NOTES

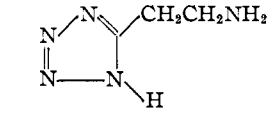
5-β-Aminoethyltetrazole

By C. Ainsworth

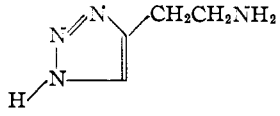
Received May 23, 1953

In connection with the investigations of compounds structurally related to histamine,[1] 5-β-aminoethyltetrazole (I) has been synthesized and examined for pharmacological activity.[2]

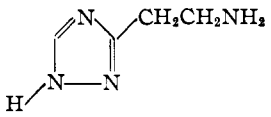
4-β-Aminoethyl-1,2,3-triazole (II)[3] has only moderate histamine-like activity on isolated smooth muscle strips and on blood pressure, whereas, the isomeric 3-β-aminoethyl-1,2,4-triazole (III)[4] is relatively highly active in these tests. The tetrazole analog, I, therefore, was of special interest in that it represented a replacement by nitrogen of two of the ring carbon atoms of histamine (IV) and could be considered as an analog of each of the compounds, II, III and IV.



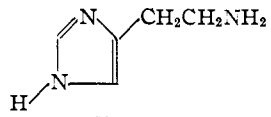
I



II

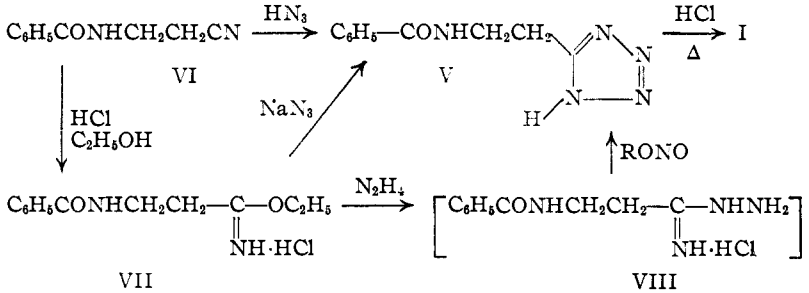


III



IV

Compound I was prepared from 5-β-benzamidoethyltetrazole (V) which, in turn, was obtained from β-benzamidopropionitrile (VI) by three different methods, as indicated in the accompanying reaction scheme



VII VIII

The yields of V were low (about 10%) by each method. Hydrolysis of V with dilute hydrochloric acid gave I which was isolated as the hydrochloride.

Preliminary pharmacological tests have indicated that I, even at high doses, has no histamine-like activity on isolated smooth muscle tissue and on blood pressure.

Acknowledgments.—The author is grateful to H. M. Lee and J. H. Tilden for the pharmacological data; to H. E. Boaz, D. O. Woolf and J. W. Forbes for physical measurements; and to W. L. Brown, H. L. Hunter and G. M. Maciak for the microanalyses.

Experimental[5]

Ethyl β-Benzamidopropionimidate Hydrochloride[6] (VII). —This compound was prepared in quantitative yield by the general procedure for obtaining iminoesters of McElvain and Nelson.[7]

A solution, formed from 8.7 g. (0.05 mole) of β-benzamidopropionitrile,[8] 3 ml. (0.05 mole) of ethanol, 1.8 g. (0.05 mole) of hydrogen chloride and 25 ml. of dioxane, was allowed to stand at 5° for three days. The heavy precipitate of ethyl β-benzamidopropionimidate hydrochloride which formed melted at 120–122°.

Anal. Calcd. for $C_{12}H_{16}N_2O_2 \cdot HCl$: N, 10.92. Found: N, 10.76.

5-β-Benzamidoethyltetrazole (V). (a) **Reaction of Ethyl β-Benzamidopropionimidate Hydrochloride and Hydrazine followed by Amyl Nitrite.**[9]—To 3.2 g. (0.1 mole) of water-free hydrazine in 50 ml. of ethanol was added, portionwise, with stirring, 25.6 g. (0.1 mole) of ethyl β-benzamidopropionimidate hydrochloride. During the addition the temperature was maintained between −20 and −5° by means of a methanol–Dry Ice-bath. After one hour approximately 15 g. of solid [presumably the hydrazidine hydrochloride (VIII)] was collected on a buchner funnel. The solid was dissolved in 100 ml. of ethanol, the solution cooled to −10° and treated with 10 ml. (0.1 mole) of amyl nitrite. It became pink then red in color, and the temperature of the reaction mixture rose rapidly to 40°. The product (3.5 g.), which separated after standing at 5° for three days, was collected by filtration. After recrystallization from water, 2.2 g. (10%) of 5-β-benzamidoethyltetrazole was obtained as white irregular prisms; m.p. 206°; pK'_a 6.15 (66% dimethylformamide); λ_{max} 224 mμ, log ε 4.06 (methanol).

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10. Found: C, 55.23; H, 5.25.

5-β-Benzamidoethyltetrazole was soluble in 1 *N* sodium hydroxide and was reprecipitated upon the addition of acid. It formed a water-insoluble silver salt.

(b) **Reaction of Ethyl β-Benzamidopropionimidate Hydrochloride and Sodium Azide.**—A mixture of 2.5 g. (0.01 mole) of ethyl β-benzamidopropionimidate hydrochloride, 1 g. (0.015 mole) of sodium azide and 25 ml. of acetic acid was heated under reflux for 24 hours. Sodium chloride (0.4 g.) was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was dissolved in a minimum amount of hot water and, after cooling, 0.21 g. (10%) of 5-β-benzamidoethyltetrazole separated. The identity with the product obtained by procedure (a) was shown by mixed melting point and infrared spectra.

(c) **Condensation of β-Benzamidopropionitrile and Hydrogen Azide.**[10]—A water-free solution of hydrogen azide (from 25 g. of sodium azide) in xylene was prepared according to the procedure of Herbst.[11] To this was added 10 g.

(1) (a) H. M. Lee and R. G. Jones, *J. Pharmacol. Exptl. Therap.*, **95**, 71 (1949); (b) R. G. Jones and M. J. Mann, This Journal, **75**, 4048 (1953).

(2) This problem was suggested by Dr. Reuben G. Jones.

(3) J. C. Sheehan and C. A. Robinson, This Journal, **71**, 1436 (1949).

(4) C. Ainsworth and R. G. Jones, *ibid.*, **75**, 4915 (1953).

(5) Melting points were taken on a Fisher–Johns block.

(6) Reported without physical data by A. A. Goldberg and W. Kelly, British Patent 605,952 [*C. A.*, **43**, 672 (1949)].

(7) S. M. McElvain and J. W. Nelson, This Journal, **64**, 1825 (1942).

(8) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(9) W. Oberhummer, *Monatsh.*, **63**, 285 (1933), prepared 5-methyltetrazole by this procedure.

(10) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950), reported the conversion of nitriles to tetrazoles by heating them with hydrogen azide in a sealed tube.

(11) E. K. Harvill, R. M. Herbst and E. G. Schreiner, *ibid.*, **17** 1597 (1952).

of β-benzamidopropionitrile and the solution was heated under reflux for four days. The solvent was evaporated and the residue was extracted with 50 ml. of 1 *N* sodium hydroxide. The extract was made acidic with dilute hydrochloric acid and was concentrated to dryness under reduced pressure. The resulting solid was extracted with absolute ethanol which, in turn, was evaporated, and the residue was recrystallized from 10 ml. of water. There was obtained 0.2 g. of 5-β-benzamidoethyltetrazole. Approximately 9 g. of starting material was recovered.

5-β-Aminoethyltetrazole (I) Hydrochloride.—5-β-Benzamidoethyltetrazole (1.5 g.) suspended in 25 ml. of dilute hydrochloric acid was heated under reflux for 6 hours. Benzoic acid, which precipitated on cooling, was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. After recrystallization from ethanol–ether, 5-β-aminoethyltetrazole hydrochloride was obtained in quantitative yield as prisms; m.p. 128–129°; pK'_a 5.0, 10.0 (66% dimethylformamide); no $\lambda_{max} > 210$ mμ; mol. wt., 152 (by titration).

Anal. Calcd. for $C_3H_7N_5 \cdot HCl$: C, 24.09; H, 5.39; Cl, 23.70. Found: C, 24.34; H, 5.95; Cl, 23.88.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA

Biosynthesis and Characterization of 11β-Hydroxytestosterone[1]

BY L. R. AXELROD AND G. ARROYAVE[2]

RECEIVED JUNE 15, 1953

The introduction of an hydroxyl group at the 11-position of some steroid compounds by adrenal gland preparations has been reported. Hechter, *et al.*,[3] demonstrated this bioöxidation in the perfused adrenal gland. Other investigators[4,5] have obtained essentially the same results using brei, homogenates and more purified preparations.

Various steroids of the C_{21} and C_{19} types have been shown to undergo this bioöxidation. Consequently, it was considered of interest to investigate the potentiality of the adrenal gland to introduce a C_{11}-hydroxyl group in steroids which are recognized as major secretory products of other endocrine glands, since normally these compounds are present in the circulation and constitute potential substrates for this adrenocortical enzymatic system.

As a representative of these naturally occurring steroids, testosterone was perfused in homologous blood through isolated beef adrenal glands freshly obtained from the abattoir. In other experiments testosterone was incubated with fresh beef adrenal gland brei and homogenates. For the latter experiments the tissue was suspended in a modified Krebs–Ringer phosphate buffer at *p*H 7.4 (calcium ions were omitted), containing sodium fumarate and ATP as cofactors[6] and incubation was continued for two hours at 37° under an atmosphere of 95% oxygen and 5% carbon dioxide. The steroids were extracted from the incubation medium by dialysis according to a technique developed in these laboratories[7] and separated by paper chromatography.

Among several steroids isolated from the perfused medium and incubation mixture, one has been characterized as 11β-hydroxytestosterone (I), hitherto unreported in the literature.

The compound was purified by paper chromatography and crystallized twice from methanol–ether–pentane. White crystals were obtained which melted at 234.5–235.5°; $[\alpha]^{25}D$ 142° (2 mg. in 1.00 ml. of methanol). The infrared absorption spectrum of I is shown in Fig. 1.

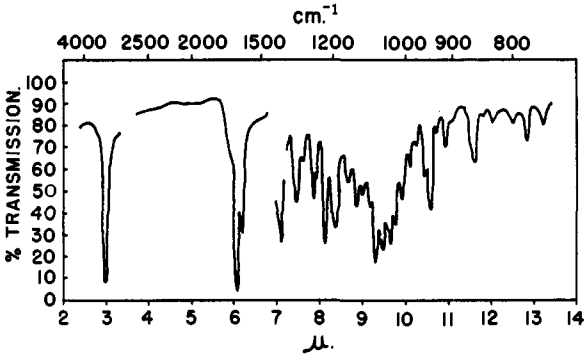


Fig. 1.—Infrared absorption spectrum of 11β-hydroxytestosterone: cell, 0.025 mm.; temp., 23°; concn., 3 mg. in 2 drops of Nujol.

Some characteristics of the compound are presented in Table I.

TABLE I

SOME CHARACTERISTICS OF 11β-HYDROXYTESTOSTERONE

Test	Result	Responsible structure
Modified Zimmerman	Blue	C_3-keto group[8,9]
Modified Lund	Orange	Δ^4-3-keto group[9]
Ultraviolet absorption maxima, mμ	242	α,β-Unsaturated ketone
Triphenyltetrazolium chloride	No reaction	Absence of reducin side chain
Rf value, benzene–formamide	0.07	.....

Chromic acid oxidation of I yielded adrenosterone (II) which was characterized by comparison with an authentic sample, showing the same chromatographic behavior in two different solvent systems, and identical color spot tests, sulfuric acid chromogen absorption spectrum, and ultraviolet

TABLE II

CHARACTERISTICS OF THE OXIDATION PRODUCTS OF 11β-HYDROXYTESTOSTERONE

Compound	Modified Zimmerman reaction	Modified Lund reaction	Ultraviolet absorption max., mμ	*Rf* value, benzene–formamide
II (adrenosterone)	Purple[a]	Orange	238	0.56
III	Blue	Orange	238	.24

[a] Indicative of a C_{17}-keto group.[8,9]

(1) This investigation was supported principally by a research grant from the Jane Coffin Memorial Fund for Medical Research and is based in part on work performed under contract with the United States Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York.

(2) John Simon Guggenheim Memorial Foundation Fellow.

(3) O. Hechter, R. Jacobsen, R. Jeanloz, H. Levy, C. N. Marshall, G. Pincus and V. Schenker, THIS JOURNAL, **71**, 3261 (1949), and *Arch. Biochem.*, **25**, 457 (1950).

(4) K. Savard, A. A. Green and L. A. Lewis, *Endocrinology*, **47**, 418 (1950).

(5) M. Hayano and R. I. Dorfman, *J. Biol. Chem.*, **201**, 175 (1953).

(6) M. Hayano, R. I. Dorfman and R. V. Yamada, *ibid.*, **193**, 175 (1951).

(7) L. R. Axelrod and A. Zaffaroni, unpublished data.

(8) C. D. Kochakian and G. Stidworthy, *J. Biol. Chem.*, **199**, 607 (1952).

(9) L. R. Axelrod, *ibid.*, in press.

absorption maxima of a methanol solution. The characteristics are summarized in Table II.

The melting point was the same as that of an authentic sample (222.5–224°) and the mixed melting point showed no depression.

Acetylation of I followed by chromic acid oxidation and hydrolysis yielded a new compound III which on simultaneous paper chromatography with the original steroid I and adrenosterone (II) was shown to possess an *Rf* value intermediate between the two. The results of color spot tests and spectrophotometric studies on this compound III are presented in Table II. The presence of an α,β-unsaturated ketone is demonstrated by its ultraviolet absorption maximum at 238 mμ. Further chromic acid oxidation of III yielded adrenosterone. Table III illustrates the characteristics of the sulfuric acid chromogen absorption spectra of compounds I–III.

TABLE III

CONCENTRATED SULFURIC ACID CHROMOGEN ABSORPTION SPECTRA

Compound	Maxima, mμ	O.D.	γ/ml.
11-β-Hydroxytestosterone (I)	295	1.80	30
	385	0.28	
Adrenosterone (II)	280	1.35	25
11-Ketotestosterone ? (III)	285	1.80	30
	355	0.08	

The elementary analysis and the degradation to adrenosterone (II) proved that I is a steroid containing 19 carbons and 3 oxygens, with the oxygen functions at positions 3, 11 and 17, and that the oxygen function on carbon 3 was thereby established to be a Δ^4-3 keto structure. This was substantiated by the characteristic color spot tests and the spectrophotometric data.

The nature of the oxygen moieties on carbons 11 and 17 was deduced from the results of the chromic acid oxidation of the acetate of I followed by hydrolysis to III and the subsequent oxidation of III to adrenosterone (II). The fact that III was chromatographically and qualitatively different from the original steroid was interpreted as indicating that the 11-oxygenated function is a β-oriented hydroxyl group, since the closely related compounds 11α-hydroxytestosterone and 11-ketotestosterone would have remained unchanged upon this treatment. The fact that III was not adrenosterone, but yielded adrenosterone upon oxidation proved that the oxygen function on carbon 17 is an hydroxyl radical. Finally, the β-orientation of this hydroxyl group at position 17 in testosterone was taken as presumptive evidence that the same configuration is present in the biosynthetic product I derived from it.

A brief outline of the procedures is given in the experimental section.

Experimental

Paper Chromatography.—Two chromatographic systems were applied: benzene–formamide[10] and methylcyclohexane–propylene glycol.[9] When chromatographic positions were to be compared for the purpose of identification, quantities of steroids between 25 and 50 γ per cm. width of paper were applied. All chromatograms were run at constant temperature (26°). The position of the spots was determined by cutting strips 0.3 cm. in width from the middle and the sides of the chromatogram and developing with modified Zimmerman reagent[8,9] and modified Lund reagent[9] or by using a fluorescent scanner.[11]

Extraction and Isolation of 11β-Hydroxytestosterone. (a) **Dialysis.**—The blood perfusate or incubation mixture was mixed with 1 part water and 1 part absolute methanol, introduced into Visking tubing (1 inch diameter) and dialyzed against 40% methanol in 250-ml. cylinders. The dialysate was collected each day for 8 days, pooled, brought to 10% methanol by volume with water and extracted five times with 15% by volume of C.P. chloroform.

(b) **Chromatography.**—Aliquots of the chloroform extract were chromatographed using the system benzene–formamide. Whatman No. 1 filter paper strips 17 cm. wide were impregnated with formamide by dipping them in a mixture of formamide and absolute methanol (1:1 by volume), removing the excess of solvents by blotting between two sheets of filter paper and evaporating off the methanol by fanning for 2 to 3 minutes in the air. In a 12-hour chromatogram, run under the conditions described above, 11β-hydroxytestosterone separated from other steroids present in the mixture moving to a position 9 to 12 cm. from the starting line. The steroid was eluted from the paper with absolute methanol and the eluate was evaporated down to dryness at 45° *in vacuo* under a stream of nitrogen. The dry residue was dissolved in warm ether by the addition of a few drops of methanol, pentane was added and the mixture was allowed to stand in the refrigerator overnight. Crystals were obtained m.p. 234.5–235.5°. Recrystallization from the same solvent mixture caused no change in the melting point.

Anal.[12] Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 75.40; H, 9.10.

Chromic Acid Oxidation.—This was done essentially according to the technique described by Zaffaroni, *et al.*[13] Two mg. of I was treated with 1 ml. of 90% acetic acid and 2.5 mg. of chromic anhydride. The mixture was stoppered and allowed to stand at room temperature (24°) for 16 hours. Three ml. of distilled water was then added followed by extraction with four 1-ml. portions of chloroform. The chloroform extract was evaporated to dryness at 45° under nitrogen. Aliquots were taken for the different characterization tests.

Oxidation and Hydrolysis of I Acetate.—One and a half milligrams of I, thoroughly dried, was treated in a 10 × 75 mm. test-tube with 1 ml. of pyridine and 1 ml. of acetic anhydride. The tube was stoppered and the mixture allowed to stand at room temperature (approximately 24°) for 14 hours. The solution was then evaporated to dryness at room temperature under a stream of nitrogen. Several small portions of absolute methanol were added to aid the evaporation of the reagents. The residue was then submitted to chromic acid oxidation as previously described. Extraction of the oxidized acetate from the reaction mixture was carried on with three 0.5-ml. portions of ethyl acetate and three 0.5-ml. portions of chloroform. The combined extracts were evaporated to dryness at 45° under a stream of nitrogen. The residue, containing the acetate, was then treated with 1 ml. of 0.1 *N* sodium hydroxide through which nitrogen had been previously passed in order to displace the dissolved oxygen. The reaction mixture was covered with an atmosphere of nitrogen, stoppered tightly and allowed to stand for 14 hours at room temperature. After addition of four times its volume of distilled water, the free steroid was extracted with four 1-ml. portions of chloroform. The chloroform extract was evaporated to dryness *in vacuo* at 45° under a stream of nitrogen and chromatographed in benzene–formamide. Oxidation of III to adrenosterone was done using the same technique previously described for the chromic acid oxidation of I.

Absorption Spectra of Sulfuric Acid Chromogens.—The technique previously described by Zaffaroni, *et al.*,[14] was applied. A 90 to 100 γ dry sample of the steroid was treated with 3 ml. of concentrated sulfuric acid. After 2 hours standing at room temperature the absorption spec-

(10) R. Burton, A. Zaffaroni and E. H. Keutmann, *J. Biol. Chem.*, **189**, 765 (1951).

(11) W. J. Haines and N. A. Drake, *Federation Proc.*, **9**, 180 (1950).

(12) Analysis was performed by Dr. D. Ketchum, Rochester, N. Y.

(13) A. Zaffaroni and R. Burton, *J. Biol. Chem.*, **188**, 749 (1951).

(14) A. Zaffaroni, THIS JOURNAL, **72**, 3999 (1950).

trum between 220 and 600 mμ was read in a DU Beckman spectrophotometer.

DEPARTMENT OF RADIATION BIOLOGY AND
DEPARTMENT OF BIOCHEMISTRY
SCHOOL OF MEDICINE AND DENTISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK

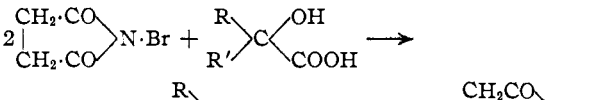
Action of N-Bromosuccinimide on Aliphatic α-Hydroxy Acids

BY MOHAMED ZAKI BARAKAT AND MOHAMED FATHY ABD EL-WAHAB

RECEIVED MAY 4, 1953

It has already been shown that N-bromosuccinimide functions as an oxidizing agent, *e.g.*, it converts primary and secondary alcohols into the corresponding aldehydes and ketones, respectively,[1,2] and in many cases the action is highly selective. Fieser and Rajagopalan have reported high selectivity in the oxidation of the 7α-hydroxyl group of cholic acid and the 6β-hydroxyl group of cholestane-3β,5α,6β-triol by use of N-bromosuccinimide. Whereas 3-hydroxyl groups usually resist attack by N-bromosuccinimide in aqueous acetone, methyl 3α-hydroxy-9α,11α-oxidocholanate[3] is oxidized to the 3-ketone. Selective oxidation of a 3-acyl derivative of methyl cholate[4] to the 7-ketone can be accomplished in high yield with N-bromosuccinimide.

There appears to have been no report on the action of this reagent with α-hydroxy acids. We have shown that N-bromosuccinimide reacts readily on heating in an aqueous solution with aliphatic α-hydroxy acids, *e.g.*, glycolic, lactic, mandelic and benzilic acids, yielding aldehydes or ketones containing one carbon atom less, *e.g.*, formaldehyde, acetaldehyde, benzaldehyde and benzophenone, respectively. Evolution of carbon dioxide and bromine was demonstrated in all cases. Succinimide has been isolated in the reaction with lactic and benzilic acids.



$$2\left|\begin{matrix}CH_2\cdot CO\\ CH_2\cdot CO\end{matrix}\right\rangle N\cdot Br + \begin{matrix}R\\ R'\end{matrix}\rangle C\langle\begin{matrix}OH\\ COOH\end{matrix} \longrightarrow \begin{matrix}R\\ R'\end{matrix}\rangle C{=}O + CO_2 + Br_2 + 2\left|\begin{matrix}CH_2CO\\ CH_2CO\end{matrix}\right\rangle NH$$

R = R′ = H : glycolic acid ⟶ formaldehyde
R = CH_3, R′ = H : lactic acid ⟶ acetaldehyde
R = C_6H_5, R′ = H ; mandelic acid ⟶ benzaldehyde
R = R′ = C_6H_5; benzilic acid ⟶ benzophenone

Compared with the fatty acids the corresponding α-hydroxy acids possess higher dissociation constants, and this may explain why such a reaction takes place; an analogous case may be the degradation of aliphatic dicarboxylic acids, *e.g.*, oxalic acid,[5] by N-bromosuccinimide in aqueous medium at room temperature.

The conversion of benzilic acid to benzophenone when treated with N-bromosuccinimide provides a new route to pass from α-diketones, *e.g.*, benzil, to aromatic ketones, *e.g.*, benzophenone.

Experimental

Action of N-Bromosuccinimide on Aliphatic α-Hydroxy Acids. (1) **Isolation of Aldehydes.** (a).—N-Bromosuccinimide (1.78 g., 2 moles) and glycollic acid (0.38 g., 1 mole) or lactic acid (0.43 cc., 1 mole) or mandelic acid (0.76 g., 1 mole) in distilled water (20 cc.) were refluxed in the apparatus previously described (Schonberg, Moubasher and Mostafa[6]) in a stream of carbon dioxide for 20 minutes. The receiver contained an ice-cold solution of 2,4-dinitrophenylhydrazine sulfate (0.6 g.) in alcohol (20 cc.). Yellow or orange crystals deposited and were recrystallized from the proper solvent (ligroin, alcohol and ethyl acetate) to give the 2,4-dinitrophenylhydrazone of formaldehyde, acetaldehyde and benzaldehyde, respectively, in 50% yields, identified by their m.p. and mixed m.p. with authentic samples.

(b) **Formation of Bromine, Carbon Dioxide and Succinimide in the Degradation.**—N-Bromosuccinimide (1.78 g.) and lactic acid (0.43 cc.) in distilled water (20 cc.) were heated for 20 minutes; the mixture was then concentrated by heat to a small volume (about 2 cc.) and allowed to cool; the colorless crystals which deposited were pressed on a porous plate and recrystallized from benzene. They were proved to be succinimide by m.p. and mixed m.p. (yield 0.5 g.).

The evolution of bromine and carbon dioxide during the degradation was demonstrated by passing the gases evolved during the reaction, first into 10% silver nitrate solution acidified with nitric acid and then into baryta water. A yellowish-white precipitate of silver bromide deposited, while the baryta water became turbid.

(2) **Isolation of Ketones.**—It is sufficient to describe one example in detail to illustrate the procedure.

N-Bromosuccinimide (1.78 g., 2 moles) and benzilic acid (1.14 g., 1 mole) in distilled water (100 cc.) were refluxed for 30 minutes. The reaction started after heating for 2 minutes with evolution of bromine vapor. The N-bromosuccinimide and benzilic acid gradually dissolved and an oil began to separate. At the end of the reaction, the mixture was allowed to cool and extracted with ether. The aqueous layer was concentrated to a small volume (about 5 cc.) and on standing deposited colorless crystals of succinimide, which after recrystallization from benzene were identified by m.p. and mixed m.p. (yield 0.6 g.).

