523. *Synthetic Plant Hormones. Part V.* (+)- and (−)-2 : 4-Dichlorophenoxy-fluoro- and -difluoro-acetic Acid.*

By (Miss) M. H. Maguire and G. Shaw.

(±)-2 : 4-Dichlorophenoxy-fluoro- and -difluoro-acetic acid have been prepared by reaction of sodium 2 : 4-dichlorophenoxide with ethyl chlorofluoroacetate and ethyl chlorodifluoroacetate respectively. The racemic monofluoro-acid was resolved with strychnine and (+)-α-methylphenethylamine.

Substitution in the α-position of aryloxyacetic acids by alkyl groups has been shown to give compounds in which the growth-regulating properties are retained although sometimes modified,[1,2] and in which activity is governed by the stereochemical configuration.[3] In this series, enhanced activity is shown by the (+)-isomers whereas the (−)-enantiomorphs have negligible activity or may even possess anti-auxin properties. By contrast, αα-dialkyl derivatives are generally without growth-regulating properties, though exceptions are known.[2]

These results have been generalised in the so-called α-hydrogen effect,[2] the anomalies being ascribed to biological demethylation by a process such as $-CMe_2 \cdot CO_2H \longrightarrow -CMe(CO_2H)_2 \longrightarrow -CHMe \cdot CO_2H$. The inactivity of 2 : 4-dichlorophenoxymalonic acid[4] and the failure of biochemical experiments to support this scheme make it more attractive to postulate the scheme $-CMe_2 \cdot CO_2H \longrightarrow -CMe(CHO) \cdot CO_2H \longrightarrow -CHMe \cdot CHO \cdot \longrightarrow -CHMe \cdot CO_2H$. So we have prepared α-fluoro-derivatives of 2 : 4-dichlorophenoxyacetic acid since substitution of fluorine for hydrogen *in vivo* would be unlikely.

Sodium 2 : 4-dichlorophenoxide and ethyl chlorofluoroacetate in hot ethanol readily gave ethyl 2 : 4-dichlorophenoxyfluoroacetate and thence the acid, which was resolved into its optical enantiomorphs with strychnine and (+)-α-methylphenethylamine. The difluoro-acid was obtained with some difficulty by using ethyl chlorodifluoroacetate.

Preliminary biological tests by Mr. C. G. Greenham, Division of Plant Industry, C.S.I.R.O., Canberra; indicate that (+)-2 : 4-dichlorophenoxyfluoroacetic acid has pronounced auxin activity but less than that of 2 : 4-dichlorophenoxyacetic acid; the racemic acid has less and the (−)-isomer negligible activity. Incomplete tests of the

* Part IV, *J.*, 1957, 311.

[1] Wain, "Plant Growth Substances," Roy. Inst. Chem. Monograph, 1953; Fawcett, Osborne, Wain, and Walker, *Ann. Appl. Biol.*, 1953, **40**, 232.
[2] Fawcett, Wain, and Wightman, *Ann. Appl. Biol.*, 1955, **43**, 342.
[3] Smith, Wain, and Wightman, *ibid.*, 1952, **39**, 295.
[4] Cavill and Ford, *J.*, 1954, 1388.

difluoro-acid indicate very slight auxin activity. These results appear to parallel the behaviour of the alkyl derivatives but it would be fallacious to draw further conclusions.

Experimental

Ethyl 2 : 4-Dichlorophenoxyfluoroacetate.—Ethyl chlorofluoroacetate was prepared from chlorotrifluoroethylene by reaction with ethanol and hydrolysis of the 2-chloro-1-ethoxy-1 : 1 : 2-trifluoroethane so formed;[5] the ester was kept over anhydrous potassium carbonate. Solutions of sodium (8·2 g.) in dry ethanol (80 ml.) were boiled with 2 : 4-dichlorophenol (58 g.) and ethyl chlorofluoroacetate (50 g.) in ethanol (300 ml.) for 2 hr., then kept for 4 days at room temperature. Sodium chloride was filtered off and washed with ethanol, and the filtrate evaporated to an oil which was added to water (300 ml.). An oil separated and was extracted with ether (4 × 50 ml.). The extract was washed with 4% sodium hydroxide solution (25 ml.) and water (6 × 10 ml.), then dried and evaporated to an oil (48 g.) which was distilled *in vacuo*, giving a low-boiling fraction (2 : 4-dichlorophenol) and then *ethyl 2 : 4-dichlorophenoxyfluoroacetate* (40·6 g.), b. p. 121—122°/1·5 mm., $n_D^{14\cdot5}$ 1·5108 (Found: C, 45·2; H, 3·5; Cl, 26·5. $C_{10}H_9O_3Cl_2F$ requires C, 44·95; H, 3·4; Cl, 26·5%). Positive tests for fluoride were obtained after sodium fusion.

