temperature for the pH readings was maintained at 25.0 ± 0.2° by the use of water-jacketed beakers. The basic solutions were protected from atmospheric carbon dioxide with an Ascarite tube. To ensure good pH response by the glass electrode, the immersion time of the electrodes in the solutions was kept to a minimum and the electrodes were allowed to stand in distilled water before each measurement.[32] Sodium ion corrections, when needed, were taken from the nomograph for aqueous solutions which was supplied with the electrode. The actual pH values were measured at the same time as the spectral measurements were recorded.

All absorbencies were measured with a Beckman DU Model 2400 spectrophotometer using the hydrogen lamp. The cell compartment temperature was maintained at 25.0 ± 0.2°. The pK_a measurements were made at several different wavelengths, which covered a range of 240–296 mμ. The value of A^0 was obtained in pure solvent and A^{eq} was determined in a series of solutions with accurately known sodium hydroxide concentrations and pH values that spanned both sides of the pK_a value. All solutions were maintained at constant ionic strength of 0.600 by adding the appropriate volume of a stock potassium chloride solution. All of the tertiary hydroperoxides were stable under the basic conditions, with the exception of 1,1-diphenylethyl and trityl hydroperoxide. For the latter hydroperoxides, A^{eq} slowly increased with time if the pH of the solution was near the pK_a. In neutral or strongly basic solutions (pH *ca.* 13.7), the absorbencies were constant. Hydrogen peroxide was stable in neutral solutions, but displayed a marked decrease in A^{eq} with time as the pH increased. Therefore, the sample of hydroperoxide or hydrogen peroxide was added just prior to absorbance and pH measurements. In the event that A^{eq} did change with time, it was graphically extrapolated back to the time of mixing. Since no isosbestic points were observed, constancy of pK_a with wavelength was taken as evidence for the absence of absorbing impurities.

(32) Reference 11, p 324.

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Reactions between Aliphatic Dihalides and Amines. I. Kinetic Study of the Reaction between 2-Phenyl-2-cyclohexyl-4,5-dibromovaleronitrile and Diethylamine

E. DE HOFFMANN,* J. P. SCHMIT, AND J. J. CHARETTE

Departments of Industrial Chemistry and Molecular Physics, Lovanium University of Kinshasa, Kinshasa, Democratic Republic of the Congo

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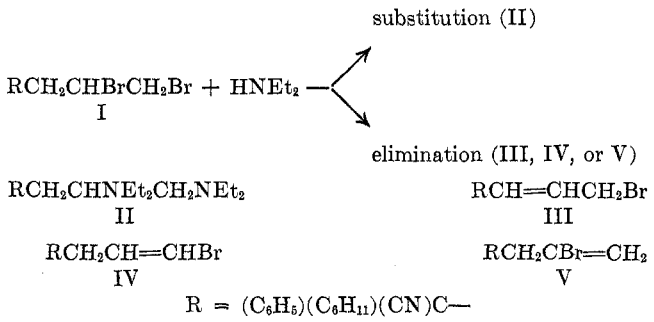
The kinetics of the action of diethylamine with 2-phenyl-2-cyclohexyl-4,5-dibromovaleronitrile in butyl alcohol as a solvent has been studied by use of conventional methods. This reaction gives two products whose structures are shown to be those of 1-bromo-4-cyclohexyl-4-phenyl-1-pentenenitrile (elimination) and ~2-cyclohexyl-2-phenyl-4,5-bis(diethylamino)valeronitrile (substitution). The ratio of the concentrations of elimination to substitution products is independent of the temperature, the time, and the initial concentrations of reactants. Hence, both reactions have the same rate-determining step with a rate equation (A). The mechanisms of these reactions are discussed.

$$V = \frac{k}{h}Te^{-29.4/R}e^{-18.4\times10^3/RT}[\text{dibr}][\text{amine}] \qquad (A)$$

The action of secondary amines on aliphatic dihalides may theoretically give competitive elimination and substitution reactions. Up to now, these reactions have received very little attention. In one instance, Attenburrow[1] has indeed treated the 2,2-diphenyl-4,5-dibromovaleronitrile with morpholine. He has mentioned only one diaminated substitution product with a yield of 70% and one elimination product of unknown structure.

