redistillate marihuana oil. Considering, accordingly, only the amounts of active principle which were recovered from hemp seeds after saponification of its chloroform extractives, hemp seeds would appear to possess about $^1/_{5000}$ the potency of the marihuana oil employed as standard of reference. This, according to our bio-assays of a great variety of cannabis tops, would signify that hemp seeds were about $^1/_{10}$ to $^1/_{30}$ as potent as the carefully ground and screened parts of dried cultivated tops from various (*e. g.*, Roumanian, Manchurian, Italian) varieties of *Cannabis sativa*, or $^1/_{30}$ to $^1/_{100}$ as potent as herbs from the illegitimate marihuana trade.

CONCLUSIONS

Qualitatively, these experiments give evidence of the presence of an active principle in hemp seeds which is similar in its pharmacological action to that of marihuana oil. Quantitatively, the value of potency found in the present preparation may help to explain why, in quite a number of attempts, we were unable to elicit "marihuana-like" action with less intricately prepared extracts from either total, or crushed, or defatted cannabis fruits, but this potency figure cannot be considered as conclusive with respect to the amount of active principle present in the starting material of our preparation. It is hardly more than a minimum value, and it is open for further investigation to determine how much of the active principle originally contained in the fruits may be lost in preparing this non-saponifiable fraction either by reasons of chemical destruction or due to insufficiencies of the procedures of fractionation.

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"Nothing would be done at all if a man waited till he could do it so well that no one could find fault with it."—John Henry Newman.

Alkyl Nitrites. VII

Synthesis of Some Organic Nitrites and Nitrates*

By Sylvan E. Forman, C. Jelleff Carr and John C. Krantz, Jr.

In the course of certain studies on the pharmacology of nitrites (1, 2, 3) and nitrates (4, 5), it was necessary to synthesize a number of organic compounds. We are reporting in this paper the data accumulated on the chemistry of these substances.

The nitrites were prepared from the corresponding alcohols and nitrous acid in the same manner as described for the preparation of 2-ethyl-*n*-hexyl-1-nitrite. Myristyl, cetyl and *n*-octadecyl alcohols were dissolved in diethyl ether before they were treated with nitrous acid. Nitrite nitrogen was determined in these compounds by the nitrometer method described for the assay of amyl nitrite in the U. S. Pharmacopœia X, page 49. In the analysis of myristyl, cetyl and octadecyl nitrites, the aqueous potassium iodide solution had to be replaced with potassium iodide solutions in 75 per cent ethanol, because of the greater insolubility of these nitrites in water.

Propyl, butyl and heptyl glycollates were prepared by fractionating mixtures of glycollic acid, benzene and a little sulfuric acid with an excess of the corresponding alcohol as in the description of the preparation of the propyl ester.

The nitrates were prepared in the manner described for the preparation of isoamyl lactate nitrate. In some cases it was necessary to pour the nitrating mixtures into ice water to obtain the product. These compounds were analyzed by the well-known modification of the Kjeldahl method which employs salicylic acid and sodium thiosulfate to reduce the nitrates.

In addition to the compounds listed in the experimental portion, the following were also prepared but the analyses indicated that they were not obtained pure: *n*-nonyl-

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1-nitrite, b. p. 63° C./2 mm.; 5-ethyl-*n*-nonyl-2-nitrite, b. p. 67° C./2 mm.; lauryl nitrite, b. p. 90° C./2 mm.; 7-ethyl-2-methyl-*n*-hendecyl-4-nitrite, b. p. 87° C./2 mm.; myristyl nitrite, b. p. 110° C./1 mm.; cetyl nitrite; heptyl glycollate nitrate, b. p. 146° C./17 mm.; glycerin 1, 3 diacetate-2-nitrate; pinite nitrate; adonitol pentanitrate; polygalitol tetranitrate; sorbitan tetranitrate. All of these compounds were liquids, but the last four were syrups.

EXPERIMENTAL

2-Ethyl-n-hexyl-1-nitrite.—One hundred and forty-three Gm. of 2-ethyl-hexan-1-ol were poured over 220 ml. of 6*N* hydrochloric acid and the mixture was cooled to 0° C. One hundred and ten Gm. of sodium nitrite in 550 ml. of water were added with stirring. The aqueous layer was separated from the upper layer which was dried with magnesium sulfate. The liquid distilled at 63° C./19 mm. The yield was 159 Gm. (91%), specific gravity $\frac{22°}{23°}$ C. 0.878./ml. in air. *Analysis.*—Calcd for $C_8H_{17}NO_2$: N, 8.80. Found: N, 8.69.

n-Octadecyl Nitrite.—The liquid was distilled at a pressure below 1 mm. between 138° and 144°. *Analysis.*—Calcd. for $C_{18}H_{37}NO_2$: N, 4.68. Found: N, 4.61, 4.66.

