733. *Chemistry of the Higher Fungi. Part VI.* Isomerisation Reactions of Naturally Occurring Allenes.*

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When treated with alkali, nemotinic acid and nemotin both undergo prototropic rearrangements resulting in the disappearance of the allene groups. Nemotinic acid gives (−)-4-hydroxyundeca-6 : 8 : 10-triynoic (*iso*-nemotinic) acid, but with nemotin the isomerisation involves opening of the lactone ring and gives undec-4-ene-6 : 8 : 10-triynoic acid (nemotin A). The latter is also obtainable by treatment of the lactone of *iso*nemotinic acid with alkali. Reasons for the different behaviour in alkali of the known naturally occurring allenes are considered.

One of the most striking properties of the antibiotics nemotinic acid and nemotin described in the original papers [1] was their instability towards aqueous alkali. The neutral compound, nemotin, with the absorption spectrum of an enediyne, was rapidly converted at pH 10 into nemotin A, thought to be a neutral compound,[1] with the ultraviolet absorption spectrum of an enetriyne.[1a] The conjugated unsaturation of the molecule thus increased by two double-bond equivalents; the change in light absorption spectrum is most conspicuous (cf. Table 1) as new bands of high intensity appear. The behaviour in aqueous alkali of nemotinic acid (having the same chromophore as nemotin) was quite different; in a much slower reaction, the specific absorption of nemotinic acid gradually disappeared, without any new bands appearing in the spectrum. No reaction product was isolated.

Table 1. *Ultraviolet absorption spectra.*

Substance	Absorption max. (Å) and log ε (in parentheses)									
Nemotin	—	—	2085 (4·74)	—	2365 (3·79)	2490 (4·03)	2625 (4·19)	2780 (4·09)	—	—
Nemotin A	2045 (4·41)	2115 (4·37)	2230 (infl.) (4·47)	2300 (4·77)	2410 (4·93)	2580 (3·44)	2720 (3·78)	2885 (4·07)	3070 (4·19)	3280 (4·04)
Methyl nemotin A	2045 —	2120 —	2230 (infl.) —	2300 —	2410 —	2570 —	2720 —	2880 —	3070 —	3280 —
*iso*Nemotinic acid			2075 (5·05)	—	2390 (2·34)	2540 (2·45)	2685 (2·56)	2850 (2·56)	3050—3080 (2·40)	—
*iso*Nemotinic lactone	—	—	2060 (5·11)	—	2400 (2·16)	2530 (2·28)	2680 (2·42)	2850 (2·41)	3040 (2·20)	—

Publication [2] in 1952 of the work of Celmer and Solomons on mycomycin and its rearrangement in alkali to *iso*mycomycin provided support for the idea that nemotinic acid and nemotin might owe their high optical activity and alkali-instability to the presence of allene groups, a view which was confirmed when we showed these compounds to be (I) and (II) respectively.[3] However, detailed investigation of their isomerisations has revealed that these are not fully analogous to the rearrangement of mycomycin.

When nemotinic acid is treated with alkali (0·1N-sodium hydroxide) a product, *iso*-nemotinic acid, can be isolated from the neutralised solution by ether-extraction. After purification, this acid shows the absorption spectrum of a conjugated triyne (Table 1); the maxima are of such low intensity that they are easily masked and were consequently not observed by the earlier workers. The product forms colourless, highly photosensitive needles; it is optically active ($[\alpha]_D^{20}$ −3°) but its specific rotation is very much less than that of nemotinic acid ($[\alpha]_D^{20}$ +320°). Apart from the absence of the sharp allene peak at 1960 cm.$^{-1}$, it shows infrared absorption very similar to that of nemotinic acid. Bands

* Part V, Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

[1] Anchel, Polatnick, and Kavanagh, *Arch. Biochem.*, 1950, **25**, 208; Kavanagh, Hervey, and Robbins, *Proc. Nat. Acad. Sci. U.S.A.*, 1950, **36**, 1.

[1a] Anchel, *J. Amer. Chem. Soc.*, 1952, **74**, 1588.

