fore, within experimental error, was 1-phenylcyclohexene.[16,17]

Decomposition of Trimethyl-*trans*-2-phenylcyclohexylammonium Hydroxide.—In a manner essentially identical with that employed with the *cis* isomer, trimethyl-*trans*-2-phenylcyclohexylammonium iodide (2.5 g.) was carried through the Hofmann degradation. The hydrocarbon ultimately obtained weighed 0.84 g. (73%) and had the constants: $n^{20}D$ 1.5690, log ϵ_{246} 4.083 (ϵ 12,120). The material was, in our hands, indistinguishable from 1-phenylcyclohexene.[16,17]

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Synthesis of Oxindole-3-propionic Acid by Ring Rearrangement

BY H. A. LLOYD AND E. C. HORNING

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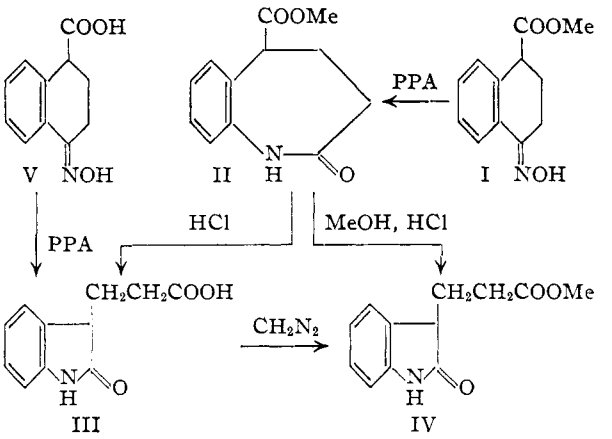
An example of an intramolecular exchange reaction in which a seven-membered lactam is converted to a five-membered system has been investigated. This reaction provides a new method for the preparation of the oxindole ring.

Intermolecular ester–amide or amide–amide exchange reactions occur frequently. Intramolecular reactions of this kind might also be expected to occur in polyfunctional cyclic systems, but comparatively few reactions of this kind have been studied. One of these is involved in the reactions of oxindole-3-acetic acid; this problem and its solution are described in the recent excellent paper of Julian.[1] It is known that esters of oxindole-3-acetic acid are converted into 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid under acidic hydrolysis conditions. Similarly, the hydrolysis of oxindole-3-malononitrile leads to the same quinolone, and this reaction most likely involves an exchange between an acid and an amide group. The nature of the final product indicates that a six-membered cyclic amide system has an increased stability when compared with the corresponding five-membered cyclic amide.

We have been interested in the application of exchange reactions in the synthesis of heterocyclic systems and have investigated a related case of ring-exchange leading to the preparation of oxindole-3-propionic acid. Incorrect reports dealing with the supposed preparation and reactions of this compound have appeared in the literature, but the recent work of Julian[2] has established the nature of authentic oxindole-3-propionic acid and the sources of error in previous work. The present study was based on the prediction that oxindole-3-propionic acid and its esters should contain a more stable ring system than that of the isomeric seven-membered cyclic lactam-ester II or the corresponding acid.

The ester II was prepared by the Beckmann rearrangement of the oxime of 4-carbomethoxytetralone-1, using polyphosphoric acid under conditions developed earlier.[3] An advantage of this reagent lies in the fact that the ester group is not disturbed during the rearrangement. When the ester II was heated in methanolic hydrochloric acid, the product was an isomeric methyl ester which was proved to be methyl oxindole-3-propionate (IV). When the ester II was heated with hydrochloric acid, hydrolysis as well as rearrangement occurred and the product was oxindole-3-propionic



acid. It seems likely that the ring contraction in each case is due to an acid-catalyzed exchange reaction rather than to hydrolysis to an aminodicarboxylic acid or ester, followed by cyclization. This belief is strengthened by the observation that the oxime of 4-carboxytetralone-1 (V) is converted by polyphosphoric acid directly to oxindole-3-propionic acid. It is highly unlikely that hydrolysis of the lactam-acid expected from the Beckmann rearrangement occurred in the presence of polyphosphoric acid, but an acid-catalyzed rearrangement is not improbable under these conditions. Unfortunately, the yield of oxindole-3-propionic acid obtained by this direct method is lower than that obtained through the ester II.

