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STUDIES ON PLANT GROWTH REGULATORS—XX.*

STRUCTURE/ACTIVITY RELATIONSHIP OF *AC*-ALKYL-HYDRO-1-NAPHTHOIC ACIDS AND RELATED COMPOUNDS

TOSHIO FUJITA, KAZUYOSHI KAWAZU, TETSUO MITSUI and MASAYUKI KATSUMI†

Department of Agricultural Chemistry, Kyoto University, Kyoto, Japan

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Abstract—The auxin activities of the *cis*- and *trans*-isomers of 2-methyl-1,2,3,4-tetrahydro-1-naphthoic acid and 2-alkyl-1-indancarboxylic acids were estimated by the pea straight-growth test. The activity difference between the stereoisomers was attributed to their conformational difference due to the alicyclic ring conversion. The activities of 2-alkyl-3-indene-carboxylic acids were also examined. For the latter acids, where both the carboxyl group and the alkyl substituent can conjugate with the aromatic ring system, an electronic effect of the substituent was suggested to be decisive for activity.

PREVIOUS publications in this series have dealt mainly with the relationships between chemical structure and auxin activity of the hydro-1-naphthoic acids and their related compounds.[1–3] For various series of the related compounds, the auxin activities were found to be highly dependent on the steric configuration of the carboxyl group[1, 3] although, for some series, the activities seem to correlate best to electronic structure of the molecule.[2, 3] In order to gain further insight into significance of these structural features, in particular, the effect of a group adjacent to the carboxyl on the activity, we have synthesized a number of *ac*-alkyl-substituted hydro-1-naphthoic acids and their analogs and estimated their auxin activities by pea straight-growth test. In this paper, we wish to report their activities and analyse them in terms of their molecular structures.

The plant growth activities of *cis*- and *trans*-2-methyl-1,2,3,4-tetrahydro-1-naphthoic acids are shown in Fig. 1. The *trans*-isomer is almost as active, whereas the *cis*-isomer is about three to four times as active as the parent tetrahydro-acid. In Table 1, their activities are compared with those of the parent acid and related compounds. The *cis*-isomer is ranked as one of the most active compounds among the related compounds.

The *cis*-isomer can exist as an equilibrium mixture of the two conformers, the 1a2e and 1e2a forms, through the alicyclic ring conversion as shown in Fig. 2. Of the two conformers, the 1a2e form is regarded as the more stable form than the 1e2a form since, in the latter, a steric repulsion between 1e-carboxyl group and 8-methine group would be operative.[4] The higher activity of this compound than that of the unsubstituted tetrahydro-acid might be due to that the equatorial 2-methyl group would assist the molecule to orient properly through hydrophobic bonding on the surface of the primary site of action.

* Part XIX; T. FUJITA, K. KAWAZU, T. MITSUI, M. KATSUMI and J. KATO, *Agr. Biol. Chem.* (*Tokyo*) **30**, 1280 (1966).

† Department of Botany, International Christian University, Mitaka, Tokyo, Japan.

1 T. FUJITA, K. KOSHIMIZU, S. IMAI, T. MITSUI and J. KATO, *Agr. Biol. Chem.* (*Tokyo*) **25**, 710 (1961).
2 K. KAWAZU, T. FUJITA and T. MITSUI, *Agr. Biol. Chem.* (*Tokyo*) **30**, 261 (1966).
3 T. FUJITA, K. KAWAZU, T. MITSUI, M. KATSUMI and J. KATO, *Agr. Biol. Chem.* (*Tokyo*) **30**, 1280 (1966).
4 T. FUJITA, *J. Am. Chem. Soc.* **79**, 2471 (1957).

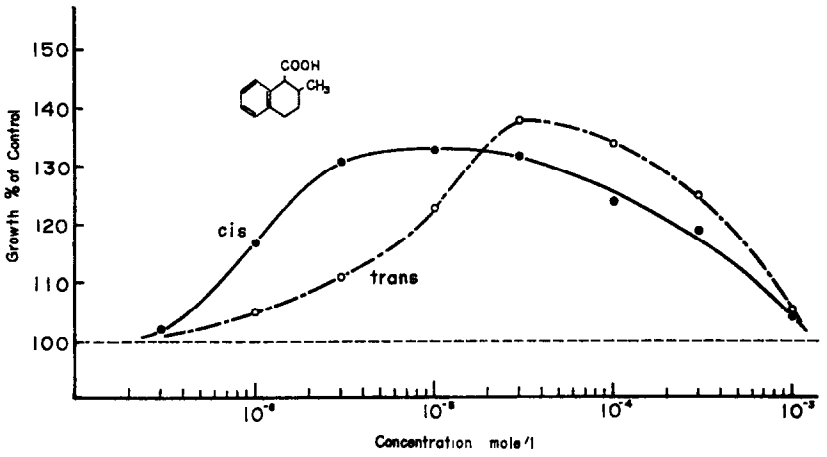

FIG. 1. THE PLANT GROWTH ACTIVITY OF *cis*- AND *trans*-2-METHYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOIC ACIDS.

