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EPIMERIZATION KINETICS FROM PROTON MAGNETIC RESONANCE DATA

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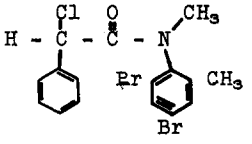
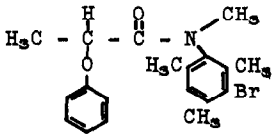
Epimerization has been studied by polarimetric techniques. It has also been studied by melting point of the epimer mixture[1], ultraviolet spectroscopy[2,3], infrared spectroscopy[4], and paper chromatography[4]. However, the use of proton magnetic resonance (PMR) to follow an epimerization has not been reported, possibly because it is difficult to find one of an epimer pair that gives a signal free of interference from other signals of its own and well separated from the signals of the other epimer. Discrete and well-separated signals can often be observed for each of the epimers of certain N-aryl-N-alkyl-α-chloro-α-phenyl acetamides that are suitably substituted in the N-aryl ring. Less favorable, but often usable, signal separation occurs with the similar α-phenoxypropionamides. The investigations of Adams and his coworkers[5] indicated that suitably long half lives should be observed for such compounds.

With these factors in mind we synthesized N-methyl-N-(2-methyl-4,6-dibromophenyl) α-chloro-α-phenylacetamide,



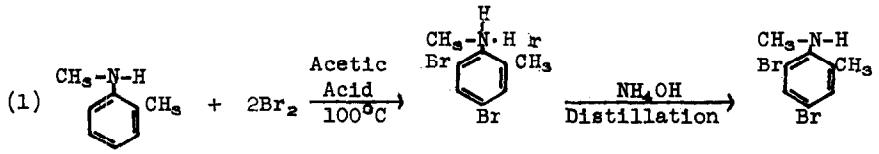
(I)

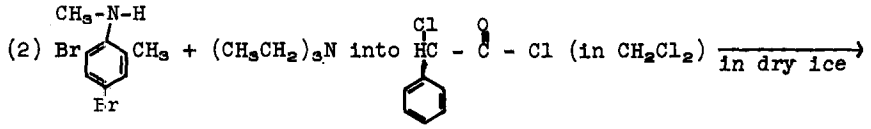
and N-benzyl-N-(2,4,6-trimethyl-3-bromo-phenyl) α-phenoxy-propionamide,



(II)

Compound I was prepared as follows:





After completion of step (2) the reaction mixture was allowed to warm to room temperature and stand overnight. It was then filtered to remove $(CH_3CH_2)_3N \cdot HCl$ and the solvent was removed by vacuum distillation. The mixture was then dissolved in boiling toluene and filtered while hot. About an equal volume of hexane was added to the filtrate and it was set aside in a bottle in the freezing compartment of a refrigerator overnight. The bulk of the product settled to the bottom of the bottle rapidly as mixed solid and separate liquid phases. However, a small quantity of crystals collected slowly on the walls of the bottle; these were separated from the bulk of the product and washed with and crystallized from ethyl ether. This part of the product we designated isomer A (Melting point = 168°C). The bulk of the product was crystallized from acetone and then from ether in deliberate small yield to give isomer B (Melting point = 164°C). Analysis showed:

Theory C = 44.5, H = 3.3, N = 3.3, Br = 37.1

Found C = 44.6, H = 3.3, N = 3.2, Br = 36.6

Compound II was synthesized by a route very similar to that used by Adams[5]. Bromomesidine, with triethyl amine as an HCl getter, was added to α-phenoxypropionyl chloride in dichloromethane, and allowed to stand overnight. After washing with water to remove triethyl amine hydrochloride, the resulting amide was crystallized from the solvent. This amide was then substituted via the conventional reaction with sodium hydride in refluxing xylene to produce II. Compound II was isolated by molecular distillation at $<10^{-4}$ mm and 190°C to give nearly pure II which formed as a white crystalline solid in the receiver. This distillate was an equimolar mixture (by PMR) of isomers which we designated C and D. Isomer C was easily isolated by crystallization from a variety of solvents* (Melting point = 128°C). Analysis showed:

Theory C = 66.4, H = 5.8, N = 3.1, Br = 17.7

Found C = 66.3, H = 5.7, N = 3.0, Br = 17.2

However, for some unexplained reason we have not been able to isolate isomer D in pure form or even in a fraction richer in D than the equimolar mixture.

