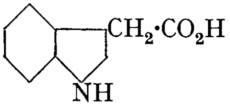
356. *Thionaphthen-2-acetic Acid.*

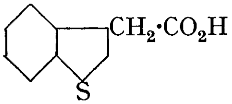
By Eric M. Crook and William Davies.

Thionaphthen-2-acetic acid (II) has been synthesised. Its growth-stimulating action on plants is less than that of the structurally related and naturally occurring indole-3-acetic acid (I). An isomeric thionaphthenacetic acid of unknown constitution has also been prepared and is slightly biologically active.

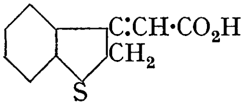
Indole-3-acetic acid or "heteroauxin" (I) has a great growth-stimulating action on plants as shown by the Avena and pea-curvature tests (*Ann. Reports*, 1935, 426) and is sometimes regarded as a "plant hormone." In view of the chemical similarities existing between some indole and thionaphthen derivatives, thionaphthen-2-acetic acid (II) has been prepared and its biological activity compared with that of (I). A preliminary communication on its hormonal action has been published by Crook, Davies, and Smith (*Nature*, 1937, **139**, 154).



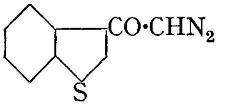
(I.)



(II.)



(III.)



(IV.)

The reaction product of indole and ethylmagnesium iodide condenses with chloroacetonitrile to give in excellent yield a nitrile which on alkaline hydrolysis gives (I) (Majima and Hoshino, *Ber.*, 1925, **58**, 2042). The analogous process with thionaphthen, however, when carried out either in ethyl ether or in anisole, gave no thionaphthen derivative. Accordingly the method (D.R.-P. 562,391) for introducing the acetic acid group directly (from halogenoacetic acids and their derivatives) into aromatic hydrocarbons was investigated with a view to applying it to thionaphthen. The experiments were carried out in glass vessels. Refluxing naphthalene with ethyl bromoacetate in the presence of aluminium powder ultimately yielded a mixture of acids melting at 115—120° and a ketonic material forming a *p*-nitrophenylhydrazone. The action of ethyl chloroacetate and aluminium chloride on naphthalene in boiling nitrobenzene solution gave no crystalline material. When naphthalene was boiled for 64 hours with a large excess of ethyl bromoacetate, a crude mixture of acids was obtained in small yield, from which α-naphthylacetic acid, m. p. 130°, was isolated. As shown by the equivalent weight, only a small quantity of naphthalenediacetic acid was produced; this is in marked contrast to the action of thionaphthen under the same conditions, where the main acid produced was shown by the equivalent weight (129·5) to consist largely of thionaphthendiacetic acid ($C_{12}H_{10}O_4S$ requires equiv. 125). Finally the presence of copper powder in the thionaphthen–ethyl bromoacetate mixture gave rise to a thionaphthenacetic acid, m. p. 141°, of which the constitution is not yet known.

The oxygen of indoxyl condenses with certain active methylene groups (D.R.-P. 255,691). Accordingly thioindoxyl was heated with malonic acid under various conditions with the object of preparing (III), which on isomerisation would give (II). The results were negative.

It is difficult to form a Grignard reagent from 2-bromothionaphthen in the ordinary way (cf. Komppa and Weckman, *J. pr. Chem.*, 1933, **138**, 109), but it can be done by Grignard's device (*Compt. rend.*, 1934, **198**, 625) of using a large quantity (more than 2 mols.) of a readily reactive halide, with the appropriate amount of magnesium to form compounds with both halides. In the present case the action of carbon dioxide on the mixture of 2-thionaphthenylmagnesium bromide and methylmagnesium iodide produced a 70% yield of thionaphthen-2-carboxylic acid. The corresponding acid chloride was converted by diazomethane into the diazo-ketone (IV); this on gradual treatment in alcoholic solution with small quantities of silver oxide (Arndt and Eisert, *Ber.*, 1935, **68**, 200; 1936, **69**, 1106, 1805) formed an ester which on hydrolysis gave the desired thionaphthen-2-acetic acid (II), m. p. 109°. This work on thionaphthen derivatives is being continued.

EXPERIMENTAL.

