brown mass was extracted with ether and the residue recrystallized from water with the aid of Norite; yield, 9.9 g. (63%); m. p. 210°.

In the preparation of 2-cyanomethylbenzimidazole, only intractable gums are obtained if too high a temperature is used or if the heating period is too long.

**Preparation of 2-Benzimidazoleacetic Acid. (1) Acid Hydrolysis of 2-Cyanomethylbenzimidazole.**—Five grams (0.032 mole) of the cyano compound was refluxed for two hours in 50 cc. of 1:1 sulfuric acid. On cooling, colorless needles of the sulfate separated. The sulfate was dissolved in water, made basic with ammonium hydroxide and then acidified with acetic acid. Small, colorless needles of 2-benzimidazoleacetic acid separated; yield, 4.8 g. (88%); m. p. 116° with decarboxylation, solidification and remelting at 176° (2-methylbenzimidazole).

*Anal.* Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.91. Found: C, 61.24; H, 4.64; N, 15.98.

**(2) Alkaline Hydrolysis of 2-Cyanomethylbenzimidazole.**—2-Cyanomethylbenzimidazole (1.57 g., 0.01 mole) was added to 20 cc. of a water solution containing 1.2 g. of sodium hydroxide and 3 cc. of ethyl alcohol and refluxed for two hours or until no more ammonia was evolved. The solution was then acidified with acetic acid; yield, 1.65 g. (94%); m. p. 116° with decarboxylation.

**Reaction of 2-Benzimidazoleacetic Acid with Thionyl Chloride.**—This reaction produced only highly insoluble, amorphous solids which could not be identified.

**Preparation of Ethyl 2-Benzimidazoleacetate.**—Five grams (0.032 mole) of the cyano derivative was added to 75 cc. of 9% alcoholic hydrogen chloride and refluxed for ninety minutes. The solution was filtered and the filtrate evaporated. The residue was treated with bicarbonate solution and recrystallized from alcohol with the aid of Norite. Colorless crystals were obtained by slow evaporation of the solution; yield, 4.8 g., (74%); m. p. 128.5–129.5°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.73. Found: C, 64.49; H, 6.03; N, 13.60.

**Preparation of 2-Benzimidazoleacetamide.**—One gram of the ethyl ester was refluxed for ten minutes with 20 cc. of concentrated ammonium hydroxide. On cooling a 70% yield of the amide separated. Colorless crystals were obtained by recrystallization from alcohol with the aid of Norite; m. p. 244–247° dec.

*Anal.* Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.19; N, 24.00. Found: C, 61.63; H, 5.20; N, 23.93.

N-Methyl-2-benzimidazoleacetamide (m. p. 214–216.5° decomp.), N-*n*-butyl-2-benzimidazoleacetamide (m. p. 209.5–212.5 decomp.), and N-(β-methoxyethyl)-2-benzimidazoleacetamide (m. p. 183.5–185° dec.) were also prepared by similar methods.

## Summary

1. 2-Benzimidazolecarboxylic and 2-benzimidazoleacetic acids have been prepared and their reactions studied.

2. 2-Benzimidazolecarboxylic acid is shown to form a diketopiperazine derivative when treated with thionyl chloride. The cleavage of this compound has been studied as a method for the preparation of derivatives of 2-benzimidazolecarboxylic acid.

3. Derivatives of 2-benzimidazoleacetic acid were prepared from the corresponding 2-cyanomethylbenzimidazole and from the ethyl ester of the acid.

PHILADELPHIA, PENNA. RECEIVED JANUARY 22, 1943

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

# The Synthesis of a Pyridine Analog of Hydnocarpic Acid and of a Lower Homolog

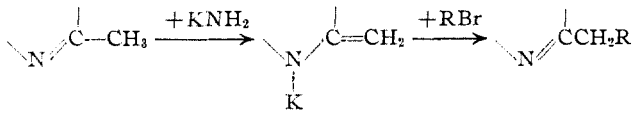
BY FREDERICK BRODY AND MARSTON TAYLOR BOGERT

Although there seems to be a considerable difference of opinion as to the curative value of chaulmoogric and hydnocarpic acids and their numerous derivatives in the treatment of leprosy, the fact remains that no drug has yet been discovered which is any more effective in combating this dread disease.

