[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Elimination Reactions in Cyclic Systems. II. *cis* Eliminations Promoted by the Sulfonate Group[1]

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Barium *trans*-2-bariosulfatocyclopentanesulfonate (I) was observed to undergo an elimination reaction in alkaline solution to give barium 1-cyclopentene-1-sulfonate and barium sulfate. This is a *cis* elimination, since elimination of *trans* groupings would have given rise to barium 2-cyclopentene-1-sulfonate. The reaction appears to follow zero-order kinetics and apparently occurs on the surface of the barium sulfate being precipitated. The *cis* isomer of I reacted more rapidly (*trans* elimination) to give the same product. The dipolar ion, *trans*-2-(1-proto-1-pyridyl)-cyclopentanesulfonate (V), also undergoes *cis* elimination with hydroxide ion. In this instance the reaction appears to be third order. Two open chain analogs of V were observed to undergo eliminations following second-order kinetics.

In the preceding paper[3] it was established that electrical effects may be more important than steric relationships in deciding the course of base-catalyzed elimination reactions. The dominant role played by electron-withdrawing groups in influencing the course of such reactions was first suggested by the observation that barium *trans*-2-bariosulfato-1-cyclopentanesulfonate (I)[4] reacted with hydroxide ion to give barium 1-cyclopentene-1-sulfonate (II) (*cis* elimination) rather than barium 2-cyclopentene-1-sulfonate (III) (*trans* elimination).[5] The *cis* isomer of I, barium *cis*-2-bariosulfato-1-cyclopentanesulfonate[4] (IV), also underwent elimination under the influence of hydroxide ion to give the same product, barium 1-cyclopentene-1-sulfonate (II). The observation that the *cis* isomer underwent elimination more rapidly than did the *trans* isomer (*trans vs. cis* elimination of H– and $-OSO_3^-Ba^{++}/2$) is consistent with the usual preference for *trans* elimination, and supports the structures of I and IV originally assigned.[4] In acid solution I and IV hydrolyze to the corresponding *trans*- and *cis*-hydroxy sulfonates[4]; no reaction occurs in neutral solution. The hydroxy sulfonates are stable in basic medium under the conditions used for the elimination reactions of I and IV.

The dipolar ion, *trans*-2-(1-proto-1-pyridyl)-cyclopentane-1-sulfonate (V),[4] also underwent an elimination reaction with hydroxide ion to give II. Once again *cis* elements have been eliminated in preference to a possible *trans* elimination. The rate of this reaction was considerably slower than comparable eliminations with the open-chain analogs, 2-(1-proto-1-pyridyl)-1-hexanesulfonate[4] (VI) [n-$C_4H_9CH(\overset{+}{N}C_5H_5)CH_2SO_3^-$], and 2-phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate[4] (VII), which is not surprising, since VI and VII may undergo *trans* eliminations.

In the cyclohexane series barium *cis*-2-bariosulfato-1-cyclohexanesulfonate (analog of IV) was observed to undergo elimination under comparable conditions to give barium 1-cyclohexenesulfonate (*trans* elimination).

The possibility that the reaction course for I and V involved *trans* elimination to barium 2-cyclopentene-1-sulfonate, and rearrangement of this to II, is rendered very unlikely by the good yield and purity of the samples of II obtained from I and V, and by the fact that β,γ-unsaturated sulfonates generally do not rearrange to α,β-unsaturated sulfonates to an appreciable extent in alkaline medium.[6] As a further check on this point barium 2-cyclohexene-1-sulfonate was refluxed for 12 hours with 1.5 N barium hydroxide, and shown to be essentially unchanged.

Attempts to establish the kinetic order of these elimination reactions were, for the most part, unsuccessful. The rate of reaction of barium *cis*-2-bariosulfatocyclopentanesulfonate (IV) with hydroxide ion actually *increased* with time for about the first 25% of the reaction, and then remained reasonably constant (followed to 70–80% completion). The reaction thus adheres closest to zero order, being independent of both the hydroxide ion and the sulfonate ion concentrations. The sodium salt proved to be much less reactive, less than 3% of reaction having taken place at 75° in five hours (the barium salt had reacted to an extent greater than 50% under comparable conditions). The much greater rate of reaction of the barium salt as compared to the sodium salt, and the fact that the rate at first increases and then follows approximately a zero-order rate expression suggests

(1) An account of this work was given at the Milwaukee Meeting of the American Chemical Society in April, 1952; see Abstracts, p. 84K.

