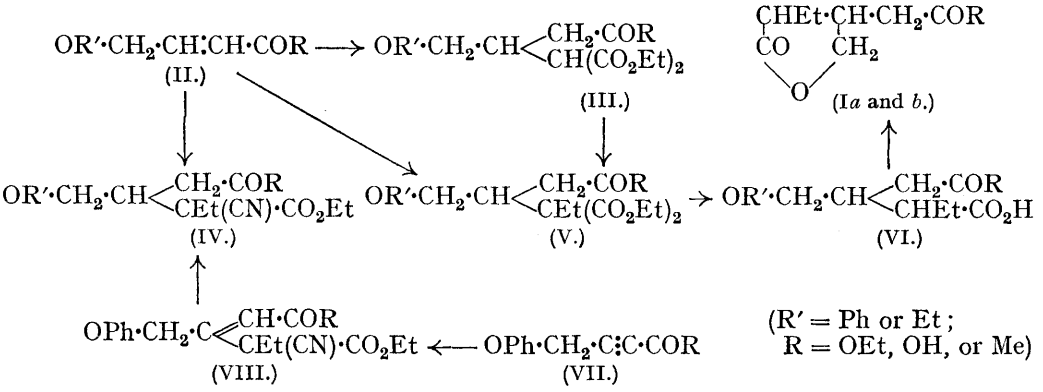
222. *The Jaborandi Alkaloids. Part I. The Synthesis of Homo- and* iso*Homo-pilopic Acids and of* r-*Pilocarpidine and* r-iso*Pilocarpidine by New Methods and the Resolution of* r-*Pilocarpine.*

By A. N. Dey.

Starting with ethyl ethylsuccinate and ethyl formate, Tschitschibabin and Preobrashenski (*Ber.*, 1930, **63**, 460) synthesised *r*-pilopic (β-ethylparaconic) and *r-iso*pilopic acids; they also showed that *d-iso*pilopic acid is identical with the *iso*pilopic acid obtained by Jowett (J., 1901, **79**, 1331) by the oxidation of *iso*pilocarpine (see also Pinner and Kohlhammer, *Ber.*, 1900, **33**, 2357; 1901, **34**, 730; Langenbeck, *Ber.*, 1924, **57**, 2072). From these two acids, Preobrashenski, Poljakowa, and Preobrashenski (*Ber.*, 1934, **67**, 710; 1935, **68**, 844, 850) synthesised the homologues, *r*-homopilopic and *r-iso*homopilopic acids. They also pre-

pared *d*-homopilopic acid by another method and showed that it is identical with the homopilopic acid produced by the oxidation of pilocarpine (Jowett, *loc. cit.*). Since Preobrashenski and Preobrashenski (*Ber.*, 1933, **66**, 1187, **1536**) had already converted homopilopic and *iso*homopilopic acids, obtained by the oxidation of pilocarpine and *iso*pilocarpine respectively, into *d*-pilocarpidine and *d-iso*pilocarpidine, and thence by methylation into *d*-pilocarpine and *d-iso*pilocarpine, the synthesis of the four bases has been fully achieved.

The present paper describes the synthesis of *r*-homo- and *r-iso*homo-pilopic acids and of *r*-pilocarpidine and *r-iso*pilocarpidine by new methods and the resolution of *r*-pilocarpine by means of *d*- and *l*-tartaric acids.



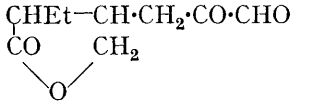
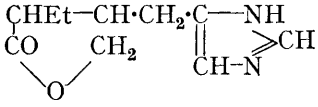
Synthesis of r-*Homo- and* r-iso*Homo-pilopic Acids.*—Elimination of hydrogen bromide from the easily available *ethyl α-bromo-γ-phenoxybutyrate* gave a poor yield of *ethyl γ-phenoxycrotonate* (II; R = OH, R′ = Ph). Therefore this ester was prepared from the corresponding *acid*, obtained in a yield of 60% by condensing phenoxyacetaldehyde with malonic acid. On condensation with ethyl cyanoacetate and ethyl iodide, the unsaturated ester gave *ethyl α-cyano-β-phenoxymethyl-α-ethylglutarate* (IV; R = OEt, R′ = Ph), which on hydrolysis furnished the cis- and trans-*glutaric acids* (VI; R = OH, R′ = Ph); these were separated by means of acetyl chloride. On hydrolysis with hydrobromic acid the *cis*- and the *trans*-acid gave *r*-homopilopic and *r-iso*homopilopic acid (I*a* and *b*, R = OH) respectively. The glutaric acids (VI) were obtained in better yield from the *carbethoxyglutaric* ester (V; R = OEt, R′ = Ph), prepared from *ethyl β-chloro-γ-phenoxybutyrate* or its *nitrile* and ethyl malonate and ethyl iodide. The hydrolysis of the phenoxy-group of the phenoxyglutaric acids, however, did not proceed smoothly and usually a poor yield of the final lactonic acids resulted. A higher temperature was more effective, but led to isomerisation of the lactonic acids. The corresponding cis- and trans-*ethoxyglutaric acids* (VI; R = OH, R′ = Et) were therefore prepared from ethyl γ-ethoxycrotonate (II; R = OEt, R′ = Et); they were separated by means of acetyl chloride as well as by the difference in solubility of their copper salts. The ethoxy-group was easily hydrolysed by hydrobromic acid and *r*-homopilopic and *r-iso*homopilopic acids were obtained in yields of 60%.