TABLE 1. PLANT GROWTH ACTIVITY OF THE HYDRO-1-NAPHTHOIC ACID DERIVATIVES

Compound	Activity†
1,4-Dihydro-	6×10^{-7}*
1,2,3,4-Tetrahydro-	2×10^{-6}*
3,4-Dihydro-	10^{-4}*
4-Me-1,2,3,4-tetrahydro-	3×10^{-5}
6-Me-1,4-dihydro-	4×10^{-6}*
6-Me-1,2,3,4-tetrahydro-	8×10^{-5}*
6-Me-3,4-dihydro-	5×10^{-4}*
8-Me-1,4-dihydro-	2×10^{-5}*
8-Me-1,2,3,4-tetrahydro-	10^{-5}*
8-Me-3,4-dihydro-	10^{-5}*
cis-2-Me-1,2,3,4-tetrahydro-	6×10^{-7}
trans-2-Me-1,2,3,4-tetrahydro-	3×10^{-6}

† Minimum concentration in mole/l. causing a 10 per cent elongation of pea stem in 24 hr. Those asterisked were taken from Ref. 1.

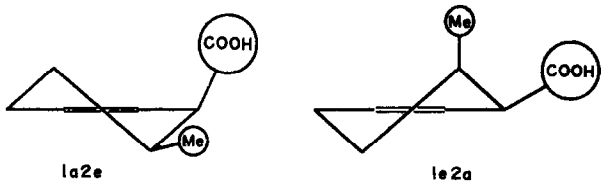

FIG. 2. DIAGRAMMATIC REPRESENTATION OF RING CONVERSION OF *cis*-2-METHYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOIC ACID.

(The condensed benzene ring is not shown in the drawings.)

As to the *trans*-isomer, the conformational equilibrium can occur between 1a2a and 1e2e conformers as shown in Fig. 3. From the observation of the coupling constant between hydrogens at 1 and 2 positions in NMR spectrum ($J_{1,2}=8{\cdot}5$ c/s), this compound is expected to exist almost entirely as the 1e2e conformer in chloroform solution where the spectrum has been taken.

Thus, the difference in activity between the two isomers seems to be attributable to either the difference in the three-dimensional molecular architecture itself or the difference in some physicochemical properties such as dissociation constant accompanied with it. It has been shown that the ionization constant of the carboxyl group varies with the axial or equatorial nature, i.e. the axial carboxyl is less acidic than the equatorial carboxyl as found in *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acids.[5] At any rate, that the axial conformation of the carboxyl group is more favorable to the activity than the equatorial conformation is not incompatible with our previous findings on the related compounds.[1,3] However, the *trans*-isomer where the carboxyl group supposedly takes the unfavorable equatorial conformation does exhibit almost the same activity as the unsubstituted tetrahydro-acid where the carboxyl group exists almost in the favorable axial position. If the equatorial 2-methyl group is efficient

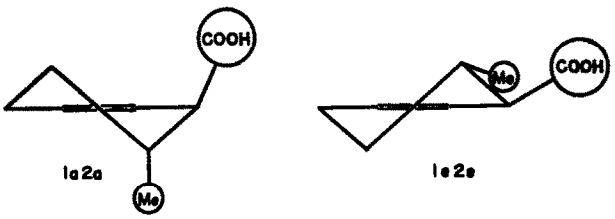

FIG. 3. DIAGRAMMATIC REPRESENTATION OF RING CONVERSION OF *trans*-2-METHYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOIC ACID.
(The condensed benzene ring is not shown in the drawings.)

in making the molecule fit properly at the site of action, then this might counteract the defect of the functionally inefficient equatorial carboxyl group. This discrepancy might be also due to that the mode of conformational equilibrium is different at the site of action from in chloroform solution. The *trans*-isomer might take the 1a2a conformation at the site of action more frequently than in the solution.