(2) Procter and Gamble Predoctoral Fellow, 1949–1951.

(3) F. G. Bordwell and R. J. Kern, THIS JOURNAL, **77**, 1141 (1955).

(4) For a discussion of the nomenclature and stereo configurations of these compounds see F. G. Bordwell and M. L. Peterson, THIS JOURNAL, **76**, 3957 (1954), and preceding papers.

(5) It should be noted that *trans* 1,2-groups and their carbons (*e.g.*, $^-O_3S-O-C-C-SO_3^-$ in I) are not all coplanar in the cyclopentane series, whereas they are for *trans* "axial" (polar) 1,2-cyclohexane derivatives. Differences in rates of elimination reactions in cyclopentane and cyclohexane compounds will be discussed in a later paper in this series.

(6) C. M. Suter and F. G. Bordwell, THIS JOURNAL, **65**, 507 (1943).

that the reaction is occurring on the surface of the barium sulfate being precipitated. That the reaction occurs more rapidly with the *cis*-barium salt than with the *trans*-barium salt (I) is apparent from the fact that the reaction of the latter with 1.0 *N* sodium hydroxide was only about 20% complete after 7.5 hours at approximately 100°, whereas the *cis* isomer reacted with 0.02 *N* sodium hydroxide to this extent in less than 1.5 hours at 85°.

The rates of reaction of 2-(1-proto-1-pyridyl)-1-hexanesulfonate (VI) and 2-phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate (VII) with hydroxide ion each gave good second-order plots. The rates observed were 1.3×10^{-3} sec.$^{-1}$ mole^{-1} l. for VI at 65° and 1.0×10^{-3} sec.$^{-1}$ mole^{-1} l. for VII at 20° Assuming that the rate for VII doubles for each 10° rise in temperature, its rate at 65° would be about 25 times that of VI.

The rate of elimination of *trans*-2-(1-proto-1-pyridyl)-cyclopentane sulfonate (V) (*cis* elimination) was much slower than that of VI (*trans* elimination) which supports the *trans* structure assigned to V on the assumption that it was formed by the reaction of pyridine with a β-sultone intermediate.[4] In 7 hours at 99° V had reacted to the extent of less than 10%, whereas at 65° VI had reacted to this extent in about one hour. In the few runs attempted with V the data appeared to be fitted better by a third-order rate expression (probably second order in hydroxide ion) than by a second order expression.

