949. *Amides of Vegetable Origin. Part X.* The Stereochemistry and Synthesis of Affinin.*

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The stereochemistry of affinin is considered. Infrared evidence supports a *trans*-2-linkage and analogy with neoherculin suggests an internal *cis*-6,-*trans*-8- rather than a *trans*-6,*cis*-8-diene. *N*-Isobutyldeca-*trans*-2,*cis*-6,-*trans*-8-trienamide was therefore synthesised: it was identical with natural affinin as judged by m. p., infrared spectra, and biological activity. *N*-Isobutyldeca-*trans*-2,*cis*-6,*cis*-8-trienamide was also synthesised. Nuclear magnetic resonance spectroscopy confirms the *trans*-2-assignment to affinin.

Affinin, an aliphatic triene-isobutylamide, was first isolated from *Heliopsis longipes* (A. Gray) Blake, a member of the Compositae, as an oil [1] (in earlier literature the source is incorrectly identified as *Erigeron affinis* DC [2]). Affinin was shown to be insecticidally active [1] and in later work was found to crystallise (m. p. 23°).[3] Some years after, the compound was found to be the same as spilanthol [4] from *Spilanthese oleracae* Jacq., for which various structures have been proposed.[5,6] Degradative evidence,[1] and synthesis of the all-*trans*-compound,[7] has led to structure (I) for affinin but the stereochemical position is less certain.[3] The amide gives no crystalline Diels–Alder adduct with maleic

(I) $Me{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}[CH_2]_2{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i$

$Me{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}[CH_2]_2{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i$ (II)

anhydride, suggesting that the diene is not *trans*-6,*trans*-8. There were infrared bands [3] at 976 and 943 cm.$^{-1}$ and the presence of these is consistent with a *trans*-6,*cis*-8- or *cis*-6,*trans*-8-system. This view was strengthened by replacement of the doublet by one band at 985 cm.$^{-1}$ when natural affinin is stereomutated to the all-*trans*-compound.[3] It has been suggested [3] that the 2-linkage is *cis*, but the results available are just as easily accommodated if the linkage is *trans*, for this would have a band near 980 cm.$^{-1}$ which would coalesce with one member of the *trans*–*cis*-diene pair. Two considerations led us to favour the *trans*-2-configuration. The first is analogy with known compounds of this class,[8,9] and the second is the position of the stretching frequency of the 2-unsaturation (1671 cm.$^{-1}$) in a specimen of spilanthol isolated from Indian *Spilanthes acmella* [6] by Dr. B. P. Griffin in our laboratory. The *trans*-2 vibration in this class of compound is normally here, whereas the *cis*-2-linkage absorbs near 1658 cm.$^{-1}$.[8] This difference of about 10—15 cm.$^{-1}$ has been noted now in a number of examples in our work.[8,9] Interference from the stretching vibrations of the internal diene does not occur, as they are very weak compared with those of a double bond conjugated with a carbonyl dipole.[8,9] Two isomers, the *trans*-2,*trans*-6,*cis*-8- and the *trans*-2,*cis*-6,*trans*-8-form of (I) were therefore entertained. We have earlier [9] found the structure of neoherculin to be *N*-isobutyldodeca-*trans*-2,*cis*-6,-*trans*-8,*trans*-10-tetraenamide (II), and the latter stereochemistry was therefore favoured for affinin. Synthetic work to this end was begun.

cis–*trans*-Pentenyne mixture was prepared and separated,[10] the purity of the isomers

* Part IX, *J.*, 1957, 2767.

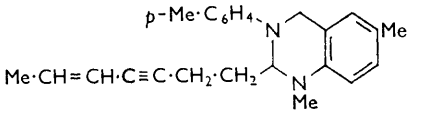
[1] Acree, Jacobson, and Haller, *J. Org. Chem.*, 1945, **10**, 236, 449.
[2] Jacobson, Acree, and Haller, *J. Org. Chem.*, 1947, **12**, 731.
[3] Jacobson, *J. Amer. Chem. Soc.*, 1954, **76**, 4606.
[4] Jacobson, *Chem. and Ind.*, 1957, 50.
[5] Asano and Kanematsu, *J. Pharm. Soc. Japan*, 1927, **47**, 521; *Ber.*, 1932, **65**, 1602; Aihara, *J. Pharm. Soc. Japan*, 1950, **70**, 43; Aihara and Suzuki, *J. Pharm. Soc. Japan*, 1951, **71**, 1323; Jacobson, *J. Amer. Chem. Soc.*, 1956, **78**, 5084.
[6] Gokhale and Bhide, *J. Indian Chem. Soc.*, 1945, **22**, 250; Pendse, *Current Sci.*, 1945, **14**, 37.
[7] Jacobson, *J. Amer. Chem. Soc.*, 1955, **77**, 2461.
[8] Crombie, *J.*, 1952, (*a*) 2997, (*b*) 4338.
[9] Crombie, *J.*, 1955, 995; Crombie and Tayler, *J.*, 1957, 2760.
[10] Allan and Whiting, *J.*, 1953, 3314.