The argument that the activity difference between the two 2-methyl-tetrahydro-acids is due to conformational difference of the carboxyl group would be supported by the fact that both the *cis*- and *trans*-isomers of 2-methyl- and 2-ethyl-1-indancarboxylic acids exhibit almost the same activities as the unsubstituted acid as shown in Fig. 4. Since, in the indane derivatives, the alicyclic ring conversion is not significant if any,[6] the conformational difference of carboxyl group is regarded to be small between *cis*- and *trans*-isomers. The fact that the *trans*- and *cis*-2-isopropyl-1-indancarboxylic acids are only weakly active, however, would suggest that the larger the dimensions of the 2-alkyl group, the less favorable is the orientation of the molecule at the site of action. The activity difference between the two isomers may indicate that, when the dimensions of alkyl substituent are increased, the conformational difference would be amplified. That the *cis*-isomer is more active than the *trans*-isomer would show that the conformational effect of the 2-isopropyl group on the carboxyl is similar to

[5] R. D. STOLOW, *J. Am. Chem. Soc.* **81**, 5806 (1959).
[6] C. W. BECKETT, N. K. FREEMAN and K. S. PITZER, *J. Am. Chem. Soc.* **70**, 4227 (1948).

that of the 2-methyl group in the 2-methyl-tetrahydro-acids. A geminal dimethyl substitution at the 2-position makes the molecule completely inactive as is seen in 2,2-dimethyl-1-indancarboxylic acid. The lack of activity of this compound may suggest that the total thickness of the susbtituent(s) at the 2-position also should not be too large for the molecule to fit the receptor.

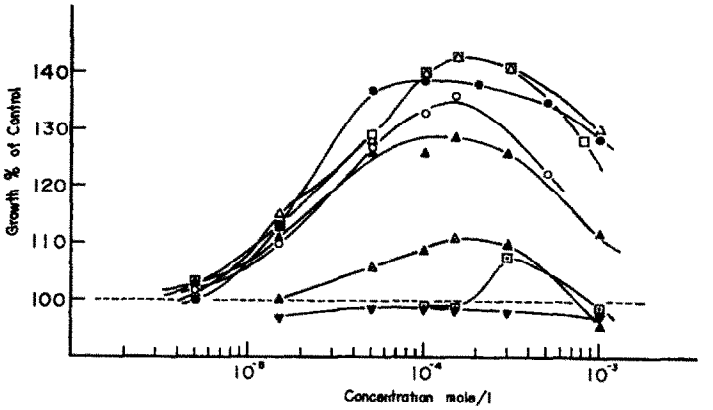

FIG. 4. THE PLANT GROWTH ACTIVITY OF 2-ALKYL-1-INDANCARBOXYLIC ACIDS.

—●—: Indancarboxylic; —▲—: *trans*-2-Ethyl-;
—□—: *cis*-2-Methyl-; —△—: *cis*-2-Isopropyl-;
—△—: *trans*-2-Methyl-; —□—: *trans*-2-Isopropyl-;
—○—: *cis*-2-Ethyl-; —▼—: 2,2-Dimethyl-.

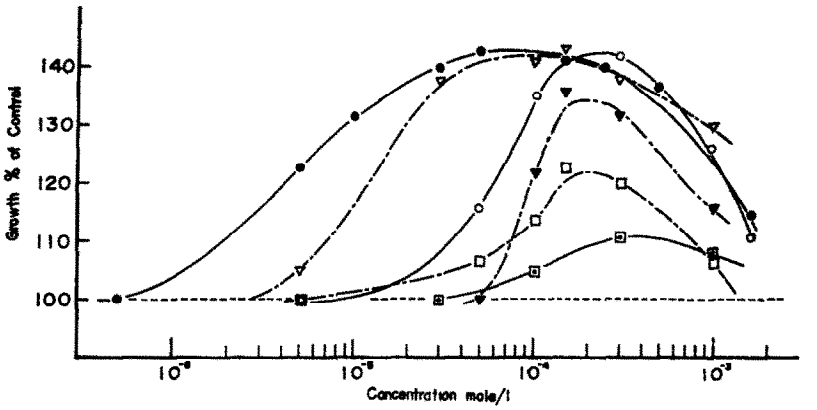

FIG. 5. THE PLANT GROWTH ACTIVITY OF 4-ALKYL-HYDRO-1-NAPHTHOIC ACIDS.

—●—: 1,2,3,4-Tetrahydro-; —▽—: 1,2-Dihydro-;
—○—: 4-Methyl-tetrahydro-; —▼—: 4-Methyl-dihydro-;
—□—: 4-Ethyl-tetrahydro-; —□—: 4-Ethyl-dihydro-.