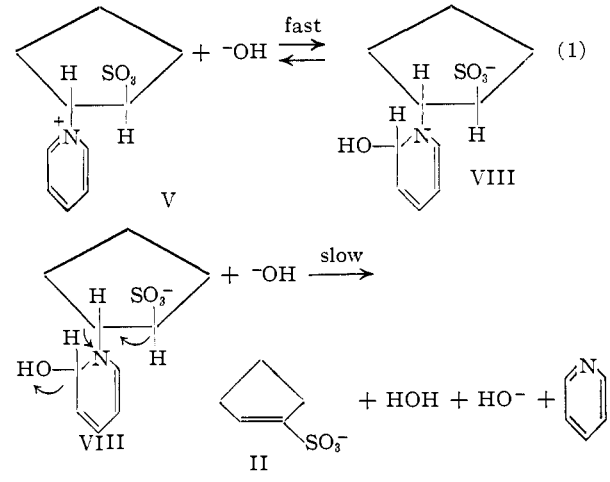
Discussion

The fact that in base-catalyzed elimination reactions of I and V an α-hydrogen *cis* to the bariosulfato ($-OSO_3^-Ba^{++}/2$) or 1-proto-1-pyridyl ($-\overset{+}{N}C_5H_5$) groups, rather than a γ-hydrogen *trans* to these groups, was involved appears to be most reasonably attributed to the greater acidity of the α-hydrogen. Despite the presence of a full negative charge on the sulfonate group ($-SO_3^-$) this group is electron attracting (since the second ionization constant of *p*-sulfobenzoic acid (*p*-$HO_3SC_6H_4COOH$) is greater by a factor of about 2 than that of benzoic acid[7]), and should activate the α-hydrogen. Also, the presence of the sulfonate group in 2-haloethanesulfonates has been shown to effect a lowering of the activation energy in elimination reactions of the order of 3–6 kcal. relative to the activation energies of alkyl halide eliminations,[8] probably by virtue of a loosening of the α-hydrogen–carbon bond, and increased conjugation in the transition state.

The evidence pointing to heterogeneous catalysis in the elimination reaction observed for IV makes it difficult to suggest a mechanism for the reaction, but the qualitative observation of a preference for *cis* rather than *trans* elimination under the influence of an electron-attracting group is comparable to the results discussed in the preceding paper for E2 eliminations.[3] The failure of salts of *trans*-2-hydroxycyclopentanesulfonic acid to form II on treatment with hydroxide rules out displacement of $-OSO_3^-$ by hydroxide followed by *trans* elimination of H– and –OH as a possible mechanism. Participation of the sulfonate group in the reaction to give a β-sultone intermediate, which reacts with hydroxide ion in a *trans* elimination to give II also is unlikely. This β-sultone is probably an intermediate in the reaction of cyclopentene and the dioxane–sulfur trioxide complex,[4] and the solution containing this intermediate does not give appreciable quantities of II when treated with alkali.[9]

Elimination of pyridine from VI, *n*-BuCH($\overset{+}{N}C_5H_5$)$CH_2SO_3^-$, and VII, $C_6H_5CH(\overset{+}{N}C_5H_5)CH_2SO_3^-$ occurs by an E2 mechanism.[10] The approximately 25-fold figure favoring elimination in VII at 65° in water is comparable to the data for eliminations with $RCH(\overset{+}{S}Me_2)SH_3$ initiated by ethoxide ion in ethanol at 64°, where the rate when R is phenyl is 9 times that when R is ethyl.

The much slower third order elimination of pyridine from V may proceed by a process such as that shown involving an intermediate addition product VIII.



Experimental[11]

Elimination of Sulfate from the Barium and Sodium Salts of *trans*-2-Hydrosulfatocyclopentanesulfonic Acid (I).—The barium salt was that prepared by sulfation of barium *trans*-2-hydroxycyclopentanesulfonate[4] (the latter does not eliminate water on refluxing for 12 hr. in 1 *N* barium hydroxide solution). A solution containing 0.215 g. of salt in 50 ml. of 1 *N* sodium hydroxide liberated 16% of barium sulfate when heated on the steam-bath for 7.5 hours, and bromate–bromide titration indicated the presence of 24% of unsaturated sulfonate. After refluxing a solution containing 0.173 g. (0.000454 mole) of the salt in 50 ml. of 1 *N* sodium hydroxide for 11 hours and removing the precipitated barium sulfate and silica, titration of the filtrate indicated the presence of 93% of unsaturated sulfonate. The end-point in these titrations was sharp, which is characteristic of α,β-(but not β,γ)-unsaturated sulfonates. Oxidation with potassium permanganate gave large amounts of sulfate, which is also characteristic of α,β(but not β,γ)-unsaturated sulfonates.[6] In a similar experiment, starting with

(7) R. Wegscheider, *Monatsh.*, **37**, 219 (1916). Recently H. Zollinger, *Nature*, **172**, 257 (1953), has assigned a Hammett σ-value of +0.31 to the *m*-SO_3^- group.

(8) E. F. Landau, W. F. Whitmore and P. Doty, THIS JOURNAL, **68**, 817 (1946).

(9) M. L. Peterson, Doctoral Dissertation, Northwestern University, June, 1951.

(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.

(11) Microanalyses were by Miss Joyce Sorensen. Melting points are uncorrected.