The ethereal layer was dried over anhydrous sodium sulfate for 12 hours, filtered and concentrated to yield an oil which soon crystallized. The solid was recrystallized from aqueous alcohol to give benzophenone (m.p. and mixed m.p.) in 85–90% yield. The evolution of carbon dioxide during the reaction was demonstrated as above.

Acknowledgment.—The authors thank Dr. M. M. El-Sadr for his interest in this work and acknowledge their gratitude to the National Aniline Division, New York 6, New York, for supplying N-bromosuccinimide.

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(3) L. F. Fieser, H. Heymann and S. Rajagopalan, THIS JOURNAL, **72**, 2306 (1950).

(4) L. F. Fieser and S. Rajagopalan, *ibid.*, **72**, 5530 (1950).

(5) M. S. Barakat, *J. Pharm. and Pharmacol.*, **4**, 882 (1952).

(6) Schönberg, Moubasher and Mostafa, *J. Chem. Soc.*, 176 (1948).

BIOCHEMISTRY DEPARTMENT
IBRAHIM PASHA EL-KEBIR UNIVERSITY
FACULTY OF MEDICINE
ABBASSIA, CAIRO, EGYPT

The High Field Conductance of Aqueous Solutions of Ammonia at 25°[1]

BY DANIEL BERG AND ANDREW PATTERSON, JR.

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The high field conductance of aqueous solutions of ammonia, between 1.3 and 1.5 × 10^{-3} *M*, has been measured at 25.00° relative to potassium chloride. The high field conductance data are

(1) Contribution No. 1166 from the Department of Chemistry, Yale University.

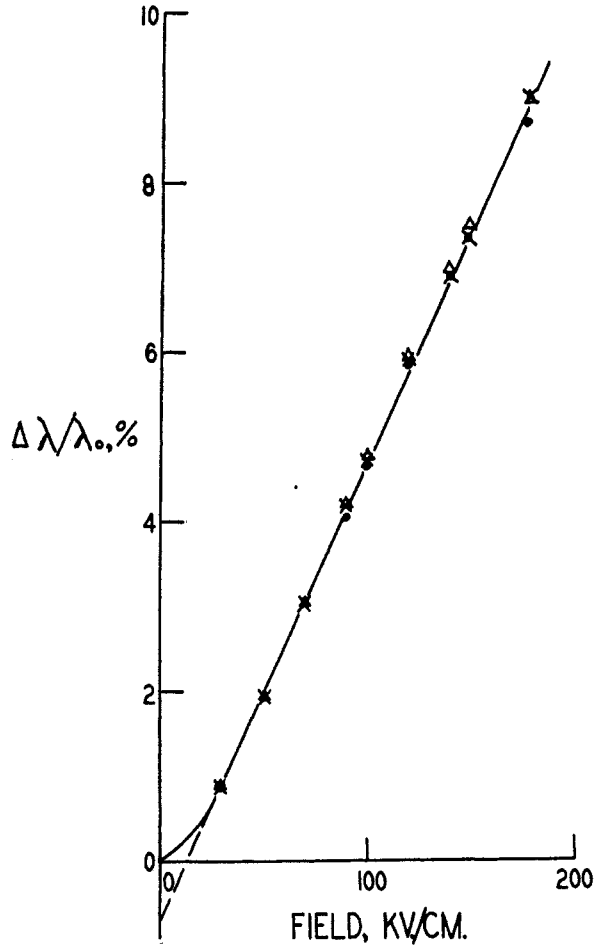

Fig. 1.—The high field conductance of ammonium hydroxide relative to potassium chloride at 25.00 ± 0.015°. The triangles refer to a 1.363 × 10^{-3} M ammonium hydroxide solution, the crosses to a 1.529 × 10^{-3} M ammonium hydroxide solution, and the dots to a 1.354 × 10^{-3} M ammonium hydroxide solution. The concentration of the potassium chloride reference solution was 3 × 10^{-4} M.

presented together with a calculation and discussion of the true ionization constant of the ammonium hydroxide in the solution.

Both low and high field conductance measurements were carried out according to the procedure of Gledhill and Patterson[2] using a differential pulse transformer bridge circuit. The ammonium hydroxide solutions were prepared in the conductance cell by addition of strong stock solution to degassed conductivity water in the cell until a desired resistance was reached. The concentration of the cell solution was then known from the weights of material used. The concentration of the strong stock solution was determined by titrating measured portions of the solution with standard hydrochloric acid using chlor phenol red as indicator. The concentration of the stock solution was 0.0431 M. All measurements were made with four microsecond pulse duration. The potassium chloride reference solution was prepared from a strong stock solution as described in reference 2. The concentration of the reference solution was 3 × 10^{-4} M. The temperature of measurement was 25.00 ± 0.015°, referred to a recently calibrated platinum resistance thermometer. Every precaution was taken to avoid introduction of carbonates, silicates or acidic contaminants with the stock solution or during the measurements. The measurements were made, however, in Pyrex glass cells.

The results are shown in Fig. 1. The dots refer to 1.354, the triangles to 1.363, and the crosses to 1.529 × 10^{-3} M solutions of ammonia in water. At 200 kv./cm. the fractional high field conductance quotient is 10.0%. The intercept of the extrapolated curve is −0.68%.

Ammonia is the first base for which we have reported measurements. There is no evidence of difficulty with the conductance measurements due to reaction of the ammonia with the Pyrex glass from which the conductance cells are constructed, when using solutions of 10^{-3} M concentration over a period of several days to a week. It is also notable that it was not found necessary or desirable to use a solution of a strong base as reference electrolyte; potassium chloride was entirely satisfactory. This is in contrast with our measurements on acetic acid[3] and with carbon dioxide,[4] for both of which it was necessary to use hydrochloric acid as reference electrolyte to make impedance balancing possible. In spite of the apparent cancellation of differential polarization between measured and reference electrolytes through the use of an acid for reference, with both acetic and carbonic acids at higher fields there was a downward curvature of the high field conductance quotient *vs.* field plot which has been explained[3] in terms of polarization due almost entirely to the hydrogen ion, and to its effect on the high field gradient to which the measured and reference electrolytes are subjected. Any such effects as these just mentioned with acids were absent with ammonium hydroxide in the range of concentrations and at the one temperature studied.

The curve of Fig. 1 is almost identical with that for the experimental results of reference 3 at 25°. The ionization constants reported for acetic acid, 1.754 × 10^{-5}, and for ammonia, 1.774 × 10^{-5}, are almost identical.[5,6] However, the concentration of ammonia, 1.4 × 10^{-3} M, is appreciably higher than that of acetic acid, 7 × 10^{-4} M, required to obtain the same conductivity; this would be expected since the limiting molecular conductance of acetic acid is appreciably higher than that of ammonia. The curve of Fig. 1 is quite different from that for carbon dioxide solutions, reference 4; the $\Delta\lambda/\lambda_0$ *vs.* field plot for carbon dioxide solutions has a smaller slope in keeping with the larger true ionization constant of carbonic acid.

With ammonia solutions in water it is thought that there is a set of equilibria of the type

$$NH_3(\text{dissolved}) + H_2O \rightleftarrows \{H_3N\text{-}H\text{-}OH\}^0 \quad (1)$$

$$\{H_3N\text{-}H\text{-}OH\}^0 \rightleftarrows NH_4^+ + OH^- \quad (2)$$

(2) J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, **56**, 999 (1952).

(3) F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4756 (1952).

(4) D. Berg and A. Patterson, *ibid.*, **75**, 5197 (1953).

(5) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1950.

(6) R. G. Bates and G. D. Pinching, THIS JOURNAL, **72**, 1393 (1950).

The formula $\{H_3N\text{–}H\text{–}OH\}^0$ has been written to suggest that an un-ionized molecular entity similar to an ion pair exists in solution; this entity arises from the presumed hydrogen bonding between the nitrogen and oxygen atoms from the ammonia and water molecules. While this series of equilibria is reminiscent of a similar set for carbon dioxide and water, reference 4, there is no evidence and little reason to believe that with ammonia any of these steps is slow. Indeed, reaction 1 is undoubtedly a fast one to which only a Langevin time lag could be attributed; the same is true of reaction 2. Nevertheless, and presumably this may be attributed to the enhanced stability conferred by the hydrogen bond, there is a finite concentration of dissolved but unhydrated ammonia in the solution together with an amount of undissociated ammonium hydroxide, and, finally, an equilibrium concentration of ions, as is represented by equations 1 and 2. These facts were clearly established by Moore and Winmill,[7] from whose work on ammonia and alkyl substituted amine solutions the hydrogen bond concept arose.

The ratio of the concentrations of ammonia and undissociated ammonium hydroxide, equation 1, is independent of concentration if the concentrations be small, and may be termed B.

$$B = [NH_3]/[NH_4OH] \quad (3)$$

The value of B may be determined by measuring at at least three temperatures the ionization and the partition of ammonia between water and an immiscible solvent such as toluene. Moore and Winmill[7] thus determined how much of the undissociated ammonia in solution was present as dissolved ammonia and how much as ammonium hydroxide. Sidgwick[8] states that at 25° the value of B is 0.885. Using the relations

$$K(0)(\text{true}) = [NH_4^+][OH^-]/[NH_4OH] \quad (4)$$

$$K(0)(\text{apparent}) = \frac{[NH_4^+][OH^-]}{[NH_4OH] + [NH_3]} = \frac{[NH_4^+][OH^-]}{[NH_4OH](1 + B)} \quad (5)$$

$$= K(0)(\text{true})/(1 + B) \quad (6)$$

and the value of $K(0)$ (apparent) at 25° from reference 6, we find that the method of Moore and Winmill gives $K(0)$ (true) $= 3.34 \times 10^{-5}$, while Moore and Winmill themselves report $K(0)$ (true) at 20° from their measurements to be $5.2 \pm 1.3 \times 10^{-5}$. Bates and Pinching[6] give the values of $K(0)$ (apparent) at 20° and at 25° as 1.710 and 1.774×10^{-5}. The difference between the computed quantity 3.34×10^{-5} and Moore and Winmill's value of $5.2 \pm 1.3 \times 10^{-5}$ is thus too large to be accounted for by the limits of error specified, and is in the wrong direction as a function of temperature, unless other unaccounted potent factors affecting the true ionization constant in a different manner than the apparent constant were present.

We may employ the method described in reference 4 to obtain $K(0)$ (true) from the high field conductance data. From a series of plots of the coefficients A_2 and A_3 against b (see eq. 21, ref. 4), the reduced slope Q and the function ρ_0 (eq. 17, ref. 4) are obtained. From the data presented in Fig. 1 ρ_0 has the average value 0.1639, and, with the value for $K(0)$ (apparent) $= 1.77 \times 10^{-5}$, $K(0)$ (true) is found to be $6.3 \pm 0.5 \times 10^{-5}$. The precision of measurement is at least ten times poorer than for carbon dioxide, as may be seen from the discussion of errors in ref. 4. This value for $K(0)$ (true) must be compared with those in the paragraph above; it is larger than any of the values of $K(0)$ (true) either quoted or computed from other data. A larger $K(0)$ bespeaks a smaller Wien effect. It is indeed possible that electrolytic impurities might cause the measurements here reported to be low, although every precaution has been taken to exclude contaminants. It seems more probable that the rapidity of reactions 1 and 2 would give a high field conductance increase larger than would truly represent the equilibrium concentrations of the several ionic species at low fields and thus a $K(0)$ (true) which is too small. This possibility hinges upon the relative speeds of reactions 1 and 2, direct information on which is not available. Experiments at a variety of pulse lengths might help elucidate this point. It is planned to extend these measurements to a range of temperatures for which values of $K(0)$ (apparent) are available in order to test the internal consistency of data derived from the high field conductance measurements.

Acknowledgment.—This work was supported by the Office of Naval Research.

DEPARTMENT OF CHEMISTRY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

(7) T. Moore and T. Winmill, *J. Chem. Soc.*, **101**, 1635 (1912); also, **91**, 1373 (1907).

(8) N. V. Sidgwick, "The Chemical Elements and their Compounds," Oxford University Press, New York, N. Y., 1950, p. 660.

Thiohydantoins of Amino Acids[1]

BY E. CAMPAIGNE AND WESLEY L. ARCHER[2]

RECEIVED JULY 22, 1953

Recent reports[3] have shown that some thiosemicarbazones have an inhibitory effect on the growth of vaccinia viruses. Thompson and Wilkin have shown that the phenylalanine antagonist, β-2-thienylalanine, prevented the multiplication of vaccinia virus in chick embryonic tissues.[4] 5-Substituted thiohydantoins possess certain structural similarities to both of these types of virus inhibitors, having an α-aminocarbonyl and an N-substituted thiourea portion in the same molecule. In pursuing a program of virus chemotherapy[5] we have synthesized a number of thiohydantoins in order to determine whether these compounds had antiviral activity. Tests conducted by Dr. R. L. Thompson at the Indiana University Medical

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(2) Abstracted from the thesis of Wesley L. Archer, to be submitted to Indiana University in partial fulfillment for the Degree of Doctor of Philosophy.

(3) *Cf.* R. L. Thompson, S. A. Minton, Jr., J. E. Officer and G. A. Hitchings, *J. Immunology*, **70**, 229 (1953); D. Hamre, J. Bernstein and R. Donovick, *Proc. Soc. Exp. Biol. Med.*, **73**, 275 (1950).

(4) R. L. Thompson and M. L. Wilkin, *ibid.*, **68**, 434 (1948).

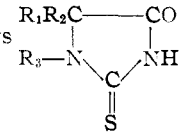
(5) *Cf.* E. Campaigne, *et al.*, THIS JOURNAL, **75**, 988 (1953).

School showed 5-phenyl-2-thiohydantoin, 5-(*p*-hydroxybenzyl)-2-thiohydantoin and the compounds described here to have no activity against several vaccinia strains.

We are reporting the synthesis of nine new thiohydantoins which are listed in Table I. The amino acids used were commercially available or easily prepared by standard methods with the exception of the 5-(2- and 3-thenyl)-thiohydantoins where the acetylated amino acids were employed. Deacetylation was acccomplished by refluxing the 1-acetyl-5-substituted thiohydantoin for one to two hours in sufficient 10% hydrochloric acid to obtain solution of the thiohydantoin. Deacetylation of 1-acetyl-5-(β-ethylmercaptoethyl)-2-thiohydantoin was accomplished without isolation of the solid acetyl intermediate.

TABLE I

5-SUBSTITUTED THIOHYDANTOINS



R_1	R_2	M.p., °C.[a]	Yield, %[b]	Nitrogen,[c] % Calcd.	Found
C_6H_5–[d]	CH_3CO	173.5–174[e]	36	11.28	11.50
p-ClC_6H_4–	CH_3CO	167–168[e]	71	9.91	10.23
p-BrC_6H_4–	CH_3CO	188–188.5[e]	65	8.56	8.46
$C_2H_5SCH_2CH_2$–	CH_3CO	58–58.5[f]	69	11.38	11.21
$C_2H_5SCH_2CH_2$–	H	99.5–100.5[g]	69	13.71	13.44
3-C_4H_3S–[h]	CH_3CO	157–158[e]	75	11.02	11.00
3-C_4H_3S–	H	177–178[g]	82	13.20	13.28
2-C_4H_3S–	CH_3CO	167–168[e]	92	11.02	11.15
2-C_4H_3S	H	197–198(dec.)[g]	93	13.20	13.09

[a] All melting points uncorrected, Fisher–Johns block. [b] Based on crude yields, the melting point of which is within 4° of that reported. [c] All analyses by Miss J. W. Dickey. [d] R_2 is methyl in this compound, H in all others. [e] Recrystallized from ethanol–water. [f] Recrystallized by slow evaporation of ethanol solution. [g] Recrystallized from water. [h] Originally synthesized by R. L. Hardin in this Laboratory.

Undoubtedly higher yields of some of the thiohydantoins could be realized if crude oily products were not sometimes encountered in the isolation. It was observed that prolonged mechanical stirring of an oily or semi-solid product in a water solution at ice-bath temperatures gave a better crystalline product. The thiohydantoins were finally recrystallized by dissolving in excess alcohol at room temperature and slowly adding water until saturation was reached, or by concentration under an air jet. Heating or extreme cooling of the recrystallizing medium led to various amounts of oily products.

Experimental

2-Thenylacetamidomalonic Acid.—Saponification of 7.7 g. (0.025 mole) of diethyl 2-thenylacetamidomalonate[6] with 25 ml. of 10% sodium hydroxide gave 5.9 g. (93.5%) of 2-thenylacetamidomalonic acid, which melted with evolution of carbon dioxide at 128.5–129°.

Anal. Calcd. for $C_{10}H_{11}O_5NS$: C, 46.70; H, 4.31. Found: C, 47.10; H, 4.49.

N-Acetyl-β-2-thienylalanine.—Decarboxylation was carried out on 5.6 g. (0.0218 mole) of 2-thenylacetamidomalonic acid in 50 ml. of water to give 4.0 g. (86%) of N-acetyl-β-2-thienylalanine, m.p. 128–129°.[7] A mixture of a sample of this compound with 2-thenylacetamidomalonic acid gave a depressed melting range.

1-Acetyl-5-(2-thenyl)-2-thiohydantoin.—The following procedure is typical of the thiohydantoin preparations. A solution of 4.0 g. (0.0188 mole) of N-acetyl-β-2-thienylalanine and 1.9 g. (0.025 mole) of ammonium thiocyanate in 5 ml. of glacial acetic acid and 25 ml. of acetic anhydride was refluxed on a steam-bath for one hour. The cooled solution was then added to 200 ml. of water with mechanical stirring to give 4.4 g. (92%) of cream colored crystals, m.p. 164–166°. Recrystallization from aqueous ethanol raised the melting point to 167–168°.

5-(2-Thenyl)-2-thiohydantoin.—A solution of 0.5 g. (0.002 mole) of 1-acetyl-5-(2-thenyl)-2-thiohydantoin in 25 ml. of 10% hydrochloric acid was refluxed for one hour, and then chilled to give 0.39 g. (93.5%) of 5-(2-thenyl)-2-thiohydantoin, which melted at 197–198° with decomposition after recrystallization from water.

5-(3-Thenyl)-2-thiohydantoin.—1-Acetyl-5-(3-thenyl)-2-thiohydantoin was prepared in an identical manner from N-acetyl-β-3-thienylalanine,[8] and readily deacetylated as above to yield white needles, melting at 177–178°.

(6) K. Dittmer, W. Herz and J. S. Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

(7) K. Dittmer, *et al.*, THIS JOURNAL, **71**, 1202 (1949), reports the m.p. to be 130°,

(8) R. G. Garst, E. Campaigne and H. G. Day, *J. Biol. Chem.*, **180**, 1016 (1949).

DEPARTMENT OF CHEMISTRY
INDIANA UNIVERSITY
BLOOMINGTON, INDIANA

The Fluoroplatinates. II. Fluoroplatinic Acid

BY ROY S. CLARKE, JR.,[1] AND THEODORE P. PERROS

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The first paper in this series dealt with the preparation and properties of certain rare earth fluoroplatinates.[2] Prior to this, the only compounds containing the fluoroplatinate ion were certain ones from the alkali group elements.[3–5]

This paper is to report the preparation and isolation of fluoroplatinic acid.

Experimental

Fluoroplatinic Acid.—Lanthanum fluoroplatinate was prepared as previously described.[2] About 60 ml. of a 0.04 *M* solution of this salt was passed through an ion-exchange column at a rate of 3–4 ml. per minute. The dimensions of the column were 3.5 × 90 cm. and it was packed with 40–60 mesh Dowex-50 resin. The resin was hydrogen charged prior to the introduction of the salt solution.

The column was eluted with water at a rate of 3–4 ml. per minute. The yellow color of the fluoroplatinate ion appeared shortly after a liter of water had passed through the column. The elution process required less than two liters for its completion. The solution was stored in a polyethylene bottle. Tests for the lanthanum ion on this solution were negative.

A portion of this solution was evaporated to dryness in a polyethylene beaker by vacuum desiccation over sodium hydroxide pellets. Yellow crystals of hydrated fluoroplatinic acid were obtained.

This acid is hygroscopic and very soluble in water. The addition of a potassium salt to a solution of this acid precipitated the yellow crystalline potassium fluoroplatinate. The characteristic color of the iodoplatinate ion appeared slowly when iodide ion was added to the acid. Hydrogen was liberated when zinc was added to the acid.

Absorption Spectrum.—The absorption spectrum of the fluoroplatinic acid was measured with a Model DU Beckman spectrophotometer using matched 1-cm. cells. The curve was identical to that previously reported for the fluoroplatinate ion, having maxima at 275 and 318 mμ (not at

(1) Abstracted from a portion of the thesis to be submitted by Roy S. Clarke, Jr., in partial fulfillment of the requirements for the degree of Master of Arts.

(2) T. P. Perros and C. R. Naeser, THIS JOURNAL, **75**, 2516 (1953).

(3) H. Schlesinger and M. Tapley, *ibid.*, **46**, 276 (1924).

(4) A. G. Sharpe, *J. Chem. Soc.*, 3444 (1950).

(5) A. G. Sharpe, *ibid.*, 197 (1953).

308 mμ as erroneously printed in the first paper of this series).

Analyses.—Aliquot portions of a stock solution of fluoroplatinic acid were titrated with 0.0219 *N* sodium hydroxide. The course of the reaction was followed with a Model G Beckman *p*H meter. The titation curve was typical of the reaction between a strong base and a strong acid.

Aliquot portions of the same stock solution were analyzed for platinum content by reduction of the acid with hydrazine. The results confirmed the existence of the dibasic fluoroplatinic acid.

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DEPARTMENT OF CHEMISTRY
THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, D. C.

Some Solvent and Salt Effects in the Solvolysis of *s*-Butyl Bromide[1]

BY W. C. COBURN, JR., ERNEST GRUNWALD AND HENRY P. MARSHALL

RECEIVED JULY 10, 1953

The solvolysis of *s*-alkyl halides proceeds by a mechanism which cannot be classified as either S_N1 or S_N2.[2,3] On the one hand, there is stereochemical evidence of partial racemization in the solvolysis of 2-bromoöctane[4] and probably of *s*-butyl *p*-toluenesulfonate,[5] suggesting the existence of a metastable solvolysis intermediate. On the other hand, there is kinetic evidence for isopropyl bromide which indicates the nucleophilic participation of solvent in systems such as ethanol–water.[2]

We now wish to report some rate studies on the solvolysis of *s*-butyl bromide, a representative member of this interesting group of reagents. First-order rate constants have been measured in a number of solvents, including acetic acid, ethanol and ethanol–water mixtures, and are equal, within a few per cent., to the corresponding rate constants for isopropyl bromide. The results are shown in Table I. Without repeating the analysis of rate constants which was made previously for isopropyl bromide,[2] we may therefore conclude that there is nucleophilic participation of solvent in the solvolysis of *s*-butyl bromide in systems such as ethanol–water.

TABLE I

COMPARISON OF SOLVOLYSIS RATE CONSTANTS FOR ISOPROPYL AND *s*-BUTYL BROMIDE

Solvent	Temp., °C.	$10^6 k$ (sec.$^{-1}$) for Isopropyl bromide	$10^6 k$ (sec.$^{-1}$) for *s*-Butyl bromide
Abs. EtOH[a]	50.0	0.112	0.098
80 Vol. % EtOH[a]	50.0	1.18	1.06
60 Vol. % EtOH[b]	80.0	70.6	74.1
Glacial HOAc	100.0	0.89	0.96

[a] Data for isopropyl bromide in abs. and 80% EtOH were taken from ref. 2. [b] M. L. Dhar, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2058 (1948).

We also tried to obtain evidence for a metastable reaction intermediate by looking for a mass-law effect.[6] The pertinent data in 75.00 wt. % ethanol–water at 50° are shown in Table II. The Table lists the rate constants for solvolysis in the presence of varying concentrations of salt for sodium bromide, a common ion salt,[6] and for sodium perchlorate and sodium *p*-toluenesulfonate, two unreactive "neutral" salts. The rate constants are generally based on at least two rate runs, and their probable errors are about 1.6%. If, to a first approximation, the neutral salt effects are treated as colligative functions of the ionic strength, the rate constants at a given salt concentration should be equal for the two neutral salts, and possible decreases below this value due to sodium bromide should measure the magnitude of the mass-law effect. As is shown in the table, the rate constants at a given ionic strength are indeed approximately equal for the neutral salts, but are greater rather than less in the presence of sodium bromide. Thus there is no evidence for a mass-law effect.

TABLE II

EFFECT OF ADDED SALTS ON THE SOLVOLYSIS RATE OF *s*-BUTYL BROMIDE IN AQUEOUS ETHANOL, 75.00 WEIGHT % ETHANOL,[a] 50.00 ± 0.02°

Salt	*M*	$10^6 k$ (sec.$^{-1}$)[b]	Salt	*M*	$10^6 k$ (sec.$^{-1}$)[b]
None	..	1.06	$NaClO_4$	0.18	1.09
NaBr	0.20	1.20		.45	1.0
	.50	1.17		.80	1.09
	.77	1.19	NaOTs	.21	1.08
				.43	1.04

[a] 79.22 vol. %. [b] Probable errors in *k*: 0.45 *M* $NaClO_4$, 4%; all other values, 1.6%.

