of the ionic strength, determined from a smoothed plot of the above data, is given in Table IV.

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COLUMBIA 1, SOUTH CAROLINA

# NOTES

## Long-chain Aliphatic Semicarbazides[1]

BY J. D. CHANLEY, STELLA KALICHSTEIN AND E. M. GINDLER

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We wish to report the synthesis of a few long-chain aliphatic semicarbazides: 4-pentadecyl- (I), 4-heptadecyl- (II), 4-octadecyl- (III) and 2-methyl-4-heptadecyl semicarbazide (IV). As far as we are aware there is no mention in the literature of any long-chain semicarbazides. The semicarbazone derivatives of ketones—obtained from them—are soluble in petroleum ether. This property may prove useful in the isolation of ketones. The combined hydrophilic and hydrophobic features of these semicarbazides render them suitable for spreading in monomolecular layers and present the possibility of employing them as carbonyl reagents at interfaces. The monomolecular film properties of these compounds and their derivatives, described below, have been investigated in these laboratories and will be the subject of a separate communication.

The syntheses of compounds I, II and IV were accomplished in good yield by the addition of anhydrous hydrazine in the first two cases and anhydrous methylhydrazine in the latter instance to the appropriate isocyanate. The reaction sequence is

$$\text{R—CO—Cl} \xrightarrow{\text{NaN}_3} \text{R—CO—N}_3 \xrightarrow{\Delta}$$

$$\text{R—N=C=O} \xrightarrow{\text{R}'\text{NHNH}_2} \text{RNHCONR}'\text{NH}_2$$

$\text{R} = \text{C}_{15}\text{H}_{31}$ (I) or $\text{C}_{17}\text{H}_{35}$ (II, IV); $\text{R}' = \text{H}$ (I, II) or $\text{CH}_3$ (IV)

The synthesis of 4-octadecyl semicarbazide (III) was accomplished, albeit in very poor yield, by the interaction of anhydrous hydrazine on the ethyl carbamate derivative of octadecylamine. The reaction sequence is

$$\text{R—NH}_2 \xrightarrow{\text{ClCOOEt}} \text{RNHCOOEt} \xrightarrow{\text{NH}_2\text{NH}_2} \text{RNHCONHNH}_2$$

$\text{R} = \text{C}_{18}\text{H}_{37}$ (III)

The monosubstituted semicarbazide reacted readily with aldehydes and ketones to give the corresponding semicarbazone derivatives in high yield. In contrast the disubstituted semicarbazide, compound IV, although reacting readily and in high yield with benzaldehyde, is very sluggish in its reactivity toward ketones. We were able, however, to obtain the cyclohexanone derivative. This difference in behavior toward ketones has previously been described by Evans and Gillam in the instance of semicarbazide and 2-methyl semicarbazide.[2] A comparison of the ultraviolet absorption spectra in 95% ethanol of the benzaldehyde derivative of compound II, $\lambda_{\max}$ 285 m$\mu$, $\epsilon_{\max}$ 19,500 and of compound IV, $\lambda_{\max}$ 293 m$\mu$, $\epsilon_{\max}$ 20,800, shows a shift to longer wave length of 8 m$\mu$, in the case of the 2-methyl-substituted semicarbazide. The same phenomenon has been observed by the above authors[2] for 2-methylsemicarbazone and semicarbazone derivatives of a variety of aromatic aldehydes.

### Experimental

All spectra were obtained in 95% ethanol with a Beckman spectrophotometer, Model DU.

Stearoyl and palmitoyl chloride were distilled before use. Octadecylamine, m.p. 53.2°, was obtained from Armour and Company, Chicago 9, Ill. The preparation of compounds I, II and IV was essentially the same and is illustrated in the instance of 4-heptadecylsemicarbazide. The isocyanates were prepared essentially according to the method given for the preparation of undecyl isocyanate,[3] except that it was found desirable to isolate the intermediate acid azide.

**4-Heptadecyl semicarbazide (II).**—To a well cooled (5–15°), vigorously stirred solution of sodium azide (3.31 g., 0.051 mole) in 22 ml. of water and 16 ml. of acetone a solution of stearoyl chloride (11 g., 0.037 mole) in 11 ml. of acetone was added at such a rate that the temperature remained between 5 and 15°. The mixture was stirred for approximately 45 minutes and the heavy white precipitate of the azide was removed by filtration, washed thoroughly with water and pressed dry; yield 17 g. The azide is quite stable and may be dried in a vacuum desiccator overnight over calcium chloride. The slightly wet azide was dissolved in benzene (125 ml.), dried overnight over sodium sulfate at 15°, filtered, refluxed for one hour, cooled in ice and 7 ml. of anhydrous hydrazine was added rapidly with hand swirling. The solid reaction product was removed by filtration, washed with benzene and water and dried overnight *in vacuo* over calcium chloride; yield 9.0 g., m.p. 90–95°. Three recrystallizations from ethanol or methanol gave 5 g. of pure material; m.p. 100–100.5°.