With excess of *p*-toluidine, *r*-homopilopic acid formed a *di*-p-*toluidide* difficultly soluble in methyl alcohol, whereas *r-iso*homopilopic acid gave only a more easily soluble *mono*-p-*toluidide*. This property was utilised to identify the two acids in their mixtures. When heated with concentrated hydrochloric acid at 200°, *r*-homopilopic acid was converted to the extent of 60% into the isomeride, but *r-iso*homopilopic acid remained unaffected. In presence of sodium ethoxide the ester of either acid underwent isomerisation. On distillation under atmospheric pressure *r*-homopilopic acid was quantitatively transformed into its isomeride.

Synthesis of r-*Pilocarpidine and* r-iso*Pilocarpidine.*—With methylzinc iodide, *r*-homopilopoyl chloride formed *β-acetonyl-α-ethyl-γ-butyrolactone* (I*a*, R = Me), and *r-iso*homopilopoyl chloride gave the isomeric *ketone* (I*b*). The constitutions of the two ketones were established by synthesis : *β-ethoxyethylideneacetone* (II; R = Me, R′ = Et), prepared either

by condensing ethoxyacetaldehyde with acetone in presence of sodium hydroxide or from γ-ethoxycrotonyl chloride and methylzinc iodide, gave, on condensation with ethyl cyanoacetate and ethyl iodide, *ethyl α-cyano-γ-acetyl-β-ethoxymethyl-α-ethylbutyrate* (IV; R = Me, R′ = Et), which on hydrolysis with fuming hydrobromic acid yielded (I*a*) and (I*b*). The same ketones were also obtained from ethyl α-cyano-γ-acetyl-β-phenoxymethyl-α-ethylbutyrate (IV; R = Me, R′ = Ph), prepared by hydrogenating the condensation product (VIII; R = Me, R′ = Ph) of *phenoxypropynyl methyl ketone* (VII, R = Me) with ethyl cyanoacetate and ethyl iodide. The acetylenic ketone itself was prepared by condensing acetyl chloride with the sodio-salt of phenyl propargyl ether.

On condensation with benzaldehyde in presence of dilute sodium hydroxide solution, the ketone (I*b*, R = Me) formed a solid *benzylidene* derivative (I*b*, R = CH:CHPh), whereas the ketone (I*a*) formed an isomeric liquid *benzylidene* derivative (I*a*, R = CH:CHPh) together with the solid isomeride. The production of the latter was due to the isomerising action of the alkali and could not be prevented. However, the acetylenic ketone produced by the condensation of *r*-homopilopoyl chloride and the sodio-derivative of phenylacetylene gave, on partial hydrogenation (Paal and Hartmann, *Ber.*, 1909, **42**, 3930), the liquid benzylidene derivative uncontaminated with the solid isomeride.

(IX*a* and *b*.)   (X*a* and *b*.)

On decomposition of their ozonides the benzylidene derivatives (I*a* and *b*, R = CH:CHPh) gave the *glyoxal* derivatives (IX*a* and *b*) respectively, which with ammonia and formaldehyde formed *r*-pilocarpidine and *r-iso*pilocarpidine respectively. These bases could not be resolved, but on methylation they gave *r*-pilocarpine and *r-iso*pilocarpine, respectively, of which the former was easily separated into its optical components by means of *d*- and *l*-tartaric acids, the *l*-acid forming an insoluble salt with the *d*-form of the base. The *d*-base thus prepared was identified with natural pilocarpine through the mixed melting points of their nitrates and hydrogen tartrates. The *l*-base, like pilocarpine, underwent isomerisation in presence of alkali, forming *l-iso*pilocarpine, which, when combined with an equal amount of *iso*pilocarpine, formed an inactive base identical with the *r-iso*pilocarpine described above.

Experimental.

Ethyl α-Bromo-γ-phenoxybutyrate.—α-Bromo-γ-phenoxybutyric acid was prepared, essentially by Fischer and Blumenthal's method (*Ber.*, 1907, **40**, 106), from β-phenoxyethylmalonic acid (Haworth and Perkin, J., 1896, **69**, 165; see also Leuchs, *Ber.*, 1911, **44**, 1507). The *ethyl* ester, b. p. 199—200°/16 mm., was prepared by the usual method (Found: Br, 27·6. $C_{12}H_{15}O_3Br$ requires Br, 27·9%).

Bromoacetal (cf. Späth, *Monatsh.*, 1915, **35**, 4).—Bromine (630 g.) was added with stirring to paraldehyde (200 g.) as fast as the reaction proceeded, the temperature being kept at 10—13°. The mixture was poured into alcohol (800 c.c.) and after 48 hours the whole was poured into a saturated solution of sodium carbonate. The oily bromoacetal (400 g.) was separated, washed, dried, and distilled, giving the pure acetal (300—350 g.), b. p. 65—68°/12 mm.

Phenoxyacetaldehyde.—Shrœtter's method (*Ber.*, 1885, **13**, 2315) gave a poor yield, so the following one was used. Bromoacetal (197 g.) and an alcoholic solution of sodium phenoxide (prepared from 94 g. of phenol, 23 g. of sodium, and 190 c.c. of alcohol) were heated (150—160°) in an autoclave for 4 hours, the solvent removed by distillation in a vacuum, the residue poured into water, and the oily product separated with ether. The residue from the ethereal solution, on distillation, gave the phenoxyacetal (150 g.), b. p. 132—134°/10 mm., which was hydrolysed with dilute sulphuric acid, and the phenoxyacetaldehyde (88 g.) formed separated with ether. It boiled at 105°/10 mm.

