# **121.** *Rearrangements of Aldoximes into Amides with Raney Nickel. Stereoisomeric Geranamides.*

By A. G. Caldwell and E. R. H. Jones.

When the oximes of tetrahydrocitral, citronellal, and citral are heated with Raney nickel, the corresponding amides are obtained in yields of 70, 50, and 40% respectively. From citraloxime, two crystalline *geranamides* are formed and these are readily separated by chromatography. Since they both yield α-*cyclo*geranamide (III) on boiling with dilute acid and both give high yields of acetone on ozonolysis, they are formulated as geometrical isomerides of the *iso*propylidene structure (I).

While studying the hydrogenation of aldoximes using a Raney nickel catalyst, Paul (*Bull. Soc. chim.*, 1937, **4**, 1116) noted the formation of small amounts of the amides of the corresponding acids. Further investigation established that the oximes of saturated aldehydes are practically quantitatively isomerised into amides on heating

$$\mathrm{R{\cdot}CH{:}NOH \longrightarrow R{\cdot}CO{\cdot}NH_2}$$

with Raney nickel at about 100°. Bryson and Dwyer (*J. Proc. Roy. Soc., New South Wales*, 1941, **74**, 471) have provided evidence for Paul's suggestion that the reaction proceeds *via* an aldoxime–nickel complex, the rearrangement of which is promoted by traces of iron or aluminium.

Under Paul's conditions the oximes of tetrahydrocitral and citronellal give the corresponding amides in yields of 70 and 50% respectively. In the latter case much charring occurs, some citronellal is produced, and it would appear that undesirable interaction takes place between the catalyst and the ethylenic linkage present in the aldoxime. This effect is still more pronounced with the doubly unsaturated citraloxime, the yields of amide being usually only about 40%. Attempts to eliminate side reactions by the use of solvents did not appear promising, much smaller conversions being obtained in boiling alcoholic and toluene solutions.

No amide of geranic acid has hitherto been described in the literature. The product of the above isomerisation was an oil, but it readily deposited some crystalline *geranamide*-I, m. p. 69—70°, from light petroleum solution. The material remaining in the mother liquors was originally partially resolved into its components by fractional distillation, but this method was laborious and extremely inefficient. Chromatography on alumina readily effected a separation of the amide mentioned above from an isomeric *geranamide*-II, m. p. 63—64°, and a repetition of the process on the liquid intermediate fraction resulted in almost complete resolution of the mixture.

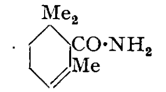
In the past the long-debated problem of the *iso*propylidene ($CMe_2{:}$) or *iso*propenyl ($CH_2{:}CMe{\cdot}$) structures of members of the terpene group has usually been complicated both by the non-crystalline nature of the open chain terpenes, and by the existence of geometrical isomerides. The isolation of these two crystalline geranamides is thus of considerable interest and four structural possibilities for these compounds had to be considered, *i.e.*, the *iso*propylidene and *iso*propenyl forms (I) and (II) and their respective geometrical isomerides.

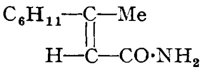
$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO{\cdot}NH_2$ (I.)

$CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO{\cdot}NH_2$ (II.)

Both geranamides were found to exhibit light absorption maxima at 2190 A., as would be expected of αβ-unsaturated amides; on refluxing with 2N-sulphuric acid, the known α-*cyclo*geranamide (III), m. p. 120—121°, was obtained in excellent yield from each isomer. From ozonolysis experiments, acetone 2 : 4-dinitrophenylhydrazone was isolated in identical yields of 84%;* in each case a trace (*ca.* 3%) of formaldehyde, estimated as the dimedon derivative, was also produced. The two amides must therefore be geometrical isomerides of structure (I), and it seems probable that, since citral is believed to consist mainly of the *cis*-isomer, citral-*a*, the more abundant geranamide-I may also be regarded as the *cis*-isomer (partial structure, IV). The light absorption intensities at the 2190 A. maxima of the two isomers are practically identical, no interconversions on irradiation are detectable, and differentiation on this basis is impossible. According to Henri and Errara (*Compt. rend.*, 1925, **180**, 2049) *trans*-isomers absorb more strongly than *cis*-isomers, but exceptions are known (Bruylants, *Bull. Acad. roy. Belg.*, 1927, **13**, 767; see also Castille, *ibid.*, 1930, **16**, 817).