*Anal.* Calcd. for $\text{C}_{18}\text{H}_{39}\text{N}_3\text{O}$: C, 68.95; H, 12.54; N, 13.40. Found: C, 69.03; H, 12.12; N, 13.70.

**4-Pentadecylsemicarbazide (I)** prepared as above from palmitoyl chloride, etc., after recrystallization from methanol or ethanol, melted at 100–101°.

*Anal.* Calcd. for $\text{C}_{16}\text{H}_{35}\text{N}_3\text{O}$: C, 67.32; H, 12.36; N, 14.72. Found: C, 67.30; H, 12.06; N, 15.02.

**2-Methyl-4-heptadecylsemicarbazide (IV)** was prepared essentially according to the method given above with the following modifications. To the benzene solution of heptadecyl isocyanate, anhydrous methylhydrazine was added. Since the semicarbazide is soluble in benzene, dry HCl was passed into the benzene solution and the precipitated mixture of semicarbazide hydrochloride and methylhydrazine hydrochloride was collected, dissolved in ethanol and decomposed with an excess of dilute aqueous sodium hydroxide

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[1] This work was supported by a Grant-in-Aid from the Permanent Science Fund of the American Academy of Arts and Sciences to Dr. Harry Sobotka.

[2] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

[3] *Org. Syntheses*, **24**, 94 (1944).

solution. The free semicarbazide was collected by filtration and recrystallized from absolute ethanol; yield 60%, m.p. 83–84°.

*Anal.* Calcd. for $C_{19}H_{41}N_3O$: C, 69.72; H, 12.53; N, 12.84. Found: C, 69.46; H, 12.28; N, 12.80.

**Preparation of 4-Octadecylsemicarbazide (III). Ethyl Octadecylaminecarbamate.**—To a well stirred ice cold suspension of octadecylamine (13.5 g., 0.05 mole) in 125 ml. of ether, contained in a three-neck flask, ethyl chloroformate (2.7 g., 0.025 mole) in 15 ml. of ether was added over a period of 30 minutes. To this mixture a solution of sodium hydroxide (2 g. in 35 ml. of water) and a solution of ethyl chloroformate (2.7 g. in 15 ml. of ether) were added simultaneously over a period of 1.5 hours. The ice-bath was removed and the mixture allowed to react for a further hour, at the end of which time a clear ether layer was obtained. The ether layer was washed with 10% sodium carbonate, water, dried over sodium sulfate and evaporated to dryness. The residue 13.3 g., m.p. 66–67°, was recrystallized from ethanol and pure material (m.p. 67–68°) was obtained as plates, which changed to needles at 60°.

*Anal.* Calcd. for $C_{21}H_{43}NO_2$: C, 73.84; H, 12.68; N, 4.10. Found: C, 74.32; H, 12.60; N, 4.11.

A sealed tube containing 3.0 g. of the above carbonate, 0.43 ml. of anhydrous hydrazine and 5 ml. of absolute alcohol was heated over a period of 22 hours at 130°. The residue after removal of excess hydrazine and alcohol was treated with ether and the ether insoluble material, Compound III, 0.26 g., m.p. 102–103°, was collected and recrystallized from ethanol; m.p. 104–106°.

*Anal.* Calcd. for $C_{19}H_{41}N_3O$: C, 69.67; H, 12.62; N, 12.83. Found: C, 69.60; H, 12.20; N, 12.62.

Dry HCl was passed through the dried ether layer and the precipitated hydrochloride (0.6 g., m.p. 103–115°) yielded after many recrystallizations from ethanol a small amount of octadecylamine hydrochloride (m.p. 159–161°) and mixed melting point with an authentic sample (m.p. 162–163°) showed no depression.

*Anal.* Calcd. for $C_{18}H_{40}NCl$: N, 4.58. Found: N, 4.48.

The final ether solution, after washing with 10% NaOH, water and drying over sodium sulfate yielded on evaporation, 1.8 g. of the original carbamate (m.p. 67–68°).

All the derivatives listed below were prepared in essentially the same manner, except as indicated, and the procedure is illustrated by the following example.

**Heptadecylsemicarbazone of Benzaldehyde.**—A solution of heptadecylsemicarbazide (1.0 g., 0.003 mole) and benzaldehyde (0.67 g., 0.006 mole) in 25 ml. of methanol containing two drops of glacial acetic acid was heated for a short time on a steam-bath and allowed to stand overnight. The crystalline precipitate was recrystallized from methanol and melted at 79–79.5°, yield 1.0 g., $\lambda_{max}$ 285 m$\mu$, $\epsilon_{max}$ 19,500.

*Anal.* Calcd. for $C_{25}H_{43}N_3O$: C, 74.76; H, 10.79; N, 10.47. Found: C, 75.53; H, 11.00; N, 10.36.

The semicarbazone of benzaldehyde shows $\lambda_{max}$ 282 m$\mu$, $\epsilon_{max}$ 24,000.