The effect of substitution at the 4-position on the activity of 1,2-dihydro- and 1,2,3,4-tetrahydro-1-naphthoic acids is also examined as shown in Fig. 5. Although the stereochemistry of the tetrahydro-acids is not certain, it would be anticipated that the longer the alkyl chain at this position, the less favorable becomes the fitting of molecule to the receptor. This argument is consistent with our early discussion on the *ar*-substituted hydro-1-naphthoic

acids that the length of the molecule in transverse direction of the hydronaphthalene ring should be restricted for the molecule to exert the activity.[1]

According to Veldstra, the essential structural requirement for the plant growth activity is the presence of a lipophilic ring system and a hydrophilic carboxyl group in a very definite spatial relation to each other (as perpendicular and peripherical as possible), possessing an appropriate lipohydrophilic balance.[7] Although the weak activity for the ethyl hydro-1-naphthoic acids and isopropylindancarboxylic acids seems also due to a shift in the lipohydrophilic character beyond optimum, the lipohydrophilic character of the molecule for the other compounds seems to be still in an optimal range. Thus, the activities of alkyl-substituted hydro-1-naphthoic acids and 1-indancarboxylic acids seem to conform to the Veldstra hypothesis.

The auxin activities of substituted indene-3-carboxylic acids are shown in Fig. 6. It is observed that methyl and ethyl substitutions at the 2-position enhance the activity of the

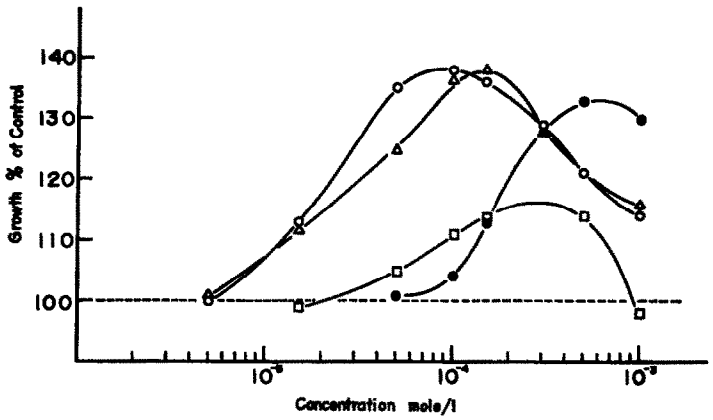

FIG. 6. THE PLANT GROWTH ACTIVITY OF 2-ALKYL-INDENE-3-CARBOXYLIC ACIDS.
——●——: Indene-3-carboxylic; ——○——: 2-Ethyl-;
——△——: 2-Methyl-; ——□——: 2-Isopropyl-.

parent acid about ten times. The effect of the 2-substituent could have been assumed to twist the carboxyl group from the ring plane so that it takes more favorable position to exert the activity as discussed earlier for the 2- and 8-substituted 1-naphthoic acids[8] and 8-substituted 3,4-dihydro-1-naphthoic acids.[1] If the carboxyl group were twisted from the plane of the conjugate system, the carboxyl–carbonyl and also ethylenic double bond orders and hence their stretching frequencies observed in the i.r. spectra should be increased. However, the ethylenic double bond stretching frequency of the 2-methyl acid is not different from that of the parent acid and the carbonyl stretching frequencies of the 2-alkyl acids are less than that of the parent acid probably since an electron-donating character of the alkyl group would enhance the polarization of the carboxyl–carbonyl and decrease its bond order (Table 2). Therefore, the spatial relation of the carboxyl group to the ring system is reasonably considered to be similar to each other in this series.

Thus, it seems adequate to consider that the effect of substituent at the 2-position in the

[7] H. VELDSTRA, *Ann. Rev. Plant Physiol.* 4, 151 (1953).
[8] K. KOSHIMIZU, T. FUJITA and T. MITSUI, *J. Am. Chem. Soc.* 82, 4041 (1960).

indene derivatives is somewhat different from that in the indane derivatives and also tetrahydro-naphthoic acids. It might be anticipated that an electronic factor is operative in this series. In this respect the activity enhancement of indene-3-carboxylic acid by methyl substitution at the 2-position could be compared with that observed between β-methyl- and $\beta\beta$-dimethyl-atropic acids, the open analogs of the indene derivatives, where the activities have been found to correlate closely to their electronic structures by means of molecular orbital calculations recently.[2] The alkyl substituent in the indene-3-carboxylic acids may also modify the electronic structure of the parent molecule so that the alkyl substituted molecule can become attached to the receptor more properly and firmly. The weak activity of the 2-isopropyl derivative would be due to an unfavorable bulkiness of the 2-substituent similarly to the case of the 2-isopropyl-1-indancarboxylic acids.

TABLE 2. CARBONYL AND ETHYLENIC DOUBLE BOND STRETCHING FREQUENCIES IN DIOXANE (CM^{-1})

Acids	$\nu_{C=O}$	$\nu_{C=C}$
Indene-3-carboxylic	1716	1640
2-Me-indene-3-carboxylic	1708	1641
2-Et-indene-3-carboxylic	1709	—

The present results, except for the compounds where molecular dimensions and/or lipohydrophilic character interfere with the activity, would be summarized as follows:

(1) For the compounds where the carboxyl and vicinal alkyl groups do not conjugate with the ring system so that the alkyl substituent does not exert a change in the electronic structure of the aromatic ring, the steric circumstance of the carboxyl group is critical to the activity.

