hydrochloric acid, and the resulting *4-methoxy-1-phenyl-2-naphthylphenylketimine hydrochloride* was removed by filtration. To remove bromide anion, the salt was dissolved in alcohol and made basic with ammonium hydroxide. Addition of water then gave a colorless oil which was taken up in ether and reconverted to the hydrochloride by shaking with dilute hydrochloric acid. The salt was nearly insoluble in hot water, ethyl acetate, or benzene. It was easily soluble in chloroform and crystallized from a mixture of methanol and ether as deep yellow prisms, m.p. 235–240°; yield 1 g.

Anal. Calcd. for $C_{24}H_{20}ClNO + CH_3OH$: C, 74.0; H, 5.92. Found: C, 74.11; H, 5.37.

The ketimine salt was quite resistant to hydrolysis, but when 0.6 g. of it was boiled for 15 min. with 5 ml. of 50% acetic acid containing a few drops of hydrochloric acid, it gave 0.5 g. of 3-benzoyl-1-methoxy-4-phenylnaphthalene, identical (mixed melting point and infrared spectrum) with the compound obtained before.

Acknowledgment. The author thanks Mrs. O. Hamerston for analytical results.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Cleavage of 10-Substituted 1,2-Benzanthracenes[1-3]

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The acid-catalyzed cleavage of 10-substituted 1,2-benzanthracenes has been observed and investigated.

Since a recent publication[4] noted the physiological activity of 10-phenyl-1,2-benzanthracene, and since 10-methyl-1,2-benzanthracene is a carcinogen, we thought it would be interesting to prepare 10-cyclohexyl-1,2-benzanthracene and have it screened for possible carcinogenic or carcinolytic activity. In view of the extensive use made of aromatic cyclodehydration reactions to prepare *meso*-substituted 1,2-benzanthracenes,[5] we chose to attempt the preparation of 10-cyclohexyl-1,2-benzanthracene (IIa) *via* the aromatic cyclodehydration of 2-(1-naphthylmethyl)phenyl cyclohexyl ketone (Ia). This ketone was prepared by the Grignard reaction between cyclohexylmagnesium bromide and 2-(1-naphthylmethyl)benzonitrile[6] followed by acid hydrolysis.[7] The first attempts at cyclization of the ketone involved the use of the often used boiling hydrobromic–acetic acid mixture. Although 14% of the expected 10-cyclohexyl-1,2-benzanthracene (IIa) was obtained, 32% of 1,2-benzanthracene (III) was also isolated. Apparently cleavage of the cyclohexyl group occurred during the course of the reaction. We also observed cleavage in the anthracene series. The acid-catalyzed cyclization of 2-benzylphenyl cyclohexyl ketone gave 29% of the expected hydrocarbon, 9-cyclohexylanthracene, and 23% of anthracene. Several instances of the loss of aromatic groups had been observed previously in this laboratory. Vingiello and Borkovec[8] reported cleavage during the attempted preparation of some di-*ortho* substituted *meso* phenyl-1,2-benzanthracenes and Vingiello and Stevens[4] reported loss of a methoxyphenyl group when 2-(1-naphthylmethyl)-4′-methoxy benzophenone or 2-(1-naphthylmethyl)-2′-methoxy diphenyl ketimine hydrochloride was treated with a strong acid. In either case, 1,2-benzanthracene was the only product isolated. Just recently Zajac[9] observed cleavage during the acid-catalyzed cyclization of 2-(2-naphthylmethyl)-2′-chloro-5′-methylbenzophenone which gave 1,2-benzanthracene. Bradsher and co-workers[10] reported the loss of an isopropyl group during the acid-catalyzed cyclization of ketones to give 9,10-dialkylphenanthrenes. They also showed that an olefin oxide which might be expected to yield 9-isopropyl-10-isobutylphenanthrene afforded instead 9-isobutylphenanthrene. They suggested that the loss of the isopropyl group in 9-isopropyl-10-alkylphenanthrenes was probably due to the strain introduced by crowding the two groups into the rather restricted space at the 9- and 10-positions. Our observations in

(1) This paper has been abstracted in part from the Master's thesis of Thomas J. Delia presented to the Virginia Polytechnic Institute in 1959.

(2) This investigation was supported in part by a research grant (S-73) from the Bureau of State Services (Division of Sanitary Engineering Services and Division of Special Health Services) of the National Institutes of Health, Public Health Service.

(3) Presented before the Chemistry Section at the Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., November 1960.