Within the limits of present knowledge, this conclusion cannot be reversed if the salt effects are treated as specific rather than colligative. In aqueous solution salt effects on non-electrolytes often parallel either the salt polarizability or the electrostriction of the solvent due to the electrolyte.[7] The relevant values of the apparent molar refractions, *R*, and of $(\bar{V}_s^\circ - V_s)$ are summarized in Table III. The values are apparently not very sensitive to change in solvent from water to 75.00% ethanol, as is illustrated for sodium *p*-toluenesulfonate. It is seen that, on the basis of the molar refractions, the neutral salt effects ought to be nearly equal for sodium bromide and sodium perchlorate but ought

TABLE III

Salt	Solvent	$(\bar{V}_s^\circ - V_s)$[a]	*R*
NaBr	HOH	−10.5[b]	12.78[d], 12.8[e]
$NaClO_4$	HOH	− 7.5[b]	13.32[d]
NaOTs	HOH	−10[c]	43.4[c]
	75.00% Ethanol	−7[c]	43.2[c]

[a] $\bar{V}_s^\circ$ = partial molar volume of salt in very dilute solution. V_s = molar volume of (metastable) pure liquid salt. [b] Taken from W. F. McDevit and F. A. Long, THIS JOURNAL, **74**, 1773 (1952). [c] Own measurements at 25.44°. For V_s use molar volume of crystalline solid salt. (See B. Lunden, *Z. physik. Chem.*, 192, 345 (1943).) [d] Taken from K. Fajans and G. Joos, *Z. Physik*, **23**, 1 (1924).

(1) Supported in part by the Research Corporation and by the Office of Ordnance Research, U. S. Army.

(2) S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951).

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

(4) E. D. Hughes, C. K. Ingold and S. Masterman, *J. Chem. Soc.*, 1196 (1937).

(5) J. Kenyon, H. Phillips and V. P. Pittman, *ibid.*, 1072 (1935).

(6) (a) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold and N. A. Taher, *ibid.*, 979 (1940); (b) O. T. Benfey, E. D. Hughes and C. K. Ingold, *ibid.*, 2488 (1952).

(7) F. A. Long and W. F. McDevit, *Chem. Revs.*, **51**, 119 (1952).

to differ sharply for sodium *p*-toluenesulfonate. On the basis of the electrostriction of the solvent, all three neutral salt effects ought to be nearly the same. Neither of these hypotheses is consistent with the observed effects.

The present failure to observe a mass-law effect does not rule out the presence of a metastable reaction intermediate in the solvolysis of *s*-butyl bromide since the effect is a sufficient but not a necessary phenomenon. Our results are consistent with analogous observations on the solvolysis of *t*-butyl bromide[6,8] and chloride[9] where the mechanism is S_N1. Our results are not consistent with reports of small rate depressions (4–12%) due to added halide salts in the solvolysis of isopropyl bromide,[10] ethyl *p*-toluenesulfonate[11] and benzyl chloride[12] in partly aqueous media. While these rate depressions suggest that there is a mass-law effect, it must be admitted that, within present knowledge, they can also be accommodated as neutral salt effects.

Experimental Part

Materials.—*s*-Butyl bromide and isopropyl bromide, from Eastman Kodak Co., were dried over potassium carbonate and fractionated through a 30-plate all-glass column before use. Middle fractions with the following properties were used: *s*-butyl bromide, b.p. 90.6° (759 mm.), $n^{21.8}D$ 1.4353; isopropyl bromide, b.p. 58.9° (754 mm.).

Sodium bromide was Baker and Adamson C.P. material and was dried at 110° before use. Sodium perchlorate was prepared halide-free by careful neutralization of Mallinckrodt 60% perchloric acid with J. T. Baker C.P. sodium hydroxide sticks to the phenolphthalein end-point. Concentration of the solution gave crystalline material which was washed with a little alcohol and dried to constant weight over magnesium perchlorate *in vacuo*. The dry salt contained less than 0.6% water by Karl Fischer titration for water. Sodium *p*-toluenesulfonate was prepared by careful neutralization of toluenesulfonic acid monohydrate with C.P. sodium hydroxide. It was purified several times by dissolving in water and reprecipitating with ethanol. Physical properties of the vacuum-dried salt: d^{25} 1.46; $\bar{V}_s^\circ$ 122.3 (water, 25.44°); 126.4 (75.00 wt. % ethanol, 25.44°). The salt contained less than 0.1% water.

The solvents redistilled water, absolute ethanol (<0.005% water by Karl Fischer titration), and 75.00% (by weight) ethanol in ethanol–water were prepared as described previously.[2] J. T. Baker "special" acetic acid was analyzed for water by freezing point determination, and enough Eimer and Amend C.P. acetic anhydride was added to make the resultant solvent 0.1 *M* in acetic anhydride. Sodium acetate solutions in this solvent were prepared by adding the required weights of reagent grade, dry sodium carbonate.

Rate Measurements.—Rates were measured by the usual sealed ampoule technique using the procedures described previously.[2,13] The vapor space in the ampoules was kept at less than 5% of the total volume to minimize errors due to volatilization of the alkyl halides. Measurements of temperature and time and methods of preparation and titration of the reaction mixtures met customary standards for precision work.

The kinetics was first order in 75.00% ethanol. In absolute ethanol, first-order rate constants decreased somewhat with time due to reaction of the hydrogen bromide product with the solvent and were extrapolated to zero time by a method described previously.[2,14] In the acetolysis experiments, initial concentrations of the alkyl halide were 0.2 and 0.1 *M*, and of the sodium acetate were 0.02 and 0.01 *M*. Over these ranges of concentration the kinetics was first order and there was no evidence of a second-order term due to direct reaction of alkyl halide with acetate ion even though the sodium acetate concentration varied in a typical run from 0.02 to 0.001 *M*.

Measurements of *R* for Salts.[15]—Refractive indices were measured with a Bausch and Lomb immersion refractometer; densities were measured with a 50-ml. pycnometer. The *R* values are accurate to about ±2%.

(8) O. T. Benfey, Ph.D. Thesis, University College, London, 1946.
(9) C. G. Swain and S. D. Ross, THIS JOURNAL, **68**, 658 (1946).
(10) E. D. Hughes, C. K. Ingold and U. G. Shapiro, *J. Chem. Soc.*, 225 (1936).
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CHEMISTRY DEPARTMENT
FLORIDA STATE UNIVERSITY
TALLAHASSEE, FLORIDA

Polarographic Study of Various Diphenyl Disulfides

BY EUGENE L. COLICHMAN[1] AND DANIEL L. LOVE[2]

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The biologically important cystine–cysteine system has been investigated by both potentiometric and polarographic methods. Kolthoff and Lingane[3] have summarized and discussed these investigations. It is seen that the disulfide linkage is usually reduced irreversibly to mercaptans at the dropping-mercury electrode. Additional polarographic results on disulfides have been reviewed by Wawzonek.[4] The present investigation concerns the polarography of various diphenyl disulfides.

Experimental

Previously reported[5,6] polarographic investigations from this Laboratory indicate the nature of the equipment and materials employed. Measurements were at 25.00 ± 0.05° and at a drop-time equal to 3.00 sec. The polarographic half-waves on dilute solutions reported in Table I did not require maxima suppressors.

The following buffer solutions were used: (a) *p*H 6.2, buffer in 95% ethanol was 0.06 *M* sodium phthalate; (b) *p*H 7.0, buffer in 50% ethanol was 0.05 *M* potassium dihydrogen phosphate and 0.006 *M* sodium hydroxide; (c) *p*H 7.0, buffer in 95% ethanol was 0.025 *M* potassium acetate and 0.041 *M* acetic acid; (d) *p*H 8.0, buffer in 95% ethanol was 0.10 *M* potassium acetate and 0.01 *M* acetic acid. Buffer values given are reproducible, however, since *p*H measurements were made with an ordinary Beckman, Model G, *p*H Meter, values given are not absolute. This is due to the uncertain liquid junction potential existing between the alcohol solutions and the reference glass electrode–aqueous solution used in making these *p*H measurements. The "*m*" value for the capillary was 2.00 mg. per second. $m^{2/3}t^{1/6} = 1.907$ mg.$^{2/3}$ sec.$^{-1/2}$ (open circuit) at $h = 64$ cm.

o,o'-Ditolyl Disulfide.—This compound was prepared by the oxidation[7] of *o*-thiocresol (Eastman Kodak Co., White Label grade) with ferric chloride. The separated oily solid was purified by dissolving the by-product ferrous chloride in water. The disulfide was then recrystallized from ethanol. Yield was 43.7%. M.p. (reported)[8] was 38–39°; (found) 38°.

m,m'- and *p,p'*-Ditolyl Disulfides.—Same procedure was used for preparing these compounds as employed with the

(1) North American Aviation, Inc., Atomic Energy Research Dept., Downey, California.
(2) Work described herein was from a thesis submitted by D. L. Love to the University of Portland in partial fulfillment of the requirements for the Degree of Master of Science.
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(5) E. L. Colichman, THIS JOURNAL, **74**, 722 (1952).
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o-isomer. Meta isomer: yield 44.5%, m.p. (reported)[9] −22°, (found) −21°; para isomer: yield 99.6%, m.p. (reported)[10] 47°, (found) 46°.

o,o'-Dimethoxydiphenyl Disulfide.—0.24 mole of *o*-anisidine (Eastman Kodak Co., White Label grade) was dissolved in a solution of 150 g. of concd. hydrochloric acid and 450 g. of water. Enough sodium nitrite was added to give a positive starch–iodide test. While keeping the diazotized product cold (0°), 0.25 mole of 10% aqueous solution of sodium disulfide was added dropwise with constant shaking. The product formed was dissolved immediately while still cold in ethanol and then recrystallized from this solution. Unless this is done rapidly, the product will become tarry. The disulfide was freed from any ferrous chloride by the same procedure as described above. Finally it was recrystallized again from ethanol. Yield was 8.9%, m.p. (reported)[11] 119°, (found) 119°.

m,m'- and *p,p'*-Dimethoxydiphenyl Disulfides.—Procedure for preparation was the same as with the ortho isomer. Meta isomer: yield 9.0%, m.p. (found) 109°. Combustion analyses for carbon, hydrogen and sulfur agreed well with theory. *m*-Anisidine needed in preparing this isomer was obtained from *m*-aminophenol (Eastman Kodak Co., Yellow Label grade) by the procedure of Reverdin and Luc.[12] Para isomer: yield 7.4%, m.p. (reported)[11,13] 120°, (found) 119°.

The diphenyl disulfide used polarographically was Eastman Kodak Co., White Label grade.

Results and Discussion

In acidic and basic buffered and unbuffered alcoholic solutions all the diphenyl disulfides investigated (see Table I) were found to be irreversibly reduced at the dropping-mercury electrode as evidenced by the linear slope analysis plots obtained with slope values in the range 0.13 to 0.28. Similar slope analysis considerations showed that the methoxy substituted diphenyl disulfides are reduced reversibly in 50% alcohol *p*H 7 phosphate buffer solutions. Slope values equal to 0.027 to 0.031 were obtained for the various methoxy isomers indicating that 2 electrons are involved in the reduction as to be expected on the basis of: RSSR + $2H^+$ + $2e^-$ = 2RSH. The unsubstituted and methyl substituted diphenyl disulfides are irreversibly reduced in 50% alcohol *p*H 7 phosphate buffer solutions. Slope values for the linear plots of $E_{d.e.}$ *vs.* $\log I/(I_d - I)$ in these cases were 0.09 to 0.11.

TABLE I

HALF-WAVE POTENTIALS (VOLT *vs.* S.C.E.) OF THE DIPHENYL DISULFIDES IN ALCOHOL

	*p*H 6.2	7.0[a]	7.0[b]	8.0	0.1 *M* NaOH
Unsubst.					
0.0003 *M*	−0.52		−0.46		
.001		−0.53		−0.60	−0.62
o,o'-Dimethyl-					
0.0003 *M*	− .55		− .44		
.001		− .52		− .57	− .63
m,m'-Dimethyl-					
0.0003 *M*	− .56		− .47		
.001		− .55		− .61	− .64
p,p'-Dimethyl-					
0.0003 *M*	− .56		− .47		
.001		− .56		− .62	− .66
					0.02 *M* NaOH
o,o'-Dimethoxy-					
0.0003 *M*	− .97	− .88[c]	− .58		
.001		−1.02		− .85	−0.75
m,m'-Dimethoxy-					
0.0003 *M*	− .97	−0.86[c]	− .58		
.001		−1.02		− .85	− .82
p,p'-Dimethoxy-					
0.0003 *M*	− .94	−0.88[c]	− .59		
.001		−1.04		− .91	− .80

[a] *p*H 7.0, acetate buffer in 95% ethanol. [b] *p*H 7.0, phosphate buffer in 50% ethanol. [c] $E_{d.e.}$ *vs.* mercury pool, volt.

The marked influence of the methoxy group is demonstrated further by the fact that only these substituted disulfides yielded catalytic hydrogen waves (excessive I_d/C values) in 95% alcohol in all except the sodium hydroxide solutions. Diffusion currents of the unsubstituted and methyl substituted diphenyl disulfides were found to be proportional to the concentrations of reducible materials, at least over the 0.0003 to 0.0050 *M* range in all the alcoholic solutions investigated here. For example, the average I_d/C values in μa./m*M* for diphenyl disulfide were: 5.05 in 95% alcohol, *p*H 7 acetate buffer; 3.20 in 50% alcohol, *p*H 7 phosphate buffer; 5.46 in 95% alcohol, *p*H 8 acetate buffer; and 5.00 in 0.10 *M* sodium hydroxide in 95% alcohol.

It is seen that solvent, buffer components, *p*H and nature of the substituent group can all influence the polarographic results obtained on the various diphenyl disulfides.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PORTLAND
PORTLAND 3, OREGON

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Synthesis of Fluorocarbon Iodides Without the Use of Liquid Solvents or Diluents

BY G. H. CRAWFORD AND J. H. SIMONS

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A method of preparing fluorocarbon iodides which consisted of the decarboxylation of the silver salt of a fluorocarbon carboxylic acid (S) in the presence of iodine was developed by Simons and Brice.[1] The reaction mixture was kept in suspension in a fluorocarbon diluent by means of mechanical stirring. The process was carried out under strictly anhydrous conditions.

Others[2–4] prepared the iodides by heating intimate mixtures of (S) and iodine.

The method herein reported consists of bringing the iodine vapors in contact with (S) under controlled conditions of temperature and pressure without a solid or liquid diluent being present. A sharp reaction zone progresses through the material until (S) is consumed. The fluorocarbon iodide passes from the reactor and is collected as in the original method. Power stirring, and pre-purification and drying of the iodine, as well as the limitations imposed by the diluent, are eliminated. Maintenance of anhydrous conditions, recovery of silver

(1) J. H. Simons and T. J. Brice, U. S. Patent 2,554,219, May 21, 1951.
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and control of reaction temperature are facilitated. Higher product yields are obtained.

Two types of reactors are currently in use in these laboratories, each having advantages depending upon the particular situation. Procedures using these reactors are:

Procedure I: This method employs a reactor which is simple to construct and provides a quick method of obtaining small quantities of fluorocarbon iodides in the laboratory. It is also adapted to reactions of this type in which the absence of any atmosphere other than the reaction gases is desired. The reactor is a vertical Pyrex tube, closed at the bottom and stoppered at the top. An exit line attached near the top connects it through two cold traps to a vacuum source. A manometer is attached to the exit line. A KOH tube for removal of CO_2 is placed between the traps and the vacuum source. Reaction temperature is followed by means of a thermocouple or thermometer extending into the tube through the top.

Experimental.—The entire apparatus is vacuum dried. Iodine followed by phosphorus pentoxide (P) is poured into the tube. (S) may be either suspended over the iodine and (P) in a steel wire cage or poured directly into the tube with a layer of glass wool separating (S) from (P). The apparatus is flushed with dry air. The reactor tube is heated in an oil-bath. The pressure is reduced in order to provide adequate volatilization of iodine at the optimum reaction temperature (130–160°). Completion of reaction is noted by cessation of evolution of gases. The bath is heated to 185° to assure complete conversion of (S). The iodide is collected in the cold traps. All products were fractionated. Iodine was determined by peroxide decomposition and thiosulfate titration. Reaction conditions and yields are in Table I.

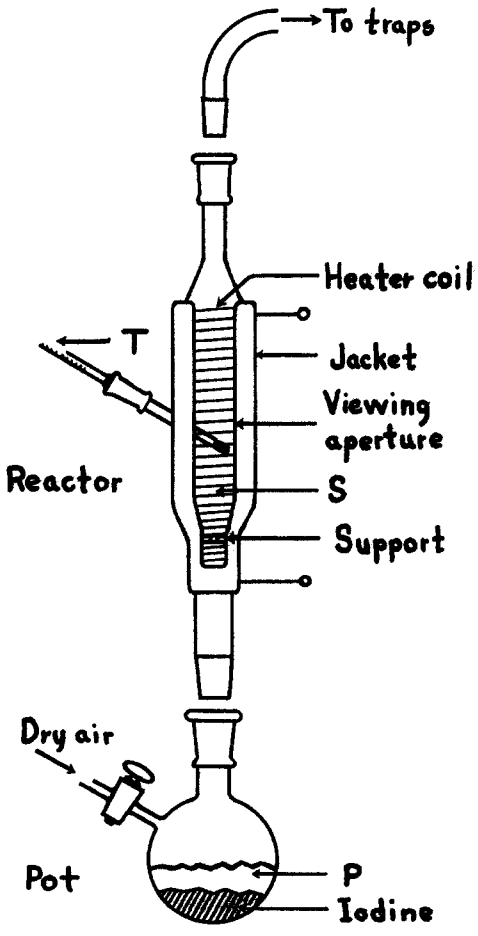

Figure 1.

TABLE I

PROCEDURE I

Starting material, g.	Heating time, min.	Operating temp., °C.	Operating pressure, mm.	Basket support	Yield, g.	Yield, %
CF_3COOAg, 75.1	60	140–145	400–450	Not used	47.6	71
C_3F_7COOAg, 15.5	80	140–145	450–500	Not used	13.1	93
CF_3COOAg, 75.4	140	150–160	400–500	Used	52.5	78
C_3F_7COOAg, 21.2	115	150–160	400–500	Used	16.5	87

Procedure II: This method is superior in cases in which relatively large amounts of various fluorocarbon iodides must be synthesized in the laboratory. The apparatus is shown in the accompanying figure. Operation is at atmospheric pressure. A stream of dry air carries the iodine vapor from the pot to the reaction zone. (S) is supported in the reactor by means of a glass "X" member and a thin layer of glass wool. The reactor and the iodine container are separate units whose temperatures are controlled independently.

Experimental.—The apparatus is assembled. (S) is poured into the reactor from the top. Final drying is effected by passing a current of dry air through the reactor while heating it to 70–80°. Excess iodine followed by (P) is placed in the pot. The iodine is heated to sublimation temperature and an extremely gentle air current started. The heat of reaction tends to increase the reactor temperature. The jacket heating is adjusted so as to maintain an optimum reaction temperature of 130–160°. The reaction requires 20–40 minutes, depending on the type and amount of (S). The iodide is collected in cold traps. Purification and identification were carried out as in procedure I. Reaction conditions and yields are in Table II.

TABLE II

PROCEDURE II

Starting material, g.	Heating time, min.	Temp., °C.	Yield, g.	Yield, %
CF_3COOAg, 33.8	21	150–160	22.3	74
CF_3COOAg, 202.1	48	150–160	161.0	90
C_3F_7COOAg, 42.0	25	130–160	36.5	94
C_3F_7COOAg, 200.4	45	150–160	175.5	95

Procedure II was used in the preparation of C_3F_7Br. No air current was employed. Reflux action of bromine was provided by an ice–water-cooled condenser on the upper end of the reactor. Reaction temperature was 130–150°. Products were fractionated and analyzed for bromine. A 67% yield was obtained.

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FLUORINE RESEARCH CENTER
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORDA

The Preparation and the Determination of Apparent Dissociation Constants of Some Substituted Aliphatic Phosphonic Acids

BY PETER C. CROFTS AND GENNADY M. KOSOLAPOFF

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In the previous paper[1] we described the acidic properties of several aliphatic phosphonic and phos-

(1) P. C. Crofts and G. M. Kosolapoff, THIS JOURNAL, **75**, 3379 (1953).

phinic acids. At this time we wish to report some results along these lines as secured with some substituted methylphosphonic acids. Specifically, we examined the effect on the dissociation constant of methylphosphonic acid that is produced by the substitution of one, two or three chlorine atoms, one chlorine, one bromine or one iodine atom, or a hydroxyl group in the aliphatic radical of this, the simplest phosphonic acid.

In the course of this work we established new melting points for several compounds that had been reported previously by other workers. These results, as well as the synthetic procedures, are given in the Experimental part of this paper.

The acids, with which we have been concerned at this time, produce on titration the expected curves with two inflection points, that are typical of phosphonic acids in general. It must be noted, however, that owing to the very considerable acid strength of the second hydrogen of trichloromethyl acid, the first inflection point, or break, is very shallow and cannot be satisfactorily determined by chemical indicators.

The results of the determination of the apparent dissociation constants, performed precisely as described earlier,[1] are given in Table I.

TABLE I

Compound	pK'_{a1}	pK'_{a2}
$ClCH_2PO_3H_2$	1.40	6.30
$Cl_2CHPO_3H_2$	1.14	5.61
$Cl_3CPO_3H_2$	1.63	4.81
$BrCH_2PO_3H_2$	1.14	6.52
$ICH_2PO_3H_2$	1.30	6.72
$HOCH_2PO_3H_2$	1.91	7.15
$CH_3PO_3H_2$[1]	2.38	7.74

It is clear that the substitution of halogens or of a hydroxyl increases the acid strength of methylphosphonic acid. This is, of course, to be expected from the general considerations. The second dissociation constant shows the steadily increasing acid properties as the number of chlorines in the molecule rises from one to three. A gradual decrease of acidic properties is also observed in the series: chlorine, bromine, iodine. The moderate increase of the dissociation constant upon the substitution of the hydroxyl on the carbon adjacent to the phosphorus is also noted; in this case the hydroxyl acts as an acid-strengthening agency.[2]

The first dissociation constants shown above indicate that the present group of acids represents very strong acids. The trend discussed above for the second dissociation constants is approximately true in this instance as well. The deviation of the trichloromethyl acid from this trend is probably not real and is caused by the relative proximity of the two dissociation constants of this acid, a situation that does not arise in the other examples. We expect to return to the consideration of this apparent anomaly at a later date, when we expect to have the necessary data on the activity coefficients of the various acids of phosphorus. Such data are not found in the literature at this time.

(2) W. D. Kumler and J. J. Eiler, THIS JOURNAL, **65**, 2355 (1943).

Experimental Part

Preparation of the Compounds. Chloromethylphosphonic Acid.—An unsuccessful attempt to prepare this acid by treatment of hydroxymethylphosphonic acid with phosphorus trichloride, followed by admission of the theoretical amount of chlorine to form phosphorus pentachloride *in situ*, was made. The preparation had to be abandoned owing to the formation of untractable semi-solid materials which could not be purified.

The compound was prepared readily from its dichloride.[3] This was obtained in 67% yield by heating 10 g. of paraformaldehyde with 71 g. of phosphorus trichloride in a sealed tube for 11.5 hours at 240–250°; the product boiled at 93° at 16.5 mm. The dichloride was added slowly to an excess of water with stirring and the resulting solution was evaporated to dryness *in vacuo*. The resulting product was redissolved in water, treated with charcoal and the clear filtrate was again taken to dryness, yielding the pure acid, which softened at 85° and melted at 88°. Kinnear and Perren[4] give m.p. 89–90°.

Dichloromethylphosphonic Acid.—Several preliminary experiments were performed in attempts to find a satisfactory preparation of this acid. Chlorination of chloromethylphosphonyl dichloride, $ClCH_2POCl_2$ (the intermediate in the previous preparation) failed to take place at 45° under ultraviolet irradiation. Some chlorination did take place in four hours at 165–169°, but the product was not homogeneous and not purifiable by fractional vacuum distillation. The reaction proceeded more readily in the presence of a small amount of iron filings, but again the product was not purifiable.

Since triethyl phosphite failed to react after many hours of refluxing with chloroform, in an attempt to prepare diethyl dichloromethylphosphonate, these two substances were heated in a glass liner of an autoclave at 160° for seven hours. None of the desired product was obtained, much triethyl phosphite (67%) being recovered along with a 12% yield of its isomerization product, diethyl ethylphosphonate. It must be concluded that the Arbuzov reaction does not occur with chloroform, in contrast to the facile reaction of carbon tetrachloride.

Dichloromethylphosphonyl dichloride was readily prepared by the method outlined by Kinnear and Perren[4] and the product was hydrolyzed with water as described above. Careful evaporation of the aqueous solution and thorough vacuum drying of the product gave the desired acid, melting at 116–119°. It must be mentioned that this acid, as well as the other halogenated derivatives cited in this paper, showed extreme hygroscopicity. This acid was previously reported with m.p. 54°.[5] In view of this discrepancy our product was analyzed.