In this work, we have investigated the action of diethylamine on 2-phenyl-2-cyclohexyl-4,5-dibromovaleronitrile (I). This reaction has a practical as well as theoretical interest. By decyanation the aminated product gives the 1-phenyl-1-cyclohexyl-3,4-bis(diethylamino)butane which is an antispasmodic drug. Hence, it may be inferred that the diaminated substitution product has the structure II.



We have determined the structure of the elimination product as well as the kinetic parameters of both reactions, in order to be able to propose a mechanism.

Experimental Section

A. Apparatus and Procedures.—Infrared spectra were recorded with Perkin-Elmer 137 and 237 spectrophotometers. The exact position of the bands was measured on the single-beam Perkin-Elmer 112G spectrophotometer. A grating with 75 grooves/mm and a blaze at 12 was used for the region 4000–600 cm^{-1} and a grating with 47 grooves/mm and a blaze at 20 for the region 600–400 cm^{-1}. Nujol and hexachlorobutadiene mulls were used for the crystalline products.

Nuclear magnetic resonance spectra were obtained using a JEOL nmr measuring instrument, at 60 Mc at a temperature of 20°, with tetramethylsilane as reference. The range of frequencies was 0 (TMS) to 510 cps.

The hydrobromic acid concentrations were determined by Volhard procedure on 1-ml samples diluted in 8 ml of 3 *N* nitric acid.

B. Materials.—2-Phenyl-2-cyclohexyl-4,5-dibromovaleronitrile (I) was obtained by bromination of the ethylenic product in $CHCl_3$, according to the method described by Attenburrow, *et al.*,[1] for the corresponding 2,2-diphenyl derivative, and was purified by recrystallization from petroleum ether to a white crystalline powder, mp 73–75°.

α-Cyclohexylphenylacetonitrile was obtained by condensing benzylcyanide in boiling benzene with cyclohexyl bromide in the

* To whom correspondence should be addressed.

(1) J. Attenburrow, *J. Chem. Soc.*, 510 (1949).

presence of sodamide as described by Vogel,[2] and purified by distillation and recrystallization from petroleum ether.

1,3-Dibromopropene was prepared by dehydration of 1,3-dibromo-2-propanol on phosphorus pentoxide as described by Lespieau,[3] and purified by distillation under low pressure.

2,3-Dibromopropene is a commercial Eastman Kodak product purified by distillation under low pressure.

1-Bromo-4-cyclohexyl-4-phenyl-1-pentenenitrile (IV) and 2-bromo-4-cyclohexyl-4-phenyl-1-pentenenitrile (V) were prepared according to the method described by Attenburrow, *et al.*,[1] for preparation of 2-bromo-4,4-diphenyl-1-pentenenitrile. α-Cyclohexylphenylacetonitrile (0.2 mol) was converted into its sodio derivative by treatment with sodamide (0.2 mol) in boiling dry benzene (300 ml). The mixture was boiled under reflux with vigorous stirring until all the sodamide had reacted. Respectively, 1,3- and 2,3-dibromopropene (0.2 mol) were added slowly to the hot suspensions and boiled under reflux for 5 hr. The cooled mixtures were washed with 1 *N* hydrochloric acid and water and were dried on Na_2SO_4. The benzene was removed and the residues were distilled. The distillates crystallized slowly on standing and were purified by recrystallization from petroleum ether. In both cases the reaction is most likely to occur with the bromine at position 3. It is worth noting that the infrared spectrum of the product before distillation has the same characteristic bands as the distilled and recrystallized one. We concluded that no rearrangement occurred during distillation. 1-Bromo-4-cyclohexyl-4-phenyl-1-pentenenitrile had mp 58–59° (yield 64%).

