In conclusion, we might point out that all of the products obtained by treating ketones and aldehydes at low temperature with phosphorus pentachloride may be logically accounted for by assuming that a chlorocarbonium ion such as V is formed. The formation of the multiplicity of products above outlined from V involves steps which appear logical in the light of our present concepts of carbonium ion behavior.

Columbus, Ohio

The Effects of Chain and Ring Substitution on the Raney Nickel-catalyzed Cleavage of 2-Arylethanols[1,2]

By Thomas W. Greenlee and William A. Bonner

A representative array of 2-phenylethanols containing alkyl or aryl substituents at C2 or containing *meta-* or *ortho–para* directing groups in the *para* nuclear position has been prepared. Each substance has been subjected to the prolonged action of Raney nickel in refluxing ethanol, and the crude reaction products resulting therefrom have been examined for their relative quantities of C1 dehydroxylation and C1–C2 cleavage products by means of vapor–liquid partition chromatography. The introduction of alkyl or aryl substituents on C2 of 2-phenylethanol progressively increased the cleavage/dehydroxylation ratio. No gross differences in the cleavage/dehydroxylation ratio was noted for 2-phenylethanols containing a *meta* directing substituent (COOMe) or an *ortho–para* directing substituent (OMe) in the *p*-position, although the over-all reaction rate was markedly slower in the latter case. When 2-(*p*-nitrophenyl)-ethanol was treated with Raney nickel, preliminary rapid reduction of the nitro group appeared to occur. The reaction products, corresponding almost exclusively to those of C1–C2 cleavage, showed the occurrence of both N,N-dialkylation of the amino group and nuclear reduction, *i.e.*, they were mainly N,N-diethyl-*p*-toluidine and 1-methyl-4-(N,N-diethylamino)-cyclohexane.

In an earlier paper[3] we have reported that the action of Raney nickel in refluxing ethanol (reductive desulfuration conditions) on 2-arylethanols leads both to simple C1 dehydroxylation producing alkylaromatics, as well as to C1–C2 carbon bond fission yielding alkylaromatics one homolog lower. More recently it has been reported that the single carbon cleavage fragment in the fission process is carbon monoxide strongly adsorbed to the nickel catalyst surface,[4] and that such C1–C2 fission is accompanied by predominant inversion of configuration[5] when the carbon atom adjacent to the aromatic nucleus is asymmetric. These observations have been qualitatively correlated by a tentative mechanism[3–5] involving concerted SN2 attack by hydrogen adsorbed on the Raney nickel surface on C2 of those 2-arylethanols undergoing C1–C2 fission. At an intermediate stage in our investigations it appeared to us that research into the cleavage/dehydroxylation ratios of substituted 2-arylethanols, particularly those bearing *p*-substituents, might afford mechanistic insight. A brief report of the results of these studies is given in the present paper.

2-Phenylethanols containing electron-withdrawing groups (NO2, COOMe) and electron-releasing groups (OMe, Br) in the *p*-position were prepared by standard methods, then subjected to the action of Raney nickel in refluxing ethanol under previously employed conditions.[3–5] The mixed reaction products were isolated as usual[3] and separated into individual components by vapor–liquid partition chromatography. The latter were finally characterized by their infrared absorption spectra and/or VLPC retention times.

In Table I are recorded the results of these experiments. The approximate composition of each

Table I

Effects of Chain and Nuclear Substitution in 2-Arylethanols on the Relative Extents of C1–C2 Cleavage and C1 Dehydroxylation
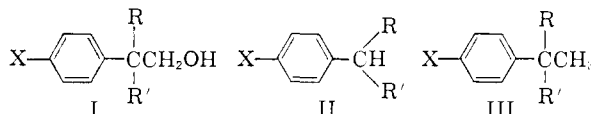
No.	Starting material, I X	R	R′	Cleavage product, II, %	Dehydroxylation product, III, %	Note
1	H	H	H	33	67	a
2	H	H	Ph	67	33	a,b
3	H	H	Me	91	9	a
4	H	Et	Me	100	0	c
5	COOMe	H	H	50	50	
6	OMe	H	H	62	38	d
7	NO2 → NH2	H	H	97	3	e
8	Br	H	H	0	0	f