(4) F. A. Vingiello and R. K. Stevens, *J. Am. Chem. Soc.*, 80, 5256 (1958).

(5) See F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, 78, 1240 (1956), and references listed there.

(6) F. A. Vingiello, A. Borkovec, and J. Shulman, *J. Am. Chem. Soc.*, 77, 2320 (1955).

(7) Again it was found that the yield of the ketone was 15–20% higher if the ketimine hydrochloride was not isolated; see Ref. 5.

(8) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, 78, 3205 (1956).

(9) W. W. Zajac, Jr., Ph.D. Dissertation, Virginia Polytechnic Institute, 1959.

(10) C. K. Bradsher and D. J. Beavers, *J. Am. Chem. Soc.*, 78, 3193 (1956); C. K. Bradsher and W. J. Jackson, Jr., *J. Am. Chem. Soc.*, 76, 4140 (1954); S. T. Amore, Ph.D. Dissertation, Duke University, 1944.

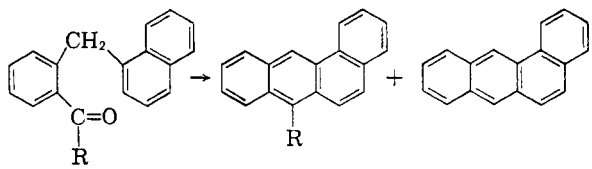
the benzanthracene series apparently involve steric strain resulting from interactions of the substituent in the 10- position with the 4- and 5-positions in the ring system itself rather than with another substituent. It is interesting to note that no cleavage was reported when 6- and 7-isopropyl-1,2-benzanthracenes were prepared by a method involving cyclization with concentrated sulfuric acid[11] nor was cleavage reported when 7-isopropenyl-1,2-benzanthracene was prepared by a method involving cyclization with hydrochloric and acetic acid.[12] This is in accord with the fact that the 6- and 7-positions are not as hindered as in the 10-position in 1,2-benzanthracene. Colonge and Bonnard[13] reported an interesting preparation of 9-isopropylanthracene which involved a variation of Bradsher's[14] original aromatic cyclodehydration reaction. They cyclodehydrated 6-isopropionyl-2,3,4,5-tetrahydrodiphenylmethane with the usual hydrobromic–acetic acid mixture and obtained 9 - isopropyl - 1,2,3,4 - tetrahydroanthracene which they dehydrogenated with sulfur to obtain the desired 9-isopropylanthracene. The geometry of the tetrahydro compounds is such as probably to afford less strain accounting for the lack of cleavage (loss of the isopropyl group). The sulfur is not acidic enough to cleave the 9-isopropylanthracene.

Although the mechanism of the loss of the cyclohexyl group during cyclization is not clear, it has been established that 10-cyclohexyl-1,2-benzanthracene is cleaved quantitatively to 1,2-benzanthracene when heated for twenty-four hours with the usual hydrobromic-acetic acid mixture. Similar treatment with only acetic acid results in recovery of the starting hydrocarbon.

Bradsher and Beavers[10] have mentioned that the acid-catalyzed dealkylation of an aromatic hydrocarbon appears to be a rare phenomenon. We sought therefore to gain further information regarding the cleavage by synthesizing a group of ketones the study of whose cyclization might give information regarding two factors thought to be important in the cleavage; namely, stability of the carbonium ion of the departing group and steric requirement of the departing group.

An interesting comparison was made regarding the stability of 10-cyclohexyl-1,2-benzanthracene (IIa), 10-phenyl-1,2-benzanthracene (IIc), and 9-benzylanthracene[15] towards a boiling mixture of hydrobromic and acetic acids. Although 10-cyclohexyl-1,2-benzanthracene was cleaved quantitatively to 1,2-benzanthracene, 10-phenyl-1,2-benzanthracene and 9-benzylanthracene were recovered unchanged. Since the cyclohexyl and phenyl groups impose essentially the same steric strain on the aforementioned 4- and 5-positions it may be that stability of the departing carbonium ion is important. Although we feel that the ability of the departing group to form a stable carbonium ion is important, it apparently is not a sufficient condition for cleavage since 9-benzylanthracene, which might be expected to form the very stable benzyl carbonium ion,[16] is not cleaved by the usual boiling hydrobromic–acetic acid mixture.