Anal. Calcd for $C_{17}H_{20}NBr$: C, 64.15; H, 6.33; N, 4.40; Br, 25.11. Found: C, 64.10; H, 6.32; N, 4.53; Br, 25.05.

2-Bromo-4-cyclohexyl-4-phenyl-1-pentenenitrile had mp 50–51° (yield 70%).

Anal. Calcd for $C_{17}H_{20}NBr$: C, 64.15; H, 6.33; N, 4.40; Br, 25.11. Found: C, 64.20; H, 6.34; N, 4.40; Br, 25.06.

Elimination and substitution products were simultaneously obtained by action of diethylamine (2.500 mol) on 2-phenyl-2-cyclohexyl-4,5-dibromovaleronitrile (0.250 mol) in 1 *N* butanol. The mixture was boiled under reflux for 48 hr. The cooled suspension was filtered and the diethylamine hydrobromide was washed with benzene. The aminated products were extracted with 1 *N* hydrochloric acid. The combined organic filtrates were washed with carbonate solution and then with water. The benzene was removed and the residual oil distilled under low pressure. After two distillations, the distillate crystallized on standing and was purified by recrystallization from petroleum ether. The yield was 62%, mp 58–59°, bp 144° (0.8 mm).

Anal. Calcd for $C_{17}H_{20}NBr$: C, 64.15; H, 6.33; N, 4.40; Br, 25.11. Found: C, 64.37; H, 6.32; N, 4.41; Br, 24.90.

C. Structure of the Products.—Like Attenburrow,[1] we have observed only one substitution product, even when reaction was interrupted before completeness. The infrared and nmr spectra of this substitution compound are in accordance with its proposed structure II.

On the other hand, the elimination product may have one of the five structures: III (cis or trans), IV (cis or trans), or V. This does not take into account the presence of asymmetric carbons. The actual structure has been established by the analysis of this infrared and nmr spectra and by comparison with those of two possible elimination products, IV and V, obtained by unambiguous synthesis. One can expect the characteristic infrared vibrations of the C=C bond to appear in the neighborhood of 1620 cm^{-1},[4,5] the intensity of this band being relatively greater for a cis isomer than for a trans, owing to the pseudosymmetry of the latter.[6] The CBr bonds are responsible for absorption in the region of 320–590 cm^{-1}.[7] The trans CHD=CHBr, for example, absorbs at 336–578 cm^{-1}. Disubstituted trans ethylenes show characteristic strong bands at 1310,[8] 935,[9,10] and 599 cm^{-1}.[5] The infrared spectrum of the elimination product exhibits indeed important bands at 1310, 939, and 591 cm^{-1} and a faint band at 1625 cm^{-1}, comparable with the values given above for the trans derivatives. Furthermore, the spectrum of the elimination product is identical with the one of the nonambiguous product IV. The 1,3-dibromopropene used for the unambiguous synthesis of the latter has the trans configuration as indicated by the presence of the characteristic bands at 1310 and 935 cm^{-1}. There is no reason to suppose that isomerization occurs in the course of the synthesis reaction. The study of the molecular models of Briegleb confirms the conclusions of the infrared measurements; the IV trans model is much less sterically hindered than the cis one.

The study of the nmr spectra of the different possible isomers confirms the conclusions of the infrared analysis. The nmr spectrum of the elimination product is also identical with the one of the synthetic product IV.

