A NEW PHOTOCHEMICAL REACTION: THE STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF ATISINE[1]

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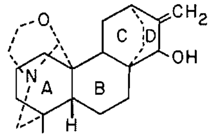
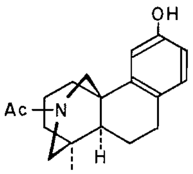
ABSTRACT

Irradiation of azides of diterpenoid acids with 1α- and 1β-carboxyl groups gave the corresponding isocyanates and ca. 25% yields of lactams. The azide of hexanoic acid under comparable conditions gave 8% of hexanamide. The reaction has been used to convert podocarpic acid to the enantiomer of the phenol III derived from atisine. This completes the structure proof of the atisine family of alkaloids, the Garrya alkaloids, and related diterpenes, and proves the absolute stereochemistry of these substances.

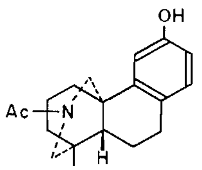
There is extensive evidence that the alkaloid atisine contains the features shown in rings B, C, and D of formula I (2, 3, 4). The evidence for the structure of ring A and the nitrogen-containing bridge was indirect, resting on the products of selenium dehydrogenation and superficial oxidation (3, 4) and on interpretation of n.m.r. spectra (3). Considerable evidence had been obtained for the relative and absolute stereochemistry shown in I (2, 3, 4). Very recently interrelation of the Garrya alkaloids, steviol, and kaurene, and extensive rotatory dispersion observations have provided confirmation of this absolute stereochemistry (5). However, since the structure of steviol and kaurene have not been rigorously proved, the ring A and hetero ring structure needed confirmation. We have now provided very direct proof of the correctness of the structure and absolute stereochemistry shown in I by partial synthesis of the N-acetyl phenol II from podocarpic acid. This proved to be the mirror image of the N-acetyl phenol III, which had been prepared earlier from atisine (2).



I



II



III

For partial synthesis of II a method was sought of substituting the angular methyl (C-17) of resin acid derivatives. A very direct possibility of doing this and immediately forming the heterocyclic system IV common to all diterpenoid alkaloids of known structure suggested itself. Thermal decomposition of acid azides leads via electron-deficient nitrogen to the isocyanate. It seemed possible that if the intermediate were generated in close proximity to a saturated carbon the nitrene or diradical might substitute this carbon. We were encouraged in this conception by the report of attack of thermally generated nitrenes from aryl azides on methyl groups, giving rise to heterocyclic rings (6), i.e. V → VI (after oxidative aromatization).

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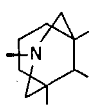
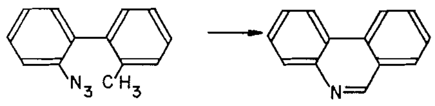
[1] *Issued as N.R.C. No. 6791.*
A preliminary report of some of this work has been published (1).

[2] *N.R.C. Postdoctorate Fellow 1960–1962.*



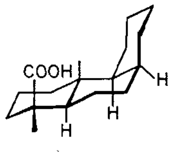
IV



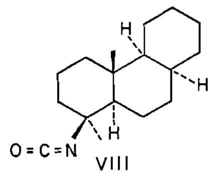
V VI

It seemed probable that the chance of attack on saturated carbon in the case of acid azides would be increased if the energy for decomposition was supplied by ultraviolet irradiation. Not only might the electron-deficient nitrogen then be more energetic, but it might be in a different electronic state (triplet rather than singlet), thus enabling the substitution reaction to compete favorably with the rearrangement.[3]

Previous work on the photolysis of acid azides had shown that isocyanates were produced as in the thermal reaction (7). It thus appeared imperative to have the saturated carbon exceptionally close to the electron-deficient nitrogen if we were to observe the desired reaction. We hence chose for study the azide of the trans-anti-cis acid VII available to us from other work (8). In this acid, ring C should provide steric compression of the angular methyl group, forcing it unusually close to the axial carboxyl.

