as confirmatory evidence for the presence of biphenylpolycarboxylic acids in the acids obtained by the oxidation of coal. The nuclei isolated in this work, phenyl, biphenyl, phthalan and "lactone," not only are indicative of the nuclear structure of the acids produced by the oxidation of coal, but may also represent some of the fundamental units which comprise the coal structure, and which were resistant to further degradation by the methods employed in this work.

Acknowledgment.—The author wishes to express his appreciation to Dr. H. C. Howard of the Coal Research Laboratory for assistance in operating the Piros-Glover distillation column. Absorption spectra were run on the Baird infrared and the Cary ultraviolet recording spectrophotometers of the Mellon Institute, Pittsburgh, Pa. The ultimate analyses were performed by the Huffman Microanalytical Laboratories, Denver, Colorado.

PITTSBURGH, PENNSYLVANIA

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Hofmann Degradation of *cis*- and *trans*-2-Phenylcyclohexylamines

BY RICHARD T. ARNOLD AND PAUL N. RICHARDSON[1]

RECEIVED MARCH 11, 1954

Pure *cis*- and *trans*-2-phenylcyclohexylamines have been prepared and characterized. Thermal decomposition of the quaternary hydroxides from each of these substances gave 1-phenylcyclohexene as the sole identifiable hydrocarbon. The data may be explained in terms of the current views relative to the mechanism of the Hofmann degradation.

Recent studies relative to the mechanism of the Hofmann degradation[2-4] have shown quite conclusively that this reaction involves a bimolecular, ionic, *trans* elimination. The elucidation of the structures assigned to the isomeric menthylamines[5] and 3α- and 3β-dimethylaminoallopregnanes[6] is based upon these considerations.

During the course of another investigation we were obliged to prepare pure *cis*- and *trans*-2-phenylcyclohexylamines (III and IV, respectively). This was accomplished by means of a Curtius degradation on carefully purified *cis*- and *trans*-2-phenylcyclohexanecarboxylic acids (I and II, respectively) since it is well recognized that no change in configuration takes place during this transformation.[7,8] Compounds I and II have been synthesized by Gutsche[9] and Alder and co-workers.[10]

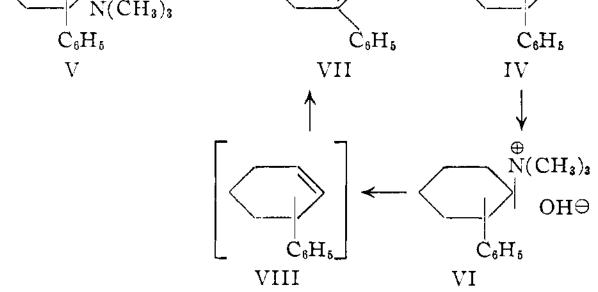
Although the latter investigators encountered difficulty in the *cis* → *trans* isomerization of methyl 2-phenylcyclohexylcarboxylate and reported no yield for this step, we have found that the *trans* ester may be obtained readily in 96% yield. This modified route would appear to be more practical than that employed by Gutsche.[9]

We have now established that 2-phenylcyclohexylamine prepared by the reduction of 2-phenylcyclohexanone oxime with sodium and alcohol,[11] or *via* the Diels–Alder reaction of ω-nitrostyrene and butadiene[12] has the *trans* configuration.

No difficulty was experienced in transforming the geometric isomeric primary amines into the corresponding tertiary compounds by methylation with formaldehyde and formic acid[13] and these were converted in the usual fashion to the isomeric quaternary salts and hydroxides.

A reaction scheme is

$C_6H_5—CH=CH—CH=CH_2 + CH_2=CH—CO_2H$



Assuming *trans* elimination, and recognizing that the most acidic hydrogen atom in the quaternary bases is attached to C_2 which holds the phenyl group, 1-phenylcyclohexene (VII) should be derived from V and 3-phenylcyclohexene (VIII) from VI.

However, examination of the ultraviolet spectra and refractive indices of the hydrocarbon samples produced from each isomeric quaternary base proved them to be essentially indistinguishable

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(1) Taken from the Ph.D. thesis of Paul N. Richardson, April, 1952.

(2) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Wolff, *J. Chem. Soc.*, 2093 (1948).