We have, therefore, undertaken the synthesis of compounds of analogous constitution, in which the cyclopentene nucleus of hydnocarpic and chaulmoogric acid has been replaced by various heterocyclic nuclei, and this first paper describes the synthesis of a pyridine analog (VIII). A later paper will report similar experiments leading to a thiazole analog. Pharmacological tests with the pyridine compound on rat leprosy are now being carried out at the National Institute of Health, Bethesda, Md., and the results will appear elsewhere.

Since both leprosy and tuberculosis are due to acid-fast bacteria, the discovery of curative drugs for the one may point the way to the synthesis of remedial medicinals for the other.

α-Picoline (II) was selected as source material because of the reactivity of its methyl group with alkali amides in liquid ammonia solution resulting in the formation of metallic derivatives which in turn react with halides, in a manner somewhat resembling the acetoacetic ester synthesis



Bergstrom[1] found that the yield of Li or Na picolyl in such cases was low, and that although potassium picolyl was formed quite readily, it failed to react with ethyl bromide in the way desired.

Chichibabin,[2] however, following a different route, added his alkyl halide to a mixture of the picoline and sodamide, in the absence of any solvent, and at room temperature. In this way, the halide interacted immediately with the small amount of sodium picolyl continuously being formed in the reaction mixture. Although he used this method successfully with cetyl chloride, among others, Knight and Shaw[3] were unable to duplicate his results with the higher alkyls except by carrying out the reaction at 100°.

The initial materials used in the following investigation were ethyl undecylenate and α-picoline. The undecylenate was reduced to the alcohol and the latter transformed into the corresponding chloride (I), which was then condensed with the picoline, in the presence of sodamide, following in the main the process of Chichibabin, as modified by Knight and Shaw.[3]

any solvent, and with a commercial sodamide; or in benzene solution, with a freshly prepared sodamide. But, with a freshly prepared sodamide and no solvent, at 100°, the principal product was the isomeric 12-(α-pyridyl)-dodecene-2 (IV), the olefin bond having migrated to the second C from the end.

A similar shift of a double bond under the influence of a base, has been reported by Chuit and his co-workers[4] in the case of undecylenic, dodecylenic and tridecylenic acids, although at higher temperatures and with different bases.

Insofar as our isomeric pyridyldodecenes (III and IV) are concerned, it is not clear whether the isomerization occurs in the undecylenyl chloride (I) prior to condensation, in the condensation product, or in both. The reason why the freshly prepared sodamide gave the rearranged product (IV), under conditions where the commercial amide yielded the normal compound (III), may be explained as due to the greater activity of the freshly prepared reagent, as shown in the two cases by the amount of heat developed and the rate of evolution of ammonia when the undecylenyl chloride was first added, as well as by the depth of color of the sodium picolyl formed. Further, when sodamide is prepared in liquid ammonia, by the method of Vaughn, Vogt and Nieuwland,[5]

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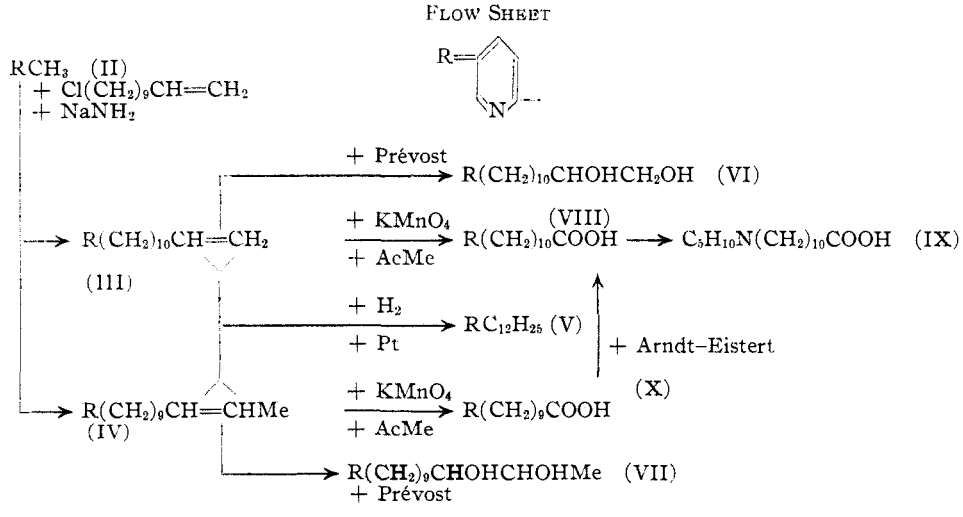


It was expected that this would result in the production of the 12-(α-pyridyl)-dodecene-1 (III), and this expectation was realized when the reaction was carried out at 100°, in the absence of any solvent, and with a commercial sodamide; or in benzene solution, with a freshly prepared sodamide. But, with a freshly prepared sodamide and no solvent, at 100°, the principal product was the isomeric 12-(α-pyridyl)-dodecene-2 (IV), the olefin bond having migrated to the second C from the end.