a Data taken from ref. 3. *b* One Ph ring reduced to cyclohexyl in the cleavage product. *c* Data taken from ref. 5. *d* Very little reaction occurred; 90% of I recovered unchanged; *cf.* Experimental. *e* Introduced as 2-(*p*-nitrophenyl)-ethanol, but apparently reduced almost immediately by Raney nickel. The cleavage products were *p*-MeC6H4NEt2 and 1,4-MeC6H10NEt2. The dehydroxylation product was *p*-EtC6H4NEt2. *f* Reaction product was exclusively 2-phenylethanol resulting from nuclear debromination. No cleavage or dehydroxylation products were noted.

crude reaction mixture with respect to cleavage and dehydroxylation products is given. Included for comparison purposes are similar data[3,5] obtained with 2-arylethanols substituted at C2 with additional alkyl or aryl substituents.

(1) This constitutes Communication XIII in the series "The Stereochemistry of Raney Nickel Action"; for XII see ref. 5.
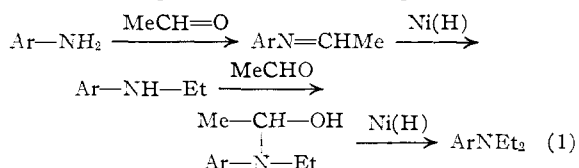
(2) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(3) J. A. Zderic, W. A. Bonner and T. W. Greenlee, This Journal, 79, 1696 (1957).

(4) W. A. Bonner and T. W. Greenlee, *ibid.*, 81, 2122 (1959).

(5) W. A. Bonner and T. W. Greenlee, *ibid.*, 81, 3336 (1959).

Table I (nos. 1 to 4) shows clearly that the progressive introduction of alkyl (or aryl) substituents on C2 in 2-arylethanols enhances the extent of C1–C2 cleavage as compared to simple C1 dehydroxylation. The presence of *meta-* or *ortho–para-* directing groups in the *para* nuclear position, however, appears to exert no unambiguous influence on the cleavage/dehydroxylation ratio. Thus nos. 5 and 6 do not differ widely with respect to this ratio, although reaction in general appeared much slower with respect to no. 6. Number 7, involving cleavage almost exclusively, is interesting in that the nitro group in the starting material appeared to reduce (spontaneous warming) almost immediately to amino, and only N,N-diethylamino compounds proved to be present among the cleavage and dehydroxylation products. The presence of N-alkylation products in such a reaction is most simply interpreted in the terms of equation 1, where the small quantity of acetaldehyde known[6] to be in equilibrium with hot ethanol in the presence of Raney nickel forms a Schiff base, which is subsequently reduced, with the amino precursor. N-Alkylation qualitatively similar to that observed in no. 7 has been noted by other investigators. Thus Mozingo has found that

$$Ar—NH_2 \xrightarrow{MeCH=O} ArN=CHMe \xrightarrow{Ni(H)}$$

$$Ar—NH—Et \xrightarrow{MeCHO}$$

$$\begin{array}{c} Me—CH—OH \\ | \\ Ar—N—Et \end{array} \xrightarrow{Ni(H)} ArNEt_2 \quad (1)$$

the action of Raney nickel on hydrazobenzene, azoxybenzene and nitrobenzene yields N-ethylaniline under reductive desulfuration conditions,[7] while Rice and Kohn have noted that a heated mixture of propanol, aniline and Raney nickel produces N-propylaniline,[8] and Rubstov has reported a high yield of N-ethylpiperidine from ethanol, pyridine and Raney nickel at elevated temperature and pressure.[9] The nuclear debromination of 2-(*p*-bromophenyl)-ethanol and subsequent lack of C1–C2 fission in no. 8 is noteworthy. In this experiment the catalyst may well have been poisoned since hydrogen bromide was noted as being associated with the spent catalyst.