(2) For the compounds where both the carboxyl group and the alkyl group conjugate with the ring system so that the alkyl substituent may intervene in the electronic structure of the aromatic ring, an electronic effect of the substituent might be decisive to the activity.

These conclusions are not inconsistent with our earlier findings on the activities of *ar*-substituted derivatives[1] and cyclic homologs of the hydro-1-naphthoic acids.[3] In order to draw general structural requirements for the auxin activity common to the hydro-1-naphthoic acid related compounds, more precise informations about the steric and electronic structures and lipohydrophilic characters of the molecules are desirable. It would also be helpful to our problem to apply an extrathermodynamic approach recently developed by Hansch *et al.* where the various effects of a given substituent are delineated in terms of substituent constants for steric, lipohydrophilic and electronic effects.[9,10]

EXPERIMENTAL

Plant growth test. Pea straight-growth test was carried out as described previously.[3]
Infra-red measurements were carried out in the same way as reported previously.[2]
*Preparation of compounds.**

* All melting points are uncorrected. NMR measurements are done using $CDCl_3$ solution and the chemical shifts are reported relative to internal tetramethylsilane.

[9] C. HANSCH and T. FUJITA, *J. Am. Chem. Soc.* **86**, 1616 (1964).
[10] C. HANSCH, E. W. DEUTSCH and R. N. SMITH, *J. Am. Chem. Soc.* **87**, 2738 (1965).

2-Methyl-1,2,3,4-Tetrahydro-1-Naphthoic Acids.

Ethyl α-cyano-α-phenyl-β-methylglutarate. Sodium (1·4 g) was dissolved in absolute ethanol (20 ml), ethyl phenylcyanoacetate[11] (10 g) and ethyl β-bromo-*n*-butyrate[12] (12 g) were added and the solution was refluxed for 9 hr at 90–110°. Water was added and the mixture was extracted with ether. The ether was driven off and the remaining viscous oil was distilled *in vacuo* to give the ester (14·2 g), b.p. 188–193° (4 mm).

α-Phenyl-β-methylglutaric acid. Ethyl α-cyano-α-phenyl-β-methylglutarate (10 g) was refluxed for 18 hr with 48% HBr (120 ml). An oil separated on cooling was taken up in ether and removal of ether afforded the dicarboxylic acid as a viscous oil which was a mixture of two diastereomers. Crystallization from benzene-*n*-hexane afforded one isomer of them as needles, m.p. 140–142°. (Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35. Found: C, 65·13; H, 6·47%.)

2-Methyl-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid. A diastereomeric mixture of α-phenyl-β-methylglutaric acid (5 g) was heated in polyphosphoric acid (80 g) at 80–100° for 40 min and the mixture was poured into water. The crude product (4 g) obtained by ether extraction was purified by being converted to the semicarbazone (2·7 g), m.p. 238–253° (dec.). The keto-acid liberated by boiling with dil. HCl weighed 1·4 g, m.p. 120–131°. Recrystallization from benzene gave one of two diastereomers of the keto-acid in needles (0·7 g), m.p. 140–142°. (Calc. for $C_{12}H_{12}O_3$: C, 70·57; H, 5·92. Found: C, 70·44; H, 5·82%.)

cis- *and* trans-*2-Methyl-1,2,3,4-tetrahydro-1-naphthoic acids.* To a solution of 2-methyl-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid, m.p. 118–124° (1·5 g), in methanol (10 ml) containing a few drops of 2 N NaOH, there was added a solution of $NaBH_4$ (0·3 g) in methanol (10 ml). After removal of methanol *in vacuo*, the residual mixture was acidified, extracted with ether. The ether extract was washed with water, dried and evaporated to give 2-methyl-4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid (1·2 g). This was boiled with 2 N HCl (15 ml) for 10 min, giving an oil (1·3 g), which was hydrogenated over platinum black in ethanol to afford a mixture of diastereomers of 2-methyl-1,2,3,4-tetrahydro-1-naphthoic acid (1·3 g). This mixture was chromatographed on an alumina column (Brockman No. 4, 2·5×16 cm) with benzene. Elution with (1:1) benzene–ethyl acetate (500 ml) furnished one of the *cis-trans*-isomers (0·62 g), which was recrystallized from *n*-hexane to prisms, m.p. 109–110°. (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·91; H, 7·52%.) The NMR signals: 3H doublet (J=6 c/s) at 1·15 ppm (methyl), overlapping 3H multiplets around 2·03 ppm (C-2-methine and C-3-methylene), 2H multiplet at 2·87 ppm (C-4-methylene), 1H doublet (J=4·5 c/s) at 3·78 ppm (C-1-methine), 4H singlet at 7·17 ppm (aromatic methines) and 1H singlet at 9·78 ppm (carboxyl-hydrogen).

