second, higher boiling fraction of 14.0 g. was obtained, b.p. 153–157°, picrate m.p. 131–136°, which was apparently a mixture of additional 4-chloropyridine and 2-chloropyridine. This decomposed on attempted refractionation.

5-Pyrid-4,3b-indole Methiodide.—γ-Carboline was synthesized from 4-chloropyridine as described by Robinson and Thornley.[4] The methiodide was prepared in ethanol and recrystallized from isopropyl alcohol–ethyl acetate; m.p. 231–232.5°.

Anal. Calcd. for $C_{12}H_{11}N_2I$: C, 46.47; H, 3.57; I, 40.92. Found: C, 46.63; H, 3.73; I, 40.66.

Other Materials.—Norharman methobromide, harman methobromide and α-carboline methiodide were analytically pure samples prepared as described earlier.[5]

pK_a Determinations.—Solutions of approximately 200 mg. of the salts in 50 ml. of carbon dioxide-free, 60% aqueous ethanol (0.01–0.015 *M*) were titrated with standard 0.1 *N* sodium hydroxide. *p*H measurements were made at 25° after each 0.2 ml. increment of the alkali, with a Model G Beckman *p*H meter.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Formation of Dihydrocarbostyril-3-acetic Acid and Esters by Rearrangement

BY H. A. LLOYD, LOUISE U. MATTERNAS AND E. C. HORNING

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A study of the synthesis of heterocyclic systems through rearrangement reactions has been continued with an examination of an acid-catalyzed amide–ester exchange involving the transformation of a seven-membered lactam to a six-membered dihydrocarbostyril system.

The seven-membered lactam 2-oxo-5-carbethoxy-2,3,4,5-tetrahydrobenzazepine may be converted into a five-membered lactam, ethyl oxindole-3-propionate, by an acid-catalyzed intramolecular exchange reaction.[1] Since it is known that esters of oxindole-3-acetic acid undergo ring expansion to 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid under similar conditions,[2] it may be concluded that the relative order of stability of these cyclic lactams is 6 > 5 > 7, in terms of the number of members in the heterocyclic ring. If this is correct, a suitably substituted seven-membered lactam should rearrange under acid-catalyzed conditions to form a dihydroquinolone.

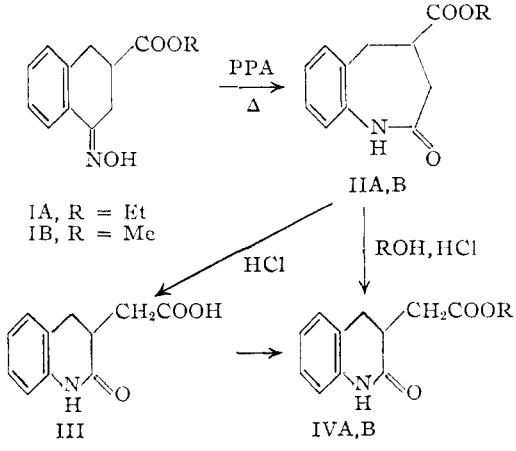
A ring contraction by amide–ester exchange was found to occur for 2-oxo-4-carbethoxy-2,3,4,5-tetrahydrobenzazepine (IIA) and the corresponding methyl ester IIB. These benzazepines were prepared by the Beckmann rearrangement of 3-carbethoxy- and 3-carbomethoxytetralone-1 oxime with polyphosphoric acid. The ester groups remained unchanged through the reaction. An intramolecular exchange reaction was carried out by heating the ester–amide in alcohol with hydrochloric acid, and the product in each case was an ester of dihydrocarbostyril-3-acetic acid (IVA, B). With concentrated hydrochloric acid, the reaction product was the corresponding acid III.

The relationship between the acid III and the ester IVB was confirmed by the esterification of the acid with diazomethane. This indicates that the acid III is indeed a dihydroquinolone rather than the isomeric seven-membered lactam-acid. A confirmation of the dihydroquinolone structure for the esters IVA, B was sought through dehydrogenation procedures. Through the use of a palladium–carbon catalyst, with or without a solvent, the ester IVA was dehydrogenated to a new substance through loss of two hydrogen atoms. This agrees with the properties expected for a dihydroquinolone; the product was ethyl carbostyril-3-acetate.