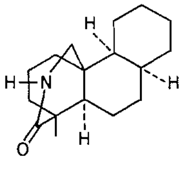


VII

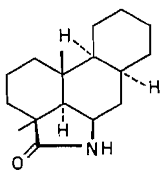


VIII

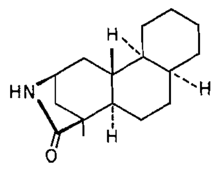
The azide of VII was prepared via the acid chloride and hydrazide. Because of its sensitivity it was not isolated, but merely characterized by its infrared absorption at 2145 and 1700 cm^{-1}. When a dry hexane solution of this was refluxed for 1 hour only the corresponding isocyanate VIII was produced. When the same solution was irradiated in a 1-cm quartz cell using a Hanovia ultraviolet lamp, at room temperature, there was steady evolution of nitrogen. After completion of the reaction the products were separated using chromatography on alumina. The isocyanate VIII, which was the main product (65%), was very readily eluted. The more strongly adsorbed products were a δ-lactam (9) ($\nu_{\max}^{\mathrm{CHCl_3}}$ 1665 cm^{-1}), in 25% yield, and a trace of γ-lactam (10) ($\nu_{\max}^{\mathrm{CHCl_3}}$ 1685 cm^{-1}), both of which gave correct analyses for $C_{18}H_{27}NO$. The δ-lactam could unambiguously be assigned the desired structure IX since the n.m.r. signal for the angular methyl group (C-17) which appeared at $\tau = 9.03$ in the spectrum of the parent acid and $\tau = 9.09$ in that of the hydrazide was missing from its spectrum (n.m.r. spectra of carbon tetrachloride solutions with tetramethylsilane as internal standard). The γ-lactam was either



IX



X



XI

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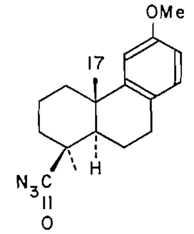
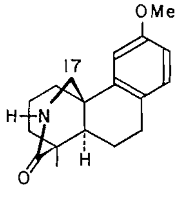
[3] *The rearrangement most likely involves migration of the alkyl group with its full complement of electrons, and hence requires a singlet state of nitrogen (nitrene).*

X or XI, but insufficient evidence was available to distinguish between these possibilities.

In order to pursue the potentialities of the substitution and to assess the importance of the steric compression discussed above we next examined the azide of the methyl ether of podocarpic acid (XII). With the flattened ring C, this should have the methyl and carboxyl functions at a more normal 1,3 diaxial distance. The photolysis of XII in hexane proceeded smoothly. To our surprise a 25% yield of a mixture of lactams was again produced. The δ-lactam which predominated crystallized on the walls of the photolysis cell. It analyzed for $C_{18}H_{23}NO_2$ and had ν_{max}^{nujol} 1655 cm^{-1}. Since the high-field signal expected for an angular methyl group (C-17) was absent from its n.m.r. spectrum it clearly had structure XIII. A 5% yield of γ-lactam (ν_{max}^{nujol} 1695 cm^{-1}) was also produced.

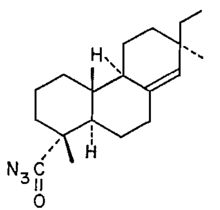


XII

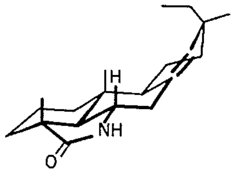


XIII

In order to examine the reaction under conditions where only secondary carbon could be substituted the azide (XIV) from dihydropimaric acid was prepared. When this was irradiated in hexane a lactam again crystallized on the walls. This analyzed for $C_{20}H_{31}NO$ and had $\nu_{max}^{CHCl_3}$ 1685 (γ-lactam). In view of the geometric limitations this can only be XV. The yield was similar (26%) to that in the methyl substitution. The reaction thus provides a new[4] and potentially valuable method for introducing substituents on ring B of the resin acids.



XIV



XV

Finally, in an attempt to observe the proportion of γ- and δ-lactams formed when equivalent methylenes were available for substitution, the azide of hexanoic acid was irradiated. An 8% yield of hexanamide was produced, probably by hydrogen abstraction from the solvent. The other products besides isocyanate were a complex mixture, which will be the object of further study.

