[CONTRIBUTION NO. 107 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE UNIVERSITY]

# On the Configuration of *N*-Substituted Benzimide-chlorides from the Beckmann Rearrangement

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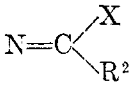
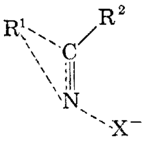
The imide-chloride prepared from 4,4′-dinitrobenzanilide with phosphorus pentachloride which has been prepared for the first time has the *anti* configuration. The Beckmann rearrangement of 4,4′-dinitrobenzophenone oxime with phosphorus pentachloride gives this imide-chloride with the *anti* configuration. As no corresponding *syn*-imide-chloride could be prepared independently, this can throw no further light on the mechanism of the Beckmann rearrangement. Similar results were obtained with the corresponding 4,4′-dibromo compounds which were prepared for the first time.

According to the mechanism proposed by Dewar[1] for the Beckmann rearrangement of oximes and oxime ethers, intermediates of the type $R^1—$



$N{=}C\begin{smallmatrix}X\\R^2\end{smallmatrix}$ are postulated, where $X^-$ is a negative group. The interpretation given is that there is a $\pi$-complex mechanism operating and that the *trans* migration follows from the fact that in the transition state one lobe of the nascent $\pi$-bond is used to bind the departing $X^-$ ion.



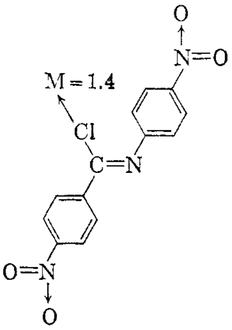
The use of phosphorus pentachloride to effect rearrangement leads to imide-chlorides as intermediates. These are isolable and stable provided moisture is excluded.

Evidently it is of interest to isolate the geometric isomers of the imide-chlorides and examine their stability. If, and only if both isomers are demonstrated to be long lived under the rearrangement conditions could their configuration be used to throw further light on the mechanism of the Beckmann rearrangement.

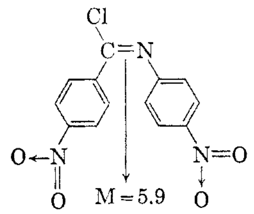
This present paper records attempts to prepare *syn* and *anti*-imide-chlorides. Unfortunately, the results indicate that such compounds change rapidly to the more stable *anti* configuration invalidating conclusions concerning the stereochemistry of the Beckmann rearrangement.

## RESULTS

The rearrangement product of 4,4′-dinitrobenzophenone oxime with phosphorus pentachloride was isolated according to the procedure described below and is a stable material melting at 130.8–131.2°. Its melting point does not change on sublimation in vacuum at 120°, on repeated recrystallizations from benzene or carbon tetrachloride, and on careful elution through an alumina chromatographic column with a 1:1 hexane-benzene mixture, where no band other than the single imide-chloride band appeared. The dipole moment of the material as determined in benzene solution at 25° was 1.20 D ± 0.5 D.[2] The value calculated for the *anti*-imide-chloride is 1.4 D and the value calculated for the *syn*-imide-chloride is 5.9 D. In calculating the dipole moments of these above models the group moments and angles for benzene derivatives were used.



*anti*-model



*syn*-model

The product obtained from treating 4,4′-dinitrobenzanilide with phosphorus pentachloride, the only other known procedure for preparing this type of imide-chloride, was isolated in pure form and its melting point and mixed melting point with the material of the Beckmann rearrangement were identical at 130.8–131.2°. This melting point was not altered by repeated recrystallizations, sublimation in vacuum, or chromatic elution.

In the same manner the product of the Beckmann rearrangement of 4,4′-dibromobenzophenone oxime was shown to be identical with the product of the reaction of 4,4′-dibromobenzanilide and phosphorus pentachloride. Both melted at 93–94° with no depression on mixing. All samples of imide-chlorides yielded the respective anilides on hydrolysis in 1:1 acetone–ammonia water.

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[1] M. R. S. Dewar, *Electronic Theory of Organic Chemistry*, Oxford, London, 1949, p. 219.