0.4 g. of salt and 25 ml. of barium hydroxide, after 11 hours the mixture was diluted to 100 ml. and the excess barium hydroxide precipitated with carbon dioxide. The filtrate was concentrated to 5 ml. and an aqueous solution of S-(*p*-chlorobenzyl)-thiuronium chloride added. The 0.2 g. (50%) of derivative, m.p. 175–180°, was recrystallized from water to give **S-(*p*-chlorobenzyl)-thiuronium 1-cyclopentene-1-sulfonate**, m.p. 180–181° (salt of II).

Anal. Calcd. for $C_{13}H_{17}O_3N_2S_2Cl$: C, 44.75; H, 4.91. Found: C, 44.67, 45.15; H, 4.55, 4.72.

A solution containing 3.16 g. (0.0109 mole) of sodium *trans*-2-sodiosulfatocyclopentanesulfonate (prepared from the barium salt and sodium sulfate) in 25 ml. of 2 *N* sodium hydroxide was refluxed for 13 hours. After removal of the silica a bromate–bromide titration of an aliquot of the filtrate indicated the presence of 74% of II. From another aliquot a 67% yield of the S-(*p*-chlorobenzyl)-thiuronium salt of II, m.p. 179–180°, was obtained.

Elimination of Sulfate from the Dianilinium Salt of *cis*-2-Hydrosulfatocyclopentanesulfonate (IV).—A solution of 5.0 g. (0.0116 mole) of the aniline salt[4] in 100 ml. of 0.5 *N* barium hydroxide was refluxed for 24 hours. The excess barium hydroxide was precipitated with carbon dioxide and the barium carbonate and barium sulfate removed. Evaporation of the filtrate gave 2.5 g. (100%) of barium 1-cyclopentene-1-sulfonate. An aqueous solution containing 2.5 g. (0.0116 mole) of this salt was treated with 0.6 g. (0.0061 mole) of sulfuric acid; the barium sulfate was removed and 1.1 g. (0.0118 mole) of aniline was added. Evaporation of the solution under reduced pressure gave a colorless salt, which on crystallization from 10% alcoholic acetone gave 1.6 g. (57%) of anilinium 1-cyclopentene-1-sulfonate, m.p. 195–198°. Further crystallization gave material melting at 201–204°, which melted at 150–180° when mixed with the dianilinium salt of *cis*-2-hydrosulfatocyclopentanesulfonate, m.p. 201–202°. An aqueous solution of the aniline salt gave a good yield of crude S-(*p*-chlorobenzyl)-thiuronium derivative, m.p. 175–181°, which did not depress the m.p. of an authentic derivative of 1-cyclopentene-1-sulfonic acid (II).

Elimination of Pyridine from *trans*-2-(1-Proto-1-pyridyl-1-cyclopentanesulfonate (V).—A solution of 0.543 g. of V in 25 ml. of 2 *N* sodium hydroxide after refluxing for 15 min. showed 25% unsaturation; after 3 hours bromate–bromide titration showed that the reaction was 88% complete. A 2.0-g. sample of V was refluxed for 6 hours in 0.2 *N* sodium hydroxide, the solution concentrated to 10 ml., and the solution made slightly acid and treated with a saturated aqueous solution of S-(*p*-chlorobenzyl)-thiuronium chloride. One crystallization from water of the 1.8 g. (59%) of colorless derivative obtained gave S-(*p*-chlorobenzyl)-thiuronium 1-cyclopentene-1-sulfonate, m.p. 180–181°, identical with the previous samples.

Elimination of Sulfate from the Dianilinium Salt of *cis*-2-Hydrosulfatocyclohexanesulfonate.—A solution of 1.9 g. (0.0042 mole) of aniline salt[4] in 20 ml. of 1 *N* barium hydroxide was refluxed for one hour, 80 ml. of water was added, and the excess barium hydroxide precipitated with carbon dioxide. After removal of the barium sulfate and barium carbonate the filtrate was treated with 0.20 g. (0.002 mole) of sulfuric acid, and the barium sulfate once again removed. The filtrate was treated with 0.5 g. (0.0054 mole) of aniline, and the solution evaporated to dryness under reduced pressure. Recrystallization of the residue from 20% alcoholic acetone gave 0.8 g. (72%) of colorless crystals, m.p. 210–215°. Further crystallization gave **anilinium 1-cyclohexene-1-sulfonate**, m.p. 216–217° (dec.). This material gave large depressions in m.p. when mixed with the original aniline salt or that of *cis*-2-hydroxycyclohexane-1-sulfonate.[4] It differs by 36° from the m.p. of anilinium 2-cyclohexene-1-sulfonate (see below).