Thionaphthenacetic Acid, m.p. 141°.—Thionaphthen (4 g.), ethyl bromoacetate (4 c.c.), and copper powder (2 g.) were refluxed for 35 hours, a further 2 g. of copper powder being added in small quantities about every 3 hours. The product was boiled with excess of alcoholic sodium hydroxide for 2 hours and diluted with cold water, and the copper compounds and unchanged thionaphthen separated. The filtrate was shaken with ether and acidified with hydrochloric acid, the organic acid extracted with ether, the extract evaporated, the tarry residue treated with hot water, and the aqueous solution purified with animal charcoal. On cooling, about 0·1 g. of brown platelets, m. p. 90—105°, separated (Found: equiv., 196. Calc. for $C_{10}H_8O_2S$: equiv., 192). Repeated crystallisation from water resolved the mixture into a less soluble fraction, m. p. 140—141°, and a more soluble impure acid, m. p. 60—90°, which crystallised in dull feathery needles. The thionaphthenacetic acid, m. p. 141°, crystallised from water in small plates with a pronounced silvery lustre and was readily oxidised by dilute potassium permanganate solution.

A thionaphthendiacetic acid, also of unknown constitution, was obtained in impure condition when thionaphthen (4 g.) and ethyl bromoacetate (5 c.c.) were refluxed in the absence of copper for 64 hours, the resulting ester hydrolysed, and the acid separated from the green fluorescent solution in the way described above for the acid, m. p. 141°. The diacetic acid finally separated from anisole in crystals, m. p. about 108°, very sparingly soluble in boiling petroleum (b. p. 80—100°) and in cold water and very soluble in cold 50% alcohol. It had no growth-stimulating action on decapitated oats (Avena test) (Found: equiv., 129·5. Calc. for $C_{12}H_{10}O_4S$: equiv., 125).

Thionaphthen-2-carboxylic Acid.—Thionaphthen, brominated in chloroform after Komppa (*J. pr. Chem.*, 1929, **122**, 319), gave a 90% yield of a very light yellow, highly refractive oil, b. p. 140°/18 mm., which remained unchanged in a corked bottle for 1½ years (according to Komppa it becomes bright red on keeping). 2-Bromothionaphthen (4 g.; 1 mol.) and methyl iodide (3 g.; 2 mols.) in ether were added to magnesium (0·9 g.; 3¼ atoms) in ether, and the mixture refluxed. After the vigorous action had subsided, the mixture was boiled for a further 15 minutes and cooled, carbon dioxide passed in, and the product decomposed by ice and hydrochloric acid and worked up in the usual way. The thionaphthen-2-carboxylic acid (2·5 g.; 70% yield) crystallised from benzene in needles having the m. p. 174—175° recorded by Komppa and Weckman (*loc. cit.*).

Warm glacial acetic acid (4 c.c.) containing 0·2 g. of thionaphthen-2-carboxylic acid was cooled, perhydrol (30%; 1·5 c.c.) added, and the mixture heated on the water-bath for ½ hour after the addition of 1 c.c. of water. The liquid, diluted with its own volume of water and kept for 2 days, deposited clusters of yellow prisms, m. p. 218° (decomp.) of thionaphthen-2-carboxylic acid *S*-dioxide, which were recrystallised from water (Found: equiv., 207·7. Calc. for $C_9H_6O_4S$: equiv., 210).

Thionaphthen-2-acetic Acid.—Thionaphthen-2-carboxylic acid was converted quantitatively by thionyl chloride into the acid chloride, which formed needles, m. p. 53—54°, from light petroleum (Komppa and Weckman, *loc. cit.*, give m. p. about 50°). The acid chloride (1·5 g.) in dry ether (20 c.c.) was added to a dry ethereal (20 c.c.) solution of diazomethane made from 2 g. of nitrosomethylurea, and kept for 24 hours. The ether was then removed under reduced pressure, the yellow 2-thionaphthenyl diazomethyl ketone [prisms, m. p. about 140° (decomp.)] dissolved in absolute alcohol (100 c.c.), and the warm solution treated with shaking during an hour with small quantities of silver oxide mixed with alcohol, 4 g. of silver oxide being used. The mixture was boiled under reflux for an hour, and the liquid filtered and refluxed for 3 hours with potassium hydroxide solution (50%; 1 c.c.) and water (30 c.c.). The solution was concentrated under reduced pressure and acidified with hydrochloric acid, and the product crystallised from water. The yield was about 1 g., m. p. 100—105°. When an aqueous solution saturated at the ordinary temperature was kept for at least 24 hours, thionaphthen-2-acetic acid separated in long thin prisms, m. p. 109° (Found: equiv., 192. Calc. for $C_{10}H_8O_2S$: equiv., 192).

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