At the time that this work was carried out, Julian's confirmation of the reported structure of Kendall's acid[4] was not published in detail. In attemping to correlate III with IV, the acid resulting from rearrangement was treated with diazomethane, and the methyl ester obtained as a reaction product was not identical with that obtained through an exchange reaction from II. It was subsequently found that this ester exists in a low-melting metastable form as well as in the normal form, and the required relationship was then established. In the case of the ethyl ester the expected relationship was demonstrated by esterification of III and comparison with the product of rearrangement in ethanol.

(1) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, THIS JOURNAL, **75**, 5305 (1953).

(2) P. L. Julian and H. C. Printy, *ibid.*, **75**, 5301 (1953).

(3) E. C. Horning, V. L. Stromberg and H. A. Lloyd, *ibid.*, **74**, 5153 (1952).

(4) E. C. Kendall, A. E. Osterberg and B. F. MacKenzie, *ibid.*, **48**, 1384 (1926).

In separate experiments the reduction-cyclization of α-(*o*-nitrophenyl)-glutaric acid also was found to yield oxindole-3-propionic acid. In this instance the expected intermediate, α-(*o*-aminophenyl)-glutaric acid, undergoes preferential cyclization to the five-membered lactam rather than to a seven-membered lactam. This suggested that alkaline hydrolysis of II, followed by acidification, should also yield oxindole-3-propionic acid, and this was confirmed by experiment. The ease with which rearrangement and hydrolysis occurs for II is in sharp contrast to the reported resistance of homodihydrocarbostyril to hydrolytic conditions.[5]

The reaction of Horner,[6] involving the addition of methyl acrylate to oxindole, followed by hydrolysis, was also carried out. The product was identical with a dicarboxylic acid obtained by the addition of methyl acrylate to IV, followed by hydrolysis. However, the product (m.p. 130–131°) was not the same as that reported by Horner[6] or Julian.[2] The analytical data indicated that this material was a half-hydrate; the acids of Horner and Julian are anhydrous. Prolonged drying *in vacuo* did not affect the compound. To confirm the nature of the product, it was esterified (ethanol), ethylated (ethyl iodide–sodium ethoxide) and hydrolyzed to 1-ethyloxindole-3,3-dipropionic acid. This product was identical with one prepared directly from 1-ethyloxindole by addition of methyl acrylate, followed by hydrolysis. This method of structure proof is described in greater detail by Julian.[2]

Since it is known that oxindole-3-acetic acid is converted by exchange conditions to a dihydroquinolone, the order of stability of ring systems in this series may be written seven < five < six, in terms of increasing stability. This leads to the conclusion that a suitable seven-membered system should undergo contraction to a six-membered system with ease. The experimental confirmation of this conclusion is described in a later paper.

Acknowledgment.—We are indebted to Mrs. Iris Siewers for the spectra measurements and to Dr. William Alford and his staff for the analytical data.

Experimental[7]

4-Carboxytetralone-1.—A mixture of 10 g. of α-phenylglutaric anhydride[8] and 30 g. of polyphosphoric acid was heated to 100–110° and kept at that temperature for 5 minutes. Another 30 g. of polyphosphoric acid was added and the mixture was heated for 10 minutes at the same temperature. The product (8 g., 80%) which separated after the addition of ice and water was dried and recrystallized from benzene, m.p. 96.5–97°. This cyclization is superior to the method employing sulfuric acid.[8]

The 2,4-dinitrophenylhydrazone was prepared; m.p. 249–251°.

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: C, 55.14; H, 3.81; N, 15.13. Found: C, 55.44; H, 3.90; N, 15.32.

