cyclo*pentanone*.—Ethyl 1-ethyl-2-oxo*cyclo*pentane-1-carboxylate [17] (9·8 g.), acetic acid (50 ml.), 48% hydrobromic acid (50 ml.), and water (25 ml.) were heated under reflux for 18 hr. About half of the mixture was removed by distillation under reduced pressure. The distillate was basified with solid sodium hydroxide and extracted with ether. The washed (sodium hydrogen carbonate) and dried (Na_2SO_4) extract gave 2-ethyl*cyclo*pentanone (4·5 g.), b. p. 152—160° (semicarbazone, m. p. 180—182°).

We are grateful to D.S.I.R. for a maintenance grant (to G. G. A.), and to Professor Prelog who kindly presented us with a specimen of *cis*-3 : 4-*cyclo*pentanopiperidine picrate.

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[*Received, May 13th*, 1958.]

[17] Case and Reid, *J. Amer. Chem. Soc.*, 1928, **50**, 3064.