Results

The stoichiometric equations of the reactions are

Substitution

$$RCH_2CHBrCH_2Br + 4HNEt_2 \longrightarrow RCH_2\underset{\displaystyle NEt_2}{\underset{|}{C}}HCH_2NEt_2 + 2HNEt_2\cdot HBr$$

Elimination

$$RCH_2CHBrCH_2Br + HNEt_2 \longrightarrow RCH_2CH{=}CHBr + HNEt_2\cdot HBr$$

Hence, the disappearance of 1 mol of dibromide results in the disappearance of 4 mol of diethylamine in the first case and only 1 mol in the second. The reactions are followed by volumetric titration of the liberated hydrobromic acid. The following relations are applicable.

$$[\text{dibr}]_i = [S]_f + [E]_f \qquad [HBr]_f = 2[S]_f + [E]_f$$

Hence

$$[HBr]_f = 2[S]_f + [\text{dibr}]_i - [S]_f$$

The subscript i indicates the initial concentration while f indicates the concentration measured at the end of the reaction; dibr, S, and E represent, respectively, the dibromide reactive, the substitution product, and the elimination product.

In all cases where the initial concentration of diethylamine allows a complete reaction, the ratio of the final concentration of hydrobromic acid to the initial concentration of the dibromide compound is 1.48. Hence the final concentrations of the substitution and elimination product are in the ratio

$$r = [S]/[E] = 0.92$$

The value of the concentrations ratio has also been determined by infrared measurement of the relative intensities of characteristic bands: 732 and 1620 cm^{-1} for the elimination product, and 1155, 1200, and 1380 cm^{-1} for the substitution product. Within the limits of experimental errors, the value of r obtained at different stages of the reaction is constant and equal to the value 0.92 ± 0.03 found above by volumetric titration at the end of the reaction. It may hence be concluded that both reactions, substitution and elimination, are of the same order.

The apparent rate constants and corresponding order for each experiment are shown in Table I. This table

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(4) J. Charette, "Etude spectroscopique des éthylènes et dérivés bromés deutérosubstitutés," Thèse, Louvain, 1955.

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(7) W. West, "Chemical Applications of Spectroscopy," Vol. IX, Interscience, New York, N. Y., 1956, pp 413.

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(9) R. N. Haszledin, *Nature*, **168**, 1028 (1951).

(10) R. E. Kitson, *Anal. Chem.*, **25**, 1470 (1953).

TABLE I[a]

No.	[dibr] 1	[A] 2	Order, apparent 3	$10^3 k_n$ (apparent)[b] 4	$10^3 V_i$ (graph)[c] 5	$10^3 V_i$ (calcd)[d] 6	k_n [dibr]^{n}[b] 7	$k_2 = V_i/cc$[e,f] 8	[S]/[E] 9
1	0.300	2.500	1.2	5.239	1.200	1.155	1.237	1.600	0.920
2	0.250	2.500	1.0	4.054	0.900	0.962	1.014	1.622	0.922
3[g]	0.250	2.500	1.0	4.009	0.833	0.962	1.002	1.600	0.922
4	0.200	2.500	1.0	3.748	0.766	0.769	0.750	1.532	0.923
5	0.100	2.500	1.0	3.814	0.350	0.385	0.381	1.524	0.923
6	0.250	3.750	0.9	4.548	1.006	1.443	1.366	1.393	0.924
7	0.250	2.500	1.0	4.054	0.900	0.962	1.014	1.622	0.922
8[g]	0.250	2.500	1.0	4.009	0.833	0.962	1.002	1.600	0.922
9	0.250	1.860	1.2	3.633	0.716	0.716	0.692	1.539	0.923
10	0.250	1.250	1.3	2.596	0.417	0.481	0.428	1.398	0.923
11	0.250	0.712	2.0	4.301	0.253	0.274	0.269	1.512	
12	0.250	0.620	2.2	5.171	0.240	0.238	0.209	1.548	

[a] Average deviation on the rate constants is less than 10%. [b] n = apparent order. [c] V_i(graph) = initial graph speed, dx/dt. [d] V_i(calcd) = k_2[dibr]$_i$[amine]$_i$. [e] cc = product of initial concentrations. [f] T = 95°. [g] With 0.0125 mol^{-1} l. of hydroquinone.