(1) H. A. Lloyd and E. C. Horning, THIS JOURNAL, **76**, 3651 (1954).

(2) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *ibid.*, **75**, 5305 (1953).

In the course of this work it was possible to make a number of comparisons of infrared spectra for seven- and six-membered lactam systems related to II and IV. In chloroform solution, the carbonyl–amide band in a seven-membered lactam system was found uniformly at 5.97 μ. This was true for 2-oxo-2,3,4,5-tetrahydrobenzazepine and its 4- and 5-substituted esters. The corresponding band for dihydrocarbostyrils, in chloroform solution, was at 5.95–5.97 μ. It therefore was not possible to follow the rearrangement by infrared measurements near 6 μ. For comparison, it may be noted that the carbonyl band of 1-ethyloxindole falls at 5.97 μ (chlf.). The oxindole acid and esters described in a previous paper show overlapping bands in the 5.77–5.97 μ range. For example, ethyl oxindole-3-propionate shows broad absorption over 5.77–5.87 μ (chlf.; in dilute solution the peak appears at 5.80 μ).



Experimental[3]

3-Carbethoxytetralone-1 Oxime (IA).—A 27-g. sample of 3-carboxytetralone-1[4] was esterified by heating a mixture of the acid, excess ethanol, benzene and a few drops of sul-

(3) All melting points were taken on a Kofler stage. Spectra measurements were carried out by Mrs. Iris Siewers. Analyses are by Dr. William Alford and his staff.

(4) E. C. Horning and G. N. Walker, THIS JOURNAL, **74**, 5148 (1952).

furic acid for 12 hours. The solvents were removed, the product was placed in ether and the solution was washed with 10% potassium carbonate solution and with water. The ether solution was dried and the ether was removed; the residual colorless keto-ester was added to a mixture of 125 ml. of dry ethanol, 125 ml. of dry pyridine and 25 g. of hydroxylamine hydrochloride. After refluxing for 3 hours, the solvents were removed and the residue was treated with water. The crystalline, slightly discolored oxime (24 g., m.p. 85–87.5°) was recrystallized from hexane–benzene and cyclohexane; m.p. 88–88.5°. This oxime is not stable on long standing.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.97; H, 6.31; N, 6.01.

3-Carbomethoxytetralone-1 Oxime (IB).—A solution of 5.0 g. of 3-carboxytetralone-1 in 250 ml. of dry methanol was saturated with hydrogen chloride and allowed to stand overnight. The neutral product was isolated and converted to the oxime in pyridine–methanol, using 6.5 g. of hydroxylamine hydrochloride. The product (3.6 g.) was recrystallized from benzene–cyclohexane, m.p. 138–138.5°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.10; H, 6.05; N, 6.30.

2-Oxo-4-carbethoxy-2,3,4,5-tetrahydrobenzazepine (IIA).—A mixture of 5.0 g. of 3-carbethoxytetralone-1 oxime and 150 g. of polyphosphoric acid was heated to 110° and maintained at that temperature for 5 minutes. After treatment with ice and water, a solid product separated. This was removed by filtration, washed well and dried. The yield was 4.3 g. (86%), m.p. 138–140°. An analytical sample was obtained by recrystallization from ethyl acetate, m.p. 141–142°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.98; N, 6.00. Found: C, 66.98; H, 6.49; N, 6.14.

2-Oxo-4-carbomethoxy-2,3,4,5-tetrahydrobenzazepine (IIB).—The rearrangement of 3-carbomethoxytetralone-1 oxime was carried out in the same way in 50% yield. The crude product (m.p. 118–119°) was recrystallized from cyclohexane–benzene; m.p. 120.5–121°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.60; H, 5.82; N, 6.37.

2-Oxo-1,2,3,4-tetrahydroquinoline-3-acetic Acid (III).—A solution of 2.0 g. of IIA in 25 ml. of concd. hydrochloric acid was heated under reflux for 2 hours. The mixture was cooled and filtered. The dried product amounted to 1.75 g. (99%); m.p. 195–203°. Recrystallization from water yielded an analytical sample, m.p. 206–208°.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.59; H, 5.37; N, 6.52.

Ethyl 2-Oxo-1,2,3,4-tetrahydroquinoline-3-acetate (IVA). By Rearrangement.—A solution of 2.0 g. of lactam IIA in ethanol–benzene containing a few drops of concd. hydrochloric acid was heated under reflux for 12 hours. The product was 1.95 g. of colorless needles; the m.p. was 100–100.5° on recrystallization from hexane.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.96; H, 6.19; N, 6.16.

