The auxin activities of the homologs of racemic and enantiomeric \( \alpha \)-alkylphenylacetic acids were estimated by pea straight growth test. The \( \alpha \)-methyl, -ethyl and -propyl acids were moderately active whereas the longer and branched alkyl chain were found to make the molecule inactive. The more active enantiomers were shown to have the same configuration as the more active enantiomers in the other series of the optical active synthetic auxins.

Although the auxin activities of \( \alpha \)-alkylphenylacetic acids have been examined by several workers, the works are not extensive and have not provided a comprehensive set of the activity data.\(^1\) The purpose of this paper is to estimate the auxin activity of homologous series of the \( \alpha \)-alkylphenylacetic acids and to provide unequivocal informations for the analysis of structure/activity relationships in the related plant growth regulators including the highly active hydro-l-naphthoic acids, the condensed ring analogs of the \( \alpha \)-alkylphenylacetic acids.\(^2\) The auxin activity of racemic \( \alpha \)-alkylphenylacetic acids obtained by pea straight growth test is shown in Fig. 1. Phenylacetic acid is found to be weakly active. The \( \alpha \)-methyl substitution enhances the activity of the parent acid about 10 times. The result is consistent with the early finding by Koepfli et al. in the pea curvature test.\(^3\) The \( \alpha \)-methyl substitution would enhance the activity by making the molecule fit the receptor surface more properly, i.e., a hydrophobic bonding with the \( \alpha \)-methyl group to the receptor surface would make the neighboring carboxyl group to take a more proper position to exert the activity. The \( \alpha \)-methyl group would also make the molecule more lipophilic so that the lipohydrophilic balance of the molecule would be made optimal for partitions between lipoidal and aqueous phases on the passages to reach the site of action.

The \( \alpha \)-ethyl acid has almost the same activity as the methyl acid. The \( \pi \)-propyl acid is less active than its lower two homologs and the other acids tested with a longer or

\(^1\) For example, see B. "Aberg, Kgl. Lantbrukskôglesk. Ann., 29, 3 (1963).
branched chain are inactive.

In the $\alpha$-$\eta$-alkyl acids, the side chain is considered to exist preferably in an extended structure and the terminal methyl group seems to be located far from both the benzene ring and the carboxyl group so that the steric repulsions between them are reduced to a minimum. Therefore, even if the length of the side chain changes, the spatial relation of the carboxyl group to the ring may not change appreciably. The carboxyl group is rising up from the plane of the benzene ring in these compounds. However, as the molecular dimensions increase due to elongation or branching of the side chain, fitting of the molecule to the site of action may be hindered, and the lipohydrophilic character would be made supraoptimal. The fall off observed in the activity beyond the $\eta$-propyl acid would be ascribed to the above-mentioned steric and/or lipohydrophilic characters of the molecule.

The growth activities of the optical active acids are shown in Figs. 2 and 3. It has been found that in various series of the optical active auxins, the more active antipodes possess the same absolute configuration, the same arrangement of four substituents around the central assymmetric carbon atom: aromatic ring system, carboxyl group, side chain and hydrogen atom as shown by the projection formula.41

![Projection formula](image)

For the $\alpha$-alkylphenylacetic acids, the absolute configurations of the methyl, ethyl, $\eta$-propyl, $\eta$-butyl and $\eta$-amyl acids have been established by Petterson51 by means of the quasi-racemate method applied to the corresponding acid amides that all of the (+)-antipodes of these acids have the same configuration as shown in the above projection formula. As to the auxin activity, the (+)-methyl acid has been known to be more active than the (-)-acids. Now, the (+)-antipodes of the ethyl and $\eta$-propyl acids are found to be more active than the other antipodes, while both antipodes of the $\eta$-butyl and $\eta$-amyl acids are inactive. The results are consistent with the other series of the optical active auxins.

In the (+)-antipodes, the activities of the methyl, ethyl and propyl acids are almost the same. The activity, however, falls suddenly by further elongation of the side chain. This all-or-nothing response observed in the activity may strongly suggest that, among the effects exhibited by the $\alpha$-alkyl substitution, the steric factor would be the most important. The molecular envelope should not be beyond a certain area on the receptor surface for the

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activity. The slight activities observed for the \((-\))-antipodes of the methyl and ethyl acids may be due to the \((+\))-antipodes which is considered to exist in the samples as impurity (at most ca. 1%), since the optical resolution may not be absolutely complete. Otherwise, the slight activities may suggest that, although the configuration is functionally inefficient, the molecular dimensions are not too large to be inactive.