Experimental

Experiments in Table I.—Each of the starting materials in Table I were subjected to the action of Raney nickel[10] in refluxing ethanol for about 6 hours in the manner fully described previously.[3] The crude products were isolated as before and separated into individual components by vapor–liquid partition chromatography. The components were characterized as before by comparison of their infrared spectra and/or VLPC retention times with those of authentic samples. The approximate relative quantity of each component was estimated as before by its relative VLPC peak height or, in later experiments, its VLPC peak area. Only those experiments requiring additional comment will be described further here.

In no. 5 the methyl *p*-(2-hydroxyethyl)-benzoate starting

material was prepared by the following reaction sequence. 2-Phenylethyl acetate was nitrated with cold fuming nitric acid after the procedure of Ferber.[11] Methanolysis of the resulting nitroester afforded 2-(*p*-nitrophenyl)-ethanol. The latter was catalytically reduced to 2-(*p*-aminophenyl)-ethanol by the method of Woodburn and Stuntz.[12] The amino derivative was diazotized and treated with cuprous cyanide according to the general procedure of Clarke and Read.[13] The resulting 2-(*p*-cyanophenyl)-ethanol was subjected to alkaline hydrolysis, affording a sample of *p*-(2-hydroxyethyl)-benzoic acid having m.p. 126–127.5° in agreement with the literature.[14] The acid was converted to its methyl ester by action of ethereal diazomethane.[15] The crude ester was distilled at 130–138° (2 mm.), boiling mainly at 137° (2 mm.), $n^{25}D$ 1.5323.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.28, 66.44; H, 6.75, 6.92.

When this ester (no. 5) was subjected to the action of Raney nickel in refluxing ethanol in the usual fashion the cleavage product was methyl *p*-toluate and the dehydroxylation product methyl *p*-ethylbenzoate. About 10% of the crude product appeared to be unreacted starting material, but it was not characterized fully.

In no. 6 the 2-(*p*-anisyl)-ethanol starting material was prepared by action of ethylene oxide on *p*-anisylmagnesium bromide. After the usual 6-hour treatment with Raney nickel four peaks beyond residual solvent were noted on the VLPC trace. The efflux times of these corresponded to starting material (90%), *p*-ethylanisole (dehydroxylation product) (3%), *p*-methylanisole (cleavage product) (5%) and anisole (2%). The presence of the *p*-methoxy group in no. 6 thus appeared to decrease markedly the rate of reaction of this substrate with Raney nickel.

In No. 7 2-(*p*-nitrophenyl)ethanol (2.00 g.), prepared by the method of Ferber,[11] was added to a mixture of Raney nickel slurry (15 g.) and absolute ethanol (50 ml.). The temperature of the mixture rose spontaneously to about 45°, suggesting that rapid reduction of the nitro group had occurred and that 2-(*p*-aminophenyl)-ethanol was the compound subsequently undergoing the cleavage reaction. After reflux for a 6-hour period the catalyst (still pyrophoric) was filtered and rinsed with ethanol. The filtrate was freed of ethanol through a fractionating column. Addition of hydrochloric acid (3 ml.) to the ethanol distillate, followed by evaporation, yielded no residue. The residue from the above fractionation was subjected to VLPC at 200° on the previous[3] 4-foot Silicone–Celite column, resulting in 6 peaks whose retention times and relative peak heights are given parenthetically: 7-1, residual ethanol (1 min.), 7-2, hydrocarbon (4 min., 2); 7-3, hydrocarbon (6 min., 2); 7-4, 1-methyl-4-(N,N-diethylamino)-cyclohexane (9 min., 21) [*Anal.* Calcd. for $C_{11}H_{23}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 78.11, 78.25; H, 13.75, 13.69; N, 7.98, 8.12]. 7-5, N,N-diethyl-*p*-toluidine (14 min., 16), VLPC retention time and infrared spectrum identical with those of an authentic sample; 7-6, *p*-(N,N-diethylamino)-ethylbenzene (19.5 min., 1), characterized, because of its small quantity, only by the identity of its retention time with that of an authentic sample. Peaks 7-2 and 7-3 represented products present in too minute quantity for convenient characterization. Sufficient of each was isolated, however, to establish their odors as hydrocarbon-like rather than amine-like. Ethylbenzene, ethylcyclohexane, toluene and methylcyclohexane had retention times of around 5 minutes under similar VLPC conditions, and presumably the two hydrocarbons trivially noted have identities among these four possibilities. The action of Raney nickel on 2-(*p*-nitrophenyl)-ethanol thus led to a complex mixture of products including mainly those of cleavage with and without accompanying ring reduction, and to lesser extents those of dehydroxylation and deamination.