By Esterification.—A 2.0-g. sample of the acid III was esterified in ethanol–benzene. The yield of neutral product was 2.2 g. (97%); m.p. 88–90.5°. Recrystallization from benzene–hexane gave colorless needles of the ester, m.p. and mixed m.p. 100–101°.

Methyl 2-Oxo-1,2,3,4-tetrahydroquinoline-3-acetate (IVB).—The reaction of diazomethane in ether–methanol with 3.6 g. of the acid III provided 3.6 g. (93%) of colorless neutral product; m.p. 148–149°. Recrystallization from benzene gave an analytical sample, m.p. 150.5–151°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.07; H, 6.02; N, 6.19.

The same ester was obtained when the lactam IIB was heated under reflux (16 hours) in methanol containing a few drops of concd. hydrochloric acid.

Ethyl Carbostyril-3-acetate.—A mixture of 200 mg. of the ethyl ester IVA and 100 mg. of 5% palladium–carbon catalyst was heated to 250° and maintained at that temperature for 15 minutes. After cooling the mixture, the product was separated with hot benzene to yield 140 mg. (70%) of colorless needles, m.p. 185–187°. An analytical sample was obtained by recrystallization from benzene; m.p. 186.5–187°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.71; H, 5.81; N, 5.88.

It was found that this dehydrogenation could be effected in 74% yield by a solvent procedure with *p*-cymene. A mixture of 1.5 g. of ester IVA, 0.8 g. of 5% palladium–carbon catalyst and 15 ml. of cymene was heated under reflux for 3 hours. The catalyst was removed by filtration and washed with hot ethyl acetate. The combined solvents were reduced in volume and the product was allowed to crystallize.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Experiments in the Colchicine Field. III.[1] A New Method for the Synthesis of Tricyclic Fused Ring Structures[2]

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2-(β-Phenylethyl)-benzaldehyde was converted to the hydrazone, the hydrazone was oxidized to the diazo compound, and the diazo compound was cyclized to a mixture of 2-phenylindane and 6,6a-dihydro-5*H*-cyclohepta[*a*]naphthalene (V). The proof of structure of V rests on carbon and hydrogen analysis, ultraviolet spectrum, formation of a maleic anhydride adduct, hydrogenation to a hexahydro derivative, and dehydrogenation of the latter to 8,9,10,11-tetrahydro-7*H*-cyclohepta[*a*]naphthalene (VII) which also was prepared by an unequivocal route. Compound V is of interest in that it possesses a phenylcycloheptatriene structure incorporated in a tricyclic system, a feature present in colchicine.

The ring enlargement of aromatic nuclei by means of carbomethoxydiazomethane (diazoacetic ester) was discovered and extensively studied by Buchner and his co-workers.[3] More recently diazomethane itself has been shown to undergo a similar reaction with a variety of aromatic nuclei,[4,5] and experiments in this Laboratory[6] and elsewhere[7] have shown that phenyldiazomethane also can act as a ring-enlarging agent for aromatic nuclei. The present communication concerns a derivative of phenyldiazomethane which, by virtue of an appropriate *ortho* substituent, undergoes in-

(1) The earlier articles by C. D. Gutsche and K. L. Seligman, THIS JOURNAL, **75**, 2579 (1953), and by C. D. Gutsche and F. A. Fleming, *ibid.*, **76**, 1771 (1954), are to be considered as papers I and II of this series.

(2) This work was supported, in part, by grants-in-aid from: (a) The Monsanto Chemical Co., (b) The Petrolite Corp., (c) The American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

(3) *Cf.* N. L. Drake and T. R. Sweeny, *J. Org. Chem.*, **11**, 67 (1946), for a bibliography of Buchner's contributions.

(4) W. von E. Doering and L. H. Knox, THIS JOURNAL, **72**, 2305 (1950); **73**, 828 (1951).

(5) W. von E. Doering and L. H. Knox, *ibid.*, **75**, 297 (1953).

(6) C. D. Gutsche and E. J. Jason, unpublished observations.

(7) W. Treibs and M. Quarg, *Angew. Chem.*, **67**, 76 (1955).