Thermal Cyclization of Certain Carbinol Quaternary Ammonium Ions to Form Phthalans[1]

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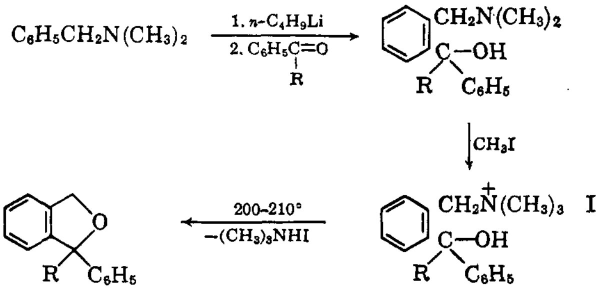
Benzyldimethylamine recently has been metalated with *n*-butyllithium in ether to form the *o*-lithioamine, which was condensed with benzaldehyde and benzophenone to give the corresponding carbinolamines.[2] The methiodides of these compounds (Ia and b)[3] have been cyclized thermally to produce phthalans IIa and b in yields of 76 and 56%, respectively; trimethylamine hydroiodide was eliminated.

SCHEME A



IIa, R = H
b, R = C_6H_5

Ia, R = H
b, R = C_6H_5

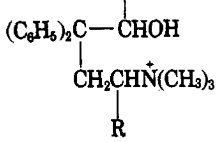
Structures IIa and b were supported by elemental analysis and by physical and chemical evidence. Their infrared spectra showed bands for a cyclic ether at 1036 and 1022 cm.$^{-1}$ for IIa and at 1022 and 1013 cm.$^{-1}$ for IIb.[4] Oxidations (alkaline permanganate) of IIa and IIb afforded *o*-benzoylbenzoic acid and 3,3-diphenylphthalide, respectively.

The n.m.r. spectrum[5] of phthalan IIa[6] showed the expected ABX system[7] which could be closely approximated by a first-order approach. The chemical shifts were, for the methylene hydrogens, $\omega_A = -242 \pm 1$, $\omega_B = -228 \pm 1$, and, for the benzhydryl hydrogen, $\omega_X = -287 \pm 1$ c.p.s.; the coupling constants were $J_{AB} \cong 12.3$ c.p.s. and $J_{BX} = J_{AX} \cong 2.1$ c.p.s. Phthalan IIb gave a quite simple n.m.r. spectrum[6] consisting of a singlet at -230 ± 1 c.p.s., assigned to the methylene hydrogens, with only an aromatic multiplet centered at approximately -356 c.p.s.

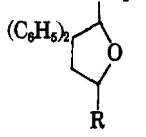
Phthalans IIa and b have been prepared earlier, but the reported boiling point of the former[8] and melting point of the latter[9] differ somewhat from our values. The purity of our IIa was indicated by a single peak in its vapor phase chromatogram, and that of our IIb by its sharp melting point.

One earlier method for the preparation of phthalan IIa involved an acid-catalyzed cyclization of 2-hydroxymethylbenzhydrol,[10] and another method a base-catalyzed cyclization of the carbinol quaternary ammonium ion represented in Ia.[8] In the latter method methiodide Ia was made by a process much less convenient than that shown in Scheme A and converted to the corresponding quaternary hydroxide, which was refluxed with 50% sodium hydroxide.[8] Phthalan IIb previously has been prepared by acid-catalyzed cyclization of 2-hydroxymethyltriphenylcarbinol, which was obtained from phthalide and phenylmagnesium bromide.[9]

It should be mentioned that the related thermal cyclization of carbinol quaternary ammonium ion III to form furan IV has been reported previously.[11]



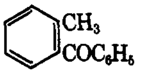
III



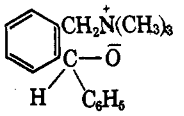
IV

R = H, CH_3

In connection with the present work, the earlier[8] method for IIa involving the carbinol quaternary ammonium hydroxide corresponding to Ia was repeated. Interestingly the reaction afforded not only phthalan IIa but also the isomeric ketone V in the ratio of 7:3 as determined by v.p.c. Actually V was isolated as its 2,4-dinitrophenylhydrazone.