In no. 8 2-(*p*-bromophenyl)-ethanol (4.00 g.), prepared by the method of Gilman and Melstrom,[14] Raney nickel (15 g.) and absolute ethanol (50 ml.) were heated under reflux

(6) W. A. Bonner, This Journal, **74**, 1033 (1952); R. Paul, *Bull. soc. chim.*, **8**, 507 (1941).

(7) R. Mozingo, P. Wolf, S. Harris and K. Folkers, This Journal, **65**, 1013 (1943).

(8) R. Rice and E. Kohn, *ibid.*, **77**, 4052 (1955).

(9) M. Rubstov and E. Nikitskaya, *Zhur. Priklad. Khim.*, **29**, 1887 (1956); *C. A.*, **51**, 7366i (1957).

(10) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(11) E. Ferber, *Ber.*, **62**, 183 (1925).

(12) H. Woodburn and C. Stuntz, This Journal, **72**, 1361 (1950).

(13) H. Clarke and R. Read, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 514.

(14) H. Gilman and D. S. Melstrom, This Journal, **70**, 4177 (1948).

(15) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 166.

for 6 hours. Customary processing gave 1.23 g. of a product showing only a single VLPC peak. The efflux time and infrared spectrum of the collected sample corresponded to those noted for 2-phenylethanol, indicating that nuclear

debromination without C1–C2 cleavage was the predominant reaction occurring in this experiment.

STANFORD, CALIF.

# The Stereochemistry of Ketonization. X.[1] Enols from α-Haloacids[2]

BY HOWARD E. ZIMMERMAN AND THEODORE W. CUTSHALL

Both stereoisomers of 1-bromo-2-phenylcyclohexanecarboxylic acid have been prepared and subjected to reduction with zinc and a proton donor. Evidence is presented that the reaction does proceed *via* the enol of the debrominated acid. Also, for the first time it has proved possible to determine the temperature dependence of the stereoselectivity of ketonization with sufficient precision to decide whether this selectivity stems from an entropy or an enthalpy effect.

In paper VI[3] of this series[1,3–10] dealing with our investigations of the stereochemistry of ketonization of enols, the behavior of the enol I of 2-phenylcyclohexanecarboxylic acid was described. For this study enol I was generated as an unstable intermediate by the decarboxylation of 2-phenylcyclohexane-1,1-dicarboxylic acid. There were several reasons why a second study seemed of interest, one in which an attempt would be made to generate enol I by debromination of the corresponding α-bromoacid II.
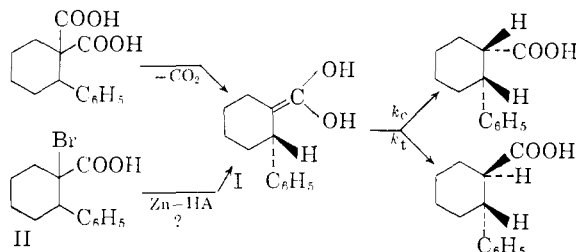
Most important, in our decarboxylation study an attempt had been made to study the temperature dependence of stereoselectivity so that it might be ascertained whether the observed selectivity stemmed from an energy or instead from an entropy effect. Unfortunately, the experimental scatter obscured any temperature dependence which might have been present.[11] However, in

analogy to the facile debromination of α-bromoketones with zinc and a proton donor[1,4,6,10] the zinc debromination of 1-bromo-2-phenylcyclohexanecarboxylic acid promised to provide a means of generating enol I relatively free of by-products, allowing improved precision.