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When this activity of the fresh amide was moderated somewhat by the use of benzene as a

(1) Bergstrom, THIS JOURNAL, **53**, 4065 (1931).

(2) Chichibabin, *Bull. soc. chim.*, [5] **3**, 1607 (1936); [5] **5**, 429, 436 (1938).

(3) Knight and Shaw, *J. Chem. Soc.*, 682 (1938).

(4) Chuit, Boelsing, Hausser and Malet, *Helv. chim. acta*, **9**, 1074 (1926); **10**, 113 (1927).

(5) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

solvent, as noted above, the isomerization was suppressed and a 73% yield of the normal compound (III) was secured.

**Acknowledgments.**—Our thanks are due to Dr. Lyndon F. Small and Assistant Director L. F. Badger of the National Institute of Health, Bethesda, Md., through whose courtesy certain physiological tests are being conducted with the 11-(α-pyridyl)-undecanoic acid. We are indebted also to the generosity of E. I. du Pont de Nemours & Co., Inc., for a supply of α-picoline received from Dr. George B. Bradshaw, Asst. Manager of their Fine Chemicals Division. The analytical results we owe to the services of Mr. Saul Gottlieb.

## Experimental

All melting points are corrected for exposed thermometer stem.

**Undecylenyl alcohol (1-hendecene-11-ol)** was prepared from ethyl undecylenate by the method of Bouveault and Blanc,[6] as modified by Grün and Wirth,[7] except that *n*-butyl was used instead of ethyl alcohol as the reduction medium. The yields were 77–82%, b. p. 131–132° (14 mm.), $n^{25}D$ 1.4481 (literature yields, 70–91.5%;[7] b. p. 132–133° (15 mm.)[6]; $n^{19}D$ 1.4506).[4]

**Undecylenyl chloride** (I) has been obtained by Meyer[8] from the above alcohol by the action of thionyl chloride, in the presence of dimethylaniline as solvent and catalyst. In our work, however, the use of this catalyst resulted in the formation of considerable tar, and the following procedure therefore was adopted, based partly on the experience of Noller and Bannerot[9] in preparing oleyl chloride.

To a mole of the undecenol containing 0.5 cc. of pyridine and kept in an ice–salt mixture, there was added slowly with stirring 2 moles of thionyl chloride, and the mixture was then heated at 130–140° until the evolution of sulfur dioxide ceased. Excess of thionyl chloride was distilled off under diminished pressure, and the residue was washed first with a saturated aqueous sodium chloride solution, then with a 10% sodium carbonate solution, and finally again with the sodium chloride solution. The oil was taken up in ether, the solution dried, and distilled under reduced pressure. The yield of chloride was 83%; b. p. 113–115° (12 mm.); $n^{25}D$ 1.4487 (lit.[8] yield, 80%; b. p. 120° (15 mm.).

**12-(α-Pyridyl)-dodecene-1 (III).**—When a mixture of undecylenyl chloride, picoline, and a good grade of commercial sodamide was kept at room temperature for six days with frequent stirring, the yield of pyridyldodecene was practically zero. At 100°, however, the reaction proceeded smoothly; the process was the following:

To 46.5 g. (0.5 mole) of α-picoline was added 20 g. (0.5 mole) of commercial sodamide which had been pulverized under mineral oil and washed free of oil with dry ether. There was then added 62.8 g. (0.33 mole) of undecylenyl chloride and the mixture was heated at 100° for thirty-six hours with frequent stirring. The hot mixture was deep red, which is the color of the sodium picolyl when in sufficient concentration. On cooling overnight, the color faded to a tan. The evolution of ammonia, which was considerable at the beginning of the heating, decreased as the reaction progressed, but was still in evidence after thirty-six hours, although but little was evolved during the cooling periods.