γ-Phenoxycrotonic Acid (II; R = OH, R′ = Ph).—A mixture of ethyl α-bromo-γ-phenoxybutyrate (50 g.) and freshly distilled diethylaniline (150 g.) was heated (170—180°) for 12 hours and poured into dilute hydrochloric acid; the product on fractional distillation gave *ethyl γ-phenoxycrotonate*, b. p. 182—184°/12 mm., in 20% yield (Found: C, 69·8; H, 6·6. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·9%).

On hydrolysis with alcoholic potassium hydroxide, and acidification of the resulting potassium salt with dilute hydrochloric acid, *γ-phenoxycrotonic acid* was obtained. It crystallised from dilute alcohol in needles, m. p. 138°, insoluble in water and difficultly soluble in benzene (Found: C, 67·2; H, 5·3. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The same acid was obtained in better yield by heating phenoxyacetaldehyde (136 g.), malonic acid (104 g.), and pyridine (120 g.) together on a water-bath for 1 hour, pouring the mixture into dilute hydrochloric acid, and extracting the acid with ether.

Ethyl α-Cyano-β-phenoxymethyl-α-ethylglutarate (IV; R = OEt, R′ = Ph).—A mixture of ethyl γ-phenoxycrotonate (II; R = OEt, R′ = Ph) and ethyl cyanoacetate (12 g.) was refluxed for 24 hours with a solution of sodium ethoxide (from 2·3 g. of sodium) in alcohol (30 c.c.), ethyl iodide (20 g.) then added, and the mixture refluxed until it became neutral. The *cyano*-ester, b. p. 221°/8 mm., was separated in the usual way in a yield of 66% (Found: C, 65·3; H, 7·1. $C_{19}H_{25}O_5N$ requires C, 65·7; H, 7·2%). On hydrolysis with an excess of alcoholic potassium hydroxide the ester gave *α-cyano-β-phenoxymethyl-α-ethylglutaric acid*, which crystallised from dilute alcohol in small needles, m. p. 194°, insoluble in benzene and water, but soluble in ether, acetone, and methyl alcohol (Found: C, 61·6; H, 5·7. $C_{15}H_{17}O_5N$ requires C, 61·9; H, 5·8%).

β-Phenoxymethyl-α-ethylglutarimide.—The above cyano-acid (10 g.) was refluxed for ½ hour with concentrated hydrochloric acid (50 g.), and the solution cooled and extracted with ether. The extract was washed with dilute sodium carbonate solution (alkaline washing *A*), dried, and distilled, the *imide* (34 g.) being obtained as a thick oil, b. p. 245°/12 mm. (Found: C, 68·0; H, 6·6; N, 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%).

cis- *and* trans-*β-Phenoxymethyl-α-ethylglutaric Acids* (VI; R = OH, R′ = Ph).—The cis-*acid* was obtained as an oil on hydrolysis of the above imide with concentrated hydrochloric acid (Found: C, 62·9; H, 6·5. $C_{14}H_{18}O_5$ requires C, 67·7; H, 6·5%). By acetyl chloride or acetic anhydride in the cold it was converted into the *anhydride*, b. p. 222—224°/18 mm. (Found: C, 67·6; H, 6·4. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). The *p*-toluidic acid could not be obtained as a solid product, but the p-*tolylimide* was prepared by heating equimolecular quantities of the anhydride and *p*-toluidine at 150° for 1 hour; it crystallised from dilute alcohol in long needles, m. p. 215° (Found: C, 74·4; H, 6·6. $C_{21}H_{23}O_3N$ requires C, 74·8; H, 6·8; N, 4·2%).

When the alkaline washing (*A*) was acidified, the trans-*acid*, mixed with a little of the *cis*-acid, separated as an oil. This was removed in ether and mixed with an equal volume of acetyl chloride; after ½ hour the excess of acetyl chloride was removed over sodium hydroxide in a vacuum at the ordinary temperature, the residue dissolved in ether, and the solution washed with dilute aqueous sodium bicarbonate. Acidification of this washing gave the pure *trans*-acid as an oil (Found: C, 63·2; H, 6·7%). It was quantitatively transformed into the anhydride of the *cis*-acid by boiling acetic anhydride or acetyl chloride.

r-*Homopilopic Acid* (Ia, R = OH).—A mixture of the *cis*-glutaric acid (VI; R = OH, R′ = Ph) (10 g.) and fuming hydrobromic acid (50 g.) was refluxed for 6 hours, the solution evaporated to dryness under reduced pressure, and the residual mixture of acids esterified by refluxing with alcohol (100 c.c.) saturated with hydrogen chloride. On fractional distillation of the esters, ethyl *r*-homopilopate, b. p. 181°/17 mm., was obtained in 20% yield (Found: C, 59·8; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). The other product was mostly the ester of the unchanged glutaric acid. On hydrolysis of the ethyl ester with concentrated hydrochloric acid, *r*-homopilopic acid was obtained as a thick oil, b. p. 199°/1·5 mm. It was obtained crystalline, m. p. 99—100°, by solution in the minimum quantity of ether and precipitation with light petroleum (Preobrashenski gives m. p. 101°) (Found: C, 55·6; H, 6·8; equiv., 172. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%; equiv., 173). The *di*-p-*toluidide*, prepared by heating the acid chloride (1 mol.) with *p*-toluidine (2 mols.) at 150° for 2 hours, was sparingly soluble in cold methyl alcohol and was crystallised from dilute alcohol; m. p. 225° (Found: C, 75·2; H, 7·0. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4%).