being confirmed by gas–liquid chromatography. Hept-*cis*- and -*trans*-5-en-3-yn-1-ol (III; R = OH) were made by treating the sodiopentenynes with ethylene oxide, small amounts of the ether-alcohol (III; R = ·O·$[CH_2]_2$·OH) also being formed. 7-Chlorohept-2-en-4-yne (III; R = Cl) could be made by treating pentenynylmagnesium bromide with 2-chloroethyl toluene-*p*-sulphonate,[11] but this intermediate failed to form a Grignard reagent in ether or tetrahydrofuran. The two alcohols were therefore converted into their toluene-*p*-sulphonates and then into the iodides (III; R = I). On examination by gas–liquid chromatography the iodide in the *cis*-series was found to be fairly pure stereochemically but stereomutation to the extent of 19% had occurred, surprisingly, in the *trans*-case. However, repeated distillations of the *cis*-iodide could cause stereoequilibration. An interesting crystalline by-product, apparently 4,5,7-tri-iodohepta-2,4-diene was encountered in these preparations.

$Me\cdot CH{:}CH\cdot C\equiv C\cdot CH_2\cdot CH_2R$ (III)

$Me\cdot CH{:}CH\cdot C\equiv C\cdot[CH_2]_4\cdot C\equiv C\cdot CH{:}CHMe$ (IV)

$Me\cdot CH=CH\cdot C\equiv C\cdot[CH_2]_2\cdot CH=CH\cdot COR$ (VI)



(V)

The two monoiodides formed Grignard reagents which, with ethyl orthoformate, gave the expected acetals. By acid hydrolysis oct-*cis*- and -*trans*-6-en-4-ynal (III; R = CHO) could be prepared and characterised as 2,4-dinitrophenylhydrazones and semicarbazones, but yields were poor because of considerable self-coupling to give the dienediyne (IV). As an alternative, preparation of the nitriles (III; R = CN) and reduction to the aldehyde by lithium aluminium hydride was envisaged. Unfortunately, the nitriles were also formed in poor yield, so the Grignard approach was re-examined. By using dilution techniques in a cyclic reactor,[12] self-coupling was minimised and, immediately after formation, the appropriate Grignard reagent was added to the methiodide of 3,4-dihydro-6-methyl-3-*p*-tolylquinazoline [13] to give compound (V). On hydrolysis, this yielded the *cis*- or *trans*-6-en-4-ynal, according to the Grignard reagent used. The two aldehydes (in the preparative batch the *trans*-compound was not stereochemically homogeneous at this stage) were converted by Doebner reaction, followed by crystallisation, into deca-*trans*-2,-*cis*-8- and deca-*trans*-2,*trans*-8-dien-6-ynoic acid (VI; R = OH). The acetylenic acids were converted through their acid chlorides into crystalline *N*-isobutylamides (VI; R = $NHBu^i$).

By partial hydrogenation the *trans*-2,*cis*-8-acetylenic amide formed *N*-isobutyldeca-*trans*-2,*cis*-6,*cis*-8-trienamide, $\lambda_{max.}$ 227 mμ (ε 26,500), with infrared bands at 1669 (*trans*-2-olefin), 3289, 3086, 1631, 1550 (monosubstituted amide), 979 (*trans*-2-def.), 720 and 701 (*cis*-diene def.) $cm.^{-1}$. Similarly, the *trans*-2,*trans*-8-acetylenic amide gave *N*-isobutyldeca-*trans*-2,*cis*-6,*trans*-8-trienamide which softened at 21° and finally melted at 26°, $\lambda_{max.}$ 227 mμ (ε 29,200), with infrared bands at 1669 (*trans*-2-olefin), 3300, 3086, 1631, 1548 (monosubstituted amide), 980 (*trans*-2-def.), 980 and 949 (*cis*-6,*trans*-8-diene), and 727 (*cis*-6 def.) $cm.^{-1}$. Each amide absorbed three mol. of hydrogen over a catalyst to give *N*-isobutyldecanamide and each could be stereomutated to *N*-isobutyldeca-*trans*-2,*trans*-6,*trans*-8-trienamide,[7] m. p. 92°, $\lambda_{max.}$ 226 mμ (ε 36,400).

The infrared spectrum of our *trans*-2,*cis*-6,*trans*-8-trienamide was completely superimposable on that of natural affinin: the *trans*-2,*cis*-6,*cis*-8-amide was clearly distinguishable. Furthermore, Dr. M. Jacobson has kindly compared affinin and the synthetic *trans*-2,*cis*-6,*trans*-8-amide against adult *Musca domestica* in "Deobase" at

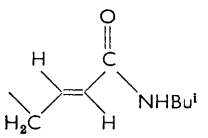
[11] Gilman and Beaber, *J. Amer. Chem. Soc.*, 1925, **47**, 518, and later papers by Gilman *et al.*

[12] Rowlands, Greenlee, and Boord, personal communication; Lawesson, *Acta Chem. Scand.*, 1958, **12**, 1.