4-Carbomethoxytetralone-1 Oxime. A. 4-Carbomethoxytetralone-1.—A solution of 10 g. of 4-carboxytetralone-1 in 100 ml. of methanol was chilled, saturated with hydrogen chloride, and allowed to stand overnight at room temperature. The residue remaining after removal of the methanol was taken up in ether and the solution was washed with 5% potassium carbonate solution, with water and dried. The ether was removed and the residue was distilled at reduced pressure to yield 7.7 g. (72%) of colorless oil, b.p. 135–136° (0.5 mm.).

The potassium carbonate extracts yielded 0.5 g. (5%) of unreacted 4-carboxytetralone-1.

The 2,4-dinitrophenylhydrazone of the ketoester was recrystallized from methyl acetate; m.p. 210–210.5°.

Anal. Calcd. for $C_{18}H_{16}O_6N_4$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.11; H, 4.22; N, 14.58.

(B) 4-Carbomethoxytetralone-1 Oxime.—A solution of 5.5 g. of the ketoester, 5.5 g. of hydroxylamine hydrochloride, 30 ml. of dry pyridine and 30 ml. of absolute methanol was refluxed for 2 hours. The solvents were evaporated and the oily residue was triturated with cold water until crystallization occurred. The oxime was recrystallized from methanol to yield 5.5 g. (93%) of product, m.p. 88–88.5°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.70; H, 5.80; N, 6.52.

4-Carboxytetralone-1 was also converted into **4-carbethoxytetralone-1 oxime** by a similar series of reactions. The colorless product was recrystallized from ethanol–water; m.p. 51–51.5°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.22; H, 6.39; N, 6.20.

2-Oxo-5-carbomethoxy-2,3 4,5-tetrahydrobenzazepine.—A mixture of 5.0 g. of oxime and 150 g. of polyphosphoric acid was stirred manually and heated to 110°; this temperature was maintained for 5 minutes. (Higher temperatures (125°) resulted in a sharply decreased yield.) The mixture was cooled and treated with ice-water; the product was extracted with chloroform. After treatment with Norit, the solvent was removed and the residue crystallized from ether to yield 4.6 g. (92%) of lactam, m.p. 141–144°. An analytical sample was recrystallized from ether–ethyl acetate; m.p. 144–145°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.04; H, 6.11; N, 6.52.

The corresponding ethyl ester, **2-oxo-5-carbethoxy-2,3,4,-5-tetrahydrobenzazepine**, was also prepared by the same method. It was crystallized from benzene; m.p. 120.5–121.5°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.23; H, 6.39; N, 6.20.

Oxindole-3-propionic Acid by Rearrangement.—A solution of 2.35 g. of the lactam II in 25 ml. of concd. hydrochloric acid was refluxed for 3 hours and then allowed to stand for 12 hours at room temperature. The product, which crystallized from the solution, was removed by filtration and washed with acetone–ether to yield 2.28 g. of acid, m.p. 161–165°. After recrystallization from ethanol the product melted at 168–170° in agreement with the value found by Julian.[2]

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.29; N, 7.00.

Methyl Oxindole-3-propionate (IV). A. By Rearrangement.—A solution of 1.51 g. of the lactam II in 100 ml. of dry methanol containing 2–3 drops of concd. hydrochloric acid was refluxed for 10 hours. The solvent was removed and the residue was dissolved in benzene. The solution was washed in the usual way and dried. Removal of the benzene gave a colorless product which was crystallized from benzene–pentane; m.p. 57.5–59°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.52; H, 5.73; N, 6.22.

This material had an infrared spectrum identical with a higher-melting ester described later, and it was found that it could be recrystallized from hexane–benzene, with seeding, to give the reported methyl ester, m.p. 78–78.5°, in close agreement with the data of Julian.[2]

(B) From III.—The treatment of 1.0 g. of the acid in 10 ml. of methanol and 50 ml. of ether with ethereal diazomethane gave a 1.0 g. (94%) yield of the methyl ester. After recrystallization from hexane–benzene the m.p. was 78–78.5°.