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from each other and practically identical with an authentic sample of 1-phenylcyclohexene.[16,17]

Although the pyrolysis of quaternary bases has long been utilized as a reliable method for the preparation of pure olefins, care must be exercised in those cases in which the newly formed carbon–carbon double bond is separated by a single methylene group from a carbon–carbon double bond present in the starting material. The formation of 1,3-pentadiene (rather than the 1,4-isomer) in the exhaustive methylation of piperidine[18] and the conversion of 3-phenylpropylamine to propenylbenzene (rather than allylbenzene)[19] represent cases in point.

We believe that the above two examples as well as that reported in this paper are the result of a base catalyzed prototropic shift which converts the first formed isolated diene into the more stable conjugated system. The isolation of 1-phenylcyclohexene (VII), rather than 3-phenylcyclohexene (VIII) from the quaternary base VI does not therefore represent evidence against the current view that the Hofmann degradation of quaternary bases proceeds by *trans* elimination.

Acknowledgment.—One of us (R.T.A.) wishes to thank Prof. Dr. W. Hückel of the University of Tuebingen for a profitable discussion on the subject of this paper.

Experimental

***cis*-2-Phenylcyclohexanecarboxylic Acid (I).**—This compound was prepared by the method of Alder, Vagt and Vogt.[10]

***trans*-2-Phenylcyclohexanecarboxylic Acid (II).**—The description of this synthesis is included here in detail because of the difficulties reported earlier.[10]

An ethereal solution of diazomethane was prepared by the addition of N-nitrosomethylurea (15 g.) to a 40% solution of potassium hydroxide (70 ml.) at 0° which was overlaid with ether (200 ml.). To this was added *cis*-2-phenylcyclohexanecarboxylic acid (20 g.) in small portions. Esterification occurred rapidly, and the excess diazomethane was destroyed by the dropwise addition of acetic acid. The solvent was removed under reduced pressure and to the residue was added a 10% solution of sodium methoxide (200 ml.) in anhydrous methanol. The resulting solution was boiled for 7.5 hours after which 10% aqueous potassium hydroxide (200 ml.) was added. Heating under reflux was then continued for an additional 12 hours. The solution was poured into water, cooled, and carefully acidified with concentrated hydrochloric acid. After several hours the product crystallized and was collected on a filter and air-dried; yield 19.2 g. (96%), m.p. 105.5–106.5°. This material is of satisfactory purity for synthetic purposes. Pure *trans*-2-phenylcyclohexanecarboxylic acid melts at 108°.[10]

***cis*-2-Phenylcyclohexylamine (III).**—The general conditions for the Curtius degradation as described by Bachmann and Fornefeld[20] were employed.

An excess of purified thionyl chloride was added to *cis*-2-phenylcyclohexanecarboxylic acid (20 g.) and the solution was allowed to stand at room temperature overnight. The excess thionyl chloride was removed under vacuum at room temperature and benzene was twice distilled from the residue in order to remove the last traces of thionyl chloride. The crude acid chloride was dissolved in acetone (225 ml.), cooled to 0°, and treated with a solution of sodium azide (20 g.) dissolved in water (135 ml.). The solution was stirred for 15 minutes, poured into water, and extracted with ether. The ethereal layer was washed first with dilute sodium bicarbonate and then with water. Acetic acid (70 ml., 70%) was added to the ether solution and the ether was removed by distillation at room temperature under reduced pressure. An additional portion of aqueous acetic acid (130 ml., 70%) was added, and the mixture was heated on the steam-bath for two hours. Afterward, concentrated hydrochloric acid (200 ml.) was added and heating was continued overnight. The cooled solution was poured into water and extracted with ether. The aqueous phase was made alkaline with sodium hydroxide, cooled and extracted with ether. The ether solution was dried with magnesium sulfate and fractionated. *cis*-2-Phenylcyclohexylamine in a yield of 8.18 g. (50.5%) was obtained, b.p. 133° (10 mm.), n^{23}_{D} 1.5457.

The free amine rapidly reacted with carbon dioxide in the atmosphere and therefore was converted with phenyl isothiocyanate into its N-phenylthioureide, m.p. 137–138°.

Anal. Calcd. for $C_{19}H_{22}N_2S$: C, 73.5; H, 7.14. Found: C, 73.8; H, 7.35.

***trans*-2-Phenylcyclohexylamine (IV).**—This compound was prepared from *trans*-2-phenylcyclohexanecarboxylic acid (19.2 g.) using the same procedure as described above for the *cis* isomer; yield 12 g. (78%), m.p. 59–60°.[11]

For analysis the amine which rapidly absorbed carbon dioxide was converted into its N-phenylthioureide, m.p. 185–186°.