The excess of sodamide was decomposed with ether and water, the aqueous layer extracted with ether, the ether extract dried with potassium carbonate and distilled. After removal of the ether and excess picoline, there was obtained a fraction, b. p. 93–95° (4 mm.), mostly unaltered undecylenyl chloride, followed by a cut, b. p. 155–165° (4 mm.). This latter was converted into its picrate, from which the base was regenerated by a 10% sodium hydroxide solution, washed, dried and distilled. The b. p. of the product was 158–159° (4 mm.), $n^{25}D$ 1.4926; yield, 43.4 g., or 53%, calculated to the undecylenyl chloride used. It decolorized a potassium permanganate solution, added bromine in a carbon tetrachloride solution, and absorbed 90% of the calculated amount of perbenzoic acid on standing four days in the refrigerator.

*Anal.* Calcd. for $C_{17}H_{27}N$: C, 83.2; H, 11.1. Found: C, 83.2; H, 11.1.

**Picrate.**—Yellow needles from alcohol, m. p. 46–46.5°.

*Anal.* Calcd. for $C_{23}H_{30}N_4O_7$: C, 58.2; H, 6.4. Found: C, 57.9; H, 6.3.

In a second series of experiments, freshly made sodamide was employed, with benzene as diluent.

A solution of 13 g. of sodium in about 300 cc. of liquid ammonia, containing a small crystal of $Fe(NO_3)_3 \cdot 6H_2O$, was stirred until its blue color disappeared, indicating the completion of the reaction. After most of the ammonia had evaporated, 52.1 g. (0.56 mole) of α-picoline was added, followed by 300 cc. of dry benzene. To the buff-colored mixture, there was added 53.2 g. (0.28 mole) of undecylenyl chloride. No appreciable evolution of ammonia occurred in the cold, but when the mixture was refluxed, it was considerable and remained so for several hours. After refluxing for twenty-four hours, the evolution of ammonia was practically negligible, and the crude product was worked up as described above. Distillation at 2.5 mm. yielded 61.6 g. of a fraction, b. p. 131–140°, which was purified through its picrate. The purified product weighed 49.9 g., or a 73% yield calculated to the undecylenyl chloride used, b. p. 158–160° (4 mm.), $n^{25}D$ 1.4924. The m. p. of the picrate, 46–47°, showed no depression when it was mixed with the picrate obtained by the first method.

**12-(α-Pyridyl)-dodecene-2 (IV).**—A solution of sodamide freshly prepared, as described above, from 13.5 g. of sodium and 300 cc. of liquid ammonia, in the presence of a small crystal of $Fe(NO_3)_3 \cdot 6H_2O$, was treated with 55.8 g. (0.6 mole) of α-picoline after most of the ammonia had evaporated. The mixture immediately turned a deep red. The rest of the ammonia was driven off by warming, and 56.6 g. (0.3 mole) of undecylenyl chloride was added slowly. A vigorous escape of ammonia ensued immediately with rise of temperature, after which the mixture was heated for twenty-four hours at 100°, by which time

(6) Bouveault and Blanc, *Bull. soc. chim.*, [3] **31**, 1210 (1904).

(7) Grün and Wirth, *Ber.*, **55**, 2208 (1922). See also "Organic Syntheses," **10**, 63, Note 8 (1930).

(8) Meyer, *Compt. rend.*, **203**, 1074 (1936).

(9) Noller and Bannerot, THIS JOURNAL, **56**, 1563 (1934).

the evolution of ammonia had practically ceased. When this mixture was worked up as described in the first series of experiments for the isomer (III), no low-boiling cut, corresponding to unchanged undecylenyl chloride, was obtained. A fraction was collected, b. p. 145–151° (3 mm.), amounting to 61.7 g. which, purified through its picrate, gave 49.3 g. of (IV), or a 67% yield, based on the undecylenyl chloride; b. p. 152–153° (4 mm.), $n^{25}D$ 1.4907.

*Anal.* Calcd. for $C_{17}H_{27}N$: C, 83.2; H, 11.1. Found: C, 83.2; H, 11.1.

**Picrate.**—Yellow needles from alcohol, m. p. 64.5–65.5°.

*Anal.* Calcd. for $C_{23}H_{30}N_4O_7$: C, 58.2; H, 6.4. Found: C, 58.1; H, 6.6.