Of course the possibility had to be entertained that the debromination of II might not afford enol I as an intermediate. Moreover, there was reason for such concern. While pointing out the general tendency for α-halocarbonyl compounds to be reduced by way of the enol,[12] Brewster had made the interesting observation[13] that zinc–acetic acid reduction[14] of α-chloro-α-phenylpropionic acid proceeds with inversion of configuration.[15] Also, subsequent to the initiation of the present research, the opinion was offered that the zinc debromination of ethyl 1-bromo-2-phenylcyclohexanecarboxylate proceeds with retention of configuration.[16]

Our investigation began with the bromination of *cis*-2-phenylcyclohexanecarboxylic acid in thionyl chloride followed by hydrolysis of the bromoacid chloride mixture in aqueous acetone. The mixture of bromoacids thus obtained was chromatographed on silica gel affording the desired 1-bromo-2-phenylcyclohexanecarboxylic acid stereoisomers, melting at 116 and 153°, as well as recovered starting material and non-crystalline bromine-containing by-products.

Due to the good fortune of isolating both *cis* and *trans* isomers of 1-bromo-2-phenylcyclohexanecarboxylic acid, a test of the reality of enol I as a debromination intermediate was possible; while inversion and retention mechanisms would produce one stereoisomer of 2-phenylcyclohexanecarboxylic acid from the 116° bromoacid and the other from the 153° bromoacid, the intervention of a common intermediate, enol I, in the debromination would require the same product distribution from the two bromoacids.

(1) For paper IX of this series see H. E. Zimmerman and A. Mais, THIS JOURNAL, 81, 3644 (1959).

(2) Abstracted from the M.S. thesis of T. W. Cutshall presented to Northwestern University.

(3) For paper I of this series and an introduction to the problem, see H. E. Zimmerman, J. Org. Chem., 20, 549 (1955).

(4) H. E. Zimmerman, THIS JOURNAL, 78, 1168 (1956).

(5) H. E. Zimmerman and H. J. Giallombardo, ibid., 78, 6259 (1956).

(6) H. E. Zimmerman, ibid., 79, 6554 (1957).

(7) H. E. Zimmerman and T. E. Nevins, ibid., 79, 6559 (1957).

(8) H. E. Zimmerman and T. W. Cutshall, ibid., 80, 2893 (1958).

(9) H. E. Zimmerman and B. S. Thyagarajan, ibid., 80, 3060 (1958).

(10) H. E. Zimmerman and W.-H. Chang, ibid., 81, in press (1959).

(11) The problem is experimentally more difficult than the usual one of obtaining the enthalpy of activation for a single process from the absolute rate equation, ln (k/T) = −(ΔH‡/RT) + ΔS‡/R + ln (k'/h), by plotting the rate constant k over T versus (1/T) and taking the slope as equal to −(ΔH‡/R). In the ketonizaton problem, stereoselectivity is controlled by the *ratio* of the two rate constants, k_c and k_t, and the rate equation becomes ln (k_c/k_t) = −(ΔΔH‡/RT) + (ΔΔS‡/R), where ΔΔH‡ = ΔH‡_c − ΔH‡_t and ΔΔS‡_c − ΔS‡_t. The quantity ΔΔH‡ is a small difference between two large numbers; hence the stereoselectivity will have a relatively small temperature dependence.

(12) J. H. Brewster, THIS JOURNAL, 76, 6361 (1954).

(13) J. H. Brewster, ibid., 78, 4061 (1956).

(14) E. Ott and K. Krämer, Ber., 68, 1655 (1935).

(15) The intriguing possibility was considered (ref. 13) that reduction of the haloacid molecule, adsorbed with the halogen atom oriented toward the metal surface, yields a carbanion which is protonated from the solution side faster than desorption can occur. Another possible mechanism is the protonation of a free enolic intermediate by the optically active α-haloacid reactant, which is the strongest acid present. Such a process could give an excess of one enantiomeric ketonization product (i.e., asymmetric induction).

(16) J. Klein and G. Levin, THIS JOURNAL, 80, 1707 (1958).