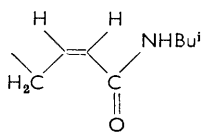
[13] Fales, *J. Amer. Chem. Soc.*, 1955, **77**, 5118.

2 mg./ml. and has found that both give complete knockdown in 10 min. and 26% mortality in 24 hours. Affinin and the synthetic amide thus have every appearance of identity. It would, however, be of interest to make the *trans*-2,*trans*-6,*cis*-8-stereoisomer for biological examination and to ensure that it is clearly distinguishable from natural affinin.

The correctness of our views on the stereochemistry of the 2-unsaturation in affinin was shown after the synthetic work had been completed. By using *N*-isobutyldec-*trans*- and -*cis*-2-enamide as models (cf. VIIa and b) [14] it was found that the τ value of the 4-methylene group was near 7·81 in the spectrum of the *trans*-2- (VIIa) and near 7·35 in the *cis*-2-compound (VIIb) where it is deshielded by the amide-carbonyl group. In affinin, the only band in this region is a multiplet centred on 7·72 which contains the four protons of the 4- and 5-methylene groups. Clearly affinin is of the *trans*-2-series. The nuclear magnetic resonance spectrum of *N*-isobutyldeca-*trans*-2,*cis*-6,*trans*-8-trienamide shows small differences from that of natural affinin in the olefin region, but these are thought to be due to impurity arising from the partial hydrogenation. Complete purification of a



(VIIa)



(VIIb)

compound of this type is extremely difficult when the impurities are close relatives. On the other hand, the nuclear magnetic resonance spectrum of the *trans*-2,*cis*-6,*cis*-8-amide is readily distinguishable from that of affinin.

Experimental

Unless otherwise stated, the following remarks apply. Solutions were dried with anhydrous sodium or magnesium sulphate and " evaporation " means evaporation under reduced pressure. Ultraviolet data were determined for ethanol solutions and infrared spectra (rock salt optics) relate to liquid films or paraffin mulls as appropriate.

Hept-cis-5-*en*-3-*yn*-1-*ol*.—Pent-*cis*-3-en-1-yne [10,14] (66·7 g., b. p. 44·8°/772 mm., n_D^{20} 1·4339) in dry ether (50 ml.) was added in 1 hr. below the liquid level of a stirred suspension of sodamide [from sodium (24·8 g.) and ferric nitrate (0·3 g.)] in liquid ammonia (500 ml.). After 2 hours' stirring, ethylene oxide (49·3 g.) in ether (60 ml.) was added similarly and the mixture was stirred under reflux for a further 4 hr. Stirring was continued under nitrogen for 24 hr. with intermittent replenishment of the ammonia. Ammonium chloride (80 g.) and ether (200 ml.) were added and the ammonia was allowed to evaporate. The solids were extracted with ether, and the dried extracts were evaporated and distilled, to give *hept*-cis-5-*en*-3-*yn*-1-*ol* (60·1 g., 54%), b. p. 88°/14·5 mm., 62—64°/3 mm., n_D^{23} 1·4982—1·4990 (Found: C, 76·35; H, 8·95. $C_7H_{10}O$ requires C, 76·35; H, 9·15%), $\lambda_{max.}$ 224·5 mμ (ε 13,000), $\nu_{max.}$ 3333, 1044 (OH), 2232 (C≡C), 1623, 721 (*cis*-CH=CH) cm.$^{-1}$. The 1-*naphthylurethane* had m. p. 92—93° (Found: C, 77·55; H, 6·4. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·15%). The higher-boiling fraction (3·0 g.), b. p. 99—122°/14 mm., n_D^{23} 1·4940, yielded on redistillation the product from reaction of pent-*cis*-3-en-1-yne with two mol. of ethylene oxide, the cis-*ether-alcohol* (III; R = O·$[CH_2]_2$·OH), b. p. 136—146°/1·5 mm., n_D^{24} 1·5060—1·5114, $\nu_{max.}$ 3378, 2230 cm.$^{-1}$, $\lambda_{max.}$ 226 mμ (ε 11,400) (Found: C, 69·9; H, 9·3. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%). Hept-*cis*-5-en-3-yn-1-ol was also made by treating the Grignard reagent from pent-*cis*-3-en-1-yne in tetrahydrofuran with ethylene oxide. Yields were poorer than in the procedure described.

The purity of the pent-*cis*-3-en-1-yne and its *trans*-stereoisomer used in the next preparation was rigorously established by both gas–liquid chromatography and infrared spectroscopy.

Hept-trans-5-*en*-3-*yn*-1-*ol*.—The sodium salt from pent-*trans*-3-en-1-yne (40·1 g.; b. p.

[14] Crombie and Manzoor-i-Khuda, *J.*, 1957, 2767.