CHART I



Ia. R = Cyclohexyl
Ib. R = *n*-Propyl
Ic. R = *i*-Propyl
Id. R = *t*-Butyl

IIa. R = Cyclohexyl
IIb. R = *n*-Propyl
IIc. R = Phenyl

III

In an attempt to gain further information regarding the cleavage of 10-substituted 1,2-benzanthracenes we prepared the three ketones Ib–Id and studied their reaction with the usual hydrobromic–acetic acid mixture. The ketone Ib gave only 9-*n*-propyl-1,2-benzanthracene with no evidence of cleavage. The ketone Ic gave only cleavage product, 1,2-benzanthracene. The ketone Id gave a very small amount, *ca.* 3%, of cleavage product, 1,2-benzanthracene, accompanied by about half of the unchanged starting ketone. This last experiment is quite revealing. Although not constituting a proof, it suggests strongly that the hydrocarbon was cleaved and not the ketone.

Cleavage can be effected by other acids such as alumina and phenyl acid phosphate. The results of the cyclization experiments are summarized in Table I together with the results of the cleavage experiments.

These data indicate that both alkyl and aryl groups may be lost from aromatic polynuclear compounds as a result of an acid-catalyzed reaction and that the stability of the carbonium ion of the departing group as well as steric strain may facilitate the cleavage.

EXPERIMENTAL[17,18]

2-(1-Naphthylmethyl)phenyl cyclohexyl ketone (Ia). A Grignard reagent was prepared from 11.0 g. (0.45 mole)

(11) J. W. Cook, *J. Chem. Soc.*, 456 (1932).
(12) J. W. Cook, *J. Chem. Soc.*, 1408 (1933).
(13) J. Colonge and L. Bonnard, *Compt. rend.*, 240, 2540 (1955).
(14) C. K. Bradsher, *J. Am. Chem. Soc.*, 62, 486 (1940).
(15) The availability of this compound in our laboratory led us to use it rather than the corresponding benzanthracene. The steric situation regarding the 4- and 5-positions is identical in both compounds. See C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, 71, 1434 (1949) for the preparation of 9-benzylanthracene. When 9-cyclohexylanthracene was heated with the usual acid mixture only anthracene was recovered.
(16) E. A. Alexander, *Principles of Ionic Organic Reactions*, Wiley, New York, 1950, p. 42.
(17) All melting points are corrected.
(18) All analyses were carried out by Geller Microanalytical Laboratories, Bardonia, N. Y.

TABLE I

CYCLIZATION AND CLEAVAGE EXPERIMENTS

Starting Compound	Reaction Conditions	Product(s) (%)
Ia	HBr, HAc, reflux, 18 hr.	IIa (26); III (57)
Ia	Heated in Carius tube, 180°, 3 hr.	III (32)
Ia	Alumina,[a] 200° (1 mm.), 3 hr.	IIa (9); III (18)
Ia	Alumina,[b] 200° (1 mm.), 1 hr.	Ia (32)
Ia	Phenyl acid phosphate,[c] 130°, 2 hr.	III (5)
Ia	Polyphosphoric acid, 110°, 24 hr.	Ia (40)
Ib	HBr, HAc, reflux, 24 hr.	IIb (35)
Ic	HBr, HAc, reflux, 2 hr.	III (19)
Ic	HBr, HAc, reflux, 24 hr.	III (33)
Id	HBr, HAc, reflux, 48 hr.	III (3); Id (40)
2-Benzylphenyl cyclohexyl ketone	HBr, HAc, reflux, 24 hr.	9-Cyclohexylanthracene (29), Anthracene (23)
IIa	HBr, HAc, reflux, 24 hr.	III (quant.)
IIc	HBr, HAc, reflux, 24 hr.	IIc (quant.)
9-Cyclohexylanthracene	HBr, HAc, reflux, 24 hr.	Anthracene (47)
9-Benzylanthracene	HBr, HAc, reflux, 24 hr.	9-Benzylanthracene (quant.)

[a] Alcoa's activated alumina, H-151, mesh 1/8, dried at 225° (1 mm.) for 2 hr. before use. [b] Fisher's adsorption alumina, 80–200 mesh, dried at 225° (1 mm.) for 2 hr. before use. [c] This was kindly given to us by the Virginia-Carolina Chemical Corp., Richmond, Va. This material is a mixture of mono- and di-hydrogen phosphate esters containing varying amounts of polyphosphates.

of magnesium turnings and 84.4 g. (0.52 mole) of cyclohexyl bromide in 300 ml. of anhydrous ethyl ether. When the Grignard reagent was formed, the ether was removed by distillation and replaced with approximately 50 ml. of anhydrous toluene. Then 40.0 g. (0.16 mole) of 2-(1-naphthylmethyl)benzonitrile in 250 ml. of anhydrous toluene was added dropwise with stirring. The mixture was heated under reflux overnight. It was then decomposed with 86 ml. of an ice-cold 20% ammonium chloride solution. The organic layer was separated and heated under reflux for 24 hr. with 150 ml. of dilute sulfuric acid (1:2). After allowing the solution to cool, the organic layer was washed with water, 10% sodium carbonate, and again with water. The organic layer was then dried, concentrated, and distilled under reduced pressure. The fraction distilling between 248–250° at 2 mm. was collected as a colorless oil; yield 41 g. (76%).