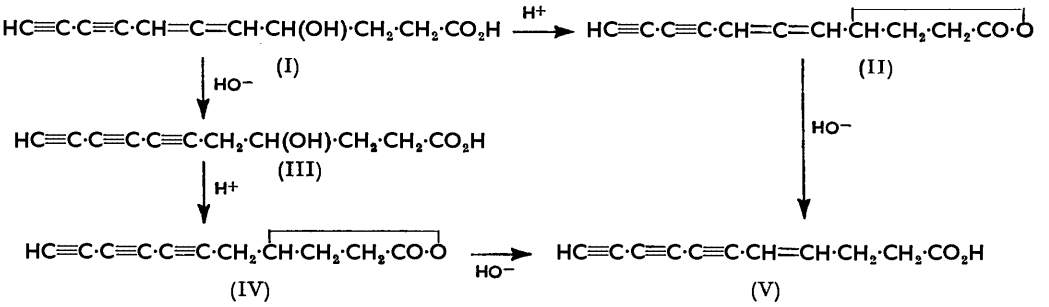
[2] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870, and later papers.

[3] Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

ascribed to hydroxyl and acetylenic hydrogen in the case of nemotinic acid are also present in the infrared spectra of *iso*nemotinic acid and its methyl ester. Like nemotinic acid, *iso*nemotinic acid is readily lactonised; the crystalline, optically active lactone ($[\alpha]_D^{20}$ −3·5°) has in its infrared absorption spectrum a carbonyl band at 1795 cm.$^{-1}$, indicative of a saturated γ-lactone ring. Hydrogenation of *iso*nemotinic acid and distillation of the product gives (+)-γ-undecanolactone (identified as 4-oxoundecanamide).

*iso*Nemotinic acid is clearly (−)-4-hydroxyundeca-6 : 8 : 10-triynoic acid (III) and its lactone is (IV).

The reported formation of a neutral enetriyne from nemotin [1] was difficult to reconcile with structure (II) for the latter; however, when the conversion of nemotin into nemotin A was repeated, it was found that the crystalline enetriyne (ultraviolet absorption spectrum, Table 1) was a carboxylic acid, with pK_a 4·70 (*i.e.*, not αβ-unsaturated). Though nemotin A is quite photosensitive, it proved to be the most easily handled compound of this series and gave reasonably good analyses for $C_{11}H_8O_2$; this is important as it may be prepared indirectly from nemotinic acid as well as from nemotin and so characterises both compounds. The infrared spectra of nemotin A and its methyl ester show the acetylenic hydrogen band at 3280 cm.$^{-1}$ and carbonyl bands at 1708 and 1742 cm.$^{-1}$ respectively, but no allene or hydroxyl band is present; nemotin A has no measurable optical activity. Hydrogenation converts nemotin A into undecanoic acid directly, so that nemotin A must be undec-4-en-6 : 8 : 10-triynoic acid (V).



Just as the conversion of nemotinic acid into its lactone, nemotin, helped in establishing the structures (I) and (II) for these compounds, so it seemed desirable to correlate their isomerisation products in some way. *iso*Nemotinic acid is apparently stable in aqueous 0·1N-alkali, but it has been found that the derived lactone (IV) gives nemotin A in up to 40% yield under alkaline conditions. The remainder of the lactone is apparently hydrolysed back to *iso*nemotinic acid; nemotin A was isolated from the reaction mixture by countercurrent distribution and characterised spectroscopically as the methyl ester.

The alkali-catalysed isomerisation reactions of mycomycin, nemotinic acid, and nemotin are three variants of the simple allene–acetylene rearrangement, –CH=C=CH– ⇌ –CH_2·C≡C–, which has been extensively studied by various workers.[4] The mycomycin ⟶ *iso*mycomycin change involves the migration of two protons, the isomerisation of nemotinic acid is a simple prototropic change, and the conversion of nemotin into nemotin A combines the rearrangement with an elimination. These diverse reactions can be reconciled by consideration of the initial step, which in every case is presumably the removal of a proton from the allene group. Of the two allenic hydrogen atoms, that which is the more acidic will be removed preferentially. Thus in the isomerisation of nemotinic acid (Fig. 1), the hydrogen atom *b* is allylic only to an enediyne system, whereas the other (*a*) is allylic both to the diyne group and to a double bond. Consequently the latter is removed and rearrangement proceeds as shown. In the rearrangement of mycomycin (Fig. 2) hydrogen atom *a* is allylic to diyne and triene groups, and hydrogen atom *b* is allylic to enediyne and diene groups; removal of the latter gives the more highly conjugated anion (the diyne

[4] Jacobs, Akawie, and Cooper, *J. Amer. Chem. Soc.*, 1951, **73**, 1273; Eglinton, Jones, Mansfield, and Whiting, *J.*, 1954, 3197 *et seq.*

system being considerably less polarisable than the enediyne system) and so in mycomycin this is the initial point of attack, the rearrangement of the cumulene intermediate probably proceeding as shown. In the isomerisation of nemotin the first step involves the same hydrogen atom as in nemotinic acid (Fig. 3), but the subsequent course of the reaction is determined by the elimination of the neighbouring oxycarbonyl group, so that nemotin A is formed as shown. Such an effect would be much less likely in the case of nemotinic acid

FIG. 1.