Anal. Calcd. for $C_{12}H_{17}O_3NS$: C, 56.44; H, 6.71. Found: C, 56.70; H, 6.92.

A small portion of the aniline salt was treated in aqueous solution with S-(*p*-chlorobenzyl)-thiuronium chloride to give a derivative melting at 177–181°. Recrystallization from water gave **S-(*p*-chlorobenzyl)-thiuronium 1-cyclohexene-1-sulfonate**, m.p. 182.5–183.5°.

Anal. Calcd. for $C_{14}H_{19}O_3N_2S_2Cl$: C, 46.33; H, 5.28. Found: C, 46.53; H, 5.61.

A solution of 1.7 g. (0.0038 mole) of the dianilinium salt of *cis*-2-hydrosulfatocyclohexanesulfonate in 15 ml. of 1 *N* barium hydroxide was refluxed for one hour. The barium sulfate and excess barium hydroxide were removed, and the solution concentrated to 10 ml. Addition of 0.8 g. (0.0038 mole) of S-benzylthiuronium chloride to the hot solution gave, on cooling, 0.8 g. (66%) of derivative, m.p. 178–182°. Recrystallization from water gave **S-benzylthiuronium 1-cyclohexene-1-sulfonate**, m.p. 182–183°.

Anal. Calcd. for $C_{14}H_{20}O_3N_2S_2$: C, 51.19; H, 6.14. Found: C, 51.56; H, 6.08.

Barium 2-Cyclohexene-1-sulfonate.—A solution of 13.0 g. (0.158 mole) of cyclohexene in 50 ml. of ethylene chloride was added slowly to a sulfonating reagent prepared from 12.6 g. (0.158 mole) of sulfur trioxide and 13.9 g. (0.158 mole) of dioxane in 100 ml. of ethylene chloride kept at −45°. This mixture was stirred at −50 to −40° for 2 hr. and at 0° for one hour and then hydrolyzed with water. Analysis of aliquots of the aqueous layer showed the presence of 0.225 equivalent of acid, 0.0845 mole (53%) of barium sulfate (mainly from hydrolysis of the hydrogen sulfate ester of *cis*-2-hydroxycyclohexanesulfonate[4]), and 27% of unsaturated sulfonate (57% on the basis of the cyclohexene reacting). The aqueous solution was neutralized with barium carbonate, the insoluble barium salts removed, and the solution evaporated to dryness under reduced pressure to give 14.0 g. of salts which contained 53% (bromate–bromide analysis) of unsaturated sulfonate. A 9.0-g. portion of the salts was refluxed in 60 ml. of 80% ethanol, the solution filtered to remove 0.9 g. of undissolved salts and the solution cooled. A first crop of crystals was collected and further crops were collected after subsequent partial evaporations. Titration for unsaturation gave the following results: crop 1, 1.1 g., 88%; crop 2, 1.0 g. (81%); crop 3, 1.6 g. (63%); crop 4, 2.7 g. (24%). To a hot solution of 0.5 g. of the first crop in 10 ml. of water was added a saturated aqueous solution containing an equimolar quantity of S-(*p*-chlorobenzyl)-thiuronium chloride. On cooling 0.5 g. (65%) of product, m.p. 156–158°, separated. Crystallization from water gave **S-(*p*-chlorobenzyl)-thiuronium 2-cyclohexene-1-sulfonate**, m.p. 159–160°.

Anal. Calcd. for $C_{14}H_{19}O_3N_2S_2Cl$: C, 46.33; H, 5.28. Found: C, 46.45; H, 5.37.