Anal. Calcd. for $CH_3O_3Cl_2P$: Cl, 43.0. Found: Cl, 42.53.

The identity of the acid was further confirmed by perfect agreement of the breaks in its titration curve with the calculated values.

Trichloromethylphosphonic Acid.—A small amount of this acid was prepared by hydrolysis of the corresponding phosphonyl dichloride, which was secured from carbon tetrachloride, phosphorus trichloride and aluminum chloride.[4] We found, however, that for preparation of this acid in moderate quantities the above method is not too satisfactory, owing to some undesirable characteristics of the dichloride.

Therefore, the acid was prepared by hydrolysis of its diethyl ester which is readily obtainable from triethyl phosphite and carbon tetrachloride.[6]

The ester (20 g.) was refluxed for 6 hours with 100 ml. of concentrated hydrochloric acid and 50 ml. of water, and the resulting solution was carefully evaporated, after treatment with charcoal. The crude acid, m.p. 80–82°, was recrystallizable from a minimum amount of water at −15° and the product melted at 85–87°. This material was then dried over phosphorus pentoxide at approximately 0.05 mm. after which the pure product melted at 163.5°, softening at

(3) M. I. Kabachnik and E. S. Shepeleva, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 185 (1951).

(4) A. M. Kinnear and E. A. Perren. *J. Chem. Soc.*, 3437 (1952).

(5) A. Ya. Yakubovich and V. A. Ginzburg, *Doklady Akad. Nauk S.S.S.R.*, **82**, 273 (1952).

(6) G. M. Kosolapoff, THIS JOURNAL, **69**, 1002 (1947).

161°. The above-mentioned melting point of the hydrate agrees with that cited earlier,[5] but the present melting point of the anhydrous acid is given for the first time. The acid liberates a considerable amount of heat when placed in contact with water.

Bromomethylphosphonic Acid.—In an attempt to form bromomethylphosphonyl dibromide, formaldehyde and phosphorus tribromide were heated in a sealed vessel precisely as described above for the chloro analog. Very considerable decomposition took place and the only identified products were unchanged phosphorus tribromide and a small amount of methylene bromide. Bromine failed to react after many hours with methylphosphonyl dichloride under ultraviolet irradiation at 120–125°. A similar failure was recorded in a reaction of hydroxymethylphosphonic acid with phosphorus pentabromide, obtained *in situ* by addition of bromine to phosphorus tribromide.

Ford-Moore and Williams,[7] in describing the Arbuzov reaction of triethyl phosphite with methylene bromide, state that: "the reaction is very slow with a poor yield of the diphosphonate, the monophosphonate being almost absent." We carried out this reaction under somewhat drastic conditions and obtained rather satisfactory results. Triethyl phosphite (126 g.) and methylene bromide (162 g.) were heated in an autoclave at 172° for four hours. The resulting mixture was distilled under reduced pressure and yielded 23 g. of diethyl bromomethylphosphonate, b.p. 50° at 0.05 mm., $n^{20}D$ 1.4592, d^{20}_4 1.4363, *MR* 43.99 (calcd. *MR* 43.92). The product also boils at 66° at 0.25 mm. The compound was reported previously with b.p. 99° at 1 mm., d^{20}_{20} 1.4474, $n^{20}D$ 1.4587.[8]

The ester was hydrolyzed by refluxing for nine hours with 48% hydrobromic acid, the solution was concentrated under reduced pressure and the residue was taken up in water. Re-evaporation under reduced pressure after treatment with charcoal, yielded an uncrystallizable sirup. A small portion of this was seeded with a tiny crystal of chloromethylphosphonic acid; this resulted in rapid crystallization of the product. A small portion of this was then used to seed the main batch. After drying *in vacuo* over phosphorus pentoxide the resulting acid melted at 62°, softening at 54°.

Anal. Calcd. for CH_4O_3BrP: P, 17.71; Br, 45.68. Found: P, 17.96; Br, 44.71.

Iodomethylphosphonic Acid.—Diethyl iodomethylphosphonate was prepared conventionally from methylene iodide and triethyl phosphite; b.p. 61° at 0.01 mm. The ester (23.6 g.) was dissolved in 100 ml. of concentrated hydrochloric acid and 50 ml. of water and refluxed for one day. After the usual treatment with charcoal, evaporation and drying under reduced pressure a brownish product was obtained which contained free iodine. This evidently originated in partial hydrolysis of the halogen and formation of hydriodic acid. The iodine was removed by prolonged evacuation of finely powdered product, which then melted at 75–82°. It was then recrystallized from ethylene chloride and after drying under reduced pressure melted at 89°, softening at 86°.

Anal. Calcd. for CH_4O_3IP: P, 13.96. Found: P, 13.9.

Attempted Preparation of Fluoromethylphosphonic Acid.—Diethyl iodomethylphosphonate (25 g.) was added to 40.3 g. of thoroughly dried silver fluoride and the mixture was slowly heated in a distillation apparatus to 125° over five hours at about 30 mm. The distillate (2.3 g., b.p. 89–93° at 20 mm.) was redistilled, yielding a product which boiled at 91–92° at 21 mm. The physical constants and a qualitative examination showed this to be diethyl methylphosphonate, formed apparently by a reductive process from the iodo derivative. This was the only recoverable product from the reaction.

Hydroxymethylphosphonic Acid.—This acid is readily prepared by the method outlined by Page.[9] Its purification is a rather tedious process. Crystallization from alcohol-ethyl acetate mixture proposed by Page is rather wasteful of the product. We noted that this acid has a negative coefficient of solubility in ethyl acetate with temperature. It dissolves quite readily in dry ethyl acetate at about −15° and separates from it in the form of fine crystals on warming to room temperature. After thorough drying the product melts at 99–100°. Previously reported highest melting point is 98–99°.[10]

Page[9] stated that in qualitative tests run in the cold this acid inhibits the precipitation of the yellow phosphomolybdate precipitate from solutions containing phosphates. We examined this effect under the normally used conditions of analytical procedure (hot solution in the presence of much ammonium nitrate) and found that such inhibition does not take place under these conditions.

Determination of Apparent Dissociation Constants.—Both the procedure of the determinations and the method of calculation were precisely the same as reported in the previous paper.[1] In all cases the locations of the breaks in the titration curves agreed excellently with the calculated values; no evidence of cleavage of the carbon–phosphorus link in the trichloromethyl acid was observed The approximate locations of the breaks, which may be of interest for titrations with visual indicators were as follows: hydroxymethylphosphonic acid *p*H 5 and 9.5; chloromethylphosphonic acid 4.5 and 8.5; dichloromethylphosphonic acid 4 and 8.5; trichloromethylphosphonic acid 3.5 (very slight) and 7.5; bromo- and iodomethylphosphonic acids 4.5 and 9.

Acknowledgment.—We wish to express our gratitude to the Research Corporation for a Frederick Gardner Cottrell grant that made this study possible.

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(8) A. Ya. Yakubovich, V. A. Ginzburg and S. P. Makarov, *Doklady Akad. Nauk S.S.S.R.*, **71**, 303 (1950).

(9) H. J. Page, *J. Chem. Soc.*, **101**, 423 (1912).

(10) M. I. Kabachnik and E. S. Shepeleva, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 185 (1951).

ROSS CHEMICAL LABORATORY
ALABAMA POLYTECHNIC INSTITUTE
AUBURN, ALABAMA

The Preparation of Ethyl *o*-Cyanocinnamate and *o*-Carbethoxycinnamonitrile

BY JAMES W. CURRY[1,2]

RECEIVED JUNE 26, 1953

Interest in the anomalous conversion of *p*-quinonemonoxime to *p*-azoxyphenol brought about by treatment with benzenesulfonyl chloride in pyridine and subsequent heating[3–5] suggested an examination of the behavior of the isomeric oximes of 1,2-naphthoquinone under the same conditions. It was possible to obtain the benzenesulfonic esters of 1,2-naphthoquinone-1-oxime and 1,2-naphthoquinone-2-oxime when these oximes were treated with benzenesulfonyl chloride and pyridine, followed by isolation through aqueous dilution of the reaction mixture, and recrystallization from a non-hydroxylic solvent. When attempts were made to recrystallize the benzenesulfonic esters from 95% ethanol, smooth conversions were effected to products which did not contain sulfur. Microanalysis indicated that the isomeric products had the composition $C_{12}H_{11}NO_2$, and infrared analysis showed the presence, in both compounds, of conjugated C≡N and conjugated ester C=O groupings. On the basis of the participants in the conversions and analyses of the products, structure III, ethyl *o*-cyanocinnamate, can be assigned to the product, m.p. 76–77°, obtained from the benzenesulfonic ester of 1,2-naphthoquinone-1-oxime (I). Simi-

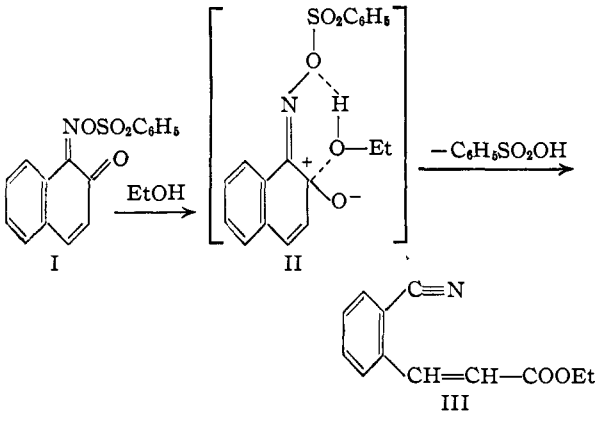
(1) U. S. Atomic Energy Commission Predoctoral Fellow, 1951–1952.

(2) Dow Corning Corporation, Midland, Michigan.

(3) N. J. Leonard and J. W. Curry, *J. Org. Chem.*, **17**, 1071 (1952).

(4) R. A. Raphael and E. Vogel, *J. Chem. Soc.*, 1958 (1952).

(5) E. Beckmann and O. Liesche, *Ber.*, **56**, 1 (1923).



larly, the product, m.p. 45–46°, from the benzenesulfonic ester of 1,2-naphthoquinone-2-oxime, is *o*-carbethoxycinnamonitrile.

The assignment of structure III is consistent with the finding of Werner and Piguet[6] that *trans*-*o*-cyanocinnamic acid was formed by treating 1,2-naphthoquinone-1-oxime (I) with benzenesulfonyl chloride in pyridine solution, followed by acidification of the reaction mixture with dilute sulfuric acid. Also, the product obtained by Beckmann and Liesche,[5] when they subjected 1,2-naphthoquinone-2-oxime to similar reaction conditions, has been identified as *o*-carboxycinnamonitrile.[7] A logical mechanism for the facile ethanolysis of the benzenesulfonic ester of 1,2-naphthoquinone-1-oxime (I) probably involves a cyclic six-membered transition state (II), and a similar transition state can be pictured to account for the formation of *o*-carbethoxycinnamonitrile. One might expect *cis* products to result from these conversions, but isomerization to the *trans* compounds is readily possible in the acidic medium (liberation of benzenesulfonic acid) either at the transition stage or on equilibration of the product. On the basis of the infrared evidence, it is probable that the *trans* forms of both esters were obtained.[8] The spectrum of ethyl *o*-cyanocinnamate showed a band at 967 cm.$^{-1}$, and the same band, though less intense, was found in the spectrum of *o*-carbethoxycinnamonitrile. In neither spectrum was there a band indicative of a *cis* configuration.[9]

Experimental[10]

Benzenesulfonic Ester of 1,2-Naphthoquinone-1-oxime.—A mixture of 12.6 g. (0.073 mole) of 1,2-naphthoquinone-1-oxime[11] and 12.9 g. (0.073 mole) of benzenesulfonyl chloride in 70 ml. of pyridine was allowed to stand until the heat of reaction had subsided. The reaction mixture was diluted to 500 ml. with water, and the precipitate which formed was filtered, washed with water and dried. The product was recrystallized from chloroform–carbon tetrachloride as yellow needles which possessed two melting points. The material melted at 86.5–89°, almost immediately resolidified and melted again at 139.5–141.5° (dec.), (reported[12] for the benzenesulfonic ester of 1-nitroso-2-naphthol, 124–125° and 141°); yield 5.8 g. (26%).

Anal. Calcd. for $C_{16}H_{11}NO_4S$: C, 61.35; H, 3.54; N, 4.37. Found: C, 60.45; H, 3.63; N, 4.31.

The infrared spectrum showed an absorption band at 1648 cm.$^{-1}$, indicating the presence of conjugated C=O.

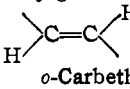
Benzenesulfonic Ester of 1,2-Naphthoquinone-2-oxime.—This compound was prepared from 1,2-naphthoquinone-2-oxime[13] in the same manner as was the benzenesulfonic ester of the 1-oxime. The material was recrystallized as yellow platelets from carbon tetrachloride, m.p. 118–121° (dec.); yield 12.3 g. (54%).

Anal. Calcd. for $C_{16}H_{11}NO_4S$: C, 61.35; H, 3.54; N, 4.37. Found: C, 61.27; H, 3.79; N, 4.56.

Absorption bands at 1685 and 1592 cm.$^{-1}$ in the infrared spectrum indicated the presence of conjugated C=O and conjugated C=N, respectively.

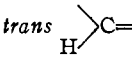
Ethyl *o*-Cyanocinnamate.—To 150 ml. of 95% ethanol was added 5.0 g. (0.016 mole) of the benzenesulfonic ester of 1,2-naphthoquinone-1-oxime. The mixture was boiled until all the material had gone into solution, then for five minutes longer. The solution was decolorized with Norite, filtered and poured into a large excess of cold water. The mixture was cooled to crystallization and the product was separated by filtration. Recrystallization from dilute ethanol gave colorless needles, m.p. 76–77° (reported[8] 57°); yield 2.6 g. (82%).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.41; H, 5.42; N, 6.91.

The infrared spectrum showed absorption bands at 2220, 1714, 1636, and 967 cm.$^{-1}$, indicative of conjugated C≡N, conjugated ester C=O, conjugated C=C, and *trans*  , respectively.

***o*-Carbethoxycinnamonitrile.**—This ester was obtained from 5.0 g. (0.016 mole) of the benzenesulfonic ester of 1,2-naphthoquinone-2-oxime by the procedure described above for the synthesis of ethyl *o*-cyanocinnamate. Recrystallization from dilute ethanol gave colorless needles, m.p. 45–46°; yield 2.5 g. (79%).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.78; H, 5.78; N, 7.16.

The infrared spectrum showed the presence of conjugated C≡N (2212 cm.$^{-1}$), and conjugated ester C=O (1712 cm.$^{-1}$). There was also a weak band at 967 cm.$^{-1}$, indicative of *trans*  .

(6) A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904).

(7) J. W. Curry, Ph.D. Thesis, University of Illinois, 1952.

(8) Ethyl *o*-cyanocinnamate of m.p. 57° has been reported previously (G. Komppa, *Oversikt. Finska Vetenskaps-Soc. Forh.*, **36**, 121). Komppa did not state whether the compound he obtained was the *cis* or the *trans* isomer.

(9) F. A. Miller, in Gilman's "Organic Chemistry. An Advanced Treatise," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 122.

(10) Melting points are corrected.

(11) C. S. Marvel and P. K. Porter, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., Second Edition, 1941, p. 411.

(12) C. A. Edwards, *J. Chem. Soc.*, 813 (1926).

(13) Chao-Lun Tseng and Mei Hu, *J. Chinese Chem. Soc.*, **3**, 60 (1935).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

Ruthenium Isotope Abundances[1]

BY LEWIS FRIEDMAN AND A. P. IRSA

RECEIVED JUNE 17, 1953

Mass spectrographic investigations of the abundances of the ruthenium isotopes have been carried out by Aston[2] and Ewald.[3] Ewald's work, which has been tentatively accepted by the N.R.C. Subcommittee on Nuclear Constants,[4] involved a photographic plate calibration using cadmium abundance data which subsequently have been

(1) Research carried out under the auspices of the U. S. Atomic Energy Commission.

(2) F. W. Aston, *Proc. Roy. Soc.* (*London*), **A132**, 487 (1931).

(3) H. Ewald, *Z. Physik*, **122**, 686 (1944).

(4) K. T. Bainbridge and A. O. C. Nier, Preliminary Report #9, Nuclear Science Series (1950).

revised. Unfortunately insufficient data are available to permit a correction of Ewald's values.

In view of this and the fact that a sizable discrepancy exists between the accepted atomic weight, 101.7,[5] and that calculated from Ewald's data, 101.03, we have reinvestigated the isotope abundances of ruthenium using electrical rather than photographic methods of ion detection.

One of the difficult aspects in determination of the isotopic abundances of ruthenium was the scarcity of volatile compounds from which a stable molecular beam for ionization could be obtained. With the discovery and synthesis of ruthenocene, ($C_{10}H_{10}Ru$),[6] this difficulty is easily circumvented; and isotope abundance measurements can be made easily in a mass range free of background and under circumstances in which errors due to voltage discrimination, fractionation of isotopic molecules, etc., are minimized.

A Nier type mass spectrometer manufactured by the General Electric Company was used. The sample, kindly supplied to us by Prof. Geoffrey Wilkinson of Harvard University, consisted of a few milligrams of solid $C_{10}H_{10}Ru$ which was synthesized from $RuCl_3$ obtained from the American Platinum Works, Newark, N. J. It was placed in a glass tube which could be sealed directly on the head of the mass spectrometer with a waxed ball joint. One end of this tube opened directly to the gas inlet port of the ionization chamber; the other, sample-containing end, was sealed off and projected downward at right angles to the spectrometer tube. The sample was cooled with liquid nitrogen during preliminary evacuation of the spectrometer. An adequate vapor pressure was obtained at room temperature and lower. Runs reported here were made at 15°. The spectrum was taken originally with 50-volt ionizing electrons, 2000-volt ion accelerating potential and magnetic scanning. Isotopic abundances were measured with 10-volt ionizing electrons to eliminate dissociative ionization processes. The technique was calibrated by determining the isotopic composition of mercury with identical sampling and operating procedures. Results on mercury were in agreement with those of Nier[7] within 0.5% except at the relatively rare Hg^{196} and here the values checked to within 1%.

The mass spectrum of ruthenocene obtained with 50-volt electrons from Ru^+ up to and including the molecular ion is presented in Table I. The spectrum reported was partially resolved into a monoisotopic spectrum based on Ru^{104}, C^{12} and H^1. The most interesting features of the spectrum are the relatively large yield of molecular ions, appreciable amounts of doubly charged ions, and the alternation in relative probabilities for the processes involving loss of one, two, three and four carbon fragments. These features are observable in the mass spectra of aromatic fused ring systems, naphthalene and anthracene. Another feature of some practical importance in the determination of isotopic abundances is the extremely small probability of loss of hydrogen from the molecular ions.

(5) E. Wichers, THIS JOURNAL, **74**, 2447 (1952).
(6) G. Wilkinson, *ibid.*, **74**, 6146 (1952).
(7) A. O. C. Nier, *Phys. Rev.*, **79**, 450 (1950).

TABLE I

Mass	Relative intensity	Probable ion formula	Mass	Relative intensity	Probable ion formula
234	100	$C_{10}H_{10}Ru^{104}$	155	1.8	$C_4H_8Ru^{104}$
208	2.6	$C_8H_8Ru^{104}$	143	5.2	$C_3H_8Ru^{104}$
206	5.0	$C_8H_6Ru^{104}$	142	2.8	$C_3H_2Ru^{104}$
193	0.3	$C_7H_5Ru^{104}$	141	14.0	C_3HRu^{104}
180	3.5	$C_6H_6Ru^{104}$	130	1.2	$C_2H_2Ru^{104}$
179	3.5	$C_6H_5Ru^{104}$	117	7.5	$C_{10}H_{10}Ru^{104++}$
169	24.0	$C_5H_5Ru^{104}$	104	6.0	Ru^{104+}

The observed polyisotopic spectrum of the molecular mass from which isotopic abundances were computed is presented in column 1 of Table II. The data were averaged from 14 scans, with average deviations as indicated. Since no detectable ions involving loss of hydrogen from $C_{10}H_{10}Ru^{96}$ were observed with 10-volt electrons the only corrections necessary are those for C^{13} and H^2. The abundance of the latter was assumed to be 0.015% or "natural abundance." A statistical distribution of C^{12} and C^{13} was assumed in computing the natural abundance of C^{13} from the 226 and 227 ($C_{10}^{12}H_{10}^{1}Ru^{96}$ and $C_9^{12}C^{13}H_{10}^{1}Ru^{96}$) peak intensities. The value 1.105% C^{13} was obtained, in excellent agreement with the accepted 1.108%.[4] The experimentally determined C^{13} abundance was used to compute the contribution of molecules containing $2C^{13}$ atoms to the polyisotopic spectrum. Errors arising from the assumption on the relative abundance of H^2, and neglect of more than two C^{13} molecules could have been detected in the internal consistency of peaks computed for ions of mass 231 and 233, $C_9^{12}C^{13}H_{10}Ru^{102+}$ and $C_9^{12}C^{13}H_{10}Ru^{104+}$. The agreement between computed and observed peaks at these masses was better than 1% indicating an approximate 0.1% error in the isotope abundances arising from the C^{13} and H^2 corrections. In turn, 0.1% may be set as an upper limit for the relative abundances of Ru^{97} and Ru^{103}. This particular system is not well suited for the purpose of detecting rare isotopes because of these interferences. The Ru^+ ion yield and doubly charged ruthenocene ions were not useful in estimating isotope abundances because of relatively weak intensity and large backgrounds in these spectral regions.

The abundances of Ru isotopes computed by starting at Ru^{96} and removing the 1.1% C^{13} and 0.015% H^2 from successively higher masses are presented in column 4 of Table II. The work of

TABLE II

Mass	Polyisotopic ruthenocene molecule ions Relative intensity	Mass	Relative abundances ruthenium isotopes This work	Ewald
226	4.923 ± 0.018[a]	96	5.50	5.68
227	0.557 ± .006			
228	1.73 ± .01	98	1.91	2.22
229	11.57 ± .01	99	12.70	12.81
230	12.56 ± .05	100	12.69	12.70
231	16.57 ± .03	101	17.01	16.98
232	30.03 ± .06	102	31.52	31.34
233	3.23 ± .04			
234	16.97 ± .06	104	18.67	18.27
235	1.854 ± .016			

[a] Average deviation.

Ewald is presented in the fifth column. In general the agreement is good, with differences in the direction expected from the revision of Nier's cadmium data. That is, low abundance nuclides are moderately reduced with higher abundance nuclides correspondingly increased. There is a moderately large percentage difference at Ru^{98}. This was a weak line in Ewald's spectrum and most susceptible to error in plate calibration and densitometry. Variations in the natural abundance of Ru^{98} are of interest as a possible means of detection of natural Tc^{98}.

The atomic weights computed from these data and Ewald's are in good agreement. Using the packing fraction listed by Mattauch[8] and the chemical conversion factor of 1.000275 a value of 101.08 is obtained. This agrees with the value of 101.08 obtained by Gleu and Rehm[9] from studies on the decomposition of $RuCl_3 \cdot 5NH_3$ but seriously diverges from the accepted value, 101.7, obtained from studies on oxide decomposition.

The authors wish to thank Prof. Geoffrey Wilkinson for his coöperation in supplying us with a sample of pure ruthenocene.

(8) T. Mattauch and S. Fluegge, "Nuclear Physics Tables," Interscience Publishers, Inc., New York, N. Y., 1942.

(9) K. Gleu and K. Rehm, *Z. anorg. Chem.*, **235**, 352 (1938).

CHEMISTRY DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, LONG ISLAND, N. Y.

Competitive Interaction between Proteins and Surface Active Anions Demonstrated by Electrophoresis[1]

BY JOSEPH F. FOSTER AND JEN TSI YANG

RECEIVED MAY 23, 1953

Both ovalbumin[2] and serum albumin[3] possess a strong affinity for anionic detergents which is manifested in the formation of an "all-or-none"[4] complex. This complex formation is thought to involve denaturation of the protein and the denatured complex can be resolved from the native protein electrophoretically. The authors have shown recently[5] that ovalbumin (O) yields the all- or none reaction at lower detergent concentrations than does bovine serum albumin (A).

It occurred to the authors that it should be possible to demonstrate this difference in reactivity directly through electrophoretic studies of mixtures of the proteins. The technique used was to mix one of the native proteins with the dodecylbenzene sodium sulfonate complex of the other. After allowing the mixed solution to stand for two days at 2° it was dialyzed for two days against the electrophoretic buffer (either glycine–NaCl, *p*H 10.0, Γ/2 0.1 or veronal–NaCl, *p*H 8.5, Γ/2 0.1) and subjected to electrophoresis. Some typical results are summarized in Fig. 1.