In separate experiments it was found that the acid could also be esterified with methanol and hydrochloric acid.

4-Carboxytetralone-1 Oxime (VI).—4-Carboxytetralone-1 (10 g.) was converted into the oxime (VI) by refluxing with

(5) J. v. Braun, *Ber.*, **40**, 1843 (1907).

(6) L. Horner, *Ann.*, **548**, 117 (1941).

(7) All melting points were taken on a Kofler stage.

(8) E. C. Horning and A. F. Finelli, THIS JOURNAL, **71**, 3204 (1949).

hydroxylamine hydrochloride, pyridine, and ethanol. The yield was 10 g. (93%); recrystallization from methanol provided an analytical sample, m.p. 188–189°.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.40; H, 5.40; N, 6.83.

Rearrangement of the Oxime VI.—A 2.0-g. sample of VI in 60 g. of polyphosphoric acid was heated at 105–110° for 5 minutes. A 0.4 g. (20%) yield of oxindole-3-propionic acid, m.p. 163–166°, was obtained. After recrystallization the m.p. and mixed m.p. was 167–169°.

Alkaline Hydrolysis of II.—A 0.4-g. sample of the methyl ester-lactam II in 10 ml. of methanol and 10 ml. of 10% sodium hydroxide solution was refluxed for 2 hours. The methanol was removed by distillation and the reflux period was continued for 0.5 hour. The acidic product was isolated and found to consist of 0.3 g. of oxindole-3-propionic acid.

Ethyl Oxindole-3-propionate. (A) By Esterification.—Oxindole-3-propionic acid (9.0 g.) was esterified in a mixture of 75 ml. of dry ethanol, 75 ml. of dry benzene and 3 drops of concd. hydrochloric acid, using an 11-hour reflux period. There was obtained 7.0 g. of ester, m.p. 67–69°. An analytical sample was recrystallized from pentane–benzene; m.p. 69.5–70°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.97; H, 6.54; N, 5.93.

(B) **By Rearrangement.**—A solution of 1.5 g. of II in 50 ml. of dry ethanol and 50 ml. of dry benzene containing 3 drops of concd. hydrochloric acid was refluxed for 10 hours. The neutral product was isolated to yield 1.4 g. of ester, m.p. 65–67°, not depressed on mixture with the sample obtained by direct esterification.

Reduction-Cyclization of α-(*o*-Nitrophenyl)-glutaric Acid.—α-(*o*-Nitrophenyl)-glutaric acid[9] was prepared by the hydrolysis-decarboxylation of 1-(*o*-nitrophenyl)-propane-1,3,3-tricarboxylic acid triethyl ester with hydrobromic acid. The tricarboxylic ester was prepared by the Michael addition of diethyl methylenemalonate to ethyl *o*-nitrophenylacetate.

A mixture of 2.4 g. of the acid, 10 ml. of concd. hydrochloric acid and 2.4 g. of tin was heated at 100° for 2 hours and then allowed to stand overnight. The acid product was isolated and found to be 0.6 g. (31%) of oxindole-3-propionic acid.

(9) M. Kotake, T. Sakan and T. Miwa, THIS JOURNAL, **72**, 5086 (1950).

Oxindole-3,3-dipropionic Acid. A. From Oxindole.—The Michael addition of methyl acrylate and oxindole was carried out according to Horner.[6] The resulting ester was hydrolyzed in 2 *N* sulfuric acid to yield 66% of a colorless acid, m.p. 124–128°. This material was recrystallized from water and from pentane–ethyl acetate; m.p. 130–131°. Since the analytical data indicated water of hydration, attempts were made to obtain an anhydrous form by drying *in vacuo* over phosphorus pentoxide at 110°. The anhydrous acid of Horner[6] and Julian,[2] m.p. 152°, was not obtained.