**12-(α-Pyridyl)-dodecane (V).—(a) From 12-(α-Pyridyl) dodecene-1 (III).**—An alcoholic solution of 2.58 g. of the pyridyldodecene-1 (III) was reduced at atmospheric pressure with hydrogen and palladium black. After correction for absorption by the catalyst, the amount of hydrogen absorbed agreed with that calculated. The mixture was filtered, the filtrate concentrated, and the product isolated as the picrate; yield, 4.7 g., or 90%. It crystallized from alcohol as a mixture of plates and needles, which changed completely to plates when left in contact with the solvent; m. p. 64–65°. By further crystallization from alcohol or ethyl acetate, the m. p. was unchanged.

**(b) From 12-(α-Pyridyl)-dodecene-2 (IV).**—A similar reduction of the pyridyldodecene-2 (IV) (0.62 g.) by hydrogen and palladium, in alcoholic solution, resulted in the absorption of the calculated quantity of hydrogen and a yield of over 90% of the picrate of the pyridyldodecane (V). This picrate, when purified, also melted at 64–65°, looked exactly like the picrate obtained by reduction of the pyridyldodecene-1, and a mixture of the two showed no change in m. p.

Since the picrate of the pyridyldodecene-2 (IV) melts at the same point (64.5–65.5°), a mixture of these two picrates (*i. e.*, of IV and V) was tested, and the m. p. of the mixture was 56–59°, indicating their non-identity. Further, as noted above, the picrate of (IV) crystallized preferably in needles, that of (V) preferably in plates, from alcohol.

*Anal.* Calcd. for $C_{23}H_{32}N_4O_7$: C, 58.0; H, 6.8; for $C_{23}H_{30}N_4O_7$: C, 58.2; H, 6.4. Found: from (a), C, 57.8; H, 7.0; from (b), C, 58.2; H, 6.9.

The base itself (V) regenerated from the picrate of (a) was a colorless liquid, $n^{25}D$ 1.4789.

*Anal.* Calcd. for $C_{17}H_{29}N$: C, 82.5; H, 11.8. Found: C, 82.7; H, 11.7.

**12-(α-Pyridyl)-dodecane-1,2-diol (VI).**—This was prepared from the 12-pyridyldodecene-1 (III), following the general method of Prévost.[10]

To a suspension of 18 g. (0.08 mole) of silver benzoate in dry benzene, there was added 9.9 g. (0.04 mole) of iodine in benzene solution. When the iodine color had been discharged by shaking, 9.6 g. (0.04 mole) of 12-(α-pyridyl)-dodecene-1 was added, and the mixture was refluxed for three hours. The precipitated silver iodide was filtered out, the benzene distilled off, and the residual viscous oil, presumably the dibenzoate of the desired glycol, was hydrolyzed by refluxing in alcoholic potassium hydroxide for an hour. By ether extraction, the crude glycol was isolated, and was then purified by crystallization from ligroin. The pure compound formed white needles (from ligroin), m. p. 71.5–72°; yield, 6.2 g., or 60%.

*Anal.* Calcd. for $C_{17}H_{29}O_2N$: C, 73.1; H, 10.5. Found: C, 73.2; H, 10.5.

**12-(α-Pyridyl)-dodecane-2,3-diol (VII),** prepared similarly, from the isomeric pyridyldodecene-2 (IV), crystallized from benzene, or ethyl acetate, in white needles, m. p. 87–87.5°; yield, 65%.

*Anal.* Calcd. for $C_{17}H_{29}O_2N$: C, 73.1; H, 10.5. Found: C, 73.3; H, 10.4.

**11-(α-Pyridyl)-undecanoic Acid (VIII).**—A solution of 5 g. (0.02 mole) of 12-(α-pyridyl)-dodecene-1 (III) in 50 cc. of dry acetone was treated with 12 g. (0.08 mole) of powdered potassium permanganate, added in small portions, over a period of four hours, maintaining the temperature below 35°. The precipitate was removed, digested with 100 cc. of warm 10% sodium carbonate solution, the mixture filtered, and the insoluble material thoroughly washed with water. The combined filtrate and washings was concentrated to about 50 cc. and neutralized to maximum precipitation, since the product is amphoteric. The crude acid thus precipitated amounted to 4.6 g., and melted at 58–63°. Recrystallized from ligroin, 2.6 g. of brilliant colorless plates was obtained, m. p. 68.5–69.5°; yield, 50%.