**EXPERIMENTAL**

**Plant Growth Test.** Pea straight growth test was carried out as described previously.2)

**Preparation of Compounds.** Some of the compounds and optical resolutions had not previously been reported.

**\(\alpha\)-sec-Butylphenylacetic acid.** A mixture of ethyl \(\alpha\)-cyanophenylacetate (9 g)7) and sec-butyl iodide (9 g) in an ethanol solution of sodium ethylate (1.3 g of sodium dissolved in 50 ml of ethanol) was refluxed for 12 hrs. in an oil bath at 105-110°C. The mixture was diluted with water, extracted with ether, the ether was dried and removed. Distillation of the residual oil gave ethyl \(\alpha\)-cyano-\(\alpha\)-sec-butylphenylacetate (9.5 g), b.p. 115-123°C (1 mmHg). The nitrile (9.5 g) was boiled with hydrobromic acid (100 ml) for 24 hrs. to yield the acid desired (4 g), b.p. 133-137°C (2.5 mmHg), m.p. 75-76°C. Anal. Calcd. For C\(_{12}\)H\(_{16}\)O\(_2\): C, 74.97; H, 8.39%. Found: C, 74.71; H, 8.46.

**\(\alpha\)-(3'-Pentyl)-phenylacetic acid.** This acid (5 g), m.p. 78-80°C (from n-hexane) was obtained similarly from ethyl \(\alpha\)-cyanophenylacetate7) (10 g) and 3'-pentyl bromide (10 g). Anal. Calcd. for C\(_{13}\)H\(_{18}\)O\(_2\): C, 75.69; H, 8.80%. Found: C, 75.69; H, 8.72.

**Resolution of \(\alpha\)-methylphenylacetic acid.** The (+)-acid was isolated through the strychinine salt according to Raper8,9), m.p. 28-30°C, \([\alpha]_D^{+}+92.5^\circ\) (c 2.54 in benzene) (lit.9) m.p. 30.2-30.9°C, \([\alpha]_D^{+}+79.0^\circ\) (c 1.67 in abs. ethanol)). Anal. Calcd. for C\(_9\)H\(_{10}\)O\(_2\): C, 71.98; H, 6.71%. Found: C, 71.79; H, 6.55.

The acid (3.9 g), \([\alpha]_D^{+}+80.3^\circ\) (c 2.1 in benzene), recovered from the mother-liquor from the first crystallization was dissolved with (+)-\(\alpha\)-phenylethylamine (4.4 g) in ethanol (20 ml).

the precipitated salt (2.6 g) was recrystallized six times from 50% ethanol until the rotatory power of the acid reached a constant value. The salt from the last crystallization (0.6 g) was decomposed with 2N hydrochloric acid to give the \((-\))-acid, m.p. 28-30°C, \([\alpha]_D^{+}+91.3^\circ\) (c 1.2 in benzene) (lit.9) m.p. 30.3-31.0°C, \([\alpha]_D^{+}+93.1^\circ\) (c 1.544 in benzene)). Anal. Found: C, 72.12; H, 6.63.

**Resolution of \(\alpha\)-ethylphenylacetic acid.** The racemic acid (3.3 g), (+)-\(\alpha\)-phenylethylamine (1.6 g) and sodium hydroxide (0.5 g) were dissolved in a warm mixture of ethanol (15 ml) and water (15 ml). The solution was allowed to crystallize at room temperature overnight. The precipitated salt (4 g) was recrystallized from ethanol-water. The course of the resolution was tested on samples from each crystallization, from which the acid was liberated and measured in ethanol solution. After six recrystallizations the optical activity did not increase any more. The salt (0.5 g) was treated with 2N sulfuric acid to liberate the \((-\))-acid, b.p. 164-168°C (22 mmHg), \([\alpha]_D^{+}+96.8^\circ\) (c 1.37 in benzene) (lit.10) \([\alpha]_D^{+}+96.5^\circ\) (benzene)).

The recovered acid (1.2 g), \([\alpha]_D^{+}+45.5^\circ\) (ethanol), from the mother-liquor of the first crystallization was dissolved with \((-\)-\(\alpha\)-phenylethylamine (0.9 g) in a mixture of ethanol (7 ml) and water (8 ml), and the salt precipitated was recrystallized three times from 50% ethanol. The acid (0.4 g) liberated from the last salt fraction (0.8 g) had \([\alpha]_D^{+}+93.8^\circ\) (c 1.19 in benzene) (lit.10) \([\alpha]_D^{+}+96.5^\circ\) (benzene)).

**Resolution of \(\alpha\)-n-propylphenylacetic acid.** The (+)-acid was obtained by crystallization of the \((-\)-menthylamine salt, according to Pickard and Yates.11) B.p. 167.5-169°C (18 mmHg), \([\alpha]_D^{+}+91.3^\circ\) (c 1.70 in benzene) (lit.11) \([\alpha]_D^{+}+79.05^\circ\) (c 5.87 in benzene)). The acid (3.2 g), \([\alpha]_D^{+}+28.1^\circ\) (abs. ethanol), obtained from the mother-liquors of the \((-\)-menthylamine salt was dissolved with (+)-\(\alpha\)-phenylethylamine (2 g) in ethanol (25 ml), the salt precipitated was recrystallized six times from 50% ethanol, and the rotatory power of the acid reached a constant value, \([\alpha]_D^{+}+80.3^\circ\) (c 1.44 in benzene) (lit.12) \([\alpha]_D^{+}+76.4^\circ\) (c 1.355 in benzene)).

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