[2] Capacitance measurements with Type 650-A Impedance Bridge, General Radio Co., Cambridge, Mass.; Audio generator at 6000 c.p.s.; Oscilloscope detector.

TABLE I

DIELECTRIC DATA FOR 4-NITROBENZ-4-NITROPHENYL-IMINO-CHLORIDE

Capacitance of cell empty = 42.0 mmf. Temp. = 25° ± 0.1°. Capacitance of cell with benzene = 78.0 mmf

| | | | | | | |
|---|---|---|---|---|---|---|
| $N_2$ | $7.14 \times 10^{-4}$ | $1.83 \times 10^{-3}$ | $5.59 \times 10^{-3}$ | $1.09 \times 10^{-2}$ | $1.66 \times 10^{-2}$ | $2.18 \times 10^{-2}$ |
| $N_1$ | 0.999 | 0.998 | 0.994 | 0.989 | 0.983 | 0.978 |
| $\epsilon_{25}{}^{\circ}$ | 2.28 | 2.28 | 2.29 | 2.31 | 2.32 | 2.34 |
| Density | 0.875 | 0.875 | 0.877 | 0.879 | 0.881 | 0.883 |
| $P_{12}$ | 26.2 | 26.3 | 26.8 | 27.7 | 28.6 | 29.5 |
| $P_2$ | 110 | 115 | 125 | 138 | 155 | 179 |

Nothing about the stereochemistry of the Beckman rearrangement can be deduced from the results of the above experiments as the only other available preparative method for this type of imide-chloride failed to yield a *syn*-isomer. Nowhere in the literature is it reported that a pair of isomeric imide-chlorides have been prepared, all preparations yielding a single compound, presumably the *anti*-isomer. Coleman and Pyle[3] report that the imide-chlorides of benzanilide and *p*-chlorobenzanilide are identical with the imide-chlorides from the Beckmann rearrangement of the proper ketoximes.

## EXPERIMENTAL

*4,4'-Dinitrobenzanilide* and *4,4'-dibromobenzanilide* were prepared by the method of Barnett and Nixon[4]; 4,4'-dinitrobenzophenone was prepared by the method of Staedel,[5] and converted to its oxime by the method of Shriner and Fuson[6]; *4,4'-dibromobenzophenone* by the method of Montagne[7] and converted to its oxime in an identical fashion as above.

*4-Nitrobenz-4-nitrophenyl-imide-chloride. Method A.* Five grams of 4,4'-dinitrobenzanilide which had been previously dried in an oven at 110° for 3 hr. and 4 g. of finely divided phosphorus pentachloride were placed in a 10-ml. distilling flask and connected to the aspirator by means of a filter flask which also served as a receiver. The distilling flask was heated on an oil bath to 95°, whence the mass melted and the evolution of hydrogen chloride commenced. After 10 min. the reaction subsided and the pressure was gradually reduced with the aspirator. The phosphorus oxychloride distilled and the reaction mixture became solid again. The solid was dissolved in hot, dry benzene and removed from the flask by forcing it through a glass tube containing a cotton plug by means of a pressure of dry air. Large yellow crystals were deposited on cooling and were filtered from the liquor and dried under vacuum; m.p. 129–130°; yield 4.3 g., 81%.

Repeated recrystallization from benzene and/or carbon tetrachloride gave a material which melted at 130.8–131.2°.[8] Slow sublimation under a pressure of 0.5 mm. at 100° did not change this melting point. The material was dissolved in a 1:1 hexane-benzene mixture and the solution passed through a column of activated alumina. Only one band appeared and was eluted. The solid which was crystallized from various cuts of the eluent all melted at 130.8–131.2°. The equivalent weight of the material determined argentometrically[9] was 309.6 which compares with 305.5 for the calculated value.

*Method B.* Seven grams of 4,4'-dinitrobenzophenone oxime was dissolved in the minimum amount of benzene, 225 ml., at 75° in a 500-ml. distilling flask, fitted with a condenser and a receiving flask. Solid phosphorus pentachloride, 6.4 g., was added at such a rate as to produce a vigorous reaction which did not become violent. After the addition of the phosphorus pentachloride, 10–12 min., the pressure of the system was gradually reduced by connecting an aspirator to the receiving flask and the benzene and phosphorus oxychloride were removed. A solid yellow mass remained which was dissolved in benzene and isolated in the identical manner as above; yield 6.1 g., 82%, m.p. 130.5–131°. Repeated recrystallizations gave a melting point which was constant at 130.8–131.2° which was not depressed on mixing with the imidechloride prepared from the anilide.