51·5°/753 mm., n_D^{20} 1·4376) was condensed with ethylene oxide (31 g.) under experimental conditions similar to those above. The product, *hept*-trans-5-*en*-3-*yn*-1-*ol* (52·5 g., 77%), had b. p. 86°/10 mm., 67—69°/2·5 mm., $n_D^{21.5}$ 1·5021 (Found: C, 76·45; H, 9·35%), $\lambda_{max.}$ 225 mμ (ε 14,000), $\nu_{max.}$ 3333, 1039 (OH), 2232 (C≡C), 1625, 954 (*trans*-5-olefin) cm.$^{-1}$. The 1-*naphthylurethane* had m. p. 101—102° (Found: C, 77·5; H, 5·95%) and depressed the m. p. of the corresponding *cis*-derivative. A weak band was present at 721 cm.$^{-1}$ in the infrared spectrum of the alcohol and it appears to signify slight contamination by *cis*-isomer formed by stereomutation. The higher-boiling fractions (9·5 g.) gave, on redistillation, the trans-*ether-alcohol* (III; R = O·$[CH_2]_2$·OH), b. p. 136—142°/1 mm., n_D^{24} 1·5143—1·5153 (Found: C, 69·95; H, 9·3%), $\lambda_{max.}$ 225 mμ (ε 11,600).

7-*Toluene*-p-*sulphonyloxyhept*-cis-2-*en*-4-*yne*.—A warm solution of toluene-*p*-sulphonyl chloride (110 g.) in anhydrous pyridine (55 ml.) was cooled rapidly to 0° with vigorous stirring and hept-*cis*-5-en-3-yn-1-ol (51·7 g.) was added in 1 hr. After being stirred for 60 hr. at 20° the product was poured into iced 2N-sulphuric acid and extracted with ether. The extract was washed with dilute acid, sodium hydrogen carbonate solution, and water. Drying and removal of the solvent gave a brown oil (126 g.) which failed to crystallise at 0°. A portion of the cis-*toluene*-p-*sulphonate* was distilled, having b. p. 150°/0·04 mm., n_D^{24} 1·5390 (Found: C, 63·3; H, 5·95. $C_{14}H_{16}O_3S$ requires C, 63·6; H, 6·1%).

7-*Toluene*-p-*sulphonyloxyhept*-trans-2-*en*-4-*yne*.—In a similar way hept-*trans*-5-en-3-yn-1-ol (116 g.), anhydrous pyridine (176 ml.), and toluene-*p*-sulphonyl chloride (251 g.) gave the trans-*toluene*-p-*sulphonate* (234 g.), which crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 50—51° (Found: C, 63·0; H, 6·15%).

7-*Chlorohept*-2-*en*-4-*yne*.—2-Chloroethyl toluene-*p*-sulphonate (60 g.; b. p. 134—145°/10^{-2} mm.) in dry ether (50 ml.) was added slowly to pent-3-en-1-ynylmagnesium bromide prepared from ethyl bromide (19 g.), magnesium (4·1 g.), dry ether (80 ml.), and mixed *cis*- and *trans*-pent-3-en-1-yne (11 g.) in ether (20 ml.). The mixture was refluxed for 18 hr., cooled, and decomposed with dilute sulphuric acid. Extraction with ether and distillation gave 7-chlorohept-2-en-4-yne (9·4 g.), b. p. 42°/0·1 mm., n_D^{26} 1·4960—1·4968 as a *cis–trans*-mixture (Found: C, 65·0; H, 7·2; Cl, 27·45. Calc. for C_7H_9Cl: C, 65·35; H, 7·05; Cl, 27·55%). It had an ultraviolet max. at 226 mμ (ε 15,000) and $\nu_{max.}$ 2219, 2196, 1621, 953, and 733 cm.$^{-1}$.

7-Chlorohept-2-en-4-yne (2·0 g.) and sodium cyanide (0·8 g.) in ethanol (4 ml.) and water (1 ml.) were refluxed together for 67 hr. and the product was diluted with water and extracted with ether. Drying, evaporation, and distillation gave a mixture of unchanged chloride and the expected nitrile, b. p. 30—40°/0·2 mm., n_D^{23} 1·4957—1·5010 (Found: C, 72·95; H, 7·65. Calc. for C_8H_9N: C, 80·8; H, 7·6%), $\lambda_{max.}$ 224 mμ (ε 11,600). An experiment in which the chloro-compound, sodium cyanide, and sodium iodide were refluxed together in ethanol–water also gave a mixed product (infrared spectrum), b. p. 48—62°/0·2 mm., n_D^{24} 1·5244—1·5012, $\lambda_{max.}$ 225 mμ (ε 12,000).