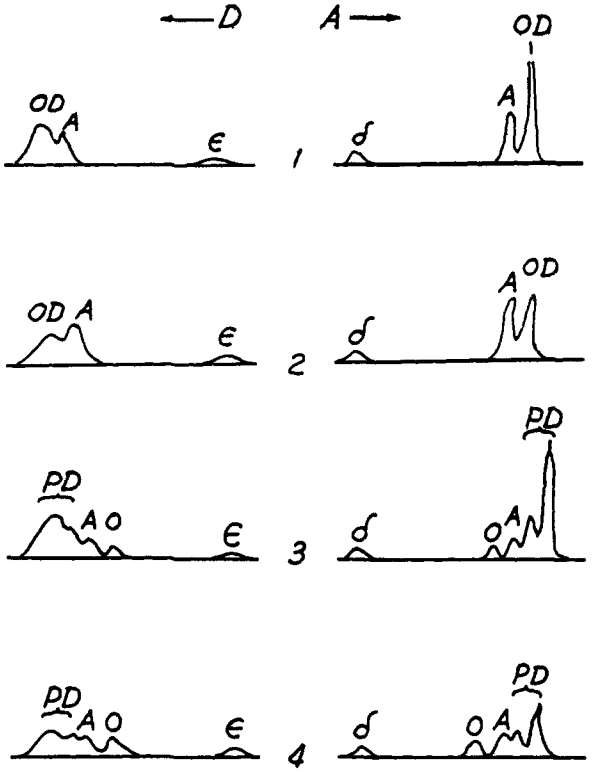


Fig. 1.—Electrophoretic analyses of albumin–SDBS mixtures in glycine–NaCl buffer (*p*H 10.0, Γ/2 0.10). Runs 1 and 2, ovalbumin–SDBS (OD) plus bovine serum albumin (A); O/A ratio 66/34 and 48/52, respectively. Runs 3 and 4, bovine serum albumin–SDBS (AD) plus ovalbumin (O); A/O ratio 66/34 and 49/51, respectively.

It will be seen in Fig. 1 that when A is added to the detergent complex of O (OD) only two components are observed and these have the mobilities characteristic of A and OD. Furthermore the relative areas under the boundaries are close to the relative composition in the original mixture. In other words the pattern is an additive function of the separate patterns on the two components. On the other hand when O is added to AD interaction is clearly revealed. Thus the area corresponding to O is greatly reduced from that which would be expected on the basis of the mixing ratio and a boundary corresponding in mobility to A appears. Similar results were obtained in the veronal buffer; however, in this buffer the patterns were complicated by a split in the protein–detergent boundary and by the appearance of a fast moving boundary anomaly in the descending pattern.

In a study of the electrophoretic analysis of detergent extracts of the corn proteins Foster, Yang and Yui[6] concluded that zein preferentially binds most or all of the detergent present. It was

(1) Journal Paper No. J-2334 of the Iowa Agricultural Experiment Station, Ames, Iowa. Proj. 978. Supported in part by a grant from Swift and Company. Taken from a thesis submitted by Jen Tsi Yang in partial fulfillment of the requirements for the degree Doctor of Philosophy, Iowa State College, 1952.

(2) H. P. Lundgren, D. W. Elam and R. A. O'Connell, *J. Biol. Chem.*, **149**, 183 (1943).

(3) F. W. Putnam and H. Neurath, *ibid.*, **159**, 195 (1945).

(4) The term "all-or-none" as applied to this reaction is in some respects perhaps unfortunate. It is now well known that different complexes are formed in the case of horse serum albumin[3] and that there may be stepwise binding both prior to and following the so-called "all-or-none" step or steps.[5] The term is used in the absence of a better one with these reservations to distinguish binding which leads to new components which are readily resolvable by electrophoresis.

(5) J. T. Yang and J. F. Foster, THIS JOURNAL, **75**, 5560 (1953).

(6) J. F. Foster, J. T. Yang and N. H. Yui, *Cereal Chem.*, **27**, 477 (1950).

thus of interest to study the behavior of mixtures of zein–detergent complex (ZD) and either O or A. Figure 2 shows that O removes a part of the detergent from ZD yielding an OI boundary whereas A yields only an additive pattern. This is again in complete agreement with the idea that O forms the all-or-none complex much more readily than A. Again similar results were obtained in the two buffer systems; however, glycine yielded better resolution of ZD and A whereas resolution of ZD and O was superior in veronal.

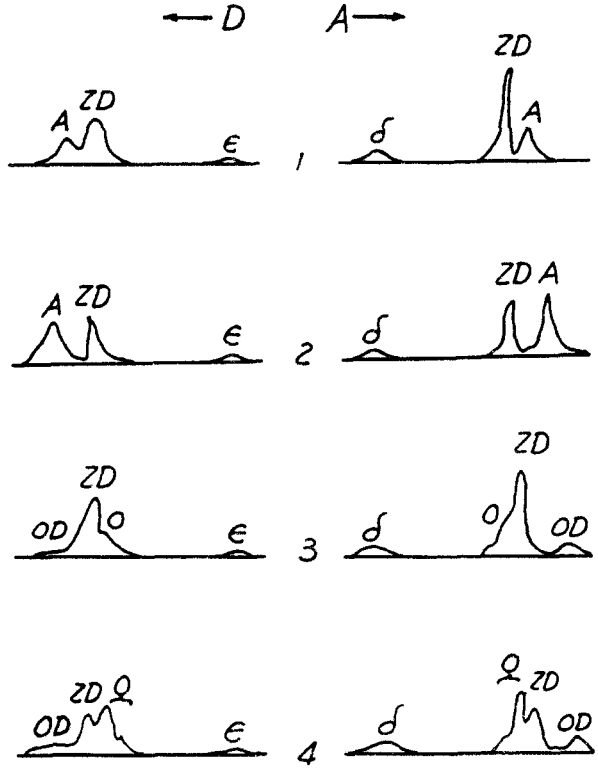


Fig. 2.—Electrophoretic analyses of mixtures of zein–SDBS (ZD) and ovalbumin (O) or bovine serum albumin (A). Runs 1 and 2, ZD plus A in glycine–NaCl buffer (*p*H 10.0, Γ/2 0.10); Z/A ratio 69/31 and 36/64, respectively. Runs 3 and 4, ZD plus O in veronal–NaCl buffer (*p*H 8.9, Γ/2 0.10); Z/O ratio 67/33 and 34/66, respectively.

Experimental

The albumin–detergent complexes were prepared from O and A by mixing 3 parts O and 2 parts A, respectively, with 1 part dodecylbenzene sodium sulfonate[7] (by weight) followed by isoelectric precipitation and redispersion of the precipitate in alkaline buffer. The complexes could also be prepared by adding a slight excess of detergent to O and A and removing the excess by prolonged dialysis against water.[8] The electrophoretic properties of the complexes prepared by either technique were substantially the same.

The zein–detergent complex was prepared by dissolving excess zein in detergent solution. Since the zein is insoluble in water a complex is formed which corresponds to the minimum detergent ratio for solubility.[9] This complex could also be prepared by dissolving zein in excess detergent and removing the excess detergent by dialysis. This procedure proved to be time consuming and tedious, however.

Electrophoretic analyses were carried out in an 11-ml. cell of the Tiselius type using a Philpot–Svenson type optical system. In the glycine–NaCl buffer O typically had a mobility of 7.4–8.3 × 10^{-5}, A 8.8–9.6 × 10^{-5} and the detergent complexes 9.6–11.3 × 10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$.

Acknowledgment.—The authors are indebted to Armour and Company and to the Corn Products Refining Company for supplying the crystalline bovine serum albumin and the zein, respectively.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

(7) Santomerse No. 3, Monsanto.

(8) Neither the composition of the complexes nor their electrophoretic mobility was found to be appreciably dependent on the extent of this dialysis. It is felt that most of the ions removed are lower homologs of the detergent which are not strongly bound[4] and that the activity of true detergent ions in equilibrium with the complex is so low that removal is negligible under these conditions.

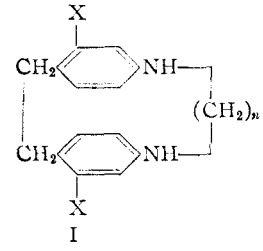
(9) J. F. Foster, *J. Phys. Chem.*, **53**, 175 (1949).

Heterocycles Containing *p*-Phenylene Units. III. Substituted Amines

BY REYNOLD C. FUSON AND HERBERT O. HOUSE[1]

RECEIVED JULY 16, 1953

Three substituted cyclic diamines of type I have been synthesized. The 2,2′-dimethyl-4,4′-(polymethylenediimino)-bibenzyls (Ia and Ib) were prepared from 4-nitro-1,2-dimethylbenzene following a sequence of reactions analogous to that previously reported.[2] Nitration of 4,4′-(hexamethylenediimino)-bibenzyl (Id) in sulfuric acid produced



I

Ia, X = CH_3, n = 4
Ib, X = CH_3, n = 6
Ic, X = NO_2, n = 6
Id, X = H, n = 6

the dinitrated heterocyclic compound (Ic). In each of the three syntheses, evidence for the formation of more than one isomer (*i.e.*, *cis* and *trans* forms) was lacking.

Experimental[3]

Cyclization of *p,p′*-Diphenylsulfonamidobibenzyl and Hexamethylene Bromide.—A solution of 9.20 g. (0.0187 mole) of *p,p′*-diphenylsulfonamidobibenzyl and 5.00 g. (0.0204 mole) of hexamethylene bromide in 200 ml. of dimethylformamide was added, in high dilution and with stirring, over a period of 12.5 hours, to a suspension of 60.0 g. (0.43 mole) of anhydrous potassium carbonate in 500 ml. of refluxing dimethylformamide. After the addition was complete, the mixture was boiled under reflux, with stirring, for an additional 12 hours and worked up as in the previous cases.[2] The residue, obtained from the chloroform extract, was recrystallized from acetic acid to give 3.18 g. (29.7%) of the cyclic disulfonamide as tan prisms melting at 201–205°. Two additional recrystallizations from acetic acid afforded the pure product as white prisms, m.p. 204–206°.

Anal. Calcd. for $C_{32}H_{34}N_2O_4S_2$: C, 66.87; H, 5.96; N, 4.86; S, 11.16. Found: C, 66.75; H, 5.75; N, 4.89; S, 11.11.

Cleavage of the Cyclic Disulfonamide.—A mixture of 2.21 g. of the cyclic disulfonamide, 5.0 g. of phenol and 75 ml. of 48% hydrobromic acid was boiled under reflux, with stirring, for 75 minutes. The isolation procedure was that outlined previously[2]; the cyclic diamine crystallized from a methanol–water mixture as white needles, m.p. 146–147°,[1] yield 0.86 g. (76%).

(1) Atomic Energy Commission Predoctoral Fellow, 1951–1953.

(2) R. C. Fuson and H. O. House, THIS JOURNAL, **75**, 1327 (1953).

(3) All melting points are corrected. The infrared spectra were determined and interpreted by Miss Helen Miklas. The microanalyses are by Mrs. Katherine Pih, Mrs. Esther Fett and Mr. Joseph Nemeth.

N,N'-Di-*p*-tolylhexamethylenediamine.—A mixture of 40.2 g. of *p*-phenylsulfonamidotoluene,[4] 22.0 g. of hexamethylene bromide, 75.0 g. of anhydrous potassium carbonate and 300 ml. of acetone was boiled under reflux, with stirring, for 2 hours. After three-fourths of the acetone had been distilled from the reaction mixture, the residue was poured into 1 l. of water. The oily product, which partially solidified when allowed to stand, was filtered. An attempted crystallization of the solid from ethanol resulted in the deposition of an amorphous white solid which could not be induced to crystallize. The material was therefore subjected to reductive cleavage; a mixture of the amorphous substance with 15 g. of phenol and 200 ml. of 48% hydrobromic acid was boiled under reflux, with stirring, for 4 hours. The cold reaction mixture, following dilution with 100 ml. of water, was extracted with two 100-ml. portions of ethyl ether and then diluted with a sufficient amount of hot water to redissolve all the amine hydrobromide which had separated during the extraction. The acidic solution, after decolorization with Norit, was rendered alkaline with aqueous sodium hydroxide. The resulting white solid crystallized from methanol as white needles, m.p. 90.5–92°, yield 1.95 g. (8.2%). An additional recrystallization of the diamine from methanol raised the melting point to 91.5–92.5°.

Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.04; H, 9.52; N, 9.45. Found: C, 81.05; H, 9.47; N, 9.75.

The infrared spectrum of the product exhibits absorption bands at 3310 cm.$^{-1}$, attributable to an N–H group; at 1520, 1584 and 1616 cm.$^{-1}$, attributable to absorption by the aromatic nuclei; and at 804 and 819 cm.$^{-1}$, attributable to a *p*-substituted benzene ring. Thus the doubling of the *p*-substitution band, formerly noted only in the heterocycles,[2] is not a property unique to the cyclic compounds.

3-Bromo-4-phenylsulfonamidotoluene.—A solution of 15.8 g. of 3-bromo-4-aminotoluene[5] in 80 ml. of pyridine was treated with 16.0 ml. of benzenesulfonyl chloride. The solution, after having been heated on a steam-bath for 15 minutes, was poured into 500 ml. of ice-water. The product was recrystallized twice from ethanol–water mixtures; yield 25.4 g. (91.4%) of white needles, m.p. 100–102°. An additional recrystallization of the sulfonamide from the same solvent pair raised the melting point to 102–103°.

Anal. Calcd. for $C_{13}H_{12}BrNO_2S$: C, 47.85; H, 3.71; N, 4.29; S, 9.83; Br, 24.50. Found: C, 47.98; H, 3.66; N, 4.38; S, 9.98; Br, 24.53.

3,3'-Dibromo-4,4'-diphenylsulfonamidobibenzyl.—To a solution of 30.0 g. (0.0612 mole) of *p,p'*-diphenylsulfonamidobibenzyl in 150 ml. of pyridine was added dropwise, with stirring, 19.8 g. (0.123 mole) of bromine. The mixture was stirred for 30 minutes, warmed on a steam-bath for 10 minutes and diluted with 500 ml. of water. After the mixture had been acidified with hydrochloric acid, the tan solid which separated was collected on a filter. The sulfonamide was extracted with aqueous sodium hydroxide and reprecipitated from the extract with hydrochloric acid. It was treated with 150 ml. of boiling ethanol to leave a white residue, m.p. 171–178°, which was recrystallized from 1500 ml. of ethanol; yield 4.49 g. (11.3%) of white needles, m.p. 175–178°. Two additional recrystallizations of the disulfonamide from large volumes of ethanol raised its melting point to 178–180°.

Anal. Calcd. for $C_{26}H_{22}Br_2N_2O_4S_2$: C, 48.02; H, 3.41; N, 4.31; Br, 24.57; S, 9.86. Found: C, 47.84; H, 3.41; N, 4.29; Br, 24.80; S, 9.57.

Since the product had been prepared by bromination in pyridine solution, a procedure known to permit facile bromination at all free positions ortho and para to the sulfonamido group,[6] the question arose as to whether both bromine atoms were borne by the same aromatic nucleus. A comparison of the infrared spectra of the benzenesulfonamides of *p*-toluidine and of 3-bromo-4-aminotoluene with those of *p,p'*-diphenylsulfonamidobibenzyl and its bromination product served to settle the question. The spectra of both bromine-free compounds exhibit an absorption band at 1510 cm.$^{-1}$, attributable to a benzene ring bearing substituents para to one another. This absorption band is absent in both brominated sulfonamides, indicating that each ring of the dibromo-*p,p'*-diphenylsulfonamidobibenzyl has an additional substituent.

2-Nitro-4-methylaminotoluene.[7]—This nitrotoluidine derivative was obtained in 97.3% yield by nitrating a solution of N-methyl-*p*-toluidine in concentrated sulfuric acid. Two additional recrystallizations from small volumes of ethanol afforded the pure nitroamine as red-orange prisms, m.p. 54–55.5°.

3-Nitro-4-methylaminotoluene.[8]—The methylation of 3-nitro-4-acetamidotoluene[9] was effected according to the procedure of Pachter and Kloetzel.[10] The intermediate amide, when hydrolyzed with a boiling ethanol–hydrochloric acid mixture, afforded the nitrotoluidine in 17.3% yield. The product crystallized from ethanol in red needles, m.p. 84–85°.

2,2'-Dinitro-4,4'-(hexamethylenediimino)-bibenzyl (Ic).—To a solution of 2.00 g. of 4,4'-(hexamethylenediimino)-bibenzyl in 30 ml. of concentrated sulfuric acid, cooled in an ice-bath, was added, dropwise and with stirring, 2.5 ml. of concentrated nitric acid. After the addition was complete, the ice-bath was removed and stirring continued for 30 minutes. The reaction mixture was poured into 300 ml. of water, and the resulting mixture filtered. The crude product, which separated when the filtrate was made alkaline with aqueous sodium hydroxide, crystallized from propanol as red prisms, m.p. 229–231°, yield 2.29 g. (87.8%). Recrystallization of the heterocyclic compound from ethanol raised its melting point to 231–232°.

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.30; N, 14.55. Found: C, 62.54; H, 6.31; N, 14.76.

The infrared spectrum of the cyclic compound, although similar to that of 2-nitro-4-methylaminotoluene, differs markedly from the spectrum of the isomeric 3-nitro-4-methylaminotoluene.

N-Methyl-N-(4-methyl-3-nitrophenyl)-glycine.—A mixture of 8.1 g. of 2-nitro-4-methylaminotoluene, 5.0 g. of chloroacetic acid, 5.3 g. of anhydrous sodium carbonate, 200 ml. of water and 100 ml. of ethanol was heated on a steam-bath, with stirring, for 2 hours. After the mixture had been cooled, the unchanged amine, amounting to 7.7 g., was collected on a filter. The *p*H of the filtrate was adjusted to 3 to liberate the amino acid, a yellow solid melting at 147–149°. The yield was 0.40 g. or 74% of the theoretical amount based upon the unrecovered amine. Two recrystallizations from water gave the pure amino acid as golden-yellow needles, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.57; H, 5.35; N, 12.74.

N,3,4-Trimethylacetanilide.—To a mixture of 10.1 g. of crude 3,4-dimethylacetanilide,[11] 20 g. of powdered potassium hydroxide and 250 ml. of refluxing acetone was added 15.0 ml. of methyl iodide in 45 ml. of acetone (methylation procedure of Pachter and Kloetzel[10]). The mixture, after being boiled under reflux, with stirring, for 5 minutes, was filtered. The filtrate was concentrated almost to dryness and then diluted with 300 ml. of water. The oil, which separated, solidified on standing and was collected on a filter. A solution of the product in a boiling methanol–water mixture, after decolorization with Norit, was chilled to give 3.68 g. (35.5%) of light tan needles melting at 68–76°. Two additional recrystallizations from petroleum ether (b.p. 30–60°) gave long, white needles, m.p. 75–76°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.51; H, 8.53; N, 7.90. Found: C, 74.80; H, 8.63; N, 8.01.

4,4'-Dinitro-2,2'-dimethylbibenzyl.[12]—A solution of 120.1 g. of 4-nitro-1,2-dimethylbenzene[13] in 2 l. of 30% methanolic

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(8) L. Gattermann, *Ber.*, **18**, 1482 (1885); G. T. Morgan, E. Jobling and R. T. F. Barnett, *J. Chem. Soc.*, **101**, 1209 (1912).

(9) G. Bacharach, THIS JOURNAL, **49**, 1522 (1927); T. L. Davis and K. C. Blanchard, *ibid.*, **51**, 1801 (1929).

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(12) A. G. Green, A. H. Davies and R. S. Horsfall, *J. Chem. Soc.*, **91**, 2076 (1907).

(13) A. W. Crossley and N. Renouf, *ibid.*, **95**, 202 (1909); P. Karrer, B. Becker, F. Benz, P. Frei, H. Salomon and K. Schopp, *Helv. Chim. Acta*, **18**, 1435 (1935); S. F. Birch, R. A. Dean, F. A. Fidler and R. A. Lowry, THIS JOURNAL, **71**, 1362 (1949).

potassium hydroxide, cooled to 7° in an ice-bath, was stirred vigorously while a rapid stream of air was introduced. After 2 hours the ice-bath was removed. The stirring accompanied by the introduction of air was continued for an additional 10 hours. The mixture was diluted with 1 l. of hot water and filtered with suction. The residue, while still on the filter, was washed first with boiling water and then with ethanol. The product crystallized from acetic acid as yellow needles, m.p. 225–227.5°, yield 85.1 g. (71.5%). Recrystallization of the dinitro compound from acetic acid raised the melting point to 227–228.5°.

4,4'-Diamino-2,2'-dimethylbibenzyl.—A mixture of 87.9 g. of 4,4'-dinitro-2,2'-dimethylbibenzyl, 200 g. of powdered iron, 500 ml. of ethanol and 500 ml. of water was heated to boiling. To this boiling mixture was added dropwise, with stirring, a solution of 12.1 ml. of concentrated hydrochloric acid in 100 ml. of 50% aqueous ethanol. The resulting mixture, after having been boiled under reflux, with stirring, for 16 hours, was made alkaline by the addition of 30 ml. of 6 *N* aqueous sodium hydroxide in 500 ml. of ethanol. The mixture was filtered while hot. The cold filtrate deposited 36.5 g. of tan needles, m.p. 164–167°. Concentration of the mother liquor afforded an additional crop of the diamine; total yield 43.5 g. (62%), A boiling ethanolic solution of the product, after decolorization with Norit, was chilled to give the pure diamine as white needles melting at 169–170.5°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.98; H, 8.39; N, 11.66. Found: C, 79.90; H, 8.12; N, 11.82.

4,4'-Diphenylsulfonamido-2,2'-dimethylbibenzyl.—A solution of 23.3 g. of 4,4'-diamino-2,2'-dimethylbibenzyl and 45 ml. of benzenesulfonyl chloride in 200 ml. of pyridine was heated to boiling. The solution, after having been allowed to cool, was poured, with stirring, into 1.5 l. of cold water. The crude sulfonamide was dissolved in warm, dilute, aqueous sodium hydroxide, the alkaline solution decolorized with Norit and the product reprecipitated with hydrochloric acid. The disulfonamide crystallized from ethanol as tan prisms; m.p. 172–174°, yield 42.3 g. (82.1%). It was obtained as colorless prisms, m.p. 173–174°, by slowly cooling a decolorized solution of the crude product in boiling ethanol.

Anal. Calcd. for $C_{28}H_{28}N_2O_4S_2$: C, 64.60; H, 5.42; N, 5.38; S, 12.32. Found: C, 64.65; H, 5.37; N, 5.33; S, 12.17.

Most attempts to recrystallize the material from ethanol resulted in the deposition of an alternative crystalline form, large rectangular prisms melting at 159–160° with a simultaneous transition to the higher melting form. The substance would melt completely only if it were plunged into a bath heated to a temperature of 161° or more. When the recrystallizing solvent was benzene or acetic acid, the lower-melting crystalline form resulted. The infrared spectra of the two forms are identical and the composition of the lower-melting form corresponds to that of the desired product.

Anal. Calcd. for $C_{28}H_{28}N_2O_4S_2$: C, 64.60; H, 5.42; N, 5.38; S, 12.32. Found: C, 64.74; H, 5.59; N, 5.31; S, 12.26.

2,2'-Dimethyl-4,4'-(hexamethylenediimino)-bibenzyl (Ib).—A solution of 30.9 g. (0.0593 mole) of 4,4'-diphenylsulfonamido-2,2'-dimethylbibenzyl and 15.0 g. (0.0614 mole) of hexamethylene bromide in 200 ml. of dimethylformamide was added in high dilution and with stirring, over a 13-hour period, to a suspension of 150 g. (1.08 moles) of anhydrous potassium carbonate in 500 ml. of refluxing dimethylformamide. After the addition was complete, the mixture was boiled under reflux, with stirring, for an additional 8 hours, cooled, diluted with 1 l. of water and poured into 3 l. of cold water. The crude product was taken up in boiling chloroform, the solution decolorized with Norit and the solvent removed on a steam-bath. A mixture of the residue, a viscous yellow oil, with 20 g. of phenol and 150 ml. of 48% hydrobromic acid was boiled under reflux, with stirring, for 1 hour. The cyclic diamine, isolated in the usual fashion,[2] crystallized from ethanol as white needles, m.p. 185.5–187.5°, yield 5.05 g. (26.4%). An additional recrystallization of the compound from ethanol sharpened the melting point to 186.5–187.5°.

Anal. Calcd. for $C_{22}H_{30}N_2$: C, 81.92; H, 9.38; N, 8.70; mol. wt., 323. Found: C, 81.66; H, 9.23; N, 8.72; mol. wt. (Rast), 352.

Concentration of the mother liquor yielded no additional material having the composition of the cyclic diamine.

The **diacetate** of the heterocyclic compound was prepared by boiling, under reflux for 4 hours, a mixture of 0.50 g. of the diamine, 1.0 g. of anhydrous sodium acetate and 20 ml. of acetic anhydride. After the excess acetic anhydride had been hydrolyzed the mixture was poured into 300 ml. of dilute, aqueous sodium hydroxide. The product separated as an oil which solidified when chilled. A solution of the compound in boiling ethanol was decolorized with Norit, the solvent removed and the residue taken up in boiling petroleum ether (b.p. 30–60°). The diamide crystallized from the cold solution as white cubes, m.p. 126–127°, yield 0.48 g. (74%).

Anal. Calcd. for $C_{26}H_{34}N_2O_2$: C, 76.83; H, 8.43; N, 6.89. Found: C, 76.93; H, 8.51; N, 6.79.