r-iso*Homopilopic Acid* (Ib, R = OH).—Hydrolysis of the *trans*-acid (VI; R = OH, R′ = Ph) in a similar manner gave *r-iso*homopilopic acid, which separated as a crystalline solid from a warm aqueous solution on passage of hydrogen chloride; m. p. 75° (Found: C, 55·5; H, 6·7%; equiv., 173). The ethyl ester boiled at 171°/17 mm. (Found: C, 59·9; H, 8·0%). The *mono*-p-*toluidide* was very soluble in methyl alcohol, but less soluble in ethyl alcohol; it separated from dilute alcohol in needles, m. p. 115° (Found: C, 68·8; H, 7·0; N, 5·6. $C_{15}H_{19}O_3N$ requires C, 69·0; H, 7·3; N, 5·4%).

The p-*Toluidides of* d-*Homopilopic and* d-iso*Homopilopic Acids.*—(i) *d*-Homopilopic acid, prepared from its methylamide derivative obtained by the ozonisation of pilocarpine, formed

a *di*-p-*toluidide*, m. p. 268° after crystallisation from alcohol (Found : C, 75·1; H, 7·2; N, 8·1. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4; N, 8·0%).

(ii) The *mono*-p-*toluidide* of *d-iso*homopilopic acid (obtained from the ozonisation product of *iso*pilocarpine) crystallised from dilute alcohol in needles, m. p. 142° (Found : C, 68·7; H, 7·2; N, 5·5. $C_{15}H_{19}O_3N$ requires C, 69·0; H, 7·3; N, 5·4%).

Isomerisation of Ethyl r-*Homopilopate*.—The ester (10 g.) was mixed with alcoholic sodium ethoxide (1 g. of sodium in 50 c.c. of alcohol) and left at the ordinary temperature for 72 hours. The solution was then exactly neutralised with alcoholic hydrogen chloride, the solvent removed under reduced pressure, and the residual ester hydrolysed with concentrated hydrochloric acid. The acid obtained was converted by thionyl chloride into the acid chloride, which was heated at 150° with an excess of *p*-toluidine. The mixture of *p*-toluidide derivatives was separated in the ordinary way and on fractional crystallisation gave two solids identical with the toluidide derivatives of *r*-homo- and *r-iso*homo-pilopic acids described above. The conversion of ethyl *r*-homopilopate into its isomeride as calculated from the proportion of the toluidides formed was 40%.

Ethyl *r-iso*homopilopate under similar conditions formed a similar mixture.

Isomerisation of r-*Homopilopic Acid*.—A mixture of the acid (10 g.) and concentrated hydrochloric acid (30 c.c.) was heated in a sealed tube for 4 hours at 200°, the solution evaporated to dryness, the residue dissolved in a dilute solution of sodium carbonate, and the alkaline solution extracted with ether to remove the neutral products. The acids reprecipitated from the alkaline solution by acidification were converted into the *p*-toluidide derivatives, which on fractional crystallisation were separated into two toluidides identical with those prepared from *r*-homo- and *r-iso*homo-pilopic acids. The conversion in this case was 60%.

β-*Hydroxy-γ-phenoxybutyronitrile*.—A solution of α-monochlorohydrin γ-phenyl ether (100 g.) in methyl alcohol (200 c.c.) was boiled under reflux (½ hour) while a solution of potassium cyanide (40 g.) in water (80 c.c.) was gradually added. After being refluxed for another hour, the solvent was distilled off, and the residue mixed with alcohol–ether (1 : 1). On removal of the solvents from the filtered solution, the *nitrile* (73 g.) was obtained as a thick oil, b. p. 201—205°/15 mm. It solidified to a felted mass, m. p. 59°, soluble in alcohol, acetone, benzene, ether, and ethyl acetate, but insoluble in light petroleum and water. For analysis it was purified by solution in the minimum quantity of ether and reprecipitation with light petroleum (Found : C, 67·5; H, 6·1. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2%).

(1) The nitrile (100 g.) was refluxed with alcohol (180 c.c.) and sulphuric acid (40 c.c.) for 6 hours, and *ethyl* β-*hydroxy-γ-phenoxybutyrate*, b. p. 189°/15 mm., obtained in a yield of 65% (Found : C, 64·2; H, 7·0. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%).

(2) By the interaction of the nitrile (17 g.) and phosphorus pentachloride (20 g.), β-*chloro-γ-phenoxybutyronitrile*, b. p. 175—177°/13 mm., was formed in a yield of 59% (Found : Cl, 18·0. $C_{10}H_{10}ONCl$ requires Cl, 18·2%).

Ethyl β-*chloro-γ-phenoxybutyrate*, obtained in 60% yield from ethyl β-hydroxy-γ-phenoxybutyrate and phosphorus pentachloride, boiled at 165—166°/10 mm. (Found : C, 59·2; H, 6·1. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·2%).