Table I gives the values of $P_2$ of 4-nitrobenz-4-nitrophenylimino-chloride as a function of concentration. $N_1$ and $N_2$ are respectively the mole-fractions of solute and solvent while $\epsilon_{25}{}^{\circ}$ is the dielective constant at 25° with a frequency of 6000 cycles per second. $P_{12}$ is the molar polarization of the mixtures while $P_2$ is that of the solute calculated on the basis that

$$P_{12} = N_1P_1 + N_2P_2 \tag{1}$$

The value for $P_1$ for benzene was of course equal to the value of $P_{12}$ at infinite dilute. The total polarization of the solute $P_2$, at infinite dilution and obtained by extrapolation, was 108. The contribution of dipole orientation, $P$, to $P_2{}^0$ was calculated from the formula

$$P_2{}^0 = P_a + P_e + P \tag{2}$$

Atomic polarization was neglected and $P_e$— was calculated from the molar refraction which was obtained from tables of refractivities given by Partington.[10] It was found to be 78. These give a value of 30 for the orientation polarization which yields a moment of 1.20 D when substituted in the moment equation.

$$\begin{aligned} P &= 108 - 78 = 30 \\ &= 0.0127 \times 10^{-18}(T \times P)^{1/2} \\ &= 1.20 \text{ D} \end{aligned}$$

*4-Bromobenz-4-bromophenylimide-chloride. Method A.* Eighteen grams of 4,4'-dibromobenzophenone oxime and 10.5 g. of phosphorus pentachloride, using the same pro-

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[3] G. H. Coleman and E. R. Pyle, *J. Am. Chem. Soc.*, **68**, 2007 (1946).

[4] E. Barnett and I. G. Nixon, *Chem. News*, **129**, 90–91 (1924).

[5] W. Staedel, *Ann.*, **283**, 168 (1894).

[6] R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202, Method A.

[7] P. J. Montagne, *Rec. Trav. Chim.*, **29**, 156 (1910).

[8] Melting points of the purified materials were measured on a micro-melting stage with thermocouple and potentiometer previously calibrated.

[9] E. H. Swift, *A System of Chemical Analysis*, Prentice Hall, Inc., New York, N. Y., 1940, p. 347.

[10] *An Advanced Treatise on Physical Chemistry*, Vol. IV, Longmans Green, and Co., Ltd., London, 1953, pp. 56–61.

cedure as above, gave 15 g. (80%) of product melting at 93.0–94.0° upon two recrystallizations from benzene.

*Method B.* The imide-chloride prepared in an identical manner as above from 2.1 g. of phosphorus pentachloride and 3.5 g. of 4,4′-dibromobenzanilide also melted at 93.0–94.0°, when recrystallized twice from benzene. This was not depressed on mixing with the material from the Beckmann rearrangement of the ketoxime; yield 2.7 g., 72%.

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[CONTRIBUTION FROM THE DIVISION OF ONCOLOGY, THE CHICAGO MEDICAL SCHOOL]

# K Region Fission and Addition Products of 7,12-Dimethylbenz[a]anthracene[1]

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The K region (5,6-positions) of 7,12-dimethylbenz[a]anthracene was cleaved by treating the appropriate dihydrodiol with sodium periodate. The resultant dialdehyde was converted to several oxygenated products as well as 5,6-dihydro-7,12-dimethylbenz[a]anthracene. This latter compound was also obtained in good yield by the hydrogenation of the parent polynuclear hydrocarbon using palladium on strontium carbonate as catalyst.[3]

The carcinogenic property of the polynuclear hydrocarbon 7,12-dimethylbenz[a]anthracene, I, has been extensively investigated.[4] This hydrocarbon has been found to be extremely potent as a skin carcinogen.[5–9] Nevertheless, very little has been reported on the metabolism of this hydrocarbon. An important factor contributing to this lack of information is the paucity of chemical studies which began with methyl-substituted polynuclear hydrocarbons in general and 7,12-dimethylbenz[a]anthracene in particular.