Isoamyl Lactate.—This compound has been synthesized by refluxing anhydrous lactic acid with isoamyl alcohol in the presence of sulfuric acid (6).

The material used in this research was prepared in the following manner: One mol of 85% lactic acid and 1 mol of isoamyl alcohol were mixed and saturated with dry hydrogen chloride. After three hours, the mixture was poured into water. The upper layer was separated and washed, first with water and then with sodium bicarbonate solution. The liquid was dried with magnesium sulfate. The fraction which distilled 96–100° C./23 mm. weighed 40 Gm. (25%).

Propyl Glycollate.—Schreiner first synthesized this compound from propyl chloroacetate and sodium glycollate (7).

The authors prepared it as follows: 76 Gm. of glycollic acid, 225 Gm. of *n*-propanol, 500 ml. of benzene and 2.5 ml. of concentrated sulfuric acid were mixed and fractionated slowly. About 500 ml. of the distillate were collected in 5 hours. The acid was neutralized with 10 Gm. of calcium carbonate and the liquid was fractionated. The material which distilled 74–75° C./20.5–21.5 mm. weighed 85 Gm. (71%).

Butyl Glycollate.—The yield from one mol of glycollic acid was 108.5 Gm. (81%) which distilled 87–88° C./20.5 mm.

Heptyl Glycollate.—The yield from 0.55 mol of glycollic acid was 57 Gm. (60%) which distilled 125–130° C./16–17 mm.

Isoamyl Lactate Nitrate.—Forty Gm. of isoamyl lactate were dissolved in 35 ml. of nitric acid (sp. gr. 1.5) which was kept cold in an ice bath. Fifty-five ml. of concentrated sulfuric acid were added slowly with stirring to prevent an excessive rise in temperature. The upper layer was separated from the acid and washed twice with water and once with sodium bicarbonate solution. The yield was dried with magnesium sulfate and fractionated. The material which distilled at 70° C./1 mm. weighed 33 Gm. (65%). *Analysis.*—Calcd. for $C_5H_{15}NO_5$: N, 6.83. Found: N, 6.78, 6.73.

Propyl Glycollate Nitrate.—Forty-eight Gm. of propyl glycollate yielded 43 Gm. (65%) of the nitrate which distilled 94–96° C./18.5–20 mm. *Analysis.*—Calcd. for $C_5H_9NO_5$: N, 8.59. Found: N, 8.30, 8.29, 8.40.

Butyl Glycollate Nitrate.—Thirty-nine Gm. of butyl glycollate yielded 37 Gm. (73%) of the nitrate which distilled 109.5–110° C./19–19.5 mm. *Analysis.*—Calcd. for $C_6H_{11}NO_5$: N, 7.91 Found: N, 7 74, 7.76, 7.83

Isomannide Dinitrate.—Fifty Gm. of isomannide yielded 45 Gm. (55%) of nitrate. The product was recrystallized from 95 per cent ethyl alcohol until it melted constantly at 65.5° C. *Analysis.*—Calcd. for $C_6H_8N_2O_8$: N, 11.86; C, 30.52; H, 3.41. Found: N, 11.54, 11.55; C, 30.44, 30.65; H, 3.45, 3.38.

Isosorbide Dinitrate.—Isosorbide dinitrate was prepared from the dianhydride of sorbitol which was prepared by dehydration of sorbitol with metaphosphoric acid in a manner analogous to the preparation of isomannide from mannitol.

Twenty Gm. of isosorbide yielded 27 Gm. (83%) of nearly pure nitrate, m. p. 50–51° C. One recrystallization from 95 per cent ethyl alcohol raised the melting point to 52° C. *Analysis.*—Calcd. for $C_6H_8N_2O_8$: N, 11.86; C, 30.52; H, 3.41. Found: N, 11.58, 11.48; C, 30.72; H, 3.44.

Erythritan Dinitrate.—Eighteen Gm. erythritan yielded 15 Gm. (45%) of nitrate which distilled 89°/1 mm. *Analysis.*—Calcd. for $C_4H_6N_2O_7$: N, 14.43. Found: N, 14.08, 14.11.

SUMMARY

The foregoing compounds, some of which are of therapeutic interest, have been synthesized.

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