Ethyl α-*carbethoxy*-β-*phenoxymethylglutarate* (III; R = OEt, R′ = Ph), obtained in a yield of 60% by condensing the preceding ester with ethyl sodiomalonate in the ordinary way, boiled at 239—240°/12 mm. (Found : C, 62·0; H, 6·9. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·1%). On ethylation through the sodio-derivative it gave *ethyl* α-*carbethoxy*-β-*phenoxymethyl*-α-*ethylglutarate* (V; R = OEt, R′ = Ph), b. p. 229—230°/11 mm., in 65% yield (Found : C, 63·8; H, 7·4. $C_{21}H_{30}O_7$ requires C, 64·0; H, 7·6%). Hydrolysis of the latter ester with concentrated hydrochloric acid gave a mixture of the *cis*- and *trans*-glutaric acids (VI; R = OH, R′ = Ph).

Ethyl α-*carbethoxy-γ-cyano*-β-*phenoxymethylbutyrate*, prepared in 60% yield from β-chloro-γ-phenoxybutyronitrile and ethyl sodiomalonate, boiled at 246°/10 mm. (Found : C, 63·8; H, 6·4. $C_{17}H_{21}O_5N$ requires C, 64·0; H, 6·6%). On ethylation through its sodio-derivative it gave a 65% yield of *ethyl* α-*carbethoxy-γ-cyano*-β-*phenoxymethyl*-α-*ethylbutyrate*, b. p. 240—242°/11 mm. (Found : C, 65·4; H, 7·1. $C_{19}H_{25}O_5N$ requires C, 65·7; H, 7·2%), which on hydrolysis furnished a mixture of the two glutaric acids (VI; R = OH, R′ = Ph).

β-*Hydroxy-γ-ethoxybutyronitrile*.—As Lespieau's process (*Bull. Soc. chim.*, 1905, **33**, 469) proved unsatisfactory for the preparation of large quantities, the nitrile was obtained by running α-monochlorohydrin γ-ethyl ether (140 g.) (Fourneau and Ribas, *ibid.*, 1926, **39**, 1584) slowly with vigorous stirring into a concentrated solution of potassium cyanide (70 g. in 70 c.c. of water) at 50—60°. The temperature, which had at first to be controlled by cooling, was finally raised to 70°, and the mixture stirred for 5 hours. It was then cooled, potassium chloride removed,

and the filtrate distilled fractionally, the nitrile, b. p. 137°/10 mm., being obtained in a yield of 65%.

Ethyl α-cyano-β-ethoxymethyl-α-ethylglutarate (IV; R = OEt, R′ = Et), obtained by the condensation of ethyl γ-ethoxycrotonate with ethyl cyanoacetate and ethyl iodide (see the corresponding phenoxy-derivative; p. 1060), had b. p. 200—204°/12 mm. (65% yield) (Found: C, 60·0; H, 8·3. $C_{15}H_{25}O_5N$ requires C, 60·2; H, 8·4%).

Ethyl α-carbethoxy-β-ethoxymethyl-α-ethylglutarate (V; R = OEt, R′ = Et), prepared by condensing ethyl γ-ethoxycrotonate with ethyl malonate and ethyl iodide in the ordinary way, had b. p. 184—185°/15 mm. (yield, 60%) (Found: C, 58·9; H, 8·5. $C_{17}H_{30}O_7$ requires C, 59·0; H, 8·7%). The intermediate ester, *ethyl α-carbethoxy-β-ethoxymethylglutarate* (III; R = OEt, R′ = Et), b. p. 190—192°/13 mm., was also isolated (Found: C, 56·3; H, 8·0. $C_{15}H_{26}O_7$ requires C, 56·6; H, 8·2%); on hydrolysis with concentrated hydrobromic acid it gave *norhomopilopic acid*, b. p. 204—206°/12 mm. (Found: C, 49·7; H, 5·4. $C_6H_8O_4$ requires C, 50·0; H, 5·6%).

Ethyl α-carbethoxy-γ-cyano-β-ethoxymethyl-α-ethylbutyrate, obtained in 60% yield by condensing γ-ethoxybutyronitrile with ethyl malonate and ethyl iodide, boiled at 192—194°/14 mm. (Found: C, 60·0; H, 8·2. $C_{15}H_{25}O_5N$ requires C, 60·2; H, 8·4%). The intermediate *ethyl α-carbethoxy-γ-cyano-β-ethoxymethylbutyrate*, b. p. 194—195°/18 mm., was isolated (Found: C, 57·3; H, 7·4. $C_{13}H_{21}O_5N$ requires C, 57·6; H, 7·7%); on hydrolysis with hydrobromic acid it also gave norhomopilopic acid.

β-Ethoxymethyl-α-ethylglutaric Acids (VI; R = OH, R′ = Et).—The esters (IV; R = OEt, R′ = Et) and (V; R = Et, R′ = Et) on hydrolysis with caustic potash (40% solution) gave the corresponding carboxyglutaric acid, which on decarboxylation furnished a mixture of the *cis*- and *trans*-glutaric acids (VI; R = OH, R′ = Et). These were dissolved in water and neutralised with ammonia, and dilute copper sulphate solution added till the precipitation of the copper salt was maximal. The filtered solution was acidified, and the cis-*acid* extracted with ether. Decomposition of the precipitated copper salt with hydrogen sulphide gave the *trans*-acid.