For some time,[10] as indicated by several reviews[11,12,13] it has been speculated that a biochemical process which occurred at the K region[14] of a polynuclear hydrocarbon was significant to carcinogenesis. Metabolism at the K region of the carcinogen dibenz[a,h]anthracene was established when the dibasic acid resulting from fission at this region was characterized as a metabolite.[15] Consequently, a variety of alteration products which involved either fission or addition to the K region of 7,12-dimethylbenz[a]anthracene have been prepared.

When starting with unsubstituted polynuclear hydrocarbons, the customary route to K region fission products has been the addition of osmium tetroxide followed by hydrolysis to the dihydrodiol.[16] Oxidation with a dichromate salt[15,17] or chromic acid[18] converted the dihydrodiol to an *ortho* quinone. The *ortho* quinone was cleaved to a dibasic acid with peracetic acid.[15,17] This route was unsuccessful when applied to 7,12-dimethylbenz[a]anthracene. Although the dihydrodiol, II, of the substituted hydrocarbon was available through the action of osmium tetroxide on 7,12-dimethylbenz[a]anthracene,[16] the oxidative step to the *ortho* quinone was fruitless.

An alternative route to K region fission products of 7,12-dimethylbenz[a]anthracene was developed. The dihydrodiol, II, when treated with sodium periodate gave the dialdehyde, III, in quantitative yield.[19] An attempt to use alkaline silver oxide for the oxidation of the dialdehyde, II, to the corresponding dibasic acid failed. An acidic product was isolated with difficulty from the reaction mixture. This product, on the basis of elemental analysis, corresponded to an alcohol acid and presumably was IV. The lactonization of IV would be in keep-

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[1] This work was supported by grant C-2399 National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Md.

[2] Present address: Department of Biochemistry, University of Wisconsin, Madison, Wis.

[3] An abstract of some of this work appeared in *Proc. Am. Assoc. Cancer Research* **3**, 25 (1959).

[4] P. Shubik and J. L. Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, Supplement I, United States Government Printing Office, Washington, 1957, p. 153.

[5] W. E. Bachman, E. L. Kennaway, and N. M. Kennaway, *Yale J. Biol. and Med.*, **11**, 97 (1938).

[6] M. Klein, *Cancer Research*, **16**, 123 (1956).

[7] V. Darchun and H. I. Hadler, *Cancer Research*, **16**, 316 (1956).

[8] H. I. Hadler, V. Darchun, and K. Lee, *J. Nat. Cancer Inst.* **23**, 1383 (1959).

[9] G. Della Porta, H. Rappaport, U. Saffiotti, and P. Shubik, *A. M. A. Archiv. Path.*, **61**, 305 (1956).

[10] O. Schmidt, *Naturwissenchaften* **29**, 146 (1941).

[11] C. A. Coulson, *Adv. in Cancer Research*, **I**, 1 (1953).

[12] G. M. Badger, *Adv. in Cancer Research*, **2**, 73 (1954).

[13] A. Pullman and B. Pullman, *Adv. in Cancer Research*, **3**, 117 (1955).

[14] The possession of a phenanthrene moiety has been accepted as a required structural feature for carcinogenic activity in a polynuclear hydrocarbon. The 9,10-double bond of the phenanthrene moiety has been termed the K region of the polynuclear hydrocarbon. This region is susceptible to 1,2-addition reactions. In 7,12-dimethylbenz[a]anthracene the 5,6-positions are the K region.

[15] P. M. Bhargava, H. I. Hadler, and C. Heidelberger, *J. Am. Chem. Soc.*, **77**, 2877 (1955).

[16] J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).

[17] E. F. M. Stephenson, *J. Chem. Soc.*, 2620 (1949).

[18] C. J. Collins, J. G. Burr, Jr., and D. N. Hess, *J. Am. Chem. Soc.*, **73**, 5176 (1951).

[19] Collins, Burr and Hess[18] reported that the K region dihydrodiol of the unsubstituted polynuclear hydrocarbon, benz[a]anthracene, was not cleaved by lead tetraacetate.