The infrared spectrum of the product closely resembles the spectrum of N,3,4-trimethylacetanilide.

2,2'-Dimethyl-4,4'-(tetramethylenediimino)-bibenzyl (Ia).—A solution of 6.10 g. (0.0117 mole) of 4,4'-diphenylsulfonamide-2,2'-dimethylbibenzyl and 3.24 g. (0.0150 mole) of tetramethylene bromide in 100 ml. of dimethylformamide was added in high dilution and with stirring, over a period of 7.5 hours, to a suspension of 55.2 g. (0.40 mole) of anhydrous potassium carbonate in 500 ml. of refluxing dimethylformamide. After the addition was complete, the mixture was boiled under reflux, with stirring, for an additional 7 hours and then worked up as in the previous case. A mixture of the crude cyclic disulfonamide, a viscous, yellow oil obtained from the chloroform extract, with 5.0 g. of phenol and 75 ml. of 48% hydrobromic acid was boiled under reflux, with stirring, for 1 hour. The cyclic diamine crystallized from a methanol–water mixture as white needles, m.p. 174–176°, yield 0.19 g. (5.5%). Recrystallization of the heterocyclic compound from aqueous methanol raised the melting point to 175.5–176.5°.

Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.52; mol. wt., 294. Found: C, 81.70; H, 8.94; N, 9.68; mol. wt. (Rast), 318.

No other product could be isolated from the mother liquor.

THE NOYES CHEMISTRY LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

The Conformation of 2-(2,3-Dimethoxyphenyl)-cyclohexane-1,2-diol, a *cis*-Glycol

BY DAVID GINSBURG[1]

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It has been shown that hydroxylation of the double bond of 1-(2,3-dimethoxyphenyl)-cyclohexene by performic acid and by osmium tetroxide leads to the same glycol, 2-(2,3-dimethoxyphenyl)-cyclohexane-1,2-diol, presumed to be a *cis*-glycol.[2] It is generally believed that the performic acid and osmium tetroxide hydroxylation methods lead to *trans*- and to *cis*-glycols, respectively. Clearly, in the case under discussion one conformation is considerably more stable than the other and therefore only one glycol is isolated.

It seems reasonable to assume that in the present case, the bulkier dimethoxyphenyl group at C_2 of the cyclohexane ring and the hydroxyl group at C_1 will both assume the equatorial conformation and will thus be *trans* with respect to each other. The hydroxyl group at C_2 must necessarily adopt the polar conformation and constitute with the adjacent hydroxyl group, a *cis*-glycol system. Although both *cis*- and *trans*-2-phenylcyclohexane-1,2-diol are known, it has been shown that the

(1) U. S. Public Health Service Postdoctoral Fellow at Harvard University 1952–1953. On leave of absence from the Weizmann Institute, Rehovoth, Israel.

(2) E. D. Bergmann, R. Pappo and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950).

latter may be readily converted to the former. Conformational analysis of the *trans*-glycol requires the arrangement: 2-phenyl (e), 2-hydroxyl (p), 1-hydroxyl (p) while in the *cis*-glycol the following arrangement obtains: 2-phenyl (e), 2-hydroxyl (p), 1-hydroxyl (e). It is implied in the work of Beckett, Pitzer and Spitzer[3] that the energy difference in similar systems between 2(p), (e) and (p), 2(e) is of the order of 1 kcal./mole. It has, indeed, been shown that the molar heat of combustion in the case of the *cis*-glycol is 1563.1 kcal. and that of the *trans*-glycol, 1564 kcal.[4]

A novel method has recently been employed by Woodward for the synthesis of *cis*-glycols[5] based upon Winstein's work on neighboring group effects.[6] The method involves the *trans* addition of iodine to a double bond followed by attack by silver acetate to give the *trans*-iodoacetoxy compound. The presence of water in the acetic acid used as solvent leads to the formation of the *cis*-glycol monoacetate. Finally, saponification leads to the *cis*-glycol.

When applied to 1-(2,3-dimethoxyphenyl)-cyclohexene, this method led to the same glycol obtained by the standard hydroxylation procedures. That the stable conformation in this case is, indeed, the *cis*-glycol was shown by the preparation of an acetonide using anhydrous copper sulfate as catalyst. Acetonide formation proceeds at a slow rate because one of the hydroxyl groups is tertiary, but is practically complete within 96 hours. Although cases of *trans*-glycols forming acetonides are known when mineral acid is used as catalyst[7] due to prior rearrangement to the *cis*-glycol, no such cases have been reported when copper sulfate is used as catalyst.

Experimental

cis-2-(2,3-Dimethoxyphenyl)-cyclohexane-1,2-diol.—1-(2,3-Dimethoxyphenyl)-cyclohexene (4.77 g.) was dissolved in analytical glacial acetic acid (100 ml.) in a three-necked flask equipped with stirrer, reflux condenser and thermometer. Silver acetate (8.22 g.) was added followed by finely powdered iodine (5.85 g.) in small portions to the vigorously stirred reaction mixture over a period of 30 minutes at room temperature. During this time the temperature rose from 26 to 33°. When all the iodine had been absorbed, as indicated by the color of the mixture, aqueous acetic acid (9.85 ml. prepared by dilution of 2.0 ml. of water up to 50 ml. with glacial acetic acid) was added and the reaction mixture was heated in a boiling water-bath with vigorous stirring for 3 hours. After cooling, sodium chloride (20 g.) was added, the mixture was stirred for 30 minutes more and the insoluble precipitate was removed by filtration. The precipitate was washed with hot benzene and the combined filtrate was evaporated under reduced pressure. The residue was treated with methanol, filtered to remove a small amount of insoluble material, and to the filtrate was added a solution of potassium hydroxide (2 g.) in methanol (10 ml.). After hydrolysis had proceeded overnight, the methanol was removed under reduced pressure, water was added and the mixture was extracted with ether. Removal of the solvent and trituration of the residue with methylcyclohexane yielded 3.2 g. (56%) of *cis*-2-(2,3-dimethoxyphenyl)-cyclohexane-1,2-diol, m.p. 104–105°, identical with the product described by Bergmann, *et al.*[2]

2-(2,3-Dimethoxyphenyl)-cyclohexane-1,2-diol Acetonide.—The glycol (2 g.) was dissolved in acetone (200 ml., distilled from anhydrous potassium carbonate) and was shaken mechanically with anhydrous copper sulfate (10 g.) for 96 hours. After filtration and evaporation of the solvent under reduced pressure, the residue was dissolved in chloroform and chromatographed over alumina. The acetonide (2.1 g.) passed through the column readily and any glycol still present remained in the column. The analytical sample of the oily acetonide was prepared by heating the material in a high vacuum at 70° for 24 hours.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.10; H, 8.16.

In the infrared spectrum, the hydroxyl band present in the glycol at 2.86 μ, was completely absent. A strong band at 9.68 μ and a band of medium intensity at 11.35 μ were present.[8]

(3) C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

(4) P. E. Verkade, *et al.*, *Ann.*, **467**, 217 (1928).

(5) We are indebted to Dr. R. B. Woodward for making this information available to us and for kindly assenting to its disclosure prior to his own publication of the details of the method.

(6) *Cf.* S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2787 (1942).

(7) *Cf.* A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 981 (1940); *C. A.*, **35**, 3603 (1941).

(8) For the position of the ether bands in the infrared *spectra* of acetonides, see R. B. Woodward, *et al.*, THIS JOURNAL, **74**, 4241 (1952).

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASS.

Reaction of Some Metallic Oxides with Liquid Dinitrogen Tetroxide. Oxides of the First and Second Periodic Groups and Lead[1]

BY JOHN R. FERRARO AND GEORGE GIBSON

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This is the first of a planned series of studies being undertaken at this Laboratory on the reaction of liquid dinitrogen tetroxide with various oxides. Other workers have studied reactions of the oxides CaO,[2] CuO and Cu_2O,[3,4] PbO,[4] HgO[4] and ZnO,[5] with gaseous or liquid N_2O_3 or N_2O_4. The oxides studied in this series are listed in Table I.

Experimental

Materials.—Pb_3O_4, PbO_2, BaO_2, BaO (71% $Ba(OH)_2$), Cu_2O, HgO, Hg_2O and $Hg(NO_3)_2$ were reagent grade chemicals. PbO, ZnO, PbO and MgO were prepared by the thermal decomposition of the respective carbonates and CaO and SrO from their oxalates. Ag_2O and CuO were prepared by precipitation from solution with NaOH, followed by drying to the oxide. N_2O_4 (cylinder) was dried before use by passing through a P_2O_5 drying tower.

Analyses.—Dinitrogen tetroxide content (as NO_2) in the reaction products was determined by cerate oxidation, as previously described.[6] Copper and mercury determinations were done by standard electrolytic procedures. Calcium, cadmium, lead, zinc and magnesium were determined gravimetrically by ignition of the reaction product to the oxide. Water analyses were done by the standard Karl Fischer procedure.

Apparatus and Procedure.—The apparatus and experimental procedure have been described elsewhere.[6] The reactants were heated to 87° at 14.5 atm. NO_2 pressure except for $Ca(OH)_2$, HgO, Hg_2O and $Hg(NO_3)_2$ which reacted completely at 25° and 1.1 atm. NO_2 pressure. All transfers or operations on the products were carried out in a dry-box.

(1) Presented in part at the 122nd Meeting of the American Chemical Society, September, 1952.

(2) M. Ostwald, *Ann. chim.*, (IX) 1, 32 (1914); J. R. Partington and F. A. Williams, *J. Chem. Soc.*, **125**, 947 (1924); E. Briner, J. P. Lugrin and R. Monnier, *Helv. Chim. Acta*, **13**, 64 (1930).

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(5) C. C. Addison, J. Lewis and R. Thompson, *J. Chem. Soc.*, 2829, 2838 (1951); C. C. Addison and J. Lewis, *ibid.*, 2833 (1951).

(6) G. Gibson and J. J. Katz, THIS JOURNAL, **73**, 5436 (1951).

TABLE I

REACTION OF OXIDES WITH LIQUID N_2O_4

Oxide	Reaction time, hr.	Oxide reacted, %	NO_2 in product, %	Metal(II) cation in product, %
PbO	7	84	Nil[a]	
Pb_3O_4	9	86[b]	Nil	
PbO_2	7	97	Nil	
Ag_2O	11	100	2.06	
ZnO	6.5	100	37.84[c]	19.14[c]
CdO	7	80	1.61	
MgO	6.5	90	26.84[c]	11.96[c]
CaO	6	50	0.81	
$Ca(OH)_2$[d]	350 days[e]	100	Nil	
SrO	14.5	0	0.22	
BaO_2	8	25	.13	
BaO[f]	14.5	99	.24	
CuO	14.5	85	31.94[c]	22.95[c]
Cu_2O	7.5	100	32.03	22.43
HgO	400 days[e]	100	19.53	47.95
Hg_2O	16 days[e]	100	16.87	

[a] Nil = 0.1% or less by weight of NO_2. [b] Residual oxide Pb_3O_4 by X-ray diffraction pattern. [c] Corrected for unreacted oxide in product. [d] $Ca(NO_3)_2 \cdot H_2O$ isolated: Found: H_2O, 9.52. Theory: H_2O, 9.88. [e] Time (in days), indicates the time the oxide remained in contact with N_2O_4 prior to analysis rather than the time for actual reaction. Observable reaction occurred in these cases in from 4 to 48 hours. [f] 71% $Ba(OH)_2$.

Results and Discussion

The data in Table I are representative of several experiments for each of the listed oxides, prepared at low temperatures. Confirming previous observations,[4,6] the oxides prepared at higher temperatures were much less reactive.

The catalytic effect of water on oxide–liquid N_2O_4 reactions is illustrated by the data for $Ca(OH)_2$ and BaO (71% $Ba(OH)_2$).

The products were either the corresponding anhydrous nitrates or the NO_2 addition compounds of the following analytical composition: $Mg(NO_3)_2 \cdot NO_2$, $Zn(NO_3)_2 \cdot 2.6$ to 3.3 NO_2, $Cu(NO_3)_2 \cdot 2NO_2$ and $Hg(NO_3)_2 \cdot 2NO_2$. These addition compounds were decomposed to the anhydrous nitrates at 10^{-5} mm. and at temperatures ranging from 90 to 140°, depending upon the thermal stability of the particular compound. The preparation of $Mg(NO_3)_2$ was not particularly successful due, we believe, to a concurrent decomposition of the $Mg(NO_3)_2$.

Zinc oxide heated in the presence of liquid dinitrogen tetroxide gave as a product a light brown, viscous oil, which solidified completely to a light yellow, waxy solid in approximately eight hours. The same solid product was obtained with zinc oxide and liquid dinitrogen tetroxide at room temperature. We believe $Zn(NO_3)_2 \cdot 2.6$ to 3.3 NO_2 represents a mixture of $Zn(NO_3)_2 \cdot 2N_2O_4$ + $Zn(NO_3)_2$ isolated at 30° whereas Addison[5] obtained $Zn(NO_3)_2 \cdot 2N_2O_4$ at 15°. In this series of addition compounds, $Zn(NO_3)_2 \cdot 2N_2O_4$ is intermediate in thermal stability between $Cu(NO_3)_2 \cdot 2NO_2$ and $Hg(NO_3)_2 \cdot 2NO_2$.

The copper(I) oxide exhibited a rather unusual behavior toward liquid dinitrogen tetroxide. At room temperature there was no observable reaction other than a slight darkening of the oxide. At 87°, however, the solid product increased in bulk volume some tenfold over that of the original oxide, producing a jade green micro-crystalline solid. In all of these experiments a considerable excess of dinitrogen tetroxide liquid was present after reaction, but in the case of the copper(I) reaction, only about 0.5 ml. of the 20 to 30 mole excess was observed as free liquid. Apparently the reaction product has the ability to absorb a large quantity of the excess dinitrogen tetroxide present; however, no reduction in the bulk volume of the solid product was observed when the excess liquid dinitrogen tetroxide was pumped off. It is interesting to note that the reaction product of copper(II) oxide did not exhibit this property.

Mercury(I) and (II) oxides and anhydrous mercury(II) nitrate reacted with the liquid dinitrogen tetroxide to produce brown viscous oils which were immiscible in the solvent. The oily product could be frozen with liquid nitrogen to a yellow glass-like solid having a conchoidal fracture. The softening point of this material was slightly below the freezing point of liquid dinitrogen tetroxide. $Hg(NO_3)_2 \cdot 2NO_2$ remained as an oil at 25 to 30° in a nitrogen dioxide gas atmosphere of 750 mm., but lost NO_2 very rapidly below this pressure at 30°, yielding a pale yellow solid having a composition approximating $Hg(NO_3)_2 \cdot 0.7NO_2$. This latter product when heated gave mercury(II) nitrate. The reaction of anhydrous mercury(II) nitrate with liquid dinitrogen tetroxide was carried out for the purpose of confirming the composition of the oily product obtained for the oxides. $Hg(NO_3)_2 \cdot 2NO_2$ is the most unstable of these nitrogen dioxide-containing compounds investigated to date. $Hg(NO_3)_2 \cdot 2NO_2$ may be the same compound reported by Boh[4] as his unidentified product obtained from the reaction of mercury(II) oxide and dinitrogen trioxide.

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DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILLINOIS

Divergent Electrophoretic Properties of Dissolved and Adsorbed Trypsin

BY ROBERTA S. HARTMAN, J. B. BATEMAN AND H. E. EDELHOCH

RECEIVED JULY 20, 1953

There is good experimental evidence that the electrophoretic mobilities of inert particles suspended in a protein solution (microscope method) are often not greatly different from the mobility of the dissolved protein, as determined by the moving boundary method under comparable conditions of *p*H, ionic strength, etc.[1] However, large differences have been noted with several proteolytic

(1) L. S. Moyer, *J. Biol. Chem.*, **122**, 641 (1938); H. A. Abramson, L. S. Moyer and M. H. Gorin, "Electrophoresis of Proteins," Reinhold Publ. Corp., New York, N. Y., 1942.

enzymes. In the case of pepsin, Herriott, Desreux and Northrop[2] found this result "to be due to the effect of decomposition products on the measurement" made by the microscope method.

The experiments to be described here are concerned with the cause of such differences in the case of trypsin. Northrop and Kunitz[3] found the isoelectric point of collodion particles suspended in a solution of trypsin to be "approximately 7 in 0.02 *M* phosphate buffer and approximately 6 in 0.02 *M* acetate buffer." Bier and Nord[4] gave the isoelectric point (pI) as 10.8 for solutions of this enzyme in 0.04 *M* glycine buffer with added $CaCl_2$, 0.03 *M*. They also reported the presence in such solutions of an enzymatically inactive component of low mobility at *p*H 7.5, which consists, in their view, of "inhomogeneous low molecular weight trypsin-split products." They suggest that the results of Northrop and Kunitz "might well be due to interference of trypsin-split products." It seemed worthwhile, as part of a more extended investigation of the electrophoresis of dissolved and adsorbed proteins, to see whether the apparent change in the pI of trypsin when adsorbed could be attributed to selective adsorption of Bier and Nord's inactive component.

Experimental

We were able to show, using an experimental arrangement described elsewhere,[5] that the pI of Pyrex particles suspended in a solution of trypsin[6] in 0.02 *M* phosphate buffer at 25° was about 7, as reported by Northrop and Kunitz. In 0.02 *M* acetate buffer the mobility remained positive even when the *p*H was increased to 6.7. This latter finding, in which our results are at variance with those of Northrop and Kunitz, was not investigated further.

For purposes of comparison with the moving boundary data of Bier and Nord, mobility measurements were made using Pyrex particles suspended in trypsin solutions in Michaelis buffer[7] with added $CaCl_2$, 0.03 *M*.[8] These results, together with the moving boundary mobility values for the inactive component obtained by Bier and Nord and in our laboratory, are reported in Fig. 1. The moving boundary data for the active component are not included, but the results of our experiment were in accord with those of Bier and Nord.

In addition to the experiments reported in Fig. 1, measurements were made at *p*H 12.5 with a Pyrex–trypsin system in 0.04 *M* glycine–NaOH buffer with added $CaCl_2$, 0.03 *M*. The average mobility, measured at 6° and converted to 0°, was -4.6×10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$; Bier and Nord found -4.85×10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$ for the inactive component in a moving boundary system under otherwise similar conditions.

As this inactive material, according to moving boundary analysis, comprised only about 8% of the total at *p*H 7.4 (and therefore probably considerably less at lower *p*H values), an attempt was made to remove it from a trypsin solution in acidified water (*p*H 2–3) by contact with an excess of Pyrex particles. When as much as 65% of the ultraviolet absorbing material had been so removed from solution, fresh Pyrex particles suspended in the treated trypsin solution after adjustment to *p*H 8.6 had about the same velocity of migration in the negative direction as particles suspended in a fresh solution of trypsin under the same conditions. On the other hand, active material would have migrated with a large velocity in the positive direction at this *p*H. In another experiment it was found that the loss of 40% of the material coincided with the disappearance of 40% of the enzymatic activity from the solution. The lost activity was not associated with the centrifuged Pyrex particles, which showed only a small degree of activity corresponding to the amount of interstitial solution.

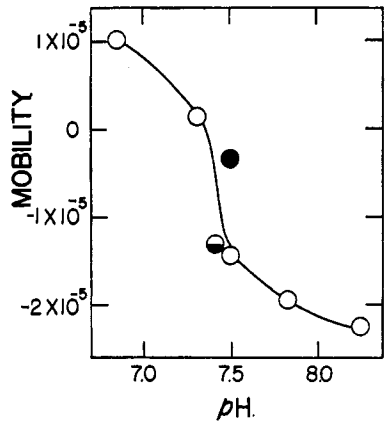

Fig. 1.—Electrophoretic mobilities of components of trypsin and of solid particles immersed in solutions of trypsin; open circles, Pyrex particles immersed in trypsin solutions; Michaelis buffer[7] with added $CaCl_2$, 0.03 *M*; half shaded circle, secondary component in trypsin solutions, moving boundary measurement in same buffer as above; solid circle, data of Bier and Nord[4] for secondary (inactive) component in trypsin solutions, moving boundary measurement in "0.04 *M* barbiturate, 0.03 *M* $CaCl_2$." Measurements by microscope method were made at 6° and converted to 0°; mobility unit: cm.^{2} volt^{-1} sec.$^{-1}$. The moving boundary measurements were made by J. H. Convey of this laboratory.

Discussion

It seems evident that there is an inactive form of trypsin, or an inactive decomposition product, differing electrophoretically from the active enzyme, which is formed at the solid–aqueous solution interface in quantities related to the interfacial area presented. No evidence as to the reversibility of the reaction has been obtained. The coincidence between the mobilities of the coated Pyrex particles and the values given by Bier and Nord for an inactive component suggests that we may be dealing with a single substance, produced relatively slowly in solution, but at an increased rate at the solid–liquid interface.

The results presented here show that considerable restraint should be exercised in interpreting apparent changes in the electrokinetic properties of substances when adsorbed. Unwarranted conclusions may be drawn unless adequate study has been devoted to the possible preferential adsorption of contaminants.

BIOLOGICAL LABORATORIES, CAMP DETRICK
FREDERICK, MD.

(2) R. M. Herriott, V. Desreux and J. H. Northrop, *J. Gen. Physiol.*, **23**, 439 (1940).

(3) J. H. Northrop and M. Kunitz, *ibid.*, **16**, 295 (1932).

(4) M. Bier and F. F. Nord, *Arch. Biochem. Biophys.*, **33**, 320 (1951).

(5) R. S. Hartman, J. B. Bateman and M. A. Lauffer, *ibid.*, **39**, 56 (1952).

(6) Crystalline trypsin was purchased from the Worthington Biochemical Laboratory, Freehold, N. J. The specific enzyme activity of this sample was 3.3 ± 0.1 [T.U.][cas] per γ, assayed by the optical density method of Kunitz, *J. Gen. Physiol.*, **30**, 291 (1947).

(7) L. Michaelis, *Biochem. Z.*, **234**, 139 (1931).

(8) Bier and Nord refer to the paper by Michaelis[7] in describing the buffer used, but it is not clear whether this buffer had the exact composition given by Michaelis (0.0268 *M* acetate, 0.0286 *M* sodium diethylbarbiturate and 0.0114 *M* NaCl, before adjustment with HCl). Tables IV and V describe the buffer as "0.04 *M* barbiturate."

Doubling of Fluorinated Chains

BY ALBERT L. HENNE

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When a molecule of $CF_3CF_2CF_2I$ is treated with zinc in acetic anhydride, a very vigorous reaction takes place at once, resulting in a doubling of the chain length with formation of normal C_6F_{14} in excellent yield. For efficient results, operation at a controlled low temperature is essential, easily accomplished by running the reaction in refluxing methylene chloride. The unused iodide is recovered in the methylene chloride fraction, which can be used in the next run after computation of its composition from its index of refraction.

A molecule of $C_3F_3Cl_4Br$[1] is doubled to $C_6F_6Cl_8$ with equal facility. Conversely, CH_3CF_2Cl and $CHCl_2CF_2CF_2Cl$ react in exceedingly poor yield, $CCl_3CF_2CCl_2CCl_3$ undergoes customary dechlorination to $CCl_3CF_2CCl{=}CCl_2$, and propyl or butyl bromide fails to give any detectable octane. These results seem to indicate that the doubling of the chain length might depend on a terminal $-CF_2X$ or $-CFClX$ group, where X is bromine or iodine, at least for a fast, efficient reaction.

Miller's report[2] that highly fluorinated organozinc derivatives were obtainable in dioxane solution, and his private remarks that they were very sensitive to protonic hydrogen, yet did not seem to condense well with carbonyl compounds prompted a search for a solvent which would not cause reduction and side reactions, as do the conventional alcohols, or delay reaction inconveniently, as does ether. All the experimental results were obtained by my collaborators, as named.

Experimental

A. Synthesis of C_6F_{14} (Robert Brown).—C_3F_7I (40 g. or 0.135 mole), granular zinc (9.3 g. or 0.142 mole), acetic anhydride (28 g. or 0.28 mole) and methylene chloride (67 g. or 50 ml.) were mixed in a 300-ml. flask provided with a sealed stirrer and a water cooled reflux condenser trailed by two Dry Ice traps. Stirring at room temperature caused only a slight cloudiness, but with external heating applied to cause refluxing at 40–45°, a white precipitate began to form; in 24 hours the precipitate was so thick that it interfered with stirring, and the reaction was worked up.

While cooling in an ice-bath, water (20 ml.) was added dropwise. It dissolved the precipitate and caused the formation of three layers. There was no gas evolved; the empty Dry Ice trap showed that $CF_3CF{=}CF_2$ had not been formed during the zinc attack, nor $CF_3CF_2CF_2H$ during the hydrolysis. The top layer (81 g.) contained acetic acid, water, acetic anhydride and zinc iodide; the middle layer (54 g.) was methylene chloride with about 4% of unused iodide; the bottom layer (17 g.) was the doubled up molecule, C_6F_{14}, quite pure. As 5.5 g. of zinc was recovered, the aggregate weights show a loss of 6.6 g. of material, attributed to mechanical handling and inexperience. There was no indication of a ketonic material which would have resulted from action of the organometallic on the solvent.