The *cis*-acid, recrystallised from hexane, melted at 78° (Found: C, 54·9; H, 8·1. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·2%). When treated with cold acetyl chloride or boiled with acetic anhydride, it formed the *anhydride*, b. p. 185°/16 mm. (Found: C, 59·8; H, 7·8. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%). The *p*-toluidic acid obtained from this anhydride and *p*-toluidine was a liquid, which, after being heated for ½ hour at 200°, formed the p-*tolylimide*, m. p. 205° (from alcohol) (Found: C, 70·3; H, 7·8; N, 4·9. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 8·0; N, 4·8%).

The *trans*-acid could not be obtained solid. It was unaffected by cold acetyl chloride, but when boiled with this reagent or with acetic anhydride it was quantitatively transformed into the anhydride of the *cis*-acid.

β-Acetonyl-α-ethyl-γ-butyrolactone (I*a*, R = Me).—A benzene solution of the acid chloride prepared from *r*-homopilopic acid (50 g.) and thionyl chloride (250 c.c.) was added slowly to a solution prepared from methyl iodide (35 c.c.), zinc–copper couple (65 g.), benzene (20 c.c.), and ethyl acetate (10 c.c.), cooled in a freezing mixture. The mixture was left in ice for 2 hours, then decomposed with ice and dilute sulphuric acid, the oily layer separated with ether, washed and dried, and the solvent removed. The residual oil on distillation gave the above *ketone*, b. p. 194—205°/12 mm., mainly at 202—205°/12 mm. (yield, 21%) (Found: C, 63·4; H, 8·1. $C_9H_{14}O_3$ requires C, 63·6; H, 8·2%). The *semicarbazone* crystallised from dilute alcohol in small needles, m. p. 184° (Found: C, 52·6; H, 7·2; N, 18·3. $C_{10}H_{17}O_3N_3$ requires C, 52·9; H, 7·5; N, 18·5%).

iso-β-*Acetonyl-α-ethyl-γ-butyrolactone* (I*b*, R = Me), obtained in 30% yield from *r-iso*homopilopic acid in a similar way, had b. p. 186—188°/13 mm. (Found: C, 63·4; H, 8·0%). The *semicarbazone* crystallised from dilute alcohol in thick needles, m. p. 164° (Found: C, 52·5; H, 7·3; N, 18·6%).

Synthesis of the Ketones (I*a* and *b*, R = Me).—(1) Ethoxyacetal (30 g.) was hydrolysed by boiling (30 mins.) with water and one drop of concentrated sulphuric acid, the solution mixed with acetone (30 c.c.), and sodium hydroxide (4 g. in 6 c.c. of water) stirred in during an hour. After being stirred for 48 hours, the mixture was extracted with ether, the extract washed with a concentrated solution of potassium chloride, and the ether removed. The residual β-*ethoxyethylideneacetone* (II; R = Me, R′ = Et), b. p. 61°/11 mm., polymerised after a few days (Found: C, 65·3; H, 9·0. $C_7H_{12}O_2$ requires C, 65·6; H, 9·3%). The *semicarbazone* had m. p. 135° after crystallisation from dilute alcohol (Found: C, 62·2; H, 5·4; N, 18·0. $C_8H_{15}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

A mixture of the above ketone (12·8 g.) and the alcoholic solution prepared from 2·3 g. of sodium, 30 c.c. of alcohol, and 12 g. of ethyl cyanoacetate was refluxed for 12 hours, ethyl iodide (15 c.c.) then added, and refluxing continued till the liquid became neutral. The product, on being worked up, gave *ethyl α-cyano-γ-acetyl-β-ethoxymethyl-α-ethylbutyrate* (IV; R = Me, R′ = Et), b. p. 187—193°/17 mm., in a yield of 30% (Found: C, 62·1; H, 8·2. $C_{14}H_{23}O_4N$ requires C, 62·4; H, 8·5%). On hydrolysis with hydrobromic acid (100 c.c.) the ester (20 g.) gave an oily mixture, which on fractional distillation yielded three fractions, (i) b. p. 200—205°/12 mm., (ii) 210—215°/17 mm., and (iii) 230—235°/17 mm. The last fraction solidified and was recrystallised from ethyl acetate; m. p. 135°; its analysis and properties indicated it to be a *dilactone* (Found: C, 61·0; H, 6·0. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). The first fraction gave a semicarbazone, m. p. 184°, identical with that obtained from the ketone (I*a*, R = Me), and the second fraction gave an isomeric semicarbazone identical with the same derivative obtained from the ketone (I*b*, R = Me).

(2) A mixture of βγ-dibromopropene (100 g.), phenol (47 g.), potassium carbonate (35 g.), and acetone (200 c.c.) was refluxed for 12 hours, the solvent removed under reduced pressure, and the residue poured into water and extracted with ether. β-Bromoallyl phenyl ether, b. p. 105°/15 mm., was obtained from the ethereal residue in 70% yield (cf. Henry, *Bull. Soc. chim.*, 1883, **40**, 324).

A mixture of β-bromoallyl phenyl ether (103·8 g.), caustic potash (42 g.), and alcohol (84 c.c.) was heated on a water-bath for 3 hours, the solution poured into water, and the oily liquid separated with ether. On distillation phenyl propargyl ether, b. p. 95—98°/23 mm., was obtained in 40% yield (cf. Henry, *loc. cit.*).