V



VI

Since phthalan IIa would presumably arise through an intramolecular displacement of trimethylamine by the alkoxide ion in VI, the formation of ketone V might appear to involve a 1,4-hydride shift within VI. Another possible mechanism would involve ionization of the benzhydrylic hydrogen of phthalan IIa and isomerization of the resulting carbanion. Indirect support for the hydride shift is the observation that phthalan IIa failed to afford ketone V with refluxing 50% sodium hydroxide. However, this mechanism is not considered established.

Experimental[12]

Cyclizations of Methiodides Ia and b.—The appropriate methiodide[2,3] was placed in a round-bottomed flask fitted with a two-

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[1] Supported by Army Research Office (Durham).

[2] F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

[3] R. L. Vaulx, G. C. Jones, and C. R. Hauser, *J. Org. Chem.*, **27**, 4385 (1962).

[4] See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 119.

[5] The authors are indebted to J. C. Randall for the determination and interpretation of these spectra.

[6] These spectra were taken using a 9% by weight solution of the phthalan in carbon tetrachloride with a cyclohexane external reference.

[7] See K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p. 30.

[8] H. W. Bersch, R. Meyer, A. v. Mletzko, and K. H. Fischer, *Arch. Pharm.*, **291**, 82 (1958).

[9] F. Seidel, *Ber.*, **61**, 2267 (1928).

[10] A. Pernot and A. Willimart, *Bull. soc. chim. France*, **20**, 321 (1953).

[11] N. R. Easton and V. B. Fish, *J. Am. Chem. Soc.*, **77**, 2547 (1955).

[12] Melting points were taken using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord 137. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Boiling points are uncorrected and vapor phase chromatograms obtained on F & M Model 500 programmed temperature gas chromatograph using an Apiezon L–Chromasorb W column.

necked adaptor for gas inlet and condenser. The system was evacuated to 1 mm. and refilled with dry nitrogen three times. After flushing the system for 30 min. with a slow stream of nitrogen (which was continued during the reaction), the flask was immersed in a Woods' metal bath which was preheated to 200–210°. After 0.5–1 hr. at this temperature, the red mixture was allowed to cool, then boiled with several portions of anhydrous ether to remove the phthalan from the solid residue. The combined etheral extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded an oil which was treated as described below.

The oil obtained from 85.9 g. (0.224 mole) of methiodide Ia was distilled to give 33.3 g. (76%) of 1-phenylphthalan (IIa), b.p. 108–110° (0.05 mm.), lit.[6] b.p. 127–129° (0.03 mm.). This product was stored under nitrogen to prevent slow decomposition.

Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.44; H, 6.30.

The oil obtained from 13.8 g. (0.03 mole) of methiodide Ib crystallized when the last trace of solvent was removed *in vacuo*. The solid was recrystallized from acetone (cooled in Dry Ice) to give 4.6 g. (56%) of 1,1-diphenylphthalan (IIb), m.p. 99–100.5°, lit.[9] m.p. 95.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.07; H, 5.88.

A sample of the solid residue left after the ethereal extractions of the reaction product was warmed with 6 *M* sodium hydroxide to evolve trimethylamine, which was bubbled through ethanolic picric acid to give the yellow picrate of this amine, m.p. 224–226°, after recrystallization from ethanol. This melting point was not depressed on admixture with an authentic sample of the picrate.

Oxidations of phthalans IIa and IIb were effected by treatment of refluxing mixtures of 0.5-g. samples of each in 25 ml. of 1 *M* sodium hydroxide with 1-g. portions of potassium permanganate until the purple persisted. After refluxing for 6 hr., ethanol was added, the suspension filtered, and the filtrate acidified. The mixture was extracted with ether, and the solvent removed from the dried ethereal extracts. The residue from the experiment with IIa was recrystallized from water–ethanol to give *o*-benzoylbenzoic acid, m.p. 128–130°, undepressed on admixture with an authentic sample. The residue from the experiment with IIb was recrystallized from hexane to give 3,3-diphenylphthalide, m.p. 116–117°, undepressed on admixture with an authentic sample.[13] The two products were further identified by comparison of their infrared spectra with the spectra of the authentic samples.