(III.)





$$\begin{array}{c} C_6H_{11}{-}C{-}Me \\ \| \\ H{-}C{-}CO{\cdot}NH_2 \end{array}$$

(IV.)

It was hoped that, by hydrolysis of the individual geranamides, stereochemically pure samples of geranic acid might be obtained. With the boiling 10% alcoholic potassium hydroxide necessary for hydrolysis at a reasonable rate, isomerisation apparently occurs, giving an equilibrated geranic acid mixture from each isomer (cf. Bennett, Ramage, and Simonsen, *J.*, 1940, 418). From an incomplete hydrolysis of geranamide-I with 5% alkali, non-crystalline neutral material was recovered, indicating that isomerisation of the amide itself probably occurs under these conditions.

In view of the fact that the ozonolysis evidence cited above indicated that the isomeric geranamides both possess the *iso*propylidene configuration, further studies of these oxidation experiments were made. No variations in the yields were observed under different conditions and a similar (3%) yield of formaldehyde was obtained on ozonolysis of the saturated tetrahydrogeranamide for an equivalent time. It has long been known that saturated compounds are slowly attacked by ozone (Blair and Wheeler, *J. Soc. Chem. Ind.*, 1922, **41**, 303; 1924, **43**, 289; Briner and Meier, *Helv. Chim. Acta*, 1929, **12**, 529). Varying proportions of formaldehyde are produced on ozonolysis of terpenoid compounds, and the necessity and significance of quantitative determinations have been emphasised by Clemo and Macdonald (*J.*, 1935, 1294). More recently Stoll and Rouvé (*Helv. Chim. Acta*, 1944, **27**, 950), as a result of detailed investigations on the ozonolysis of ethyl oleate, have obtained evidence of the occurrence of oxidation of terminal carbon atoms. It is clear that the small amounts of formaldehyde produced in the present instance arise in all probability from the oxidation of terminal or side-chain methyl groups and have little significance in so far as evidence for the existence of the geranamides in the *iso*propenyl form (II) is concerned.

## EXPERIMENTAL.

*Rearrangement of Citronellaloxime to Citronellamide.*—The oxime, obtained from citronellal and hydroxylamine acetate in aqueous methyl alcohol, had b. p. 95—97°/4 mm., $n_D^{17°}$ 1·4750 (Semmler, *Ber.*, 1893, **26**, 2255, gives b. p. 135—136°/14 mm., $n_D$ 1·4763). A mechanically stirred mixture of citronellaloxime (20 g.) and Raney nickel (*ca.* 3 g.) was heated in a bath at 100—105° for 2 hours. After dilution with ether, the catalyst was removed by filtration through activated alumina, the ether was evaporated, and the residue crystallised from light petroleum (b. p. 40—60°). This gave the amide (8·1 g.) in large plates, m. p. 81·5—82·5°, a further quantity (1·9 g.) being obtained by distillation (b. p. 160—165°/16 mm.) of the material contained in the mother liquors (Wallach, *Annalen*, 1897, **296**, 125, and Tiemann, *Ber.*, 1898, **31**, 2902, give m. p. 82—83°).