The top and middle layers were returned to the flask and neutralized with sodium carbonate. The organic layer was drained from the aqueous layer, and proved to be a clean mixture of methylene chloride with 4% of unused iodide.

The bottom layer was dried on sodium sulfate and distilled; it came over entirely at 57°, the correct boiling point for C_6F_{14}. The refractive index (1.25) was too low to be read on the available instrument; the density was found to be 1.6707 at 25° (lit. 1.6995 at 20°).

The conversion from the iodide was 74%, and as 3.4% of iodide was recovered, the net yield was 77%. A computation based on the amount of zinc consumed shows that an additional 12% might have been formed and lost.

B. Synthesis of $C_6F_6Cl_8$ (Dorothy Kraus).—$C_3F_3Cl_4Br$ (205 g. or 0.65 mole), obtained by addition of CCl_3Br to $CF_2{=}CFCl$, see ref. 1, granulated zinc (42 g.), a volume of acetic anhydride equal to that of $C_3F_3Cl_4Br$ and another volume of methylene chloride were placed together and stirred under reflux. The reaction started spontaneously and was held under control at 40–45° by external cooling; this shows that much more anhydride and methylene chloride should have been used, as in A. White salt came out progressively and the mixture remained clean and only light yellow, but when the solid accumulated, control of the temperature became inadequate, and the mixture was quenched before deterioration set in appreciably.

The working up recovered 31 g. (0.1 mole) of starting material, and 60 g. of a solid, m.p. 39–39.5°, which contained 24.1% F and 59.6% Cl (analysis by Mary Renoll); the correct values for $C_6F_6Cl_8$ are 24.2% F and 60.4% Cl. As the solid represents 0.13 mole, a 40% conversion was obtained or a 55% yield when the recovered material is taken into count.

C. Synthesis of $CCl_3CF_2CCl{=}CCl_2$ (Mary Renoll).—Crude $CCl_3CF_2C_2Cl_5$ (32 g. or 0.09 mole) was dissolved in chloroform (30 ml.) and dripped into a flask containing mossy zinc (5.85 g. or 0.09 mole) covered with acetic anhydride (75 ml.). The reaction started promptly and raised the temperature to 45–50°, where it was kept by control of the rate of addition and stirring. Addition took an hour, after which the mixture was stirred at 45–50° for another 40 minutes. The mixture remained clean, pale yellow and the salt which came down was not gummy; this is in marked contrast with the amount of resinification, decomposition and difficulty in handling which occur with other solvents.[3] After pouring into ice-water and adding 50 ml. of chloroform, the two layer mixture was kept overnight at 4° for good decantation, and recovery of 2.4 g. of zinc. This indicated that 58% of the zinc had been used. From the bottom layer, distillation separated chloroform, 12 g. of the olefin $C_4F_2Cl_6$ and 12 g. of the original paraffin $C_4F_2Cl_8$. There was no still residue. The conversion to the olefin was 45%, or after deducing recovered material, a 76% yield. There was no doubling up.

This dechlorination is to be contrasted with the difficulties reported by Newby,[3] whose maximum yields were 30% in ethanol and 10–15% in dioxane, with resinification of the balance of his material. The observed properties, b.p. 85–86° at 10 mm., d_4 1.7842 and n_D 1.5052 at 20°, MR 49.69 and AR_F 1.24 agree well with Newby's who found: m.p. −6.0 to −6.8°, b.p. 212° at 745 mm., d_4 1.7803 and n_D 1.5029 at 25°, MR 49.64 and AR_F 0.97. The last figure is miscalculated and should be 1.2, in good agreement.

D. Attempted Synthesis of *n*-Octane (John Gordon).—Butyl bromide (28 g. or 0.2 mole), granular zinc (13.1 g. or 0.2 mole), acetic anhydride (27.6 g. or 0.3 mole) with an equal volume of Skellysolve F (b.p. 35–60°) were stirred at 65° for 4 days. After that period, 12.2 g. of zinc was recovered unused, showing that practically no reaction had occurred. The working up recovered 3 g. of material b.p. 65–100° (a mixture of solvent and bromide), then 15 g. of butyl bromide, and there was less than 1 g. of a black residue. There was no indication of octane, and about 40% of the starting material was lost by decomposition.

(1) A. L. Henne and D. W. Kraus, THIS JOURNAL, **73**, 1791 (1951). Also Dorothy W. Kraus, Ph.D. dissertation, The Ohio State University, 1953.

(2) W. T. Miller, Atlantic City Meeting, September, 1952.

(3) Thomas Newby, Master's Thesis, Ohio State University, 1944, also A. L. Henne and Thos. Newby, THIS JOURNAL, **70**, 130 (1948).

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO

Ionization Constant of Fluorinated Acids. II

BY ALBERT L. HENNE AND CHARLES J. FOX

RECEIVED JULY 6, 1953

The fact that butyric acid is a little more highly ionized than its lower homolog ($K_A \times 10^{-5}$ being 1.51 and 1.34, respectively) is sometimes explained[1]

(1) J. F. Dippy, *J. Chem. Soc.*, 1122 (1938).

by ability to form a six-membered ring involving hydrogen bonding, such as $CH_2—CH_2—CH_2—C—OH$ (with H ⟵ O), and the same explanation applies to isovaleric acid (1.67) and diethyl acetic acid (1.77). These differences of acidity are quite small, and it occurred to us that the effect would be magnified in the $CF_3(CH_2)_nCO_2H$ series. We have previously reported[2] K_A for n = 0, 1 and 2. Assuming that the induction of the CF_3 group on the acid function falls substantially as the square of the distance, K_A for trifluorovaleric acid should not differ appreciably from K_A for unfluorinated valeric acid. Computations by various procedures,[3,4] give a probable value of 1.7, certainly not higher than 2. If, however, ring formation should take place, such as $CF_3—CH—CH_2—CH_2—C—OH$ (with H ⟵ O), the observed K_A should be appreciably higher than 1.7, since the hydrogen atoms on the carbon adjacent to the CF_3 group are quite acidic.

Trifluorovaleric acid, $CF_3(CH_2)_3CO_2H$, was synthesized, and from its *p*H at half neutralization, its K_A was found to be $3.2 \pm 0.03 \times 10^{-5}$, nearly twice as large as the extrapolated value of 1.7.

Experimental

1. **Preparation of $CF_3(CH_2)_3CH_2Cl$.**—$CCl_3(CH_2)_3CH_2Cl$ (210 g., 1 mole) in CCl_2=CClCCl=CCl_2 (200 ml.) is added by drops to a vigorously stirred slurry of SbF_3 (138 g., 0.77 mole) and SbF_3Cl_2 (220 g., 0.88 mole, total 65 mole % excess of fluorinating agent) in CCl_2=CClCCl=CCl_2 (30 ml.) cooled in an ice-bath. When addition is complete, more SbF_3Cl_2 (80 g., 0.3 mole) is added to promote fluorination of mono- and difluorinated products. Under these conditions of high SbF_3Cl_2 concentration and low temperature, the solvent C_4Cl_6 is left practically intact. After 2 hours the mixture is permitted to warm up and is stirred 4 hours at room temperature then hydrolyzed with HCl in ice and steam distilled. The distillate is washed with aqueous $NaHCO_3$, H_2O saturated NaCl and dried over $MgSO_4$. Distillation gives material (19 g.): b.p. 97–98°, $n^{29}D$ 1.3521, d^{29}_4 1.195; $CF_3(CH_2)_3CH_2Cl$ (11 g., 0.07 mole, 7%), b.p. 121°, $n^{27}D$ 1.3691, d^{27}_4 1.217, MR 29.6, AR_F 0.93; found, 32.40% F, 25.07% Cl; calcd., 35.6% F, 21.9% Cl, indicative of a contaminated sample; and material (27 g.), b.p. 150–152°, $n^{29}D$ 1.4070, d^{29}_4 1.264. The solvent and starting material are not readily separated. Similar reactions give identical products in the same relative amounts.

2. **Preparation of $CF_3(CH_2)_3CH_2OH$.**—Redistilled $CF_3(CH_2)_3CH_2Cl$ (43 g., 0.27 mole) in 150 ml. of dry ether is added to Mg (8 g., 0.3 mole) stirred in 150 ml. of dry ether. Reaction starts when several crystals of I_2 are added to the reaction, but not when $CF_3(CH_2)_3CH_2Cl$ (2 g.) is heated with Mg or when C_2H_5I (20 drops) is added to the reaction (although C_2H_5I reacts), and proceeds satisfactorily when heated slightly with formation of an orange precipitate. The suspension is siphoned into an addition funnel and added slowly to dry ether into which oxygen is bubbled while stirring and which is cooled in an acetone–Dry Ice-bath. When addition is complete, oxygen is slowly bubbled into the mixture for another eight hours; precipitation is voluminous. The suspension is hydrolyzed with dilute HCl and two clear layers form. The ether layer and ether extract of the aqueous layer are washed with saturated NaCl, dried over $MgSO_4$ and the ether is distilled. The residue is mixed with mercury to remove free iodine, filtered, and benzene is added and distilled to remove the water. Distillation of the residue gives crude $CF_3(CH_2)_3CH_2OH$ (18 g., 0.13 mole, 48% yield), b.p. 80–85° at 69 mm. which reacts slowly with Na but not with Lucas reagent. No further attempt at purification or identification is made, and the crude alcohol is directly oxidized to the acid.

3. **Preparation of $CF_3(CH_2)_3CO_2H$.**—$CF_3(CH_2)_3CH_2OH$ (18 g., 0.13 mole) is added by drops to a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (24 g., 0.08 mole) and 95% H_2SO_4 (15 ml., 0.34 mole) in 250 ml. H_2O stirred at 50° for 48 hours. Additional H_2SO_4 (50 ml.) is added to the cold mixture which is then continuously extracted with ether. Benzene is added to the extract and distilled to remove H_2O. Distillation under reduced pressure gives crude $CF_3(CH_2)_3CO_2H$ (11 g., 0.07 mole, 54% yield) b.p. 93–100° at 16 mm., neut. equiv., 163, which contains a small amount of H_2O insoluble material. Neutralization of an aqueous solution with NaOH and extraction with ether (3 times) removes about 0.5 g. of oil in the extract. The aqueous solution is acidified with H_2SO_4 (50 ml.), continuously extracted with ether and the extract is dried over $MgSO_4$; benzene is added and distilled to remove ether and water. Distillation under reduced pressure gives $CF_3(CH_2)_3CO_2H$ (9 g.), b.p. 93.8–95° at 15 mm.; cut b.p. 94.8–95.0° at 15 mm., has $n^{25}D$ 1.3632, d^{25}_4 1.293, MR 26.83, AR_F 1.10, neut. equiv., 155.3 (calcd. 156), found 36.9% F (calcd. 36.5%), qualitative test for Cl on fusion with Na is negative.

4. **Attempted Preparation of $CF_3(CH_2)_3CH_2OH$ from $CF_3CH_2CH_2Cl$.**—Reaction of $CF_3CH_2CH_2MgCl$ (1 mole) with ethylene oxide is carried out as described for the preparation of *n*-hexyl alcohol.[5] The reaction proceeds normally and the rearrangement occurs smoothly. However, after hydrolysis no material is isolated other than solid decomposition products. Direct oxidation with $Na_2Cr_2O_4$ and H_2SO_4 after hydrolysis also fails to give any product.

5. **Attempted Preparation of $CF_3(CH_2)_3CO_2C_2H_5$ from $CF_3CH_2CH_2Cl$.**—$CF_3CH_2CH_2Cl$ treated with $NaCH(CO_2C_2H_5)_2$ undergoes only dehydrohalogenation to CF_3CH=CH_2.

(2) A. L. Henne and C. J. Fox, THIS JOURNAL, **73**, 2323 (1951).

(3) D. A. MacInnes, *ibid.*, **50**, 2587 (1928).

(4) J. C. Greenstein, *ibid.*, **58**, 1314 (1936).

(5) "Organic Syntheses," Coll. Vol. I, 2d Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 306.

DEPARTMENT OF CHEMISTRY
OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

11-Oxygenated Steroids. VIII. The Synthesis of 16,17-Oxido-4-pregnen-11α-ol-3,20-one Acetate

BY HERSHEL L. HERZOG, CONSTANCE C. PAYNE, MARYANN E. TULLY AND E. B. HERSHBERG

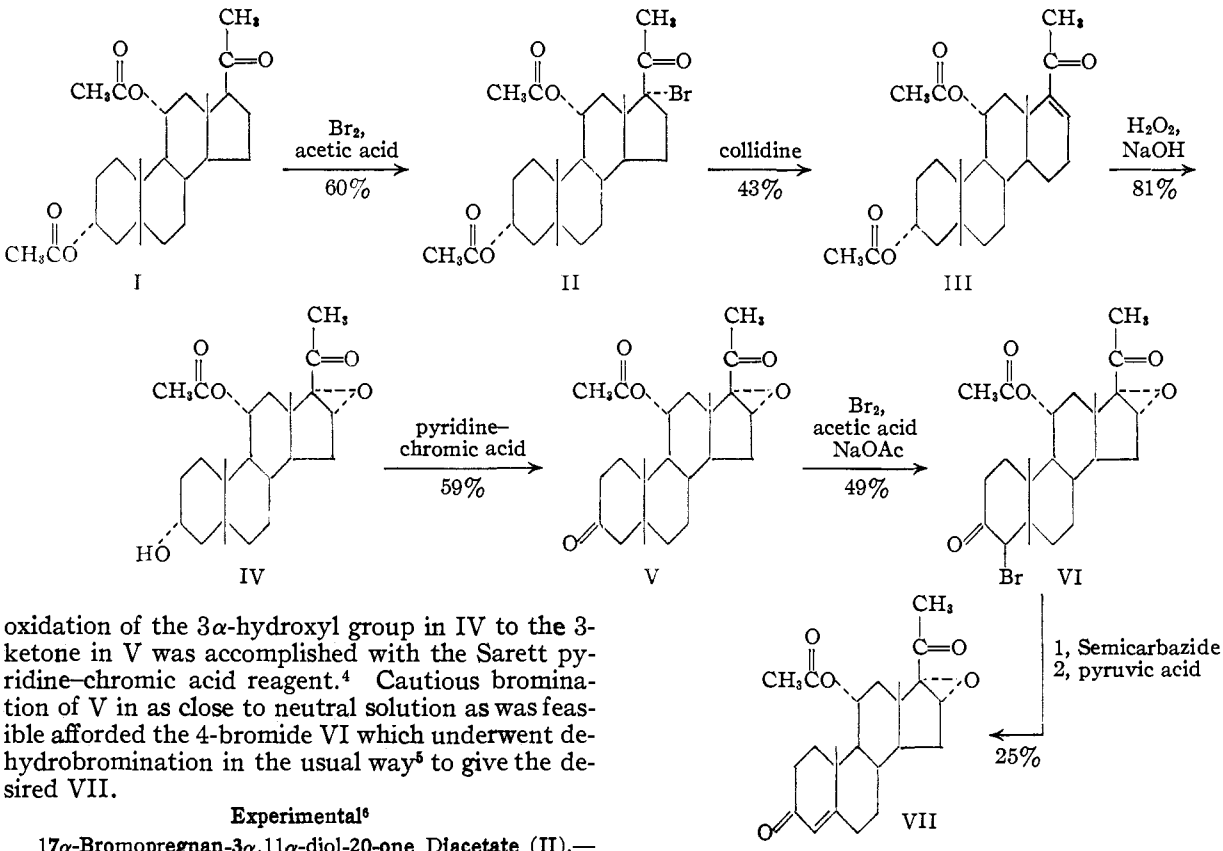
RECEIVED JUNE 12, 1953

In connection with other studies in this Laboratory 16,17-oxido-4-pregnen-11α-ol-3,20-one acetate (VII) was required. The synthesis was accomplished according to the following scheme. Pregnan-3α,11α-diol-20-one diacetate[1] (I) was brominated at the 17-position in acetic acid solution. The bromide II was dehydrobrominated by refluxing with collidine to yield 16-pregnen-3α,11α-diol-20-one diacetate (III). Epoxidation of III by the procedure of Julian[2] afforded the corresponding 16,17-epoxide IV from which the acetate group at 3-, but not at 11-, had been hydrolyzed.[3] The

(1) E. P. Oliveto, H. L. Herzog and E. B. Hershberg, THIS JOURNAL, **75**, 1505 (1953).

(2) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(3) Following the completion of this work, J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 1277 (1953), reported that potassium hydroxide could be employed to hydrolyze selectively the 3- and 21-acetate groups in allopregnan-3β,11α,17α,21-tetrol-20-one 3,11,21-triacetate. The same paper described the epoxidation of 16-allopregnen-3β,11α-diol-20-one diacetate with alkaline hydrogen peroxide; in this experiment no attempt was made to isolate 16,17-oxidoallopregnan-3β,11α-diol-20-one 11-acetate, the reaction mixture being subjected to vigorous alkaline hydrolysis prior to isolation of the product in order to remove any acetate groups which survived the initial reaction.



oxidation of the 3α-hydroxyl group in IV to the 3-ketone in V was accomplished with the Sarett pyridine–chromic acid reagent.[4] Cautious bromination of V in as close to neutral solution as was feasible afforded the 4-bromide VI which underwent dehydrobromination in the usual way[5] to give the desired VII.

Experimental[6]

17α-Bromopregnan-3α,11α-diol-20-one Diacetate (II).—To a solution of 20 g. of I in 500 ml. of glacial acetic acid and 14 drops of 0.28 *N* hydrogen bromide in glacial acetic acid was added dropwise with stirring at room temperature 2.6 ml. of bromine in 100 ml. of glacial acetic acid. The addition required two hours, and the mixture was then stirred an additional 15 minutes. Five volumes of water was then added and the resulting precipitate was collected by filtration. The filtrate was extracted with methylene chloride, and the extracts were washed free of acid and dried over magnesium sulfate. The residue from the concentration of the methylene chloride solution was combined with the precipitate previously isolated, and recrystallized from hexane. There was obtained 14.4 g. (60%) of II, m.p. 182–186° dec., which on further recrystallization melted at 185–187° dec., $[\alpha]^{25}D$ −48.1° (1% in chloroform).

Anal. Calcd. for $C_{25}H_{37}O_5Br$: Br, 16.06. Found: Br, 16.33.

16-Pregnen-3α,11α-diol-20-one Diacetate (III).—A mixture of 3.28 g. of II in 50 ml. of collidine was refluxed for 45 minutes. The reaction was then cooled, diluted with ether and filtered to remove the precipitated collidine hydrobromide. The filtrate was washed free of collidine with dilute sulfuric acid and then washed to neutrality with sodium carbonate and water. After the ethereal solution had been dried over magnesium sulfate it was concentrated to a small volume, hexane was added, and the resulting precipitate was removed by filtration. There was obtained 1.26 g. (43%) of III, m.p. 192–194.5°. Recrystallization from methylene chloride–hexane raised the m.p. to 198–200°, $[\alpha]^{25}D$ +25.8° (1% in chloroform), ϵ_{236} 9,200 (ethanol).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.39; H, 9.04.

16,17-Oxidopregnan-3α,11α-diol-20-one 11-Acetate (IV).—To a solution of 1.15 g. of III in 76 ml. of methanol at 15° was added 2.28 ml. of 4 *N* aqueous sodium hydroxide and 4.45 ml. of 30% hydrogen peroxide. The reaction mixture was stored at 5° for 40 hours. Initially a heavy precipitate of starting material formed which was almost completely in solution at the end of the reaction period. The reaction mixture was filtered and the filtrate was diluted with 325 ml. of water. The resulting solution was extracted with methylene chloride, and the extracts were washed well with water and dried. Concentration of the dried solution followed by addition of hexane gave a heavy, gelatinous precipitate which was filterable. The solid gave up the solvent upon drying at 60°, leaving 0.88 g. (81%) of IV, m.p. 191–193°. Recrystallization from methylene chloride–hexane raised the m.p. to 193–195°, $[\alpha]^{25}D$ +18.8° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.03; H, 8.97.

16,17-Oxidopregnan-11α-ol-3,20-dione Acetate (V).—A solution of 3.0 g. of IV in 30 ml. of pyridine was added slowly to a slurry of 1.5 g. of chromic acid in 15 ml. of pyridine and the resulting mixture was stirred overnight at room temperature. (Caution! In preparing the reagent the chromic acid must be added to the pyridine under controlled conditions.[4]) To the reaction was then added 4.5 g. of sodium sulfite in 45 ml. of water and stirring was continued for two hours. The reaction mixture was poured into 600 ml. of water and the resulting solution was extracted with methylene chloride. The extracts were washed neutral with dilute sulfuric acid, aqueous sodium carbonate and water, and dried over magnesium sulfate. Concentration of the dried solution followed by the addition of hexane resulted in the crystallization of 1.8 g. (59%) of V, m.p. 222–224°, $[\alpha]^{25}D$ +25.3° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.39; H, 8.52.

4-Bromo-16,17-oxidopregnan-11α-ol-3,20-dione Acetate (VI).—To a solution of 1.0 g. of V in 100 ml. of glacial acetic acid was added 1.0 ml. of 0.28 *N* hydrogen bromide in glacial acetic acid. Then there was added, dropwise with good agitation, a solution containing 412.5 mg. of bromine, 210 mg. of sodium acetate and 25 ml. of glacial acetic acid at such a rate that each drop had the opportunity to react

(4) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(5) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(6) Analyses and optical data were obtained by the Microanalytical and Physical Chemical Departments of these laboratories.

before another was added (time of addition, five hours). The reaction mixture was then poured into five volumes of water and the resulting precipitate was collected. Recrystallization from methylene chloride–hexane afforded 0.69 g. (49%) of VI, m.p. 186–188° dec. (with recrystallization at 115–120°), $[\alpha]^{25}D$ +44° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{31}O_5Br$: Br, 17.09. Found: Br, 17.04.

16,17-Oxido-4-pregnen-11α-ol-3,20-dione Acetate (VII).—To a solution of 0.5 g. of VI in 50 ml. of glacial acetic acid was added, under an atmosphere of carbon dioxide, a solution containing 272 mg. of semicarbazide hydrochloride, 195 mg. of anhydrous sodium acetate, 10 ml. of water and 10 ml. of glacial acetic acid. The mixture was agitated for ten minutes and there was then added 20 ml. of 1 *N* sodium acetate in glacial acetic acid. Agitation was continued for ten minutes longer, 2 ml. of pyruvic acid was added, and the mixture was refluxed for ten minutes. The cooled solution was diluted with water and extracted with methylene chloride. The extracts were washed free of acid with water, dried over magnesium sulfate and concentrated to a small volume. Hexane was then added to the point of opalescence and the solution was chromatographed on 20 g. of Florisil prepared with hexane. Elution with hexane and mixtures of hexane and ether stripped nothing from the column. From elution with ether there resulted five 50 ml. fractions containing a total of 0.103 g. (25%) of VII, m.p. 212–214°. Recrystallization from methylene chloride–hexane raised the m.p. to 217–218°, $[\alpha]^{25}D$ +112.9° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.55; H, 8.00.

CHEMICAL RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

The Preparation of 2-C^{14}-Adenine

BY A. R. P. PATERSON AND S. H. ZBARSKY

RECEIVED JUNE 25, 1953

As a preliminary to a study of the metabolism of the purines, with especial reference to the 2-position of the ring, the synthesis of adenine labeled in the 2-position with C^{14} was undertaken. The method described by Shaw,[1] in which 4-amino-5-imidazolecarboxamidine is formylated and the product cyclized to give adenine, appeared to be suitable since by using C^{14}-formic acid for the formylation 2-labeled adenine would be obtained. An advantage of this method is that the isotope would be introduced at a late step in the synthesis, thereby minimizing losses of radioactive material. The undesirable feature of the method, however, as far as economy of radioactive material is concerned, is that the formylation is carried out with a large excess of 98% formic acid in the presence of acetic anhydride. This would necessitate the use of an inordinately large amount of C^{14}-formate in order to obtain adenine with appreciable radioactivity.

In order to avoid the use of such a large excess of formic acid, experiments were carried out to study the feasibility of formylating the carboxamidine with an aqueous solution of formic acid, since such conditions have been used to formylate other amines.[2,3] The formylation reaction was found to proceed in 6 *M* formic acid, and by using this modification it was possible to obtain 2-C^{14}-adenine in yields of 60–65%, based on the carboxamidine used. The unreacted C^{14}-formate can be recovered almost quantitatively and used for further preparations of labeled adenine.

Method.—A solution of 0.200 g. of 4-amino-5-imidazolecarboxamidine dihydrochloride[1] in 2.0 ml. of 20% formic acid was placed in a reaction tube made from the outer member of a 24/40 standard taper joint. To this solution was added 0.170 g. of potassium formate, making the solution 6.3 *M* with respect to formate. The solution was then boiled gently under reflux for 4 hours. The formamido derivative was not isolated but was cyclized to adenine by diluting the solution to 8 ml. with water, adding sufficient potassium bicarbonate to neutralize the formic acid and to make the solution 0.5 *M* in bicarbonate, and then boiling under reflux for 1 hour. An amount of hydrochloric acid slightly less than that required to neutralize the solution was added, and the solution was concentrated under reduced pressure to a volume of 2–3 ml. On placing the solution in the refrigerator for several hours crude adenine precipitated. This material was collected by centrifugation, washed 3 times with ice-cold water and dried *in vacuo*. The supernatant and wash liquids were saved for the recovery of unreacted formate. The crude material was sublimed at 220° and a pressure of 1 mm. to give 0.083 g. of pure adenine, a yield of 61% based on the carboxamidine. Yields of 40–42% were obtained when the formylation was carried out with 4.0 *M* formic acid.