The proton magnetic resonance (PMR) signals from the aliphatic protons of isomers A and B of Compound I occurred at different fields. The positions of these signals are summarized in Table 1. All PMR measurements were made with a Varian A-60 spectrometer** with the V-6057 variable temperature accessory.

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* Acetone was particularly effective.

**Varian Associates, Palo Alto, Calif.

TABLE 1

Proton Magnetic Resonance Signals of Compound I
250 mg/ml in $CHCl_2CHCl_2$ at 40°C
Chemical Shift, ppm from tetramethylsilane

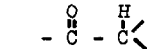
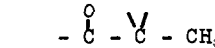
Isomer	o-methyl	N-methyl	
A	1.46	3.12	4.80
B	2.39	3.08	4.90

The N-methyl signals for the two isomers are not sufficiently separated to be easily usable for analytical purposes and no quantitative use was attempted. However, the o-methyl and α-proton signals were completely separated and could be used for independent estimates of isomer abundance in mixtures.

The PMR signals for isomers C and D of Compound II are summarized in Table 2.

TABLE 2

Proton Magnetic Resonance Signals of Compound II
222 mg/ml in $CHCl_2CHCl_2$ at 40°C
Chemical Shift, ppm from tetramethylsilane

Isomer	Methyl groups on ring*					
C	2.28	1.86	1.72	AB pattern J_{AB} = 13.6 cps, $\Delta\gamma$ = 0.095 ppm Center at 4.69	Quartet J = 6.0 cps Center at 4.32	Doublet, J = 6.0 cps Center at 1.
D	2.23	1.97	1.65	4.69	Same as isomer C	Doublet, J = 6.0 cps Center at 1.

*We have not determined the assignment of the signals to specific methy groups on the ring.

The situation is not so favorable for quantitative estimates of isomer abundance for II as for I. A slight broadening prevents a satisfactory resolution of the methyl signal at 1.72 (C) from that at 1.65 ppm (D). The methylene signals of the benzyl groups are interesting in that for C

they are a typical AB quartet, while for D a broad singlet is obtained at exactly the center of the C quartet. Evidently these protons are distinctly nonequivalent in C but equivalent or very nearly so in D*. Unfortunately there is too much overlap of signals for any but qualitative analytical purposes. The $-\overset{O}{\overset{\|}{C}}-\overset{V}{C}-CH_3$ signals are just barely separated at high resolution and therefore are not useful. The methyl signals at 1.86 (C) and 1.97 ppm (D) are almost entirely resolved and therefore of some use for quantitative purposes. However, this incomplete resolution qualifies the data derived for the epimerization of II. Our estimates of isomer ratios for II could be in error by as much as about 15% when the ratio is large; while for I a precision of about 3% was routinely achieved except for very large ratios.

The isomer ratios, A/B for I, and C/D for II, were then measured at appropriate time intervals as a means of following the epimerization reactions. The 135°C run with I was made in an evacuated sealed tube that was left in the spectrometer for the duration of the run. Only the o-methyl signals were scanned in this run. All other runs were made in evacuated, sealed tubes in constant temperature baths with periodic interruptions to make the PMR measurements at 40°C. Peak areas were measured by means of a planimeter on expanded PMR scans. The ratio of isomer A to B (or C to D) was used in all calculations rather than signal areas for the isomers individually. This technique minimizes the consequences of apparent fluctuations in signal intensity. For I the results of measurements of isomer ratios of $-\overset{O}{\overset{\|}{C}}-\overset{|}{\underset{|}{C}}-H$ proton signals and o-methyl signals were the same within experimental error. In

*In sym-tetrabromoethane as a solvent, this singlet is partially resolved into a doublet.

the final calculations the two measurements were combined, with the o-methyl results being given twice the weight of the α-proton results. This weighing recognizes the more favorable signal-to-noise ratio for the o-methyl signals. Sym-tetrachloroethane was chosen as the solvent for these determinations because of its boiling point, stability, and lack of signals at high field.