*Anal.* Calcd. for $C_{16}H_{25}O_2N$: C, 73.0; H, 9.6; N, 5.3. Found: C, 73.1; H, 9.5; N, 5.6.

The product was insoluble in water; soluble in warm petroleum ether or ligroin, insoluble cold; freely soluble in alcohol, ether, acetone, or benzene, and also in excess of 5% sodium carbonate solution or in excess of dilute mineral acid. Its precipitation range appears to be between *p*H 5.5 and 7.5, outside of which limits it remains in solution.

Oxidation of the dodecene in aqueous solution, or at higher temperatures, gave picolinic acid and other products.

**Picrate of Ethyl Ester.**—When the above acid was converted into a picrate in alcoholic solution, esterification of the acid apparently occurred, and the product was the picrate of this ethyl ester. It separated in yellow needles, m. p. 69–70°.

*Anal.* Calcd. for $C_{24}H_{32}O_9N_4$: C, 55.4; H, 6.2. Found: C, 55.5; H, 6.2.

As recorded later, it is interesting to note that the 10-(α-pyridyl)-decanoic acid gave the normal picrate in alcoholic solution and not the picrate of the ethyl ester.

**Picrate of the Acid.**—This was prepared in ether solution and crystallized from ethyl acetate. It formed yellow prisms, m. p. 79–79.5°.

*Anal.* Calcd. for $C_{22}H_{28}O_9N_4$: C, 53.7; H, 5.7. Found: C, 53.9; H, 6.0.

**Hydrochloride.**—Precipitated from anhydrous ether solution of the acid by dry hydrogen chloride, this salt dissolved in water with immediate hydrolysis and precipitation of the original pyridine acid.

**Sodium Salt.**—The dry salt was prepared by the method of McBain, *et al.*[11] An alcoholic solution of the pyridine

(10) Prévost, *Compt. rend.*, **196**, 1129 (1933).

(11) McBain, *et al.*, *J. Phys. Chem.*, **44**, 1013 (1940).

acid was titrated with sodium ethoxide, using phenolphthalein as indicator, and the alcohol was then driven off in an oven. In water, the dry salt hydrolyzed rapidly, depositing the free acid.

Because of the ready solubility of the acid in excess of dilute sodium bicarbonate solution, the acid itself was forwarded to the National Institute of Health, Bethesda, Md., for pharmacological testing. Dr. Lyndon F. Small reports that preliminary tests carried out on mice at the National Institute of Health have shown that the toxic dose of this acid is about 0.8 g. per kg., or approximately 16 mg. per mouse. Some further tests are being conducted (subcutaneous), for chronic toxicity, and to determine whether or not its effects are cumulative. It possesses a very strong local irritating action, and has a considerable narcotic effect which often progresses to complete immobility and lasts for about 24 hrs. Further experiments are underway.

**11-(α-Pyridyl)-undecanoamide,** $C_5H_5N(CH_2)_{10}CONH_2$. —A mixture of the undecanoic acid with a large excess of thionyl chloride was allowed to stand overnight in the refrigerator, and the excess of the reagent was then removed by distillation under diminished pressure. The residual white powder, presumably the chloride hydrochloride,[12] was added to an ice-cold concentrated ammonium hydroxide solution. The precipitated amide, crystallized from ethyl acetate, formed white needles, m. p. 96.5–97.5°.

*Anal.* Calcd. for $C_{16}H_{26}ON_2$: C, 73.2; H, 10.0. Found: C, 73.3; H, 10.1.

**Picrate.**—Yellow needles, from alcohol, m. p. 112.5–113°.

*Anal.* Calcd. for $C_{22}H_{29}O_8N_5$: C, 53.8; H, 6.0. Found: C, 54.0; H, 6.1.

**10-(α-Pyridyl)-decanoic Acid (X).**—Ten grams (0.041 mole) of 12-(α-pyridyl)-dodecene-2 (IV) was oxidized by potassium permanganate in acetone solution, as described above for its isomer (III). The yield of crude acid was 5.6 g., m. p. 50–55°. This was redissolved in alkali and fractionally precipitated with acid. The first fractions, precipitated from the more alkaline solution, contained the acid sought. A repetition of this procedure gave fractions melting between 55° and 57° which were further purified by crystallization from a mixture of ethyl acetate and petroleum ether and then formed white needles, m. p. 55.5–56.5°; yield, 4.4 g., or 43%.