The subsequent elution with ethyl acetate (200 ml) and ethanol (200 ml) gave no more material. The column was washed by 2 N NaOH solution (50 ml), and the alkaline solution was acidified with conc. HCl and extracted with ether. Removal of ether furnished the other isomer (0·3 g), which was recrystallized from *n*-hexane to prisms, m.p. 82–83·5°. (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·62; H, 7·64%.)

The NMR signals: 3H doublet (J=6 c/s) at 1·12 ppm (methyl), 3H overlapping multiplets around 2·00 ppm (C-2-methine and C-3-methylene), 2H multiplet at 2·83 ppm (C-4-methylene), 1H doublet (J=8·5 c/s) at 3·50 ppm (C-1-methine), 4H singlet at 7·18 ppm (aromatic protons) and 1H singlet at 10·35 ppm (carboxyl).

Conversion of the high melting acid to the low melting isomer on heating with 20% KOH suggests that the high melting isomer is a less stable *cis*-isomer. According to the Karplus equation,[13] the larger coupling constant (J=8·5 c/s) between protons at C_1 and C_2 for the lower melting isomer may be resulted from an approximate diaxial interactions. The isomer (m.p. 82–83·5°) having the larger coupling constant is therefore assigned to the *trans*-acid and the isomer (m.p. 109–110°) with the smaller coupling constant to the *cis*-acid. The values of $J_{1,2}$, 4·5 c/s for the *cis*-acid and 8·5 c/s for the *trans*-acid, are comparable with those for the *cis*- and *trans*-isomers of methyl 2-ethyl-4-oxo-1,2,3,4-tetrahydro-1-naphthoate and their 5- and 7-methoxy derivatives.[14]

2-Methyl-3-Indenecarboxylic Acid

α-Methyl-α′-phenylsuccinic acid. To a solution of sodium ethoxide (Na, 12·5 g) in absolute ethanol (200 ml) there were added ethyl phenylcyanoacetate[11] (100 g) and ethyl α-bromopropionate (100 g), and the solution was refluxed for 6 hr. After excess of ethanol was removed, water was added and the mixture was extracted with ether. The ether was removed and the remaining viscous oil was distilled *in vacuo* to give ethyl α-cyano-α-phenyl-α′-methylsuccinate (87·5 g), b.p. 135–145° (2 mm). This cyano-ester (85 g) was refluxed for 10 hr with 48% HBr (850 ml). An oil separated on cooling was taken up in ether and removal of ether afforded α-methyl-α′-phenylsuccinic acid (60 g), m.p. 180–183·5°. The melting point was raised up by recrystallizations from water to 189–192°, 189–192 (192–193°[15]).

[11] E. C. Horning and A. F. Finelli, *Org. Syn.* **30**, 43 (1950).
[12] H. Burton and C. K. Ingold, *J. Chem. Soc.* 2030 (1929).
[13] M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).
[14] Z. Horii, T. Momose and Y. Tamura, *Chem. Pharm. Bull.* (*Tokyo*) **13**, 651 (1965).
[15] N. Zelinsky and L. Buchstab, *Chem. Ber.* **24**, 1876 (1891).

2-Methyl-3-oxo-1-indancarboxylic acid. A suspension of α-methyl-α'-phenylsuccinic acid (10 g) in conc. H_2SO_4 (100 ml) was kept at 60° for 2 hr and then at room temperature overnight. The mixture was poured onto ice and the crystals separated (5 g), m.p. 149–155°, was collected, which was recrystallized from benzene, m.p. 164–165° (3·5 g). (Calc. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·26; H, 5·44%.)

3-Hydroxy-2-methyl-1-indancarboxylic acid. 2-Methyl-3-oxo-1-indancarboxylic acid (5·1 g) was dissolved in N NaOH (30 ml) and there was added $NaBH_4$ (0·5 g) in water (10 ml) containing a few drops of N NaOH. The mixture was acidified with conc. HCl to afford crystals (5 g), m.p. 172–173°. Recrystallized from ethanol, m.p. 180–181°. (Calc. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·98; H, 6·22%.)