Reaction of Carbinol Quaternary Hydroxide with Alkali.—A solution of 9.16 g. (0.025 mole) of methiodide Ia in 250 ml. of hot water was treated with 11.2 g. (0.05 mole) of silver oxide, and the resulting carbinol quaternary hydroxide treated (after filtration) with 35 g. of sodium hydroxide essentially as described previously.[8] After refluxing until trimethylamine ceased to be evolved (3 hr.), the reaction mixture was cooled, diluted with water, and extracted with ether. The solvent was removed from the dried ethereal solution and the oily residue distilled *in vacuo* to give 2.4 g. (49%) of a mixture of phthalan IIa and ketone V, b.p. 108–110° (0.05 mm.). The infrared spectrum of the mixture showed peaks at 1031 and 1019 cm.$^{-1}$ for a cyclic ether and a strong peak at 1637 cm.$^{-1}$ for a carbonyl group.[14] A vapor phase chromatogram of the mixture showed two peaks (approximate ratio, 7:3), the retention times of which corresponded to those of IIa and V,[15] respectively. A solution of a sample of the mixture in 95% ethanol was treated with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of ketone V, m.p. 179–189°, undepressed on admixture with an authentic sample, m.p. 181–189°. The infrared spectra of the two samples were identical.

The stability of phthalan IIa in refluxing 50% sodium hydroxide was demonstrated by the observation that no ketone V was obtained after 4 hr. refluxing. Recovery IIa (90%) was identified by boiling point, v.p.c., and n.m.r. spectrum.

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[13] F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3364 (1962).

[14] See ref. 4, p. 132.

[15] Authentic ketone V, b.p. 110–113° (0.6 mm.), was prepared in 83% yield from *o*-tolyl chloride and benzene by means of aluminum chloride as described previously [H. Goldschmidt and H. Stoker, *Ber.*, **24**, 2805 (1891)].

Additional Rearrangements of 5-Phenyl-1,4-benzodiazepines

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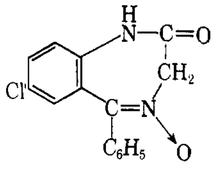
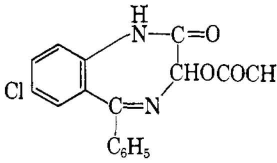
7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide (I) has been shown to undergo a Polonovski-type rearrangement upon treatment with acetic anhydride to afford 3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (II).[1] The acetyl group of II has been removed, leaving an isomer of I (III).[2] In studying the scope of this rearrangement, I was treated with *p*-toluenesulfonyl chloride and with phosphorus oxychloride. The product (IV), obtained in either case, was isomeric with I but was not III; neither was it 7-chloro-5-phenyl-4,5-dihydro-2H-1,4-benzodiazepine-2,3(1H)-dione nor 6-chloro-4-phenyl-3,4-dihydroquinazoline-2-carboxylic acid, two other isomers of I that were prepared earlier.[1]

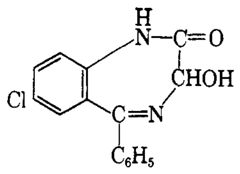
Compound IV, m.p. 255–257°, absorbed in the infrared at 3.15 and at 6.01 μ suggesting the persistence of NH and C=O in the product. The n.m.r. spectrum showed a singlet (2H) at δ 4.56.[3] The reaction conditions suggested the possibility of a Beckmann-type rearrangement. The expected product (*trans* shift) of such a rearrangement is 4-benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1H)-one, a structure consistent with the physical data.



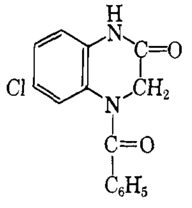
I



II



III



IV

Compound IV was hydrolyzed with hot sodium hydroxide removing the benzoyl group and affording the known 6-chloro-3,4-dihydroquinoxalin-2(1H)-one.[4] Catalytic dechlorination of IV resulted in 4-benzoyl-3,4-dihydroquinoxalin-2-(1H)-one, identical with an authentic sample made from 3,4-dihydroquinoxalin-2(1H)-one by benzoylation.[5] The structure of IV was thus established.

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[1] S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

[2] Compound III has been assigned the generic name oxazepam.

[3] N.m.r. measurements were made in deuteriochloroform (tetramethylsilane) with a Varian A-60 spectrometer.

[4] A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. J. Stacy, *J. Chem. Soc.*, 1260 (1949).

[5] S. Motylewski, *Ber.*, **41**, 800 (1908).