**4-Pentadecylsemicarbazone of benzaldehyde** after recrystallization from ethanol melted at 73–74°.

*Anal.* Calcd. for $C_{23}H_{39}N_3O$: C, 73.95; H, 10.50; N, 11.25. Found: C, 74.03; H, 10.17; N, 10.90.

**2-Methyl-4-heptadecylsemicarbazone of benzaldehyde** after recrystallization from methanol melted at 100–101°, $\lambda_{max}$ 293 m$\mu$, $\epsilon_{max}$ 20,800.

*Anal.* Calcd. for $C_{26}H_{45}N_3O$: C, 75.13; H, 10.91; N, 10.11. Found: C, 75.51; H, 10.86; N, 10.31.

**Heptadecylsemicarbazone of Formaldehyde.**—The crude product was dissolved in ether, filtered from insoluble purity, and the ether residue recrystallized several times from methanol and dried *in vacuo* over $P_2O_5$. Five grams of compound IV yielded 2.5 g. of the pure semicarbazone derivative, m.p. 66–68°.

*Anal.* Calcd. for $C_{19}H_{39}N_3O$: C, 70.09; H, 12.08; N, 12.92. Found: C, 70.18; H, 11.79; N, 12.68.

The above material on hydrogenation in glacial acetic acid with platinum oxide as catalyst absorbed the equivalent of one mole of hydrogen. However, the sought-for 1-methyl-4-heptadecylsemicarbazide could not be isolated in any state of purity.

**4-Heptadecylsemicarbazone of cyclohexanone** after recrystallization from methanol melted at 66–67°, yield 80%.

*Anal.* Calcd. for $C_{24}H_{47}N_3O$: C, 73.23; H, 12.03; N, 10.67. Found: C, 74.03; H, 11.80; N, 10.40.

**4-Pentadecylsemicarbazone of cyclohexanone** after recrystallization from methanol melted at 62–63°.

*Anal.* Calcd. for $C_{22}H_{43}N_3O$: C, 72.27; H, 11.85; N, 11.49. Found: C, 71.98; H, 10.77; N, 11.47.

**2-Methyl-4-heptadecylsemicarbazone of Cyclohexanone.**—One gram of the semicarbazide (0.003 mole) and 0.58 g. of cyclohexanone (0.006 mole) in 10 ml. of ethanol containing 3 drops of glacial acetic acid were refluxed for a few minutes and allowed to stand overnight. The alcohol was removed by evaporation and the residue treated with petroleum ether, b.p. 40–60°. The insoluble starting material was removed and the filtrate after evaporation to a small volume yielded after cooling overnight in the ice-chest 250 mg. of the slightly yellow semicarbazone, m.p. 44–48°.

*Anal.* Calcd. for $C_{25}H_{49}N_3O$: C, 73.62; H, 12.12; N, 10.32. Found: C, 73.24; H, 12.09; N, 10.48.

**4-Heptadecylsemicarbazone of cholestenone** after recrystallization from ethyl acetate–methanol mixture melted at 78–80°, $\lambda_{max}$ 273.5 m$\mu$, $\epsilon_{max}$ 25,000.

*Anal.* Calcd. for $C_{45}H_{81}N_3O$: C, 79.46; H, 12.00; N, 6.18. Found: C, 79.10; H, 11.45; N, 6.45.

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## Alkaloid Biogenesis. IV. The Non-availability of Nicotinic Acid-Carboxyl-$C^{14}$ and its Ethyl Ester for Nicotine Biosynthesis[1]

BY R. F. DAWSON,[2] DAVID R. CHRISTMAN AND R. CHRISTIAN ANDERSON

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For reasons of structural analogy and biological ubiquity, nicotinic acid has been regarded as a possible precursor of the pyridine moiety of the Nicotiana alkaloids.[3] Attempts to secure analytical increases in nicotine content of excised tobacco leaves by feeding solutions of nicotinic acid through cut stems and the transpiration stream have yielded conflicting and inconclusive results.[4] In large part, this is due to the fact, recently demonstrated, that matured excised tobacco leaves do not possess the capacity to synthesize nicotine.[4] The synthetic ability of tobacco roots, on the other hand, has been repeatedly affirmed. This fact, together with the ability of excised tobacco roots to grow indefinitely in sterile culture and to produce nicotine at predictable rates under standard conditions have provided the basis for an isotopic test of the availability of nicotinic acid and its ethyl ester as precursors for nicotine biosynthesis.

### Experimental

**Nicotinic-$C^{14}$ Acid.**—Carboxyl-labeled nicotinic acid was prepared from 3-bromopyridine, *n*-butyllithium and $C^{14}O_2$,

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[1] Research carried out under the auspices of the U. S. Atomic Energy Commission.

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[3] E. Winterstein and G. Trier, "Die Alkaloide," 2nd Ed., Borntraeger, Berlin, 1931, pp. 1031.

[4] *Cf.* R. F. Dawson, "Advances in Enzymology," Interscience Publishers, Inc., Vol. 8, 1948, for review.