A solution of 0.8 g. (0.0032 mole) of the crystals from the second crop in 20 ml. of water was treated with 0.17 g. (0.0017 mole) of sulfuric acid, and the barium sulfate removed. Addition of 0.4 g. (0.0043 mole) of aniline and evaporation to dryness under reduced pressure gave 0.6 g. (67%) of tan crystals. After decolorization and crystallization from acetone material melting at 165–170° was obtained. Further recrystallization from acetone gave **anilinium 2-cyclohexane-1-sulfonate**, m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{17}O_3NS$: C, 56.44; H, 6.71. Found: C, 56.42; H, 6.72.

The structure of barium 2-cyclohexene-1-sulfonate is indicated by its failure to form sulfate on oxidation, and by the agreement in m.p. of its S-benzylthiuronium salt, 148–149° with that reported by Sperling for the salt of an authentic sample of sodium 2-cyclohexene-1-sulfonate prepared from 3-bromocyclohexene and ammonium sulfite.[12]

Attempted Rearrangement of Barium 2-Cyclohexenesulfonate to Barium 1-Cyclohexenesulfonate.—A solution of 0.31 g. of barium salt (crop 1 above) was refluxed for 12 hr. in 20 ml. of 1.5 *N* barium hydroxide solution. After precipitation of the excess barium hydroxide with carbon dioxide and removal of the barium carbonate, 0.3 g. of S-(*p*-chlorobenzyl)-thiuronium chloride was added to the filtrate. From the solution 0.31 g. (63%) of derivative, of m.p. 154–157°, was obtained. The m.p. of a mixture of this derivative with S-(*p*-chlorobenzyl)-thiuronium 2-cyclohexene-1-sulfonate (m.p. 159–160°) was 158–160°, and the m.p. of a mixture with S-(*p*-chlorobenzyl)-thiuronium 1-cyclohexene-1-sulfonate (m.p. 182–183°) was 137–153°. The yield and purity of the derivative were practically identical with that of the untreated barium salt (see above).

Kinetic Runs with Barium and Sodium Salts of *cis*-2-Hydrosulfatocyclopentanesulfonic Acid.—Runs were made at 65°, 75°, and 85°. In every case 100 ml. of a solution

(12) The S-benzylthiuronium salt was prepared by R. S. Schiefelbein, Doctoral Dissertation, Northwestern University, June, 1950, p. 38.

TABLE I

RATES OF ELIMINATION OF SALTS OF *cis*-2-HYDROSULFATOCYCLOPENTANESULFONIC ACID

Time, min.	Acid, ml.	Concn. of base	x	$k_0 \times 10^7$	$k_1 \times 10^5$
Barium salt, standard acid 0.02726 N, T = 75°					
0	18.90	0.02067	.....	..	..
30	18.38	.02011	0.00056	3.11	1.53
90	17.05	.01865	.00202	3.74	1.90
180	13.90	.01521	.00546	5.06	2.84
300	9.35	.01022	.01045	5.78	3.91
390	6.70	.00735	.01332	5.69	4.43
480	3.90	.00427	.01640	5.69	5.48
Barium salt, standard acid 0.03380 N, T = 85°					
0	15.05	0.02035	.....	..	
15	14.80	.02001	0.00034	3.78	
45	13.76	.01860	.00175	6.49	
105	11.28	.01525	.00510	8.09	
165	8.51	.01151	.00884	8.92	
230	6.10	.00825	.01210	8.76	
285	4.20	.00568	.01467	8.56	
Sodium salt, standard acid 0.02726 N, T = 75°					
0	19.22	0.02095			
61	18.95	.02066			
150	18.80	.02049			
320	18.70	.02039			
500	18.65				

0.04194 M in the salt and 100 ml. of 0.04194 N sodium hydroxide were thermostated and mixed. Twenty-five ml. aliquots taken at approximate time intervals were removed, cooled in an ice-bath and titrated with standard hydrochloric acid.