Anal. Calcd. for $C_{19}H_{22}N_2S$: C, 73.5; H, 7.14. Found: C, 73.9; H, 7.47.

N,N-Dimethyl-*cis*-2-phenylcyclohexylamine.—*cis*-2-Phenylcyclohexylamine (5 g.), formaldehyde (5.4 g., 40%) and formic acid (43 g.) were heated together under reflux for eight hours. Concentrated hydrochloric acid (4 ml.) was added and the formic acid removed by distillation under reduced pressure. Water was added to the residue and the solution was made alkaline with dilute sodium hydroxide. The solution was extracted with ether, and the extract was dried and fractionated. The tertiary amine was obtained in a yield of 3.23 g. (55.5%), b.p. 135° (10 mm.), n^{21}_{D} 1.5370. Rapid absorption of atmospheric carbon dioxide rendered the analysis of this compound and its *trans* isomer extremely difficult. The quaternary salts, however, gave correct analyses.

N,N-Dimethyl-*trans*-2-phenylcyclohexylamine.—This compound was prepared by the methylation of *trans*-2-phenylcyclohexylamine (8 g.) using the method described above for the *cis* isomer; yield 5.9 g. (62%), b.p. 130–132° (11 mm.), n^{21}_{D} 1.5282.

Trimethyl-*cis*-2-phenylcyclohexylammonium Iodide.—N,N-Dimethyl-*cis*-2-phenylcyclohexylamine (2 g.) was dissolved in ether, treated with a slight excess of methyl iodide and allowed to stand at room temperature overnight. The product weighed 3 g. (87%), m.p. 215–217°.

Anal. Calcd. for $C_{15}H_{24}NI$: C, 52.18; H, 7.01. Found: C, 52.25; H, 7.01.

Trimethyl-*trans*-2-phenylcyclohexylammonium Iodide.—This quaternary salt was prepared from N,N-dimethyl-*trans*-2-phenylcyclohexylamine (4.87 g.) and an excess of methyl iodide dissolved in ether. After 24 hours, the product was collected on a filter and was recrystallized from absolute ethanol; yield 6.8 g. (82%), m.p. 233.5–235°.

Anal. Calcd. for $C_{15}H_{24}NI$: C, 52.18; H, 7.01. Found: C, 52.08; H, 7.21.

Decomposition of Trimethyl-*cis*-2-phenylcyclohexylammonium Hydroxide.—Silver oxide was prepared in aqueous solution from equimolar quantities of silver nitrate and sodium hydroxide.

An aqueous solution of the quaternary hydroxide was made by treating trimethyl-*cis*-2-phenylcyclohexylammonium iodide (2.5 g.) with an excess of silver oxide in water (60 ml.). The mixture was stirred for one hour, filtered, and the precipitate was washed until the filtrate was alkali free. The aqueous portions were combined, heated under reflux for one hour and then distilled. Near completion of the distillation, water in 5–10 ml. portions was added to the distilling flask and steam distillation continued until no further hydrocarbon appeared in the steam distillate. The two-phase distillate was extracted with petroleum ether (35–45°) and the latter solution was washed with hydrochloric acid (5%), water, dried and fractionated. The hydrocarbon product (0.83 g.) had the following constants: n^{20}_{D} 1.5690, $\log \epsilon_{246}$ 4.068 (ϵ 11,700). The sample, there

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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

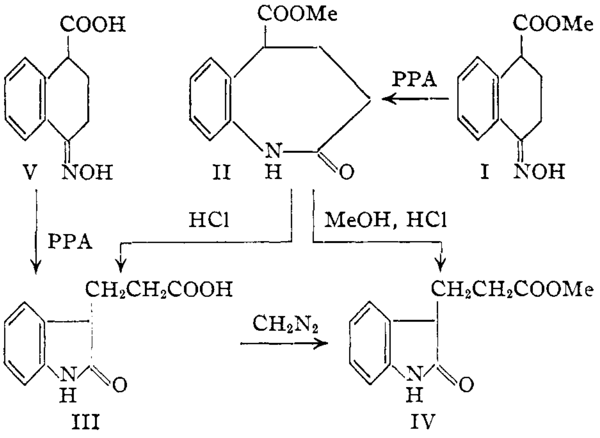
RECEIVED FEBRUARY 26, 1954

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.

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