2-Methyl-3-indenecarboxylic acid. A suspension of 3-hydroxy-2-methyl-1-indancarboxylic acid (4·7 g) in conc. HCl (130 ml) was boiled under reflux for 50 min. After cooling, the crystals were collected (3·6 g), m.p. 198·5–199·5°. (Calc. for $C_{11}H_{10}O_2$: C, 75·84; H, 5·79. Found: C, 75·99; H, 5·65%.) Three proton singlet at 2·57 (vinyl methyl) and two proton singlet at 3·56 ppm (methylene) in its NMR spectrum show that this acid is an α,β-unsaturated acid and concomitant migration of a double bond took place under the condition of dehydration. The bathochromic shift of λ_{max}^{EtOH} 270 nm (ϵ $5{\cdot}31 \times 10^3$) of the acid compared with that of 2-methyl-indene (λ_{max}^{EtOH} 266·5 nm, ϵ $5{\cdot}87 \times 10^3$) also supports this structure.

cis-2-*Methyl*-1-*Indancarboxylic Acid*

2-Methyl-3-indenecarboxylic acid (2 g) in ethanol (80 ml) was hydrogenated over platinum black to give the dihydro-acid (1·7 g), m.p. 103–106° (recrystallized from *n*-hexane). (Calc. for $C_{11}H_{12}O_2$: C, 74·97; H, 6·86. Found: C, 74·72; H, 6·74%.) The *cis*-configuration was confirmed[16] by reducing the acid to a hydrocarbon, which was shown to be identical with *cis*-1,2-dimethylindane derived from *cis*-1,2-indandicarboxylic acid.[17]

trans-2-*Methyl*-1-*Indancarboxylic Acid*

A mixture of amalgamated mossy zinc (prepared from 34 g of Zn and 3·3 g of $HgCl_2$), conc. HCl (100 ml) and 2-methyl-3-oxo-1-indancarboxylic acid (5 g) dissolved in toluene (120 ml) was heated under reflux for 20 hr, during which conc. HCl (15 ml) was added every 6 hr. Toluene layer was separated, the aqueous layer was extracted with ether, the combined solution was washed with water and extracted with $NaHCO_3$ solution. The alkaline solution was acidified, an oil separated was taken up in ether. Removal of ether left crystals (4·7 g), m.p. 80–85°, which was recrystallized from *n*-hexane to give colorless needles (2·1 g), m.p. 87°. (Calc. for $C_{11}H_{12}O_2$: C, 74·97; H, 6·86. Found: C, 75·18; H, 7·01%.) The *trans*-configuration was confirmed[16] by identity of the corresponding hydrocarbon with *trans*-1,2-dimethylindane derived from *trans*-1,2-indandicarboxylic acid.[17]

2-*Ethyl*-3-*Indenecarboxylic Acid and* -*Indancarboxylic Acids*

The ethyl-substituted acids were prepared in a similar way to that used for the methyl-substituted acids.

α-Ethyl-α'-phenylsuccinic acid, prepared from ethyl cyanophenyl acetate[11] and ethyl α-bromo-*n*-butyrate. M.p. 195–198° (from dilute ethanol) (m.p. 196°[18]). (Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35. Found: C, 65·00; H, 6·44%.)

2-Ethyl-3-oxo-1-indancarboxylic acid, m.p. 147–150°.

2-Ethyl-3-hydroxy-1-indancarboxylic acid, m.p. 167–170° (dec.) (from dil. ethanol). (Calc. for $C_{12}H_{14}O_3$: C, 69·88; H, 6·84. Found: C, 70·10; H, 6·87%.)

2-Ethyl-3-indenecarboxylic acid, m.p. 149–150° (from benzene). (Calc. for $C_{12}H_{14}O_3$: C, 69·88; H, 6·84. Found: C, 70·10; H, 6·87%.) λ_{max}^{EtOH} 270 nm (ϵ $6{\cdot}12 \times 10^3$).

cis-2-Ethyl-1-indancarboxylic acid, m.p. 108–109° (from *n*-hexane). (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·97; H, 7·65%.)

trans-2-Ethyl-1-indancarboxylic acid, m.p. 79–80° (from *n*-hexane). (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·97; H, 7·49%.)

2-*Isopropyl*-3-*Indenecarboxylic Acid*

The method of preparation was similar to that for the methyl-substituted acid.

α-Phenyl-α'-isopropylsuccinic acid, m.p. 180–183°, prepared from ethyl cyanophenylacetate[11] and ethyl α-bromo-isovalerate.[19]

2-Isopropyl-3-oxo-1-indancarboxylic acid, m.p. 109–111° (from benzene-*n*-hexane). (Calc. for $C_{13}H_{14}O_3$: C, 71·54; H, 6·47. Found: C, 71·30; H, 6·47%.)

2-Isopropyl-3-hydroxy-1-indancarboxylic acid, m.p. 117–118° (from dil. methanol). (Calc. for $C_{13}H_{16}O_3$: C, 70·89; H, 7·32. Found: C, 71·00; H, 7·34%.)