Anal. Calcd. for $C_{14}H_{15}O_5N \cdot {}^1/_2H_2O$: C, 58.73; H, 5.63; N, 4.89. Found: C, 58.96; H, 5.64; N, 4.88.

B. From Methyl Oxindole-3-propionate.—From a 1.3-g. sample of methyl oxindole-3-propionate, by addition of methyl acrylate followed by acid hydrolysis, there was obtained 1.1 g. (66% over-all yield) of the same material described above.

1-Ethyloxindole-3,3-dipropionic Acid. (A) From Oxindole-3,3-dipropionic Acid.—A 1.2-g. sample of the oxindole-3,3-dipropionic acid described above was esterified in ethanol–benzene containing a few drops of concd. sulfuric acid. The ester was isolated in the usual way and was subjected to alkylation conditions using 0.1 g. of sodium, 15 ml. of dry ethanol and 1 ml. of ethyl iodide. After a 2-hour reflux period, the neutral product was isolated. Hydrolysis was effected with boiling 2 *N* sulfuric acid. The product crystallized from the solution in colorless form in 1.0 g. (75%) yield; m.p. 133–135°. Recrystallization from water and from ethyl acetate, followed by drying *in vacuo* at 110°, gave colorless hygroscopic needles with m.p. 137–138°.

Anal. Calcd. for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.92; H, 6.54; N, 4.61.

(B) **From 1-Ethyloxindole.**—Methyl acrylate (6.2 g.) was added to 1-ethyloxindole (3.2 g.) in a sodium ethoxide solution prepared from 0.46 g. of sodium and 20 ml. of dry ethanol. The neutral product was hydrolyzed in 10% sodium hydroxide solution, and the resulting acid was crystallized directly from the solution after acidification to yield 4.3 g. (71%) of 1-ethyloxindole-3,3-dipropionic acid; m.p. 135–137°. Recrystallization from water raised the m.p. to 137–138°, not depressed on mixture with the sample described above.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diuretics. I. 3-Substituted Paraxanthines

BY F. F. BLICKE AND H. C. GODT, JR.[1,2]

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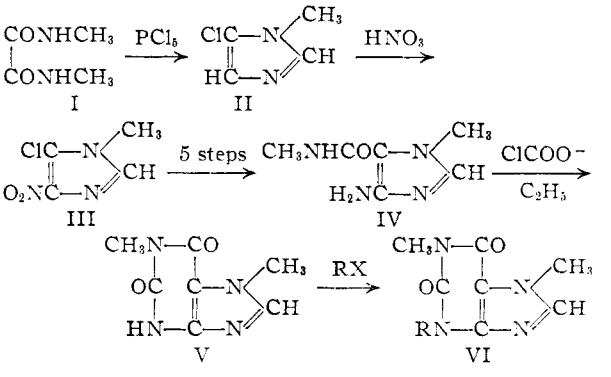
Thirteen 3-substituted paraxanthines have been obtained by alkylation of paraxanthine, and their potency as diuretics has been reported.

The 3-substituted paraxanthines were obtained by heating an aqueous alcoholic solution of paraxanthine, potassium hydroxide and the required alkyl or aralkyl halide.

It was found that the necessary paraxanthine (V) could be obtained in adequate amounts by the following eight-step process. Diethyl oxalate was converted by methylamine into N,N'-dimethyloxamide (I) in the manner described by Wallach.[3,4] The amide reacted with phosphorus pentachloride to yield 1-methyl-5-chloroimidazole (II). This reaction has been described inadequately by Wallach.[3,4] Nitration of this imidazole gave 1-methyl-4-nitro-5-chloroimidazole (III) which reacted with sodium cyanide to produce 1-methyl-4-nitro-5-cy-



(1) This paper represents part of a dissertation submitted by H. C. Godt in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1953.

(2) Monsanto Chemical Company Fellow.

(3) O. Wallach and A. Boehringer, *Ann.*, **184**, 50 (1877).

(4) O. Wallach, *ibid.*, **214**, 257 (1882).