7-*Iodohept*-trans-2-*en*-4-*yne*.—7-Toluene-*p*-sulphonyloxyhept-*trans*-2-en-4-yne (233 g.) was added to sodium iodide (154 g.) in dry acetone (900 ml.). The red-brown mixture was stirred in the dark at 20° for 84 hr. and the sodium toluene-*p*-sulphonate (145 g.) was removed. The filtrate was refluxed and stirred for 2 hr. and more sodium toluene-*p*-sulphonate (12 g.) was filtered off. Partial evaporation of the deep-red filtrate (magnetic stirring) gave khaki-coloured needles which were filtered off rapidly and washed with small volumes of acetone. The concentration, filtration, and washing were repeated a number of times. Finally, the remainder of the khaki crystals crystallised at 0° (total approx. 60 g.). The filtrate was distilled through a short Vigreux column, to give highly dispersed (mainly) 7-iodohept-*trans*-2-en-4-yne (111·7 g.), b. p. 77—81°/2·7 mm., 35°/0·1 mm., n_D^{21} 1·5675 (Found: C, 37·6; H, 4·2; I, 58·45. Calc. for C_7H_6I: C, 38·2; H, 4·15; I, 57·65%). The *trans*-iodide distilled as a pink liquid but the colour was slowly discharged. Gas–liquid chromatography showed that the iodide was not stereochemically homogeneous but contained 19% of *cis*-isomer. The iodide had $\nu_{max.}$ 2222 (C≡C), 1623, 952 (*trans*-5-acetylene conjugated olefin), and 722 (*cis*-5-olefin impurity?) cm.$^{-1}$.

Dissolution of the khaki needles (which changed to an iodine-containing sludge when kept) in warm ether gave yellow needles which, when treated with charcoal and crystallised from the same solvent, or from methanol, in the dark, gave large, nearly colourless needles, m. p. 88—89° [Found: C, 18·0, 17·8; H, 2·0, 2·15; I, 81·3, 79·6%; *M* (ebullioscopic), 457. $C_7H_6I_3$ requires C, 17·73; H, 1·91; I, 80·35%. *M*, 474]. The 4,5,7-*tri-iodohepta*-2,4-*diene* had $\lambda_{max.}$ 230,

(10,400), 270 (15,530) mμ, $\nu_{max.}$ 1631 (conj. olefin), 951 (conj. *trans*-CH=CH) cm.$^{-1}$. Khaki-coloured needles are also formed from a mixture of sodium iodide, acetone, and toluene-*p*-sulphonyl chloride.

7-*Iodohept*-cis-2-*en*-4-*yne*.—Prepared as for the *trans*-compound 7-*iodohept*-cis-2-*en*-4-*yne* (69 g. from 125·5 g. of 7-toluene-*p*-sulphonyloxyhept-*cis*-2-en-4-yne), had b. p. 52°/0·9 mm., n_D^{20} 1·5661 (Found: C, 38·50; H, 4·2%), $\lambda_{max.}$ 225 mμ (ε 12,000). On repeated distillation rising absorption in the infrared region at 954 cm.$^{-1}$ indicated slow *trans*-isomerisation.

The khaki crystals, on crystallisation from methanol (charcoal) in the dark, gave the tri-iodide, m. p. 88—89° (Found: I, 79·4%), identical with the sample obtained from the *trans*-hydrocarbon.

Oct-cis-6-*en*-4-*ynal*.—(*a*) *Dihydroquinazoline route*. A "cyclic reactor" was used.[12] Amalgamated magnesium in the column was activated with ethyl bromide (2 ml.) and iodine, and the ethylmagnesium bromide formed was washed out by recycling ether and rejected. 7-Iodohept-*cis*-2-en-4-yne (10·5 g., see above) in dry ether (50 ml.) was added during 6 hr. into a stream of recondensed ether (giving a dilution of 150 : 1), passing down the column of magnesium and into a flask containing stirred methiodide of 3,4-dihydro-6-methyl-3-*p*-tolylquinazoline (20·8 g.) in refluxing ether. The refluxing was continued in the apparatus for 12 hr. with the ether recycling through the magnesium column. The gummy red solids were thoroughly extracted with ether and chloroform. Evaporation of the extracts gave an oil which was steam-distilled from 2N-sulphuric acid to give, on redistillation, oct-*cis*-6-en-4-ynal (3·1 g., 53%), b. p. 92°/16 mm., n_D^{23} 1·4980—1·5010, $\lambda_{max.}$ 225 mμ (ε 10,000), $\nu_{max.}$ 2227 (C≡C), 1724 (CHO), 1623, 723 (*cis*-6-CH=CH) cm.$^{-1}$. The aldehyde contained 5—10% of *trans*-isomer as estimated from the band at 955 cm.$^{-1}$. The aldehyde with 2,4-dinitrophenylhydrazine gave *oct*-cis-6-*en*-4-*ynal* 2,4-*dinitrophenylhydrazone*, orange needles, m. p. 105—106° (dimorphic change 101°) after chromatography through bentonite–kieselguhr and repeated crystallisation (Found: C, 55·2, 55·8; H, 4·65, 4·75. $C_{14}H_{14}N_4O_4$ requires C, 55·6; H, 4·65%). The semicarbazone crystallised from methanol–water in needles, m. p. 103—104°.