An analytical sample was prepared by redistilling the oil and collecting the sample from the middle fraction; b.p. 223–224° at approximately 1 mm.

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.77; H, 7.37. Found: C, 87.97; H, 7.70.

The other new ketones of type I were prepared in a similar manner and are listed in Table II with their respective oiling ranges and analytical data.

TABLE II

NEW KETONES I

Ketone	Yield, %	B.P.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	76	223–224	1.0	87.77	87.97	7.37	7.70
Ib	65	195–196	1.5	87.48	87.81	6.99	7.46
Ic	75	182–184	1.0	87.48	87.67	6.99	7.11
Id	35	189–196	1.0	87.38	88.02	7.34	6.94

2-Benzylphenyl cyclohexyl ketone. (By F.A.V.). This compound was prepared using substantially the procedure given above for Ia. The reaction between cyclohexylmagnesium bromide and 2-benzylbenzonitrile[18] gave the desired product (70%), b.p. 194–197° (3 mm.).

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 85.92; H, 7.99.

Cyclization of 2-(1-naphthylmethyl)phenyl cyclohexyl ketone (Ia). A mixture of 10.0 g. of the ketone, Ia, 50 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was heated under reflux for 18 hr. On cooling white plates formed which were filtered and chromatographed on a column packed with alumina[19] using 30–60° petroleum ether as the eluent. This gave 3.98 g. (57%) of 1,2-benzanthracene identified by means of its ultraviolet spectrum, melting point, and melting point of the picrate.

The filtrate was neutralized with concd. sodium hydroxide and extracted with benzene. The benzene solution was washed with water, dried over calcium chloride, concentrated, and the resulting solid recrystallized from 95% ethanol giving 2.43 g. (26%) of 10-cyclohexyl-1,2-benzanthracene; m.p. 119–121°.

Anal. Calcd. for $C_{24}H_{22}$: C, 92.86; H, 7.14. Found: C, 93.01; H, 6.65.

Samples of pure 10-cyclohexyl-1,2-benzanthracene have been submitted to appropriate laboratories for screening for possible carcinogenic and/or carcinolytic activity.

The ultraviolet spectrum, recorded with a Perkin-Elmer Model 3000 Spectracord, 1 cm. path, of 10-cyclohexyl-1,2-benzanthracene in 95% ethanol was similar to the spectrum of 1,2-benzanthracene, as was to be expected, and does not appear worthy of further note.

Cyclization of 2-benzylphenyl cyclohexyl ketone. This experiment was conducted essentially as was the previous one. Two grams of the ketone gave 0.30 g. of anthacene and 0.55 g. of 9-cyclohexylanthracene.[20]

Anal.[21] Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 8.10.

As noted for the analogous situation regarding 10-cyclohexyl-1,2-benzanthracene, the ultraviolet spectrum of 9-cyclohexylanthracene[22] is similar to that of anthracene.

(19) The column was 18 mm. × 370 mm. and was packed with Fisher's adsorption alumina, 80–200 mesh.

(20) This compound was previously prepared by Willemart, *Compt. rend.*, 207, 532 (1938) who reported neither a yield nor analytical data for the hydrocarbon. In our hands, his method, which involved the reaction between cyclohexylmagnesium bromide and anthrone gave an 8% yield of 9-cyclohexylanthracene.

(21) The analytical sample was prepared by Mr. H. H. Hannabass.

(22) The spectrum was recorded by Mr. J. Shulman.

The other acid-catalyzed cyclizations were carried out in a similar way. The results are summarized in Table I.

Cleavage of 10-cyclohexyl-1,2-benzanthracene (IIa). A mixture of 0.3 g. of the hydrocarbon, IIa, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 24 hr. On cooling, white plates formed which were filtered and recrystallized from 95% ethanol yielding white crystals, m.p. 157–160°, identified as 1,2-benzanthracene (100%).