*Anal.* Calcd. for $C_{15}H_{23}O_2N$: C, 72.3; H, 9.3. Found: C, 72.1; H, 9.1.

**Picrate.**—Yellow needles, from alcohol, m. p. 82.5–83°.

*Anal.* Calcd. for $C_{21}H_{26}O_9N_4$: C, 52.7; H, 5.5. Found: C, 53.0; H, 5.7.

**10-(α-Pyridyl)-decanoyl Chloride Hydrochloride,** $C_5H_4N\cdot(CH_2)_9COCl\cdot HCl$.—Seventy-five mg. of the decanoic acid was converted into its chloride hydrochloride as already described for its higher homolog, and the product was similar in appearance and properties.

**9-(α-Pyridyl)-nonyldiazomethyl Ketone,** $C_5H_4N\cdot(CH_2)_9COCHN_2$.—The above acid chloride hydrochloride was added to 10 cc. of an ether solution of diazomethane, prepared from 0.5 g. of nitrosomethylurea, at −20°. After an hour at this temperature, the bath was allowed to warm up slowly to +5°, and the mixture was left overnight in the refrigerator. A small amount of resin separated, with evolution of nitrogen. The ether solution was filtered and the solvent removed under diminished pressure. The residual viscous yellow oil, presumably the diazomethyl ketone, could not be crystallized and was therefore used direct for the next step.

It was dissolved in 10 cc. of dioxane, 1 cc. of 28% ammonium hydroxide solution was added and a few drops of a 10% silver nitrate solution. The mixture was refluxed at 100° for 2 hours, filtered hot, cooled and poured upon ice. The separated oil was collected in ether, the solution dried by magnesium sulfate, and the ether driven off. The residue, crystallized twice from ethyl acetate, appeared in white needles, m. p. 95–96°.

**Picrate.**—Yellow needles from alcohol, m. p. 110–111°.

A mixture of the above amide with that prepared directly from the undecanoic acid (VIII), melted at 96–97°; and a mixture of the picrates of these two amides, melted at 112–113°.

**11-(α-Piperidyl)-undecanoic Acid (IX).**—Two grams of the pyridylundecanoic acid (VIII) was hydrogenated over a Raney nickel catalyst in a cyclohexane solution, at 180° and 1700 lb. pressure. The precipitated product was dissolved in alcohol, filtered from the catalyst, and treated with hydrogen sulfide to decompose nickel salts. The precipitated nickel sulfide was filtered out, the filtrate concentrated, and the piperidyl acid precipitated by addition of water. Recrystallized from dilute alcohol, and then from water, 1.57 g. (77% yield) of pure product was secured, in the form of white needles, m. p. 158.5–160°; practically insoluble in petroleum ether, benzene, ether, ethyl acetate or cold water; soluble in alcohol or hot water. It dissolved freely in aqueous sodium bicarbonate solution, but was practically insoluble in excess of mineral acid. The relatively high m. p., and the solubilities of this acid, suggest a high polarity for the compound.

*Anal.* Calcd. for $C_{16}H_{31}O_2N$: C, 71.3; H, 11.6. Found: C, 71.6; H, 11.5.

**Picrate.**—Prepared without using any solvent and crystallized from ethyl acetate, it formed yellow prisms, m. p. 92.5–93.5°.

*Anal.* Calcd. for $C_{22}H_{34}O_9N_4$: C, 53.0; H, 6.9. Found: C, 53.3; H, 7.1.

The fact that this picrate melts lower than the piperidyl acid itself, may be ascribed to the fact that the picrate lacks the high polarity characteristic of the free acid.

## Summary

1. By the action of undecylenyl chloride upon α-picoline, in the presence of sodamide, either 12-(α-pyridyl)-dodecene-1 or 12-(α-pyridyl)-dodecene-2 is formed, depending upon the conditions.

2. Both of these, on catalytic reduction, give the same 12-(α-pyridyl)-dodecane.

3. With the Prévost reagent, the two dodecenes yield the corresponding 1,2- and 2,3-diols.

4. Oxidation of the dodecenes with potas-

(12) Späth and Spitzer, *Ber.*, **59**, 1477 (1926).

sium permanganate, in acetone solution, results in the production of 11-(α-pyridyl)-undecanoic and 10-(α-pyridyl)-decanoic acids, the former being a pyridine analog of hydnocarpic acid.