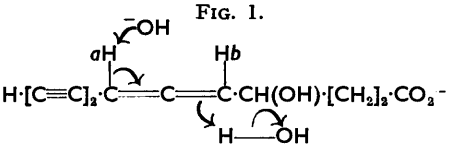


FIG. 2.

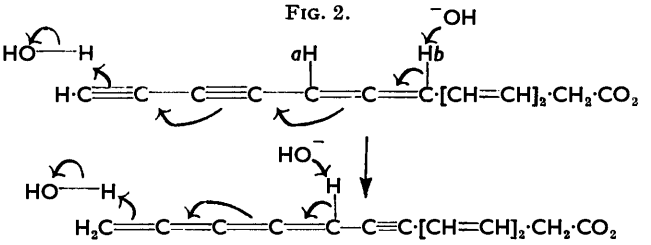
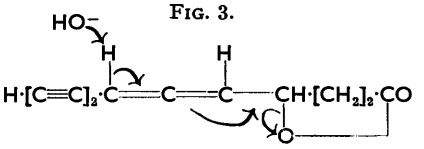


FIG. 3.



because of the lower electronegativity of the hydroxyl compared with the oxycarbonyl group; in fact only a minute amount (<1%) of nemotin A could be detected in the isomerised nemotinic acid, and this may well have been formed from traces of nemotin present in the starting material. The absence of this effect in the isomerisation of nemotinic acid may partly explain its greater stability to alkali; another factor tending to slow down the isomerisation is that it requires the approach of two anions, whereas in the isomerisation of nemotin only one of the reacting entities is charged. (The relative alkali-stabilities of nemotinic acid and nemotin may be assessed from the data in Table 2.) The isomeris-

TABLE 2. *Effect of* pH *on allene isomerisation rates.*

Reaction medium		Buffer, pH 8·4	Buffer, pH 10	M/20-NaOH
Approx. time (min.) for 50% isomerisation	Nemotin	23	3	<0·1
	Nemotinic acid	—	—	7

ation of *iso*nemotinic lactone to nemotin A can be formulated as a simple elimination following removal of the propargylic hydrogen atom. From the infrared spectra of the products, it appears that both reactions leading to nemotin A give mainly the *trans*-isomer; this accords with the reaction schemes outlined above. The reactions leading to nemotin A are to some extent analogous to those in which certain lactones [5] and β-acyloxy-esters [6] afford *trans*-αβ-unsaturated acids on treatment with alkali; in such reactions protons are removed from positions activated by alkoxycarbonyl groups. In the reactions at present under consideration the removable protons are in allylic (or propargylic) positions; the reactions proceed under far milder conditions.

In conclusion we would like to add that the statement, attributed to us in a recent review,[7] that nemotinic acid gives nemotin A on treatment with alkali, is of course incorrect.

[5] Pavly and Will, *Annalen*, 1918, **416**, 1.
[6] Linstead, Owen, and Webb, *J.*, 1953, 1211.
[7] Bohlmann, *Angew. Chem.*, 1955, **67**, 389.

Experimental

For details of general experimental methods, see Part V.[3]

Isomerisation of Nemotinic Acid.—A solution of the acid (560 mg.) in ether was shaken with 0·1N-sodium hydroxide (500 + 250 c.c.), and the combined aqueous layers were kept for 2 hr. at 20°. The ultraviolet absorption of the solution then showed no further change and indicated the presence of about 1% of enetriyne. The brown solution was acidified and extracted with ether (3 × 250 c.c.), and the combined extracts were reduced in bulk and subjected to counter-current distribution between M/15-disodium hydrogen phosphate and ether. The purified *iso*nemotinic acid (III) crystallised from methylene chloride–pentane at −80° as colourless needles, rapidly becoming purple even at −40° in the dark, $[\alpha]_D^{20}$ −3° (*c* 1), pK_a (in water) 4·75; ultra-violet absorption, Table 1.