Without the use of a cyclic reactor the yield of aldehyde fell to 25% (b. p. 86—92°/16 mm., n_D^{23} 1·4925—1·4940) and symmetrically coupled product (tetradecadienediyne) was formed (13%).

(*b*) *Ethyl orthoformate route*. Dry magnesium turnings (57 g.) were kept under a saturated dry ethereal solution of mercuric chloride for 12 hr. The Grignard reaction was initiated with ethyl bromide (1 ml.) and iodine, and 7-iodohept-*cis*-2-en-4-yne (53 g.) was added during 1 hr. with rapid stirring. After a further hour's heating and then cooling, redistilled ethyl orthoformate (178 g., 1·10 mol.) was added. The product was refluxed for 18 hr. and much of the ether and excess of ethyl orthoformate was then removed by distillation. The residue was extracted with ether and the extracts were poured into saturated ammonium chloride solution. The ethereal solution was dried, evaporated, and distilled, to give crude 1,1-diethoxy-*cis*-oct-6-en-4-yne (5·5 g.), b. p. 52—96°/0·4 mm., n_D^{22} 1·4990—1·5105. Symmetrically coupled hydrocarbon, *tetradeca*-cis-2,cis-12-*diene*-4,10-*diyne* (8·9 g.), b. p. 116—119°/2·5 mm., $n_D^{22.5}$ 1·5135, was also formed (Found: C, 89·9; H, 10·0. $C_{14}H_{18}$ requires C, 90·25; H, 9·75%). The hydrocarbon had $\lambda_{max.}$ 225 mμ (ε 23,200) with a shoulder at 233 mμ (ε 19,000), $\nu_{max.}$ 1626 and 722 cm.$^{-1}$. On hydrogenation over palladium–charcoal under light petroleum (b. p. 60—80°) 6·10 mol. of hydrogen were absorbed to give n-tetradecane, m. p. 4—5° (lit., m. p. 5·5°). The impure 8,8-diethoxy-*cis*-octenyne (5·5 g.) was added to boiling 2N-sulphuric acid (150 ml.) and was steam-distilled. The steam-distillate was saturated with salt and extracted 3 times with ether. The ethereal extract, on drying, evaporation, and distillation, gave *cis*-oct-6-en-4-ynal (1·7 g., 50%) which, from the infrared spectrum, was of poor quality. It gave a 2,4-dinitrophenylhydrazone, m. p. 105—106° (dimorphic change 101°), identical with that above.

Oct-trans-6-*en*-4-*ynal*.—(*a*) *Dihydroquinazoline route*. By procedures similar to those described under the *cis*-compound, 7-iodohept-*trans*-2-en-4-yne (25 g.) was converted into the Grignard reagent in a cyclic reactor and treated with 3,4-dihydro-6-methyl-3-*p*-tolylquinazoline methiodide (52 g.). Refluxing for 12 hr. and working up gave an oil which was steam-distilled from 2N-sulphuric acid to give stereochemically impure oct-*trans*-6-en-4-ynal (5·72 g., 41%), b. p. 84—88°/11 mm., n_D^{24} 1·4936—1·4945 (Found: C, 78·7; H, 8·15. Calc. for $C_8H_{10}O$: C, 78·65; H, 8·25%), $\lambda_{max.}$ 225 mμ (ε 13,500) in cyclohexane. Gas–liquid chromatography of this and other preparations indicated that as much as 30—50% of *cis*-isomer could be present at this stage. In the infrared region there were bands at 2715 (CHO), 2227 (C≡C), 1727 (C=O),

957 (*trans*-CH=CH), and 723 (*cis*-CH=CH) cm.$^{-1}$. The 2,4-*dinitrophenylhydrazone* was made from *trans*-aldehyde containing 10% of *cis*-contaminant. It was chromatographed and repeatedly crystallised from light petroleum (b. p. 60—80°), forming orange needles, m. p. 129—131° (Found: C, 55·6; H, 4·8%). The *semicarbazone*, crystallised from methanol–water, had m. p. 148—149°. A second form, m. p. 128—129° (Found: C, 60·25; H, 7·6. $C_9H_{14}N_3O$ requires C, 60·0; H, 7·85%), has also been encountered.

(*b*) *Ethyl orthoformate route.* 7-Iodohept-*trans*-2-en-4-yne (38·1 g.) was converted into the Grignard reagent by using amalgamated magnesium in dry ether as for the *cis*-compound, and then treated with ethyl orthoformate (130 g.). Distillation gave crude *trans*-acetal (7·7 g., 23%), b. p. 72—98°/0·45 mm., n_D^{21} 1·4651 which, on distillation with 2N-sulphuric acid gave oct-*trans*-6-en-4-ynal, b. p. 78—90°/9·5 mm., n_D^{20} 1·4952. Besides the acetal tetradeca-*trans*-2,*trans*-12-diene-4,10-diyne (9·8 g., 61%) was obtained which, when redistilled, had b. p. 154°/12 mm., n_D^{20} 1·5179 (Found: C, 89·6; H, 9·85%), $\nu_{max.}$ 2222 (C≡C), 1623 and 953 (*trans*-CH=CH) cm.$^{-1}$. Both the aldehyde and the hydrocarbon were contaminated with *cis*-isomer arising from the stereochemically impure starting iodide.