*Tetrahydrogeranamide from Tetrahydrocitraloxime.*—A solution of citral (50 g.) in alcohol (350 c.c.) was shaken with hydrogen, under 11 atmospheres pressure, and palladium on calcium carbonate (25 g.; 10%) until absorption ceased (cf. Paal, D.R.P. 298,193; Rydon, *J.*, 1939, 1544). This gave tetrahydrocitral (30 g.), b. p. 82—84°/15 mm., $n_D^{17°}$ 1·4285, giving no colour with tetranitromethane. The semicarbazone had m. p. 88—88·5° [for *d*-tetrahydrocitral, Sabetay and Bléger (*Bull. Soc. chim.*, 1928, **43**, 843) give $n_D^{17°}$ 1·4273, semicarbazone, m. p. 78—79°; Suzucki (*Chem. News*, 1929, **139**, 153) gives $n_D^{21°}$ 1·4253, semicarbazone, m. p. 78°. Rupe and Giesler (*Helv. Chim. Acta*, 1928, **11**, 665) report that the semicarbazone of *dl*-tetrahydrocitral has m. p. 92—93°]. The oxime, prepared in the usual way, had b. p. 101—102°/4 mm., $n_D^{18°}$ 1·4531.

A mixture of tetrahydrocitraloxime (7·8 g.) and Raney nickel (*ca.* 1 g.) was stirred and heated in a bath at 110—120° for 2 hours. The product was freed from catalyst as described above; crystallisation from light petroleum (b. p. 60—80°) gave tetrahydrogeranamide (5·6 g.) in large glistening plates, m. p. 108—109° (Wallach, *Annalen*, 1897, **296**, 128, gives m. p. 108—109°).

*Isomeric Geranamides from Citraloxime.*—The oxime, prepared in aqueous methyl alcohol with hydroxylamine acetate, had b. p. 110—114°/4 mm., $n_D^{13°}$ 1·5186 (Tiemann and Semmler, *Ber.*, 1893, **26**, 2716, give b. p. 143—145°/12 mm., $n_D^{20°}$ 1·5143). A well stirred mixture of citraloxime (20 g.) and Raney nickel (*ca.* 3 g.) was heated in a bath at 115—120°

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* The use of the iodometric method of acetone estimation as developed by Kuhn and Roth (*Ber.*, 1932, **65**, 1284) gives higher yields; in this case they would probably be over 95%.

for 2 hours. The catalyst was separated as described above; its complete removal is absolutely essential, otherwise extensive decomposition occurs on distillation. The product was distilled giving citral, b. p. 70—80°/4 mm., citraloxime, b. p. 110—120°/4 mm., and then a mixture of isomeric geranamides (9·9 g.) as a colourless oil, b. p. 130—132°/4 mm. An attempt to moderate the reaction by carrying it out in boiling toluene (80 c.c.) gave only 3·8 g. of the geranamide mixture.

On dissolving the mixed amides (38 g.) in light petroleum (35 c.c.; b. p. 40—60°) and keeping at 0° for 20 hours, *geranamide*-I (6·7 g.) separated in long needles, m. p. 69—70° (Found: C, 71·85; H, 10·25; N, 8·75. $C_{10}H_{17}ON$ requires C, 71·95; H, 10·25; N, 8·4%). Light absorption in alcohol: Maximum, 2190 A.; log $\epsilon$ = 4·19.

The mother liquors were evaporated, the residue was dissolved in light petroleum (300 c.c.; b. p. 60—80°) and adsorbed on a 75 × 1·5 cm. column of " Birlec " alumina. Two faint yellow bands were observed at the bottom of the column. Elution was effected with benzene, 50 c.c. portions of eluate being collected and evaporated to dryness. From the early fractions an oil (*ca.* 5 g.), probably citraloxime, was obtained, but after the yellow bands had been washed off the residue solidified readily on standing. Elution with benzene was continued until the material being eluted failed to crystallise. The solid fractions so far obtained were combined and crystallised from light petroleum (b. p. 40—60°) to give *geranamide*-II (2·6 g.) as large glistening plates, m. p. 63—64° (Found: C, 71·7; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·95; H, 10·25%). Light absorption in alcohol: Maximum, 2190 A.; log $\epsilon$ = 4·21.

Elution with benzene was continued and eventually the material removed from the column again crystallised on standing. A benzene–chloroform mixture (1 : 1) was later employed. The combined solid fractions, on crystallisation from light petroleum (b. p. 40—60°), gave 8·5 g. of geranamide-I, m. p. 69—70°.

The intermediate non-crystallising portions were combined and rechromatographed giving further quantities of the pure isomers, the final yields from 38 g. of mixed amides being 21·4 g. of geranamide-I and 5·1 g. of geranamide-II.