As discussed by Smolinsky for the thermal decomposition of aryl azides (4, 11) the photolysis of acid azides could involve the singlet nitrene XVI or the corresponding

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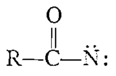
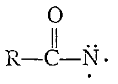
[4] *Chromic acid oxidation has been used to place oxygen on ring B of resin acids with an aromatic ring C (12), and in the case of one pimaric acid isomer (Ukita's acid) (13) selenium dioxide has been used to introduce oxygen on C-9.*

triplet diradical XVII (unpaired spins of two of the unshared electrons). He produced evidence for the triplet character of the nitrogen in the thermal reaction (11).



$$R-\overset{O}{\overset{\|}{C}}-\ddot{N}:$$

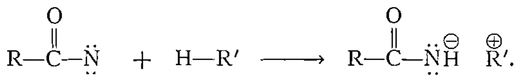
XVI



$$R-\overset{O}{\overset{\|}{C}}-\underset{\cdot}{\ddot{N}}\cdot$$

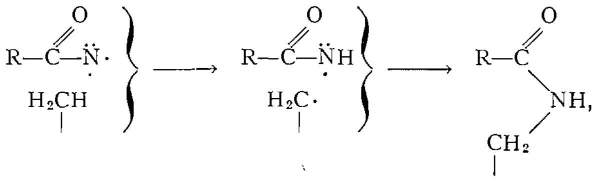
XVII

We consider that the formation of the hexanamide from the azide proves the diradical nature of the nitrogen doing the hydrogen abstraction in this photolysis. Had the nitrene state done the hydrogen abstraction the first stage would be as in (*a*):



$$R-\overset{O}{\overset{\|}{C}}-\underset{\cdot\cdot}{\ddot{N}} + H-R' \longrightarrow R-\overset{O}{\overset{\|}{C}}-\underset{\cdot\cdot}{\overset{\cdot\cdot\ominus}{N}}H\ \ \overset{\oplus}{R'}. \qquad (a)$$

The charged particles in the non-polar solvent would form an ion pair which would collapse to uncharged RCONHR′. While it seems probable by analogy that the lactam formation also involves a triplet nitrogen as shown:



the product could equally well arise from nitrene as in (*a*) or by insertion of nitrene into the C—H bond. An attempt to decompose the azide of dihydropimaric acid by energy transfer from triplet benzophenone (14), and hence get information about the mechanism, produced no change in product ratio or yield over photolysis without the benzophenone.

This reaction takes its place with the Hofmann–Loffler–Freytag reaction (15, 16) and the recently developed photolysis of aliphatic azides (17) as a means of forming nitrogen-containing rings by substitution on saturated carbon. The latter two reactions seem to preferentially form pyrrolidine rather than piperidine rings (six-membered cyclic transition state for hydrogen abstraction). The formation predominantly of piperidone in the compounds with a 1β-carboxyl when two possibilities for pyrrolidone formation were present is remarkable. This is particularly so if hydrogen is abstracted as hydride ions or hydrogen atoms, since this should be easier from secondary than from primary carbon. The proximity of the 1β-carboxylic function and the angular methyl is the most probable cause of this preferential δ-lactam formation.

With lactam XIII readily available we were now in a position to synthesize phenol II. Hydrolysis of XIII with hot constant-boiling hydrobromic acid gave the phenolic lactam, which was then reduced by lithium aluminum hydride in refluxing dioxane to the secondary aminophenol. This was acetylated, then partially hydrolyzed to the N-acetyl phenol II. This melted at 279–280° and its infrared spectrum (nujol mull) was identical with that of the N-acetyl phenol from atisine (2). However, its rotation was +112°, compared to −105° for the atisine degradation product. This proves decisively that the latter is correctly represented by III and that atisine has the structure and stereochemistry illustrated in I. Since podocarpic acid has been synthesized (18), this work opens a way to total synthesis of the mirror images of diterpenoid alkaloids.

EXPERIMENTAL

Rotations were of ethanol solutions, infrared spectra were of Nujol mulls, unless otherwise stated, and melting points were taken on a Kofler hot stage.