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2-Isopropyl-3-indenecarboxylic acid, m.p. 126–127° (from benzene-hexane). (Calc. for $C_{13}H_{14}O_2$: C, 77·20; H, 6·98. Found: C, 77·41; H, 7·08%.) λ_{max}^{EtOH} 269 nm (ϵ 10·4 × 10³).

cis-2-*Isopropyl*-1-*Indancarboxylic Acid*

By hydrogenating 2-isopropyl-3-indenecarboxylic acid. M.p. 141–143° (from *n*-hexane). (Calc. for $C_{13}H_{16}O_2$: C, 76·44; H, 7·90. Found: C, 76·22; H, 8·09%.)

trans-2-*Isopropyl*-1-*Indancarboxylic Acid*

By Clemmensen reduction of 2-isopropyl-3-oxo-1-indancarboxylic acid. M.p. 89–90° (from *n*-hexane). (Calc. for $C_{13}H_{16}O_2$: C, 76·44; H, 7·90. Found: C, 76·70; H, 8·01%.)

2,2-*Dimethyl*-1-*Indancarboxylic Acid*

2,2-*Dimethyl*-3-*oxo*-1-*indancarboxylic acid*. α,α-Dimethyl-α'-phenylsuccinic acid,[20] m.p. 164–165·5° (1·8 g), was converted to its acid chloride with thionyl chloride, and it was cyclized in the presence of anhydrous $AlCl_3$ in nitrobenzene yielding the keto-acid. Purification through its semicarbazone, m.p. 230–233° (dec.) (0·7 g), gave the keto-acid (0·5 g), m.p. 157·5–185·5° (from benzene).

2,2-*Dimethyl*-1-*indancarboxylic acid*. The keto-acid (0·4 g) was reduced by the method of Clemmensen to give the acid (0·3 g), m.p. 100–103° (from *n*-hexane). (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·69; H, 7·67%.)

4-*Methyl*-1,2-*Dihydro*-1-*Naphthoic Acid*

To a Grignard reagent prepared from Mg (0·4 g) and methyl iodide (3·4 g) in ether (50 ml) there was rapidly added under cooling methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate[21] (2·2 g), b.p. 131–136° (2 mm), in ether (30 ml.) The mixture was stirred for an hour, dilute H_2SO_4 was added and the ether solution was washed with sodium thiosulfate solution, 2 N Na_2CO_3 and water, dried (Na_2SO_4), and evaporated. The remaining yellow oil (2·7 g) was boiled with KOH (1 g) in methanol (20 ml) for an hour. The mixture was washed with ether, acidified with dil. HCl and extracted with ether. The ether extract provided a yellow viscous oil, which was distilled at 170–185° under a reduced pressure (8 mm). The distillate (0·8 g) dissolved in ether was taken up in aqueous Na_2CO_3, the alkaline solution was made acidic and the needles separated were collected. They were recrystallized twice from benzene-*n*-hexane. Yield 0·5 g, m.p. 132·5–133°. (Calc. for $C_{12}H_{12}O_2$: C, 76·57; H, 6·43. Found: C, 76·57; H, 6·49%.)

4-*Methyl*-1,2,3,4-*Tetrahydro*-1-*Naphthoic Acid*

4-Methyl-1,2-dihydro-1-naphthoic acid (0·1 g) in glacial acetic acid (12 ml) absorbed 1 mole of hydrogen in the presence of platinum black at ordinary atmosphere, yielding quantitatively the tetrahydro-acid, which was recrystallized from *n*-hexane. M.p. 86·5–87·5°. (Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42. Found: C, 75·97; H, 7·56%.)

4-*Ethyl*-1,2-*Dihydro*-1-*Naphthoic Acid*

In a same manner as used for preparation of the 4-methyl-substituted acid, this acid was prepared from methyl 4-oxo-tetrahydro-naphthoate (1 g) and ethylmagnesium iodide in 25 per cent yield. Recrystallized from *n*-hexane, the acid had m.p. 73–74·5°. (Calc. for $C_{13}H_{14}O_2$: C, 77·20; H, 6·98. Found: C, 77·41; H, 7·20%.)

4-*Ethyl*-1,2,3,4-*Tetrahydro*-1-*Naphthoic Acid*

4-Ethyl-1,2-dihydro-1-naphthoic acid in ethanol was hydrogenated over platinum black to give quantitatively the tetrahydro-acid, m.p. 66–67° (recrystallized from *n*-hexane). (Calc. for $C_{13}H_{16}O_2$: C, 76·44; H, 7·90. Found: C, 76·92; H, 8·07%.)

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