On hydrogenation in light petroleum (b. p. 40—60°) over palladium–charcoal catalyst, 6·1 mol. of hydrogen were absorbed and n-tetradecane, m. p. 3° after distillation, was isolated.

Deca-trans-2,cis-8-*dien*-6-*ynoic Acid.*—Oct-*cis*-6-en-4-ynal (3·25 g.) and malonic acid (3·5 g.) in dry pyridine (6 ml.) were shaken at 20° for 56 hr. After being heated at 100° for 1 hr. the mixture was poured into iced 2N-hydrochloric acid and extracted with ether. The ethereal extract was in turn thoroughly extracted with 2N-sodium hydroxide. The alkaline extract was acidified (to Congo Red) and extracted with ether. On drying and evaporation, the crude acid (3·6 g.) was isolated which, when repeatedly crystallised from light petroleum (b. p. 30—40°), gave *deca*-trans-2,cis-8-*dien*-6-*ynoic acid*, flat needles, m. p. 45° (Found: C, 73·05, 73·35; H, 7·3, 7·45. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·4%). It had $\lambda_{max.}$ 224 mμ (ε 18,000) with an inflexion at 234 mμ (ε 13,250), and $\nu_{max.}$ (mull) 1686, 3030, 930 (bonded acid), 2237 (C≡C), 1642, 982 (*trans*-2-olefin), 723 (*cis*-8-olefin) cm.$^{-1}$. On microhydrogenation 4·1 mol. of hydrogen were absorbed.

Deca-trans-2,trans-8-*dien*-6-*ynoic Acid.*—Oct-*trans*-6-en-4-ynal (5·23 g.; contains *cis*-impurity, see above), malonic acid (6·2 g.), and dry pyridine (10 ml.), treated as above, gave crude acid (6·0 g.). Repeated crystallisation from light petroleum (b. p. 60—80°) gave *deca*-trans-2,trans-8-*dien*-6-*ynoic acid* (2·39 g., 34%), plates, m. p. 144—145° (dimorphic change to needles at ~120°) (Found: C, 73·05; H, 7·5%). It had $\lambda_{max.}$ 225 mμ (ε 18,550) with an inflexion at 235 mμ (ε 15,100). It had infrared bands (mull) at 3030, 1689, 933 (bonded acid), 1645, 982 (*trans*-2-olefin), and 956 (*trans*-8-olefin): the acetylenic stretching vibration was not detectable on using mulls of the usual composition and thickness. By working up the mother-liquors more *trans*-2,*trans*-8-acid, m. p. 143°, was obtained, followed by *trans*-2,*cis*-8-acid, m. p. 40° (1·05 g.). The infrared spectrum of the remaining oil was almost identical with that of the *trans*-2,*cis*-8-acid.

N-*Isobutyldeca*-trans-2,cis-8-*dien*-6-*ynamide.*—Purified thionyl chloride (5·56 g.) was added to deca-*trans*-2,*cis*-8-dien-6-ynoic acid (2·55 g.) and pyridine (2 drops). The mixture was kept for 8 hr. at 20° with occasional swirling. Thionyl chloride was removed *in vacuo* and on distillation the acid chloride, b. p. 118—124°/2·5 mm., was obtained: it was immediately added dropwise to an excess of ethereal *N*-isobutylamine with shaking and cooling. After keeping overnight the mixture was washed with 2N-hydrochloric acid, sodium carbonate solution, and water. Drying and evaporation gave the crude amide (3·1 g.). By direct crystallisation at −10° from ether–light petroleum (b. p. 30—40°) N-*isobutyldeca*-trans-2,cis-8-*dien*-6-*ynamide* (191 mg.), m. p. 36—37°, was obtained as needles (Found: C, 76·7; H, 9·6; N, 6·4. $C_{14}H_{21}NO$ requires C, 76·65; H, 9·65; N, 6·4%). The mother-liquors were distilled (b. p. 142°/0·04 mm., n_D^{22} 1·5151) and the distillate then crystallised, to give the main bulk of the amide (2·28 g.) which was crystallised as above. The amide had $\lambda_{max.}$ 225 mμ (ε 23,550) with an inflexion at 235 mμ (ε 18,400): there were infrared bands at 3300, 3096, 3040, 1629, 1550 (monosubstituted amide), 2222 (C≡C), 1669, 977 (*trans*-2-olefin), and 721 (*cis*-8-olefin) cm.$^{-1}$.