*Ozonolysis of Geranamide*-I.—Geranamide-I (1·0 g.) was dissolved in " AnalaR " acetic acid (40 c.c.) (on which a completely satisfactory blank determination had been carried out) and ozonised oxygen was passed in until ozonolysis was complete (5 hours), the issuing gases being passed into water. The acetic acid solution was mixed with the wash water and the resulting solution was divided into two equal portions. (*a*) Water (50 c.c.) was added and, after being warmed until a clear solution was obtained, the mixture was distilled in steam. The steam distillate was collected in 5 c.c. portions, each of which was treated with 2 : 4-dinitrophenylhydrazine sulphate. The first two fractions yielded a heavy orange precipitate, which on crystallisation from aqueous methyl alcohol gave acetone 2 : 4-dinitrophenylhydrazone (600 mg.; 84% of theoretical), m. p. 123—125°, undepressed on admixture with an authentic specimen. (*b*) The second portion was dropped into boiling water (50 c.c.) and zinc dust (7 g.) in a distillation flask. The volatile products were passed into a saturated aqueous solution of dimedon and the solution was kept overnight. The precipitate of fluffy needles (30 mg.; 3% of theoretical) was separated and crystallised from aqueous methyl alcohol, from which the formaldehyde dimedon derivative crystallised in long needles, m. p. 187—188°, undepressed on admixture with an authentic specimen.

A similar yield of the formaldehyde dimedon derivative was obtained on ozonolysis of tetrahydrogeranamide under identical conditions.

*Ozonolysis of Geranamide*-II.—The amide (1·0 g.) was treated with ozonised oxygen exactly as described above for the first isomer. The yield of acetone 2 : 4-dinitrophenylhydrazone was 600 mg. (84%), and that of the formaldehyde dimedon derivative was 40 mg. (4% of theory).

*Alkaline Hydrolysis of the Amides.*—(a) Geranamide-I (3 g.) was refluxed with alcoholic potassium hydroxide (60 c.c.; 10%) for 16 hours giving geranic acid (2·8 g.), b. p. 90—92°/2 mm. This was split arbitrarily on a second distillation into several fractions which had $n_D^{20°}$ in the range 1·4782—1·4792 (Barbier and Bouveault, *Bull. Soc. chim.*, 1896, **15**, 1002, give b. p. 157·5°/18 mm., $n_D$ 1·4836; Bennett, Ramage, and Simonsen, *loc. cit.*, give the following values for the acid from different sources: $n_D^{25°}$ 1·4839, 1·4725—1·4783, 1·4988). Attempts to convert the geranic acid into pure crystalline derivatives were unsuccessful.

Hydrolysis of geranamide-I (2 g.) with boiling alcoholic potassium hydroxide (40 c.c.; 5%) was incomplete after 16 hours and the recovered neutral portion (1·1 g.) could not be induced to crystallise.

(b) When geranamide-II (1 g.) was hydrolysed by boiling with alcoholic potassium hydroxide (20 c.c.; 10%) for 16 hours, the geranic acid (0·9 g.) so obtained had b. p. 150°/18 mm., $n_D^{20°}$ 1·4779, and failed to yield any crystalline derivatives.

*Cyclisation of the Isomeric Geranamides.*—(a) Geranamide-I (1·9 g.) was heated under reflux with sulphuric acid (25 c.c.; 2N.) for 16 hours; on cooling, the insoluble oil crystallised. The product was separated with ether and on crystallisation from aqueous methyl alcohol gave α-*cyclo*geranamide (1·5 g.; 80%), m. p. 120·5—121°, undepressed on admixture with an authentic specimen (Barbier and Bouveault, *Bull. Soc. chim.*, 1896, **15**, 1003, and Bouveault, *ibid.*, 1910, **7**, 352, give m. p. 120—121°).

(b) Geranamide-II (100 mg.) under similar conditions gave 80 mg. of α-*cyclo*geranamide, m. p. 120—121°, undepressed on admixture with an authentic specimen.

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