Azide of VII

1β-Carboxy-1α,12β-dimethyl-*trans*-anti-*cis*-perhydrophenanthrene (8) (850 mg) in dry ether (25 ml) and pyridine (3 drops) was allowed to react with thionyl chloride (2 ml) for 2 hours at room temperature. The precipitated pyridine hydrochloride was removed by filtration and the solution evaporated *in vacuo*, yielding a pale yellow oil (870 mg) which crystallized on standing. This product showed infrared absorption at 1795 cm^{-1} (acid chloride) but none at 1695 cm^{-1} (COOH). The acid chloride was readily hydrolyzed to the parent acid.

The acid chloride (800 mg) in ether (50 ml) was added to 100% hydrazine hydrate (2 ml) in absolute ethanol (10 ml) at 0° C. The mixture was vigorously shaken for 3 minutes, poured into water, and extracted with ether. The ether extract was washed well with water, dried, and evaporated, yielding a crystalline product forming colorless needles (780 mg) from ether/*n*-hexane, m.p. 160°, $[\alpha]_D$ +47° (*c*, 0.34). Found: C, 73.14; H, 10.71; N, 10.28. Calc. for $C_{17}H_{30}N_2O$: C, 73.33; H, 10.86; N, 10.06. Infrared spectrum: ν_{max} 3400 cm^{-1}, 1600 cm^{-1} (amide).

The above hydrazide (500 mg) was dissolved in acetic acid (20 ml) and cooled to 0° C. A saturated solution of sodium nitrite (250 mg) in water was added and the mixture vigorously shaken for 1 minute. The mixture was diluted with water and extracted several times with *n*-hexane. The extract was washed with ice-cold water, 5% sodium bicarbonate, and water again, then dried with anhydrous sodium sulphate. The infrared spectrum of this hexane solution showed absorption at 2145 cm^{-1} and 1700 cm^{-1} (acid azide).

Photolysis of the Azide of VII

The hexane solution of the azide was irradiated using a Hanovia ultraviolet lamp, at room temperature, in a 1-cm quartz cell. The photolysis cell had a capacity of ca. 150 ml and was fitted with a circulating device. A similar quartz cell, through which cold water was passed, was placed between the light source and the photolysis cell to keep the reaction cool. A steady evolution of nitrogen was observed and the disappearance of the azide bands in the infrared spectrum was complete after 6 hours. The reaction mixture was evaporated, yielding a pale yellow oil (260 mg) which was chromatographed on alumina (Grade IV, 7 g) in hexane. The following fractions were obtained.

Eluant	Fraction No.	Wt. (mg)	Infrared indicates
Hexane	1, 2	163	Isocyanate
Hexane/benzene (70/30)	3–5	5	γ-Lactam
Benzene/chloroform (30/70)	10–15	62	δ-Lactam

The isocyanate (VIII) was sublimed at 90° at 10^{-4} mm, yielding colorless prisms, m.p. 64–66°, $[\alpha]_D$ +36°, (*c*, 1.07). Found: C, 78.26; H, 10.39; N, 5.56. Calc. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Infrared spectrum: ν_{max} 2250 cm^{-1} (isocyanate).

The next eluted product was the γ-lactam (X or XI), m.p. 182°, $[\alpha]_D$ +27° (*c*, 0.33), forming colorless needles from ethanol. Sublimation at 170° at 10^{-4} mm yielded the analytical sample. Found: C, 78.38; H, 10.13. Calc. for $C_{17}H_{27}ON$: C, 78.11; H, 10.41. Infrared spectrum: ν_{max} 1680 cm^{-1} (γ-lactam). The more strongly absorbed δ-lactam (IX) was crystallized twice from ether/pentane and sublimed at 120° at 10^{-3} mm to yield colorless needles, m.p. 183°, $[\alpha]_D$ +23° (*c*, 2.02). Found: C, 78.37; H, 10.13; N, 5.25. Calc. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Infrared spectrum: ν_{max} 3200 cm^{-1} ($>$NH), 1650 cm^{-1} (δ-lactam); 1665 cm^{-1} in CCl_4.