The fluoro-ester (23·3 g.) in ethanol (15 ml.) was warmed with 10% sodium hydroxide solution (200 ml.). After a few minutes a crystalline salt separated. The mixture was kept overnight, and the salt (21 g.) filtered off, dissolved in water (150 ml.) and acidified with 10N-hydrochloric acid to precipitate the *acid* (15·2 g.), needles (from benzene–light petroleum), m. p. 91—93° (Found: C, 39·95; H, 2·15%; equiv., 239. $C_8H_5O_3Cl_2F$ requires C, 40·2; H, 2·1%; equiv., 239).

A suspension of strychnine (29·8 g.) in boiling acetone (250 ml.) was added to a warm solution of the racemic acid (21·35 g.) in acetone (100 ml.) and water (150 ml.). The clear solution obtained was boiled and filtered, then treated with hot water (400 ml.), cooled to room temperature, seeded, and kept for 2 days. The strychnine salt (58 g.) was filtered off and recrystallised 8 times from acetone–water (1 : 10). After each crystallisation a portion of the salt was decomposed with 7·5N-aqueous ammonia with warming. Strychnine was filtered off and the cooled filtrate acidified to precipitate the fluoro-acid which was recrystallised from *cyclo*hexane or benzene–light petroleum and the specific rotation determined. The *(+)-acid* was finally obtained as needles, m. p. 104—105°, $[\alpha]_D^{22\cdot5}$ +57·1° ± 0·3° * (*c* 1·505 in $CHCl_3$) (Found: C, 40·1; H, 1·95%).

A solution of (+)-α-methylphenethylamine (7·6 g.) in ether (100 ml.) was added to the racemic acid (13·8 g.) in ether (150 ml.); a crystalline salt separated. This was recrystallised 6 times from chloroform–ether. Portions were decomposed with 1·5N-sodium hydroxide, the base extracted with ether, and the fluoro-acid isolated as before. The *(−)-acid* separated from benzene–light petroleum as needles, m. p. 103—105°, $[\alpha]_D^{21\cdot5}$ −57·1° ± 0·3° (*c* 1·504 in $CHCl_3$) (Found: C, 40·2; H, 2·1%).

2 : 4-Dichlorophenoxydifluoroacetic Acid.—A mixture of dry sodium 2 : 4-dichlorophenoxide (25 g.) and ethyl chlorodifluoroacetate (54 g.) was boiled under reflux for 41 hr. The semisolid residue was stirred with ether (110 ml.) and 1% sodium hydroxide solution (100 ml.); unidentified crystals were filtered off and recrystallised from acetic acid as needles, m. p. 200—203° (Found: C, 47·6; H, 2·55%). The alkaline solution was acidified with 10N-hydrochloric acid and then extracted with ether. The ether solution was extracted with sodium hydrogen carbonate solution, and the solution acidified and re-extracted with ether. The dried solution was evaporated to an acidic oil which crystallised. *2 : 4-Dichlorophenoxydifluoroacetic acid* (8·4 g.) separated from light petroleum as deliquescent needles, m. p. 68—71° (Found: C, 37·2; H, 1·5; Cl, 27·5. $C_8H_4O_3Cl_2F_2$ requires C, 37·4; H, 1·55; Cl, 27·6%). A solution in ether gave the *p-toluidine salt*, plates (from ethyl acetate–*cyclo*hexane), m. p. 134—135° (Found: C, 49·5; H, 3·8; N, 3·85. $C_8H_4O_3Cl_2F_2,C_7H_9N$ requires C, 49·45; H, 3·6; N, 3·85%).

The acid (0·73 g.) in ethanol (5 ml.) was boiled for 1 hr., then kept at room temperature for

* Limits of error in optical rotations were calculated by use of formulæ (±) $3\Sigma x/(n\sqrt{n})$ and (±) $0{\cdot}6745\sqrt{(\Sigma x^2/n)}$ where x is the residual and n the number (10) of readings.

[5] Young and Tarrant, *J. Amer. Chem. Soc.*, 1949, **71**, 2432; *Org. Synth.*, 1954, **34**, 49.

3 days. The solvent was removed and the residue dissolved in dry ether, dried (K_2CO_3), evaporated, and distilled, giving the *ethyl ester* (0·49 g.), b. p. 80—88°/0·5 mm., $n_D^{22\cdot5}$ 1·4833 (Found : C, 41·9; H, 2·85. $C_{10}H_8O_3Cl_2F_2$ requires C, 42·15; H, 2·85).

We thank the C.S.I.R.O. for a maintenance grant (to M. H. M.) and Dr. E. Challen for the microanalyses.

N.S.W. University of Technology,
Sydney, N.S.W., Australia.

[*Received, February 25th,* 1957.]