5. By the Arndt–Eistert procedure the decanoic can be converted into the undecanoic acid.

6. The undecanoic acid is being tested at the National Institute of Health, Bethesda, Md., for possible therapeutic properties.

NEW YORK, N. Y. RECEIVED FEBRUARY 19, 1943

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

# Researches on Thiazoles. XXVII. A Thiazole Analog of Hydnocarpic Acid

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In a recent paper,[1] we described the synthesis of a pyridine analog of hydnocarpic acid and of a lower homolog. The present communication records experiments carried out in the thiazole field having as their object the synthesis of a similar compound in the thiazole group.

From the therapeutic point of view, thiazole derivatives are of considerable interest, since they have proven useful in the treatment of various diseases. Vitamin $B_1$ and sulfathiazole (and its derivatives) are beneficent drugs. Some thiazoles possess antimalarial activity. In combatting the tubercle bacillus, Mayer[2] found that sulfathiazole was 6–30 times more potent than sulfanilamide or sulfapyridine, and mercaptobenzothiazole was still more active. And of a large number of organic compounds studied *in vitro* by Smith, Emmart and Westfall,[3] sulfathiazole proved third in order of tuberculostatic effectiveness. Inasmuch as the tubercle bacillus is closely related to *M. leprae*, these observations are at least worthy of note.

The preparation of thiazoles carrying long carbon chains in position 2 with a terminal carboxyl group, should be attainable by oxidation of thiazoles having a suitable hydrocarbon chain in that position, but we failed to find in the literature any satisfactory method for the synthesis of such derivatives.

The reactivity of the 2-methyl group in thiazoles has been tested for aromatic aldehydes,[4,5] but in the pyridine series aliphatic aldehydes or ketones do not condense readily unless activated.[6] An attempt to condense *n*-heptaldehyde with 2,4-dimethylthiazole, in the presence of acetic anhydride, gave such a poor yield of 1-(4-methyl-2-thiazolyl)-octene-1 that further experimentation along that line was discontinued.

The alkylation of the 2-methyl group, therefore, was undertaken with alkyl chlorides, as described by Chichibabin[7] for pyridines and used successfully by us[1] in that series. 2-Methyl- and 2,4-dimethyl-thiazole were used with undecylenyl, lauryl and cetyl chlorides, with or without benzene as diluent, and in the presence of commercial sodamide. The reactions were allowed to proceed at room temperature for several days. The product was mainly a tar, from which a yield of 10–14% of an oil could be distilled giving a crude picrate. But no pure products could be isolated.

The procedure finally adopted is shown by the Flow Sheet. Ethyl undecylenylcyanoacetate (II), from ethyl cyanoacetate and undecylenyl iodide (I) in the presence of potassium carbonate,[8] was converted into the thioamide (III) by the action of hydrogen sulfide. Since hydrogen sulfide does not add easily to higher aliphatic nitriles under ordinary conditions, the method of Ralston, Van der Wal and McCorkle[9] was tried, but the high temperature required led to considerable resinification. Using triethanolamine as catalyst, however, following the experience of Olin and Johnson,[10] a satisfactory yield of thioamide was obtained, provided that the catalyst was used in adequate amount, the stream of hydrogen sulfide was continued long enough, and the temperature was maintained at 25–60°.

Condensation of the thioamide with chloroacetaldehyde hydrate, in benzene solution, resulted in hydrolysis of the ester and elimination of

(1) Brody and Bogert, THIS JOURNAL, **65**, 1075 (1943).
(2) Mayer, *Rév. Méd. France*, 3 (1941); *C. A.* **36**, 5199 (1942).
(3) Smith, Emmart and Westfall, *J. Pharmacol.*, **74**, 163 (1942).
(4) Kondo and Nagasawa, *J. Pharm. Soc. Japan*, **57**, 909 (1937); *C. A.*, **32**, 1699 (1938).
(5) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).
(6) McElvain and Johnson, THIS JOURNAL, **63**, 2213 (1941).
(7) Chichibabin, *Bull. soc. chim.*, **3**, 1607 (1936).
(8) Robinson, *J. Chem. Soc.*, **125**, 226 (1924).
(9) Ralston, Van der Wal and McCorkle, *J. Org. Chem.*, **4**, 68 (1939).
(10) Olin and Johnson, *Rec. trav. chim.*, **50**, 72 (1931).