Thermal Rearrangement of the Azide of VII

The hexane solution of the azide from a comparable run was refluxed for 1 hour, cooled, and evaporated to yield quantitatively the isocyanate (VIII) described above.

Photolysis of O-Methyl Podocarpic Acid Azide (XII)

A hexane solution of this azide (XII) was readily prepared using the previous procedure. The hydrazide prepared during this sequence readily crystallized from ethyl acetate as colorless needles, m.p. 166°, $[\alpha]_D$ +124° (*c*, 0.38). Found: C, 71.39; H, 8.62; N, 9.51. Calc. for $C_{18}H_{26}O_2N_2$: C, 71.49; H, 8.67; N, 9.26. Infrared spectrum: ν_{max} 3350 cm^{-1} ($>$NH), 1615 cm^{-1} (amide), 1600 cm^{-1} and 1560 cm^{-1} (aromatic).

A hexane solution of XII (ν_{max} 2150 cm^{-1} and 1700 cm^{-1}) from 1 g of hydrazide was irradiated as described for VII. After 2 hours a colorless crystalline product was observed forming on the windows of the photolysis cell. After 16 hours the disappearance of the azide absorption was observed in the infrared spectrum of the solution. The hexane solution was decanted and chromatographed on alumina (Grade IV). The isocyanate was eluted with hexane as a colorless oil (500 mg) which slowly crystallized. Sublimation at 80° at 10^{-3} mm gave colorless prisms, m.p. 62°, $[\alpha]_D$ +89° (*c*, 1.32). Found: C, 75.93; H, 8.10; N, 5.05. Calc. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Infrared spectrum: ν_{max} 2260 cm^{-1} (isocyanate), 1600 cm^{-1} and 1560 cm^{-1} (aromatic). Elution with benzene/hexane (1/1) yielded a crystalline product (45 mg) forming needles from acetone, m.p. 284°. This was too insoluble for a rotation determination. Found: C, 75.92; H, 8.08; N, 4.88. Calc. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Infrared spectrum: ν_{max} 1695 cm^{-1} (γ-lactam), 1600 cm^{-1} and 1560 cm^{-1} (aromatic).

The product which crystallized on the window of the photolysis cell was collected and recrystallized from ethanol, yielding colorless prisms of XIII (190 mg), m.p. 274°, $[\alpha]_D$ +41° (*c*, 0.33). Found: C, 76.03; H, 8.14; N, 4.96; OMe, 10.80. Calc. for $C_{17}H_{20}NO(OMe)$: C, 75.75; H, 8.12; N, 4.91; OMe, 10.88. Infrared spectrum: ν_{max} 3300 cm^{-1} ($>$NH), 1655 cm^{-1} (δ-lactam), 1600 cm^{-1} and 1560 cm^{-1} (aromatic).

Thermal Rearrangement of XII

The hexane solution of the acid azide (XII) was refluxed for 1 hour and evaporated to yield quantitatively the isocyanate, $[\alpha]_D$ +89° (*c*, 0.73), described above.

Synthesis of Phenol II

A solution of the lactam (XIII) (200 mg), obtained from O-methyl podocarpic acid, in acetic acid (3 ml) and 48% hydrobromic acid (10 ml) was refluxed for 3 hours. The cooled mixture was evaporated to dryness *in vacuo*, yielding a colorless product (160 mg) which was crystallized from ethanol to yield needles, m.p. 347°. This was too insoluble for a rotation determination. Found: C, 74.97; H, 7.82. Calc. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Infrared spectrum, ν_{max} 3300 cm^{-1} ($>$NH), 3140 cm^{-1} (—OH), 1650 cm^{-1} (amide), 1600 cm^{-1} and 1560 cm^{-1} (aromatic).

The phenolic lactam (150 mg) was dissolved in hot dioxane (75 ml), and lithium aluminum hydride (100 mg) in ether (10 ml) was added at such a rate that the ether distilled off. The mixture was refluxed for 2 hours, cooled, and the excess lithium aluminum hydride was decomposed with ethereal methanol. Evaporation to dryness *in vacuo* yielded a colorless product, which was extracted several times with warm ethanol. The ethanol extract yielded a secondary amine (110 mg) which exhibited no infrared absorption in the carbonyl region but complex absorption in the 3500 cm^{-1}–3300 cm^{-1} region (amine + phenol).