The other acid-catalyzed cleavage experiments were carried out in a similar way. The results are summarized in Table I.

BLACKSBURG, VA.

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

Ionization Constants of Derivatives of Fluorene and Other Polycyclic Compounds[2]

PRESTON H. GRANTHAM, ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

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Potentiometric and spectrophotometric methods were applied to the determination of the apparent ionization constants, in 70% ethanol, of 120 polycyclic aromatic compounds. These were phenols, carboxylic acids, and chiefly amines derived from naphthalene, biphenyl, phenanthrene, chrysene, pyrene, dibenzofuran, dibenzothiophene, carbazole, diphenyl sulfide, diphenylmethane, and especially from fluorene. The effect of the substituent groups *N,N*-dimethyl-, nitro-, keto-, fluoro-, chloro-, bromo-, iodo-, acetamido-, methoxy-, hydroxy-, and amino- was established. The results are discussed in terms of inductive and steric interactions, resonance and hydrogen bonding in these molecules in relation to their structure.

Useful insight into the chemical and physical properties of molecules in the ground state can be derived from a comparative study of the ionization constants[3] of such molecules.[4,5] Relatively few compounds of the polynuclear aromatic type have been investigated in this regard. It is the purpose of this paper to present and discuss data in this field, especially in respect to derivatives of biphenyl, fluorene, and certain other tri- and tetracyclic compounds. The conclusions derived proved helpful in gaining a better understanding of the intimate molecular structure of the compounds, particularly in terms of inductive and resonance effects in the polynuclear systems. In addition, this study furnished information on the possible relationship of the ionization constants of some of these compounds to their carcinogenicity.[6] In a number of other cases a connection has been found between the pharmacologic activity in a series of related chemicals and their ionization constants.[7] In those instances the specific property assayed depended on whether the ionized or the nonionized species existed and was active at the *p*H of the living host, *i.e.* around *p*H 7.4.

The method used for the determination of the *p*K value involved the potentiometric measurement of the *p*H of a solution containing exactly equivalent amounts of a compound and its salt. This relatively simple procedure, while not of universal applicability,[7a] was found to be sufficiently accurate with the pure substances studied. The known literature values of some of the chemicals examined again in the present study (*cf.* footnotes to Tables) were reproduced without difficulty. In addition, the results obtained were corroborated in a number of cases by the spectrophotometric method. The values observed by this method were within the experimental error of those with the potentiometric procedure if the *p*K fell within the range of 3.50 to 11.80. The *p*K values of compounds outside this range were determined by the spectrophotometric method.

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) Presented in part before the 125th Meeting of the American Association for the Advancement of Science, Washington, D. C., December 1958.

(3) In this paper all ionization constants refer to the apparent acid constant, pK_a'.

(4) In order to limit the references to a reasonable number, comprehensive reviews or monographs will be cited wherever possible. Similarly, references to the preparation of known compounds will generally not be given. J. H. W. will gladly supply information on particular compounds upon inquiry by interested readers.

(5) (a) H. C. Brown, D. H. McDaniel, and O. Häfliger in E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, New York, 1955, pp. 567–662. (b) L. N. Ferguson, *Electron Structures of Organic Molecules*, Prentice-Hall, New York, 1952, pp. 189–200. (c) A. Albert, *Heterocyclic Chemistry*, Oxford University Press, Oxford, England, 1959, pp. 336–346. (d) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956, pp. 46–80. (e) G. W. Wheland, *Resonance in Organic Chemistry*, Wiley, New York, 1955, pp. 337–376. (f) B. Pullman and A. Pullman, *Les Théories Électroniques de la Chimie Organique*, Masson et Companie, Paris, 1952, pp. 316–322. (g) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, Chapters VII and IX.

(6) For reasons of chemical stability the acetyl derivatives, such as *N*-2-fluorenylacetamide, are usually tested. However, animals possess enzyme systems capable of removing the acetyl group. In those cases where both amine and acetyl derivatives were examined the biological effects were usually similar. See E. K. Weisburger, and J. H. Weisburger, *Advances in Cancer Research*, **5**, 331 (1958).

(7) (a) A. Albert, *Pharmacol. Revs.*, **4**, 136 (1952); (b) D. Libermann, *Bull. soc. chim. biol.*, **34**, 1026 (1952); (c) T. C. Butler, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 367 (1955); (d) J. J. Burns, T. F. Yu, P. Dayton, L. Berger, A. B. Gutman, and B. B. Brodie, *Nature*, **182**, 1162 (1958).