Phenyl propargyl ether (13·5 g.) was heated with finely pulverised sodium (23 g.) in toluene (100 c.c.) on a water-bath for 6 hours, the sodio-derivative separated by decantation and suspended in dry ether (200 c.c.), and, with cooling in a freezing mixture, a solution of acetyl chloride (10 g.) in ether (30 c.c.) slowly added. The mixture was left at room temperature for 2 days and poured into ice-water, and the product extracted and dried in ether, and distilled up to 150°/20 mm. The residue consisted mainly of *phenoxypropynyl methyl ketone* (VII, R = Me) and was used for further reactions; the specimen for analysis was twice redistilled, b. p. 164—166°/20 mm. (Found: C, 75·8; H, 5·7. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·8%). The *semicarbazone*, m. p. 135°, crystallised from dilute alcohol (Found: C, 62·2; H, 5·4; N, 18·0. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

The acetylenic ketone (1 mol.) was refluxed with ethyl sodiomalonate (2·3 g. of sodium, 16 g. of ethyl malonate, and 30 c.c. of alcohol) for 6 hours, ethyl iodide (16 c.c.) then added, and the mixture refluxed until it became neutral. After removal of the solvent and the excess of ethyl iodide under reduced pressure the residue was mixed with a fresh quantity of alcohol (100 c.c.) and hydrogenated in presence of palladised charcoal (Paal and Hartmann, *loc. cit.*) until 1 mol. of hydrogen was absorbed. The solvent was then removed, and the residue hydrolysed with excess of fuming hydrobromic acid. The product after separation with ether gave on distillation mainly two fractions, (i) b. p. 194—200°/17 mm., and (ii) 200—205°/17 mm., identified with the ketones (I*a*, R = Me) and (I*b*) by means of their semicarbazones.

β-Benzylideneacetonyl-α-ethyl-γ-butyrolactone (I*a*, R = CH:CHPh).—A mixture of the ketone (I*a*, R = Me) (10 g.) and benzaldehyde (6·5 g.) was left in 10% sodium hydroxide solution (35 c.c.) for 3 weeks with occasional shaking. The solution was then neutralised with acetic acid, steam-distilled to remove benzaldehyde, and extracted with ether. The residue from the ethereal solution was converted into semicarbazone and fractionally crystallised. Two solids separated, m. p. 245° (5·4 g.) and 211° (2 g.). The latter was identified with the semicarbazone of the benzylidene derivative obtained from the isomeric ketone (below). The former, the less soluble product, was the *semicarbazone* of β-benzylideneacetonyl-α-ethyl-γ-butyrolactone; after recrystallisation from water it melted at 245° (Found: C, 68·4; H, 6·4; N, 13·1. $C_{17}H_{21}O_3N_3$ requires C, 68·6; H, 6·7; N, 13·3%). The *benzylidene* derivative obtained from it by warming with concentrated hydrochloric acid was a viscous oil (Found: C, 74·0; H, 6·8. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). This compound was also obtained by the following procedure: *r*-Homopilopoyl chloride (1 mol.) was added to a well-cooled suspension of the sodio-derivative of phenylacetylene in ether (Nef, *Annalen*, 1909, **308**, 275), and the mixture shaken on a machine. After 48 hours the solvent was removed, and the residue suspended in alcohol (200 c.c.) and hydrogenated in presence of palladised charcoal (Paal and Hartmann, *loc. cit.*) until 1 mol. of hydrogen was absorbed. The alcohol was then distilled, and the residue extracted with ether. After removal of the ether from the extract the residue was steam-distilled to remove the admixed styrene, washed and dried in ether, and recovered as a thick

liquid, which was identified with the above liquid benzylidene derivative by means of its semicarbazone (yield, 30%).

iso-β-*Benzylideneacetonyl-α-ethyl-γ-butyrolactone* (I*b*, R = CH:CHPh).—When the ketone (I*b*, R = Me) was treated with benzaldehyde and sodium hydroxide solution in the way already described, the *butyrolactone* (I*b*, R = CH:CHPh) was the sole product (yield, 45%); after crystallisation from ethyl acetate–benzene, it had m. p. 105° (Found: C, 74·1; H, 6·7%). The *semicarbazone* crystallised from alcohol in thick needles, m. p. 211° (Found: C, 68·4; H, 6·5; N, 13·5%). The preparation from *r-iso*homopilopoyl chloride and sodiophenylacetylene gave ultimately only a 10% yield of the benzylidene derivative.

Ozonolysis of the Benzylidene Derivatives (I*a* and *b*, R = CH:CHPh).—Ozone was passed through a solution of the benzylidene derivative (I*a*) (10 g.) in chloroform (250 c.c.) until no more was absorbed; the solvent was then removed in a vacuum at the ordinary temperature. The residue was dissolved in ether (250 c.c.) and glacial acetic acid (10 c.c.), cooled in a freezing mixture, and decomposed with zinc (10 g.) and water (5 c.c.), added with vigorous stirring during 1 hour. The sludge was removed, the filtrate washed with dilute sodium bicarbonate solution and water and dried, the solvent removed under reduced pressure at the ordinary temperature, and the residue steam-distilled to remove benzaldehyde. The residual solution of *α-ethyl-γ-butyrolactone-β-pyruvaldehyde* (IX*a*) was used for further reactions. The pure glyoxal (2·2 g.), however, was obtained by extraction with ether and removal of the ether at the ordinary temperature by dry carbon dioxide; it was a thick oil, which reduced ammoniacal silver nitrate and gave a non-crystalline osazone (Found: C, 58·2; H, 6·2. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%).