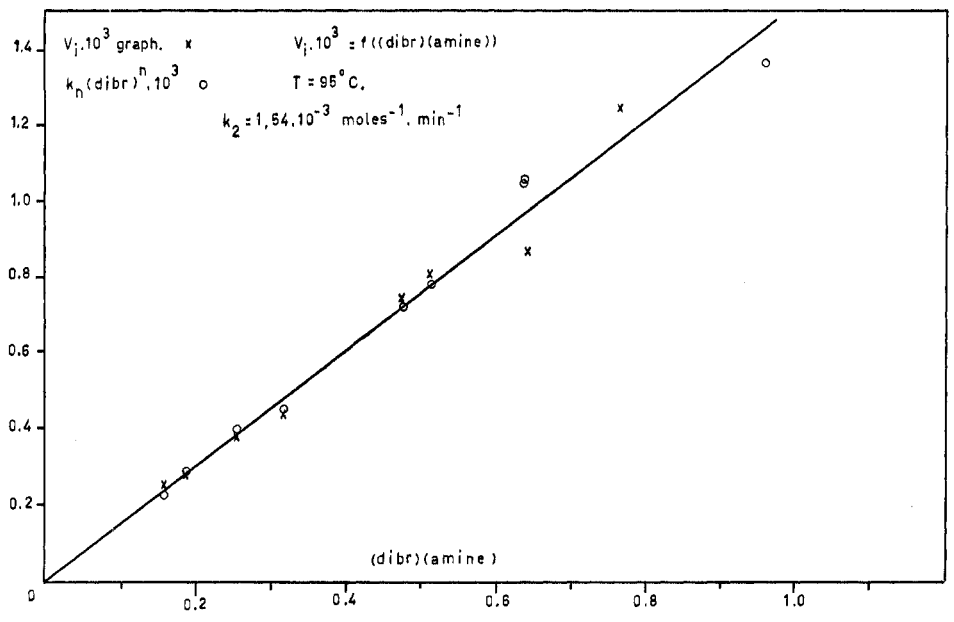

Figure 1.

gives the values of the initial rate obtained graphically from the first points of the equation

$$V_i = k_n[\text{dibr}]_i^n$$

if the amine concentration is in excess, and from

$$V_i = k_2[\text{dibr}]_i[\text{amine}]_i$$

if the initial mixture is stoichiometric: V_i = initial rate, k_n = observed rate constant, and n = observed order.

The good agreement between the graphical and calculated initial rates indicates that the initial rate law is the same as the current one. On the other hand, the graph of these initial rates *vs.* the product of the concentrations (Figure 1) gives a straight line passing through the origin. The reaction is thus first order with respect to each reactive. The slope of this graph gives the value of the second-order rate constant (at 95°).

$$k_2 = 1.54 \times 10^{-3} \text{ mol}^{-1} \text{ l. min}^{-1}$$

Rate constants and [S]/[E] ratios at different temperatures have been measured using concentrations of 0.250 mol l.$^{-1}$ of dibromide and 2.500 mol l.$^{-1}$ of diethylamine Temperatures (in °K) and corresponding observed rate constants in min^{-1} are 328, 0.075 × 10^{-3}; 330, 0.426 × 10^{-3}; 348, 0.829× 10^{-3}; 358, 1.463 × 10^{-3}; 368, 4.054 × 10^{-3}; 368, 4.009 × 10^{-3}. The ratio [S]/[E] has been found to be also independent of the temperature (0.92 ± 0.03).

The energy of activation and the action constant calculated by application of the Arrhenius relation, $k = k_0 e^{-E/RT}$, are respectively found equal to 18.4 kcal and 1.32 × 10^8 mol^{-1} l. min^{-1} or 7.92 × 10^6 mol^{-1}, cm^3 sec^{-1} in cgs units.