This amine was dissolved in pyridine (5 ml) and acetic anhydride (5 ml). The solution was refluxed for 40 minutes, cooled, and poured into 2 *N* hydrochloric acid (50 ml). The product was extracted into ether. The ether solution was washed well with water and 2 *N* hydrochloric acid, dried, and evaporated, yielding a pale yellow oil (91 mg) which showed no absorption in the hydroxyl region of its infrared spectrum but had absorption at 1738 cm^{-1} (acetate) and 1610 cm^{-1} (amide). This product was dissolved in methanol (15 ml) and water (5 ml). Potassium hydroxide (10 ml, 5%) was added and the mixture refluxed for 3 minutes. The solution was cooled and extracted with ether. The aqueous layer was acidified with 2 *N* hydrochloric acid and extracted with chloroform. The chloroform extract was dried and evaporated to yield a crystalline residue (53 mg). Recrystallization from acetone gave small colorless prisms, m.p. 279–280°, $[\alpha]_D$ +112° (*c*, 0.45). Found: C, 76.40; H, 8.34. Calc. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. The infrared spectrum of this N-acetyl phenol (II) was identical with that of the phenol (III) obtained from the degradation of atisine.

Photolysis of Dihydropimaric Acid Azide (XIV)

A hexane solution of the above azide (XIV) was prepared using the described procedure. The hydrazide formed colorless needles from aqueous ethanol (900 mg), m.p. 156–157°, $[\alpha]_D$ 7° (*c*, 0.76). Found: C, 75.64; H, 10.60; N, 8.88. Calc. for $C_{20}H_{34}N_2O$: C, 75.42; H, 10.76; N, 8.80. Infrared spectrum: ν_{max} 3380 cm^{-1} ($>$NH), 1620 cm^{-1} and 1590 cm^{-1} (amide). The hexane solution of the acid azide prepared from this hydrazide (850 mg), which showed infrared absorption at 2130 cm^{-1} and 1700 cm^{-1}, was irradiated as described for VII. After 12 hours the disappearance of azide absorption was observed and the solution was then evaporated to dryness and chromatographed on alumina (Grade IV). Hexane eluted the isocyanate (520 mg) as a colorless oil, b.p. 130–140° at 10^{-4} mm. Found: C, 79.82; H, 10.48. Calc. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37. Infrared spectrum: ν_{max} 2245 cm^{-1} (isocyanate). The benzene eluates yielded a crystalline product, XV (153 mg), forming needles from aqueous methanol with m.p. 209°. The analytical sample sublimed at 162° at 10^{-4} mm as colorless prisms, m.p. 210°, $[\alpha]_D$ 7° (*c*, 0.9). Found: C, 79.82; H, 10.51; N, 4.81. Calc. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37; N, 4.65. Infrared spectrum: ν_{max} 3250 cm^{-1} ($>$NH), 1690 cm^{-1} and 1640 cm^{-1} (γ-lactam), 1685 cm^{-1} (in $CHCl_3$, γ-lactam). Dihydropimaric acid (250 mg) in hexane (150 ml) was unchanged after photolysis for 12 hours.

Photolysis of Hexanoic Azide

Hexanoyl chloride (2 g) in dioxane (25 ml) and sodium azide (2.5 g) in water (10 ml) were vigorously shaken for 5 minutes and extracted with cyclohexane. The organic layer was well washed with water, 5% sodium bicarbonate, and water again, then dried with anhydrous sodium sulphate. This solution, which exhibited infrared absorption at 2130 cm^{-1} and 1710 cm^{-1} (acid azide), was irradiated as described for VII during 12 hours. The only product that could be readily separated from the resulting mixture was the amide of hexanoic acid (230 mg), m.p. and mixed m.p. 99–100° after sublimation at 70° at 10^{-4} mm and having the requisite infrared spectrum. Found: C, 62.90; H, 11.23; N, 12.09. Calc. for $C_6H_{13}ON$: C, 62.57; H, 11.38; N, 12.16.

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