N-*Isobutyldeca*-trans-2,trans-8-*dien*-6-*ynamide.*—The acid chloride, b. p. 126—130°/4 mm., prepared from deca-*trans*-2,*trans*-8-dien-6-ynoic acid (2·38 g.), thionyl chloride (5·55 g.), and pyridine (2 drops), was added to an excess of ethereal isobutylamine. Working up as above gave crystals (2·18 g.) which recrystallised from light petroleum (b. p. 60—80°), to give N-*isobutyldeca*-trans-2,trans-8-*dien*-6-*ynamide* (1·72 g.), needles, m. p. 105—107° (Found: C, 76·75;

H, 9·7; N, 6·3%), $\lambda_{max.}$ 225 mμ (ε 25,300), inflexion at 235 mμ (ε 20,700), $\nu_{max.}$ 3300, 3096, 1626, 1550 (monosubstituted amide), 2232 (C≡C), 1669, 975 (*trans*-2-olefin), and 955 (*trans*-8-olefin) $cm.^{-1}$.

N-*Isobutyldeca*-trans-2,cis-6,cis-8-*trienamide*.—Lindlar catalyst (900 mg.) and freshly distilled quinoline (65 mg.) were stirred in light petroleum (b. p. 80—100°, 100 ml.) under hydrogen until no more gas was absorbed. *N*-Isobutyldeca-*trans*-2,*cis*-8-dien-6-ynamide (926 mg.) was then added and 1·00 mol. of hydrogen was taken up against slight negative pressure in 54 min. Absorption was by then very slow. The product was filtered through kieselguhr and the filtrate was evaporated, dissolved in ether, washed, dried, and again evaporated. The oil [920 mg., $\lambda_{max.}$ 228 mμ (ε 24,300)] was distilled to give N-*isobutyldeca*-trans-2,cis-6,cis-8-*trienamide*, b. p. 120—125°/10^{-3} mm., n_D^{21} 1·5090 (Found: C, 75·15, 75·5; H, 10·35, 10·85; N, 6·4, 6·3. $C_{14}H_{23}NO$ requires C, 75·95; H, 10·45; N, 6·35%). On microhydrogenation the trienamide absorbed 2·97 mol. of hydrogen to give *N*-isobutyldecanamide, m. p. and mixed m. p. 37—38° (and infrared comparison).

Several attempts to stereomutate the *trans*-2,*cis*-6,*cis*-8-amide in light petroleum with iodine as catalyst failed at 20°. However, thermal stereomutation in the presence of iodine (170—200°) gave *N*-isobutyldeca-*trans*-2,*trans*-6,*trans*-8-trienamide, plates [from light petroleum (b. p. 60—80°)], m. p. 91—92° (dimorphic change to needles at approx. 80°),[3,7] $\lambda_{max.}$ 226 mμ (ε 36,400), $\nu_{max.}$ 3300, 3096, 1626, 1550 (monosubstituted amide), 1669, 987 (*trans*-2-olefin with out-of-plane vibration of *trans*-6,*trans*-8-diene on top of that of the *trans*-2-linkage: the diene stretching vibrations are weak) $cm.^{-1}$ [lit.,[7] m. p. 91·5—92·5°, $\lambda_{max.}$ 228·5 mμ (ε 37,150)].

N-*Isobutyldeca*-trans-2,cis-6,trans-8-*trienamide*.—*N*-Isobutyldeca-*trans*-2,trans-8-*dien*-6-*ynamide* (195 mg.) was partially hydrogenated in light petroleum (b. p. 80—100°) (25 ml.) over Lindlar catalyst (145 mg.). Absorption of 1 mol. of hydrogen took 8 min. The mixture was worked up to give an oil which crystallised at 0° in rosettes of needles. It was distilled, b. p. 120°/3 × 10^{-3} mm., n_D^{22} 1·5058. The distillate at once crystallised: it softened at 21°, finally melting at 26°. *N*-Isobutyldeca-*trans*-2,*cis*-6-,*trans*-8-trienamide (Found: C, 75·9; H, 10·25; N, 6·2%) had $\lambda_{max.}$ 227 mμ (ε 29,200). Jacobson gives m. p. 23°, b. p. 157°/0·26 mm., n_D^{25} 1·5134, $\lambda_{max.}$ 228·5 mμ (ε 33,700).[4] The infrared spectra of the synthetic amide and natural affinin were superimposable: the synthetic *trans*-2,*cis*-6,-*cis*-8-trienamide is easily distinguishable. Thermal stereomutation of the *trans*-2,*cis*-6,*trans*-8-trienamide gave the all-*trans*-stereoisomer, m. p. 91—92° (and mixed m. p. with the specimen above). Microhydrogenation gave *N*-isobutyldecanamide, m. p. and mixed m. p. 38°.

When tested against *Tenebrio molitor*, *N*-isobutyldeca-*trans*-2,*cis*-6,*trans*-8-trienamide was rather more toxic than the *trans*-2,*cis*-6,*cis*-8. As expected,[14,15] the two dienynes (*trans*-2,-*trans*-8- and *trans*-2,*cis*-8- VI; R = $NHBu^i$) were almost non-toxic.

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