The activation entropy has been calculated by means of the relation

$$k_{exp} = e\frac{k}{h}Te^{\Delta S^{\pm}/R}$$

where $\Delta S^{\pm} = -29.4$ eu at 95°. The general equation of the velocities is, under these conditions

$$V = e\frac{k}{h}Te^{-29.4/R}e^{-18.4\ 10^3/RT}[\text{dibr}][\text{amine}]$$

Discussion

The substitution/elimination ratio remains constant when concentrations and temperature are varied. Since the reaction is kinetically first order with respect to the amine and the dibromide, the rate-determining step implies necessarily one molecule of dibromide and

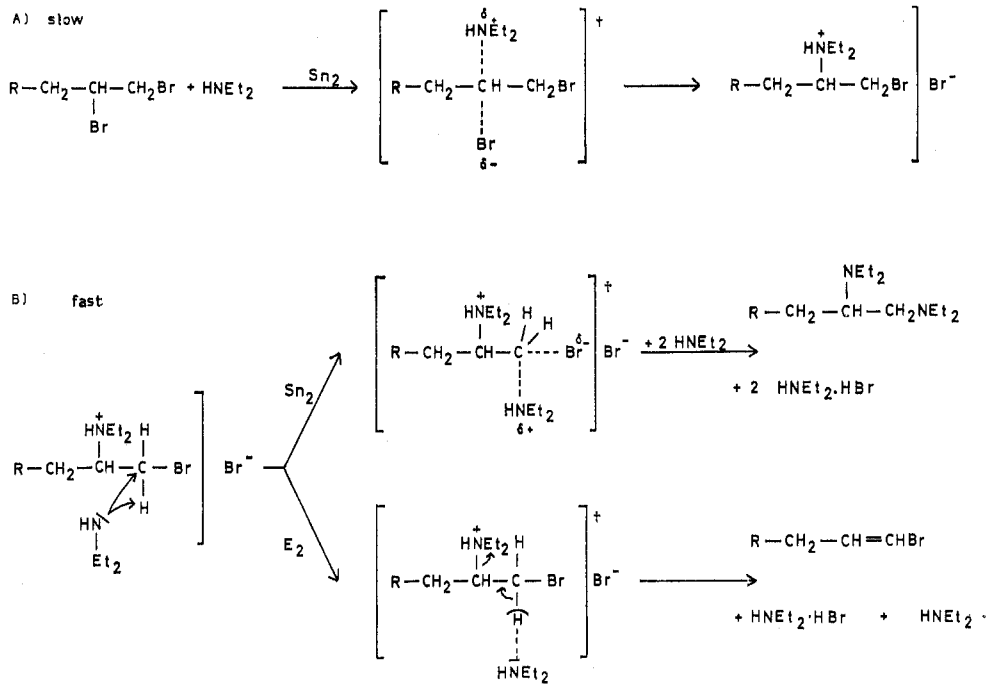

Figure 2.

one of diethylamine. Furthermore, no intermediary product nor induction period as detected. The negative entropy implies the formation, during the rate-determining step, of a highly organized complex.

On the bases of these observations two mechanisms may be emphasized. The first one includes a competition between SN2 substitution by amine and E2 attack on a proton at C-6 carbon atom, both reactions occurring on the dibromide. The E2 reaction leads directly to the elimination product by a fast bonding rearrangement, while the SN2 substitution leads to an intermediary amino bromide. The latter reacts with a new amine molecule in a second fast step leading to the disubstituted product. In this hypothesis, both reactions should be of the same order and should have exactly the same activation energy, which is unlikely for such different mechanisms.

In another mechanism, the first step (slow) is a substitution of the bromine on the C-5 carbon atom by a molecule of diethylamine, leading to the formation of a diethylammonium derivative (Figure 2). The second step (fast) is the reaction of this conjugated acid with a second molecule of diethylamine on the C-6 carbon atom itself, giving a second substitution, or on a proton linked to the C-6 carbon leading to the elimination product by rearrangement of the bonds. These reactions between an ion and a neutral molecule are very similar in their nature, and they require only a low activation energy. This makes them insensitive to temperature variations. This is in good agreement with the experimental observations.

Registry No.—I, 25517-87-7; diethylamine, 109-89-7; *trans*-IV, 25527-97-3; V, 25517-88-8.