Methyl iso*Nemotinate.*—*iso*Nemotinic acid (20 mg.) in ether was treated with a slight excess of distilled diazomethane in ether. The product was an oil, showing infrared absorption peaks at 3625 and 3470 cm.$^{-1}$ (O–H stretching) and 1737 cm.$^{-1}$ (ester-carbonyl).

iso*Nemotinic Lactone* (IV).—A solution of *iso*nemotinic acid (150 mg.) and sulphuric acid (3 c.c.) in pure dry dioxan (100 c.c.) was kept at 20° in the dark for 4 days. Water (100 c.c.) was then added and the solution neutralised with aqueous potassium hydrogen carbonate; more water (2 l.) was added and the solution extracted with ether (3 × 250 c.c.). The combined extracts were washed with water (2 × 150 c.c.), dried, and evaporated to small bulk, the product being kept in solution by addition of a little methylene chloride. iso*Nemotinic lactone* crystallised as colourless plates from methylene chloride–pentane at −70°; the crystals became pink in the dark at −40° and decomposed at 50° (Found: C, 75·6; H, 4·5. $C_{11}H_8O_2$ requires C, 76·7; H, 4·7%); $[\alpha]_D^{20}$ −3·5° (*c* 1·2); ultraviolet absorption, Table 1.

Hydrogenations.—(a) iso*Nemotinic acid.* The acid (50 mg.) in ethanol (20 c.c.) over platinum took up 5·6 mol. of hydrogen; evaporation of the solution gave an oil (47 mg.) with the odour of γ-undecanolactone. The oil, distilled under reduced pressure, had n_D^{20} 1·4516, $[\alpha]_D^{20}$ +31° (*c* 1·1), and an infrared spectrum identical with that of (+)-γ-undecanolactone {n_D^{20} 1·4540, $[\alpha]_D^{17}$ +29° (*c* 1·7)}.

(b) iso*Nemotinic lactone.* The lactone (65 mg.) in ethanol (25 c.c.) over platinum took up 5·7 mol. of hydrogen; the crude product showed $[\alpha]_D^{20}$ +24° (*c* 1·0) and after distillation showed bands at 1780 (strong) and 1710 cm.$^{-1}$ (weak). Ammonolysis of this mixture of (+)-γ-undecanolactone and undecanoic acid and oxidation of the product [3] yielded 4-oxoundecanamide (20 mg.), m. p. and mixed m. p. 130—131°.

Isomerisation of Nemotin.—A solution of nemotin (150 mg.) in ether was added to M/15-aqueous disodium hydrogen phosphate (400 c.c.), and the ether evaporated. After 16 hr. at 20°, when the ultraviolet absorption spectrum showed no further change, the solution was acidified and extracted with ether. The dried ether extracts were evaporated to dryness and the residue dissolved in ether–pentane; from this the *nemotin A* (V) crystallised at −70° as colourless photosensitive needles, decomp. 50—60° (Found: C, 76·7; H, 5·3. $C_{11}H_8O_2$ requires C, 76·7; H, 4·7%), pK_a (in 20% aqueous ethanol), 4·70; ultraviolet absorption, Table 1; the compound was optically inactive.

Hydrogenation of Nemotin A.—The acid (48 mg.) in ethanol (25 c.c.) over platinum took up 6·6 mol. of hydrogen; evaporation of the solution yielded undecanoic acid (43 mg.), identified as the *p*-toluidide, m. p. and mixed m. p. 78°.

Esterification of Nemotin A.—The acid (10 mg.) and sulphuric acid (0·3 c.c.) in methanol (10 c.c.) was kept at 20° in the dark for 4 days. The mixture was poured into water and extracted with ether; the extract was washed with sodium hydrogen carbonate solution and water, then dried. The methyl ester (ultraviolet absorption, Table 1) showed infrared absorption at 1742 (ester-CO) and 3280 cm.$^{-1}$ (≡C–H) and no bands attributable to a hydroxyl group.

Isomerisation of iso*Nemotinic Lactone* (IV).—The lactone (30 mg.) in dioxan (60 c.c.) was added to 1% aqueous potassium carbonate (60 c.c.). After 90 min. at 20°, when the ultraviolet absorption of the solution showed no further change, the mixture was acidified, poured into water (2 l.) and extracted with ether (400 c.c.). The ether extract was washed with water (2 × 100 c.c.), and its ultraviolet absorption spectrum showed peaks ascribable to a mixture of an enetriyne and a triyne. The mixture was resolved by counter-current distribution in 4 tubes between ether and M/15-aqueous disodium hydrogen phosphate. When all the enetriyne had been eluted in the ether fractions these were combined and the product was esterified (as above)

with methanol–sulphuric acid. The ester showed ultraviolet and infrared absorption spectra identical with those of the methyl ester of nemotin A.

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