The results from these runs are given in Table 3. The raw data from the 119°C runs with I are given in Figure 1 as a demonstration of the fact that identical results were obtained whether the starting isomer was pure A or pure B. In all cases the equilibrium mixture was equimolar in the two isomers (A and B or C and D). There are apparently no differences in thermodynamic properties between the two isomers of the same compound in sym-tetrachloroethane solution.

The energies of activation and kinetic data obtained for I and II are quite similar to values obtained for the racemization of active biphenyls and also to values obtained by Adams[5] for amides similar to I and II. We are inclined to agree with Adams that the rate limiting step for epimerization (or racemization as the case may be) is rotation around the benzene-to-nitrogen bond. The similarity between this process and rotation around the bond that joins the rings in a biphenyl is too great to be ignored. It should be pointed out, as we have earlier[6], however, that if the nitrogen atom is non-planar to any degree, then inversion of the nitrogen atom must accompany the rotation.

We plan to continue these investigations with studies of the effects of changing the solvent and of changing the substituents in the molecules.

These investigations were performed in the course of work under Contract AT(07-2)-1 with the U. S. Atomic Energy Commission.

TABLE 3

Rate Constants for Epimerization in $CHCl_2CHCl_2$

Compound	Temperature, °C	Rate Constant, hr^{-1}	Activation Energy, Kcal/mol	Frequency Factor, hr^{-1}
I	100	0.043 ±0.002	25	8×10^{12}
	119	0.21 ±0.01		
	135	0.74 ±0.04		
II	100	0.0014 ±0.0002	24	3×10^{12}
	119	0.008 ±0.001		
	146	0.050 ±0.007		

REFERENCES

1. G. G. Ayerst and K. Schofield, J. Chem. Soc. 3445 (1960).
2. J. C. Jochims, Ber. 96 990 (1963).
3. E. G. Remmers, G. M. Seiger, and A. P. Doerschuk, J. Pharm. Sci. 52 752 (1963).
4. N. Green and M. Geroza, J. Org. Chem. 24 761 (1959).
5. R. Adams, Record Chemical Progress 10 91 (1949).
6. T. H. Siddall and C. A. Prohaska, "Slow Inversion at the Nitrogen Atom in Certain Amides", to be published in Nature.

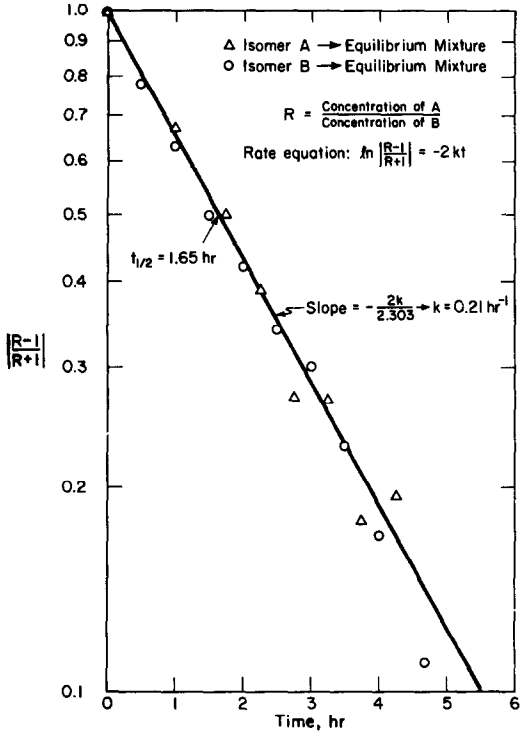


FIG. 1 KINETICS OF EPIMERIZATION OF COMPOUND IN $Cl_2CHCHCl_2$ SOLUTION AT 119°C