The benzylidene derivative (I*b*, R = CH:CHPh) similarly gave an isomeric *glyoxal* derivative (IX*b*) in almost equal yield (Found: C, 58·4; H, 6·2%). This formed an *osazone* which separated from dilute alcohol in lemon-coloured crystals, m. p. 156° (Found: C, 69·0; H, 6·1; N, 15·7. $C_{21}H_{24}O_2N_4$ requires C, 69·2; H, 6·6; N, 15·4%).

Synthesis of r-*Pilocarpidine* (X*a*).—The glyoxal (IX*a*) (2 g.) or an aqueous solution containing it was mixed with a solution of ammonia (2 c.c., *d* 0·880, specially prepared by saturating carbon dioxide-free water with the gas) and formaldehyde (2 c.c.; 40%). After 3 weeks the solution was evaporated under reduced pressure at 60°, the residue acidified strongly with hydrochloric acid and boiled for 2 hours, the solution again evaporated to dryness under reduced pressure, and the residue mixed with a concentrated solution of potassium carbonate and extracted with chloroform in a continuous extractor. On evaporation of the dried chloroform solution a thick oily base was left; this was converted by the calculated amount of nitric acid into the nitrate, m. p. 131° after crystallisation from alcohol (Found: C, 46·6; H, 5·5; N, 16·5. Calc. for $C_{10}H_{14}O_2N_2,HNO_3$: C, 46·7; H, 5·5; N, 16·3%).

Synthesis of r-iso*Pilocarpidine* (X*b*).—In the same manner the glyoxal (IX*b*) (2 g.) or a solution of it in water furnished *r-iso*pilocarpidine, of which the nitrate had m. p. 113—114° after repeated crystallisation (Found: C, 46·5; H, 5·2; N, 16·2%).

These two bases, when methylated with methyl iodide in the usual way, severally gave *r*-pilocarpine [nitrate, m. p. 150° after repeated crystallisation (Found: C, 48·5; H, 6·3; N, 15·4. Calc. for $C_{11}H_{16}O_2N_2,HNO_3$: C, 48·7; H, 6·3; N, 15·3%)] and *r-iso*pilocarpine [nitrate, m. p. 132—134° after recrystallisation from alcohol (Found: C, 48·4; H, 6·1; N, 15·1%)].

Resolution of r-*Pilocarpine*.—When a solution of *l*-tartaric acid (1 mol.) in just sufficient alcohol to dissolve it was added to a solution of *r*-pilocarpine (0·9 g.; 2 mols.) in alcohol (5 c.c.), *d*-pilocarpine hydrogen *l*-tartrate was precipitated as an oil which soon solidified; after recrystallisation from dilute alcohol it had m. p. 132° alone or mixed with the same salt of natural pilocarpine (Found: C, 50·0; H, 6·0; N, 7·8. Calc. for $C_{11}H_{16}O_2N_2,C_4H_6O_6$: C, 50·3; H, 6·2; N, 7·8%). The base obtained from the hydrogen tartrate was converted into the nitrate, which, after recrystallisation from dilute alcohol, melted at 175°, alone or mixed with the same salt of natural pilocarpine (Found: C, 48·5; H, 6·0; N, 15·6. Calc. for $C_{11}H_{16}O_2N_2,HNO_3$: C, 48·7; H, 6·3; N, 15·5%). It had $[\alpha]_D^{19°}$ 81·3° in water (c = 1·165, l = 0·5).

The filtrate from the *d*-pilocarpine hydrogen *l*-tartrate was treated with an equal quantity of *d*-tartaric acid (1 mol.) and the precipitate (0·25 g.) of *l*-pilocarpine hydrogen *d*-tartrate was filtered off and recrystallised from alcohol; m. p. 132° (Found: C, 49·9; H, 6·2; N, 7·9%). The base obtained from it after repeated crystallisation was converted into the nitrate, m. p. 175° after crystallisation from alcohol (Found: C, 48·5; H, 6·0; N, 15·6%). It had $[\alpha]_D^{19·5°}$ = — 82·17° in water (c = 0·925, l = 0·5).

The pure active bases (0·005 g. of each) were mixed together in dry ether; the base recovered

by evaporation of the solution under reduced pressure was converted into the nitrate, m. p., after recrystallisation, 150° alone or mixed with the nitrate of *r*-pilocarpine.

Conversion of l-*Pilocarpine into* l-iso*Pilocarpine*.—*l*-Pilocarpine (0·25 g.) was mixed with an alcoholic solution of sodium ethoxide (0·3 g. of sodium in 20 c.c. of alcohol) and after a few days the mixture was warmed for 1 hour on the water-bath, the alkali neutralised with alcoholic hydrochloric acid, the solution evaporated under reduced pressure, and the residue made strongly alkaline with sodium carbonate solution and extracted with chloroform. The base obtained from the dried chloroform solution was converted into the nitrate, m. p. 156—158° (dilute alcohol) (Found : C, 48·5; H, 6·0; N, 10·1. Calc. for $C_{11}H_{16}O_2N_2,HNO_3$: C, 48·7; H, 6·3; N, 10·3%). It had $[\alpha]_D^{17\cdot0°}$ — 53·1° in water (c = 1·216, l = 0·5). The *r*-base obtained from the two active *iso*pilocarpines in ether formed a nitrate, m. p. 134° alone or mixed with *r-iso*pilocarpine nitrate.

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