Rates of Elimination of Pyridine from 2-(1-Proto-1-pyridyl)-1-hexanesulfonate and 2-Phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate.—Portions of 100 ml. each of a 0.04284 N sodium hydroxide solution and 0.04284 M aqueous solution of the dipolar ion, which had been equilibrated at 65.0° were mixed. Samples of 25.0 ml. of the reaction mixture were pipeted into an excess of 0.03380 N hydrochloric acid, and the solution back-titrated with the standard base solution using phenolphthalein indicator. This run gave $k_2 = 1.31 \times 10^{-3}$ l. sec.$^{-1}$ mole^{-1}. A similar run using a two molar quantity of base gave $k_2 = 1.26 \times 10^{-3}$. An analogous experiment with equimolar concentrations of 2-phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate (VII) and sodium hydroxide gave $k_2 = 1.05 \times 10^{-3}$ l. sec.$^{-1}$ mole^{-1}.

Rate of Elimination of Pyridine from *trans*-2-(1-Proto-1-pyridyl)-1-cyclopentanesulfonate (V).—In one experiment 10-ml. portions of a 0.04387 N solution of V were added from a buret to test-tubes each containing 10.0 ml. of 0.04387 N sodium hydroxide. The tubes were tightly stoppered with rubber stoppers, and were heated in an insulated vessel through which steam was passed. The temperature was maintained at 99.0 ± 0.5°. At appropriate time intervals, the samples were removed and added to an excess of 0.03229 N hydrochloric acid, and the acid was back-titrated with the standard base. The third-order constant calculated from these data, $k_3 = 6.0 \times 10^{-2}$ l. sec.$^{-1}$ mole^{-2}, had an average deviation in the constant of 5%. The values calculated for a second order "constant" × 10^4 were: 6.4, 5.6, 5.5, 4.6, 4.4, 3.8, 3.6.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Condensation of Aryl Carboxylic Acid Hydrazides with Orthoesters

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Nineteen 2-aryl-1,3,4-oxadiazoles, or 2-alkyl-5-aryl-1,3,4-oxadiazoles, were prepared by the condensation of aryl carboxylic acid hydrazides with orthoesters. In two examples the 1-acyl-2-ethoxymethylenehydrazine intermediate was isolated. Thiobenzoic acid hydrazide and ethyl orthoformate formed 2-phenyl-1,3,4-thiadiazole. 3-Pyrazolecarboxylic acid hydrazide and ethyl orthoformate gave pyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one rather than the oxadiazole.

Although 2,5-disubstituted-1,3,4-oxadiazoles have been prepared by dehydration of 1,2-diacylhydrazines,[1] no reference to 2-substituted-1,3,4-oxadiazoles of the type represented by I, appears in the literature. These latter compounds have now been made in good yield by the condensation of an aromatic carboxylic acid hydrazide with *excess* ethyl orthoformate. Extension of this reaction to higher orthoesters has led to the formation of 2-alkyl-5-aryl-1,3,4-oxadiazoles.

$$ArCONHNH_2 + HC(OC_2H_5)_3 \longrightarrow \underset{I}{\text{2-Ar-1,3,4-oxadiazole}} + 3C_2H_5OH$$

In carrying out this process experimentally, the reactants were heated under mild reflux after which the excess orthoester was removed and the oxadiazole purified by distillation or recrystallization. The compounds listed in Table I were prepared in this fashion. The starting aromatic carboxylic acid hydrazide may be carboxylic or heterocyclic.

(1) For a leading reference covering the older literature see R. Stolle, *J. prakt. Chem.*, [2] **68**, 130 (1903).

It is interesting to note that the dihydrazide of terephthalic acid reacts with ethyl orthoformate to give *p*-phenylene-bis-(1,3,4-oxadiazole-2).

In two examples, compounds of the type represented by II were isolated. Picolinic acid hydrazide with excess ethyl orthoformate, heated under re-

$$\underset{II}{RCONHN{=}CHOC_2H_5} \qquad R = \text{IIa or IIb}$$

flux overnight, gave rise to 1-ethoxymethylene-2-picolinylhydrazine (IIa). Compound IIa lost ethanol when heated at 200° and formed 2-(2-pyridyl)-1,3,4-oxadiazole. This suggests that II is an intermediate in the formation of I, perhaps through its enol III.

Two products were obtained from 3-(or 5)-pyrazolecarboxylic acid hydrazide and ethyl orthoformate. The properties of one were in agreement