Anal. Calcd. for $C_5H_5N_5$: C, 44.44. Found: C, 44.27.

The compound formed a picrate which melted with decomposition at 286–287°.[1] Admixture with picrate prepared from authentic adenine did not depress the m.p. The ultraviolet absorption spectrum and R_f values obtained by paper chromatography[4] were identical with those of authentic adenine.

2-C^{14}-Adenine was prepared by using C^{14}-potassium formate in the above procedure. In a typical experiment, adenine having a specific activity of 1.055×10^6 c.p.m. per m*M* was synthesized and the formate recovered from the reaction mixture had a specific activity of 1.025×10^6 c.p.m. per m*M*.

The unreacted C^{14}-formate in the supernatant fluid and washings after separation of the crude adenine was recovered almost quantitatively by steam distillation.[5] For further use in preparing radioactive adenine, the steam distillate was titrated with standard potassium hydroxide solution and concentrated to small volume under reduced pressure. The concentrate was then transferred to the reaction tube and evaporated to dryness. The appropriate amount of 4-amino-5-imidazolecarboxamidine dihydrochloride was added, followed by hydrochloric acid equivalent to the formate present less the amount of hydrochloric acid present as the dihydrochloride salt. The procedure outlined above was then followed for the remainder of the synthesis.

Acknowledgment.—This work was supported by grants from the National Research Council of Canada.

(1) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950).
(2) V. M. Clark and H. M. Kalckar, *J. Chem. Soc.*, 1029 (1950).
(3) R. Abrams and L. Clark, THIS JOURNAL, **73**, 4609 (1951).
(4) J. D. Smith and R. Markham, *Biochem. J.*, **46**, 509 (1950).
(5) S. Weinhouse and B. Friedmann, *J. Biol. Chem.*, **197**, 733 (1952).

DEPARTMENT OF BIOCHEMISTRY
FACULTY OF MEDICINE
THE UNIVERSITY OF BRITISH COLUMBIA
VANCOUVER 8, BRITISH COLUMBIA, CANADA

The Tetrachlorophthalic Anhydride Derivatives of Some Alkylbenzenes

BY GEORGE F. LEWENZ[1a] AND KASPER T. SERIJAN[1b]

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In a previous note[2] the authors reported the phthalic anhydride derivatives of several substituted alkylbenzenes. In general these derivatives distinguish satisfactorily among the alkylbenzene hydrocarbons. However, it is not possible by

(1) Present addresses: (a) The Texas Co., Beacon, N. Y.; (b) Armour and Co., Chicago, Ill.
(2) G. F. Lewenz and K. T. Serijan, THIS JOURNAL, **75**, 4087 (1953).

TABLE I

THE *o*-AROYLTETRACHLOROBENZOIC ACID DERIVATIVES OF BENZENE AND VARIOUS MONO-, DI- AND TRIALKYLBENZENES

o-Aroyltetrachlorobenzoic acid	Molecular formula	Neut. equiv. Calcd.	Neut. equiv. Found	Chlorine, % Calcd.	Chlorine, % Found	Melting point, °C. Observed	Melting point, °C. Literature
Benzene	$C_{14}H_6O_3Cl_4$	364	362	38.96	38.91	[c]	200[a]
Toluene	$C_{15}H_8O_3Cl_4$	378	388	37.51	37.79	174.9–175.8	174.5[b]
Ethylbenzene	$C_{16}H_{10}O_3Cl_4$	392	400	36.17	36.55	176.3–177.1	172–173[g]
1,2-Dimethylbenzene	$C_{16}H_{10}O_3Cl_4$	392	391	36.17	36.31	182.3–182.8	177.5–178.5[g]
1,3-Dimethylbenzene	$C_{16}H_{10}O_3Cl_4$	392	386	36.17	36.38	231.1–231.7	222–224[g]
1,4-Dimethylbenzene	$C_{16}H_{10}O_3Cl_4$	392	392	36.17	36.40	245.2–247.2	244–246[g]
n-Propylbenzene	$C_{17}H_{12}O_3Cl_4$	406	415	34.92	34.76	159.2–160.0	
i-Propylbenzene	$C_{17}H_{12}O_3Cl_4$	406	394	34.92	34.71	187.9–189.0	
1,2,3-Trimethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	396	34.92	34.58	208.6–209.8	
1,3,5-Trimethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	412	34.92	34.65	233.3–233.8	
1,2,4-Trimethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	395	34.92	34.60	[d]	
1-Methyl-2-ethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	413	34.92	34.69	173.0–173.9	
1-Methyl-3-ethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	405	34.92	34.60	168.8–170.1	
1-Methyl-4-ethylbenzene	$C_{17}H_{12}O_3Cl_4$	406	405	34.92	34.59	170.4–171.6	
1,2-Diethylbenzene	$C_{18}H_{14}O_3Cl_4$	420	414	33.76	33.50	164.5–165.7	
1,3-Diethylbenzene	$C_{18}H_{14}O_3Cl_4$	420	415	33.76	33.92	[e]	
1,4-Diethylbenzene	$C_{18}H_{14}O_3Cl_4$	420	404	33.76	33.57	147.0–148.9	
n-Butylbenzene	$C_{18}H_{14}O_3Cl_4$	420	420	33.76	33.16	146.5–147.5	
s-Butylbenzene	$C_{18}H_{14}O_3Cl_4$	420	412	33.76	33.11	165.3–167.0	
i-Butylbenzene	$C_{18}H_{14}O_3Cl_4$	420	414	33.76	33.15	178.7–179.4	
t-Butylbenzene	$C_{18}H_{14}O_3Cl_4$	420	431	33.76	33.24	228.9–229.5	
1,3-Dimethyl-5-ethylbenzene	$C_{18}H_{14}O_3Cl_4$	420	418	33.76	33.65	248.6–249.4	
1-Methyl-4-*i*-propylbenzene	$C_{18}H_{14}O_3Cl_4$	420	418	33.76	33.88	188.5–189.7	
1-Methyl-2-*t*-butylbenzene	$C_{19}H_{16}O_3Cl_4$	434	444	32.67	31.90	205.8–206.3	
1-Methyl-3-*t*-butylbenzene	$C_{19}H_{16}O_3Cl_4$	434	443	32.67	32.44	207.1–208.5	
1-Methyl-4-*t*-butylbenzene	$C_{19}H_{16}O_3Cl_4$	434	425	32.67	32.24	206.1–207.0	
1-Methyl-3,5-diethylbenzene	$C_{19}H_{16}O_3Cl_4$	434	431	32.67	33.10	160.3–161.7	
1,3,5-Triethylbenzene	$C_{20}H_{18}O_3Cl_4$	448	457	31.64	31.73	[f]	

[a] H. Meyer, *Monatsh.*, **25**, 1198 (1904). [b] A. Hofmann, *ibid.*, **36**, 805 (1915). [c] Two crystalline modifications were observed: (1) 190.2–191.7; (2) 203.0–203.5. [d] Two crystalline modifications were observed: transition point: 209.2; m.p. 218.2–218.8. [e] Two crystalline modifications were observed: (1) 167.3–168.5; (2) 178.8–179.3. [f] Three crystalline modifications were observed: (1) 173.4–174.1; (2) 178.4–178.8; (3) 187.0–187.9. [g] H. Underwood, Jr., and W. Walsh, THIS JOURNAL, **57**, 940 (1935).

means of the benzoylbenzoic acids to identify 1,3-dimethylbenzene and 1,4-dimethylbenzene or *s*-butylbenzene and isobutylbenzene. No phthalic anhydride derivative was obtained from 1,4-diethylbenzene and 1-methyl-4-ethylbenzene, and the derivative of isopropylbenzene could not be obtained in sufficient purity to report. Therefore, the authors investigated the tetrachlorophthalic anhydride derivatives reported in the present work. The *o*-aroyltetrachlorobenzoic acids are suitable derivatives to identify 1,3- and 1,4-dimethylbenzene, *s*- and isobutylbenzene, isopropyl- and *n*-propylbenzene, and satisfactory derivatives have been obtained for 1,4-diethylbenzene and 1-methyl-4-ethylbenzene. By means of the *o*-aroylbenzoic acids or the *o*-aroyltetrachlorobenzoic acids or a combination of the two classes, as in the case of the butylbenzenes, it is possible to identify each of the alkylbenzene hydrocarbons investigated except 1-methyl-4-ethylbenzene. This hydrocarbon did not give a derivative with phthalic acid and its derivative formed with tetrachlorophthalic anhydride is identical to that formed with 1-methyl-2-ethylbenzene.

In the present work the tetrachlorophthalic anhydride derivatives of 28 mono-, di- and trisubstituted alkylbenzenes are described. Of these 22 are reported for the first time. Melting points, neutralization equivalents and chlorine analyses or all compounds are presented in Table I. All derivatives were recrystallized until successive recrystallizations gave no significant change in melting point. The melting points available from the literature are given in Table I and are generally in good agreement with the values obtained in this work.

In those instances where the melting points of derivatives of isomeric hydrocarbons were similar, mixed melting points were determined. In this way it was found that a common derivative was obtained from the three isomeric methyl-*t*-butylbenzenes. Similarly, 1-methyl-2-ethylbenzene and 1-methyl-4-ethylbenzene gave the same halogenated keto acid, which was, however, not the same as that derived from 1-methyl-3-ethylbenzene. This fact was indicated by the observation that a mixed melting point taken of the derivative of the 1,2- with that of the 1,3- gave a 15–20° depression and that a similar depression occurred on mixing the derivatives of the 1,3- and the 1,4- substituted hydrocarbons. On the other hand, a mixture of the derivatives of the 1,2- and the 1,4- showed no depression on melting. This could either mean rearrangement into the same keto acid, or the formation of solid solutions. If the former alternative is assumed, the difference of about 2° between the melting points of the 1,2- and the 1,4- might be explained by the formation of a trace of the 1,3-form, just enough to depress the melting point 2–3°.

In the case of the tetrachlorophthalic anhydride

derivatives of 1,2,3- and 1,2,4-trimethylbenzene a mixed melting point showed a slight depression; however, the degree of depression was not sufficient to permit a definite conclusion as to whether rearrangement of the hydrocarbon had or had not occurred.

In this series as in the previously reported one, several derivatives were observed which had at least two crystalline modifications. This phenomenon was exhibited by the tetrachlorophthalic anhydride derivatives of benzene, 1,2,4-trimethylbenzene, 1,3-diethylbenzene and 1,3,5-triethylbenzene.

Experimental

The starting materials and procedures were the same as in the previous work with the following exceptions: (1) The tetrachlorophthalic anhydride used was Eastman Kodak Co. practical grade. (2) The *o*-aroyltetrachlorobenzoic acids were recrystallized by dissolving them in a small volume of hot glacial acetic acid and adding sufficient water to cause precipitation as the solution cooled. (3) The percentage chlorine was determined by burning the acid in a Parr oxygen bomb and then titrating with silver nitrate and potassium thiocyanate using ferrous ammonium sulfate as an indicator.

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LEWIS FLIGHT PROPULSION LABORATORY
NATIONAL ADVISORY COMMITTEE FOR AERONAUTICS
CLEVELAND, OHIO

The Preparation of N-Dialkylphosphorylated Glycine

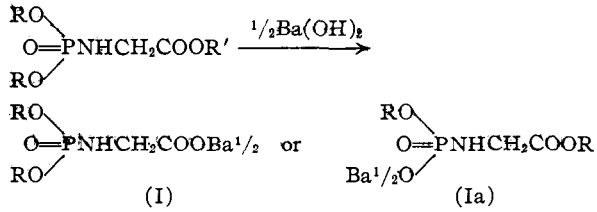
BY T. LIEB, R. E. PLAPINGER AND T. WAGNER-JAUREGG

RECEIVED JUNE 15, 1953

Various N-dialkylphosphorylated amino acid esters have been described recently.[1-3] Attempts to saponify the carboxylic ester group in compounds of this type have been unsuccessful.[1,3] Therefore it has been claimed that the phosphorylation of the α-amino group greatly increases the stability of the carboxylic ester linkage.[1]

By saponification of the esters of N-dialkylphosphorylglycine with one equivalent of barium hydroxide at room temperature we have been able to obtain the corresponding monobarium salts. These were transformed for further characterization into the crystalline guanidine salts.

The question arises as to whether the barium salts formed have the structure I or Ia.

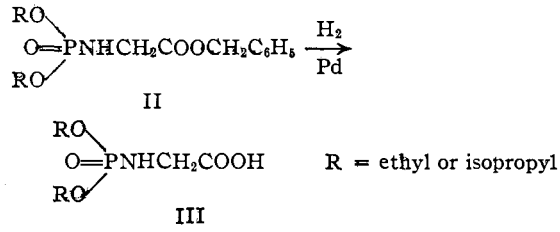


(I) (Ia)

When R and R′ are different alkyl groups (for instance R = butyl or isopropyl and R′ = methyl or ethyl) it was possible to exclude structure Ia as a possible product by elementary analysis of the guanidine salts. In the case where both R and R′ are ethyl groups the isolation of a product corresponding to structure I could be established by the absence of a positive hydroxamate test, a reaction characteristic of carboxylic acid esters.

By treatment of an aqueous solution of the guanidine salt of N-diethylphosphorylglycine with an ion-exchange resin the corresponding free acid can be liberated. Its titration curve indicates a pK_a of 3.8, which is in agreement with the expected value. The free acid corresponding to the barium salt of the structure Ia should have a lower pK_a. The aforementioned results demonstrate that the assumption of a greatly increased stability of the carboxylic ester linkage in N-dialkylphosphorylated α-amino acid esters is unjustified.[4]

N-Diethyl- and N-diisopropylphosphorylglycines (III) also were prepared from the corresponding benzyl esters II by hydrogenolysis.



II

III

No well-defined product could be obtained in the attempted hydrolysis of N-diphenylphosphorylglycine ethyl ester with barium hydroxide. Since the odor of phenol can be detected after addition of 0.5 mole of $Ba(OH)_2$ a hydrolytic attack on the O–P linkage has to be assumed.

The N-dialkylphosphorylglycine esters used for this investigation were prepared by the reaction of glycine esters with dialkylphosphoryl chlorides. N-Diethylphosphorylglycine ethyl ester (IV) is formed also during the reaction of glycine ester with tetraethyl pyrophosphate (TEPP). Previously[2] the interaction of these substances had been tentatively formulated as yielding N,N-bis-diethylphosphorylglycine ester, $H_5C_2O_2CCH_2N[PO(OC_2H_5)_2]_2$ (V). However, material presented in the Experimental Part of this paper makes it evident that a mixture of approximately two moles of IV with one mole of TEPP is obtained. This correction eliminates an apparent exception to the reaction of TEPP with amino compounds. It demonstrates that in the case of glycine ester also, the ordinary monophosphorylation takes place with a tetralkyl pyrophosphate, as originally shown by Atherton and Todd.[5]

Experimental

N-Diethylphosphorylglycine Ethyl Ester (IV).—This substance was obtained by treating glycine ester with diethylphosphoryl chloride in a manner analogous to that of the reaction of diisopropylphosphoryl chloride with amino acid esters.[2] The product obtained had a boiling point of 123–128° (0.3 mm.), $n^{30}D$ 1.4338.

(1) L. J. Sciarini and J. S. Fruton, THIS JOURNAL, 71, 2940 (1949).
(2) T. Wagner-Jauregg, J. J. O'Neill and W. H. Summerson, *ibid.*, 73, 5202 (1951).
(3) Si-Oh Li, *ibid.*, 74, 5959 (1952).
(4) N-Diisopropylphosphorylglycine methyl ester produced one equivalent of acid with a commercial horse serum at pH 7.6 and 38°, while glycine ethyl ester remained unattacked. We did not investigate whether this hydrolysis was due to the presence of an esterase or a phosphatase.
(5) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

Anal. Calcd. for $C_8H_{18}O_5NP$ (239.3): N, 5.9; P, 13.0. Found: N, 5.43; P, 13.3.

Barium Salt of N-Diethylphosphorylglycine (I, R = C_2H_5).—To 2.2 g. (0.009 mole) of N-diethylphosphorylglycine ethyl ester was added a solution of 0.77 g. (0.0045 mole) of barium hydroxide in 18 ml. of water. The *p*H of the resulting solution fell to 5.5 after about one-half hour at room temperature. The solvent was evaporated off under vacuum. The resulting sirup was dissolved in a small quantity of absolute ethanol. Fractional precipitation with dry ether yielded the salt as a finely divided white solid, which was collected by centrifugation and dried at 100° in a vacuum over phosphorus pentoxide.

Anal. Calcd. for $C_{12}H_{26}O_{10}N_2P_2Ba$: OC_2H_5, 32.3; N, 5.0; P, 11.1; Ba, 24.6. Found: OC_2H_5, 30.6; N, 4.8; P, 11.1; Ba, 25.8.

Guanidine Salt of N-Diethylphosphorylglycine.—To 2.4 g. (0.01 mole) of N-diethylphosphorylglycine ethyl ester was added a filtered solution of 0.85 g. (0.005 mole) of barium hydroxide in 20 ml. of water. The *p*H of the resulting solution dropped instantly to 8, and after five minutes the solution was approximately neutral. Addition of 0.9 g. (0.005 mole) of guanidine carbonate, $(CH_5N_3)_2H_2CO_3$, in a small amount of water precipitated barium carbonate, which was filtered off. Evaporation of the filtrate under vacuum to dryness yielded a solid, which was washed with acetone and recrystallized 3 times from absolute ethanol. Dried over phosphorus pentoxide in a vacuum the colorless crystals melted at 159–160°, yield 51%.

Anal. Calcd. for $C_7H_{19}O_5N_4P$ (270.2): P, 11.2; N, 20.7; C, 31.1; H, 7.1; OC_2H_5, 33.3. Found[6]: P, 11.8; N, 20.9; C, 31.7; H, 7.0; OC_2H_5, 31.8.

Guanidine Salt of N-Diisopropylphosphorylglycine.—(a) Prepared in the same manner as above from N-diisopropylphosphorylglycine ethyl ester[2] the salt melted at 167–168.5° after one recrystallization from anhydrous ethanol and vacuum drying over phosphorus pentoxide, yield about 50%.

Anal. Calcd. for $C_9H_{23}O_5N_4P$ (298.3): P, 10.4; N, 18.8; C, 36.2; H, 7.8; OC_3H_7, 39.5. Found: P, 10.9; N, 19.2; C, 36.2; H, 7.8; OC_3H_7, 38.6.

(b) The guanidine salt of N-diisopropylphosphorylglycine prepared from N-diisopropylphosphorylglycine methyl ester (b.p. 114–120° (0.1–0.2 mm.), $n^{27}D$ 1.4314) melted at 166–167°.

Anal. Calcd. for $C_9H_{23}O_5N_4P$ (298.3): P, 10.4; N, 18.8; C, 36.2; H, 7.8; OC_3H_7, 39.5. Found: P, 10.3; N, 19.3; C, 35.2; H, 7.3; OC_3H_7, 38.5.[7]

Guanidine Salt of N-Dibutylphosphorylglycine.—The hydrolysis of N-dibutylphosphorylglycine methyl ester (b.p. 145–147° (0.15 mm.), $n^{26}D$ 1.4392) with 0.5 mole of $Ba(OH)_2$ was best accomplished in the cold. The guanidine salt melted at 156.5–157° after recrystallization from ethanol and ether.

Anal. Calcd. for $C_{11}H_{27}O_5N_4P$ (326.3): C, 40.4; H, 8.33; N, 17.15; P, 9.48; OC_4H_9, 45.7. Found: C, 39.8; H, 8.1; N, 17.2; P, 9.6; OC_4H_9, 44.1.

N-Diisopropylphosphorylglycine Benzyl Ester (II, R = (II, R = Isopropyl).—Glycine benzyl ester was liberated from 5.0 g. of its hydrochloride[8] by neutralization with triethylamine. To a cooled solution of the free base in 10 cc. of dry ether was added a solution of 5.0 g. of diisopropyl chlorophosphate in 5 cc. of dry ether with stirring. An immediate reaction took place in the course of which triethylamine hydrochloride was precipitated. After stirring for 1 hour the triethylamine hydrochloride (3.0 g.) was removed by filtration and the ether solution concentrated. A yellow oil (7.6 g.) remained which did not solidify when kept at 20° overnight. This material gave a faint test for halogen. Extraction of an ethereal solution of this material with ice-water removed the halogen.

Anal. Calcd. for $C_{15}H_{24}O_5NP$: N, 4.24; P, 9.38. Found: H, 4.30; P, 9.40.

(6) All CH determinations were obtained by combustion in the presence of V_2O_5; compare T. Wagner-Jauregg and H. Griesshaber, *Ber.*, **70**, 1458 (1937).

(7) The low analytical values found for carbon and alkoxy probably indicate that hydrolysis of the phosphate ester linkage took place to a certain extent.

(8) H. K. Miller and H. Waelsch, THIS JOURNAL, **74**, 1092 (1952).

Debenzylation of N-Diisopropylphosphorylglycine Benzyl Ester.—Diisopropylphosphorylglycine benzyl ester (3.0 g.) in 100 ml. of absolute alcohol containing 3.0 g. of 5% Pd–C catalyst was catalytically hydrogenated at a pressure of 60 lb./in.^{2} for 36 hours at room temperature. Removal of the catalyst by filtration and concentration of the alcohol yielded a sirup. This material was dissolved in cold aqueous sodium bicarbonate and the water solution extracted with ether. Acidification of the aqueous solution in the cold, followed by extraction with ether and drying, yielded the product, a colorless viscous oil which was strongly acidic (III, R = isopropyl).

Anal. Calcd. for $C_8H_{18}O_5NP$: C, 40.17; H, 7.58; N, 5.85; P, 12.95; equiv. wt., 239.2. Found: C, 40.3; H, 7.4; N, 5.3; P, 13.2; equiv. wt. (by titration with NaOH), 239.7.

Diethylphosphorylglycine Benzyl Ester (II, R = Ethyl).—*Anal.* Calcd. for $C_{13}H_{20}O_5NP$: N, 4.64; P, 10.28. Found: N, 4.75; P, 10.18.

Diethylphosphorylglycine (III, R = Ethyl).—*Anal.* Calcd. for $C_6H_{14}O_5NP$: N, 6.63; P, 14.67; equiv. wt., 211.2. Found: N, 6.75; P, 14.80; equiv. wt. (by titration with NaOH), 211.5, 212.2.

The titration curve of an aqueous solution of this acid gave a pK_a 3.85, identical with that of a sample obtained from the guanidine salt by treatment with Dowex-50. On standing of the solution a change in the titration curve could be observed, first noticeable after 4 hours, and complete within 22 hours. This demonstrates that N-diethylphosphorylglycine slowly hydrolyses.

Interaction of Glycine Ethyl Ester with Tetraethyl Pyrophosphate (TEPP).—A substance with the formula V and a 2:1 mixture of N-diethylphosphorylglycine ethyl ester (IV) and TEPP have almost the same analytical composition so that no exact distinction is possible by elementary analysis. Since the boiling points of IV and TEPP are almost the same at reduced pressure, a separation by distillation is not possible. Differentiation between V and a 2:1 mixture of IV and TEPP could be made in favor of the latter mainly by a determination of the molecular weight. The comparison of the reaction product (R) of glycine ethyl ester with TEPP described previously[2] with a mixture (M) prepared from two moles of N-diethylphosphorylglycine ethyl ester (IV) and one mole of TEPP gave the values

Reaction product	Mixture
Boiling point 120–125° (0.5 mm.)	124–125° (0.5 mm.)
Refractive index $n^{28}D$ 1.4275–1.4290[2]	$n^{28}D$ 1.4281
Molecular weight[9] 270.4	267.8; calcd. for M, 256 (calcd. for V, 375)
LD_{50} for rabbits[10] 0.17 mm.^{3}/kg. (i. v.), in propylene glycol	0.2 mm.^{3}/kg. (i. v.), in propylene glycol

For an aqueous solution of R an LD_{50} = 1 mg./kg. rabbit has been reported.[2] Since R is a mixture of IV and TEPP, the low toxicity found previously was due to the rapid hydrolysis of TEPP when water, rather than propylene glycol, was used as the solvent.

Acknowledgment.—The diethyl and dibutyl chlorophosphates used were kindly furnished by Victor Chemical Works, Chicago 4. The analytical determinations were performed by Cpl. Patrick Tetta of this Branch and by the Analytical Branch, Cml C Chemical and Radiological Laboratories. We wish to thank Mr. B. E. Hackley, Jr., for the manometric determination of the enzymatic hydrolysis of N-diisopropylphosphorylglycine methyl ester.

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(9) Determined by a modified Signer method; see C. A. Rush, J. J. Schrock and D. H. Rosenblatt, Abstracts 123rd Meeting Am. Chem. Soc., Los Angeles, Calif., March, 1953, page 5B.

(10) Determined by the Field Toxicology and the Pharmacology Branches, Cml C Med Labs.

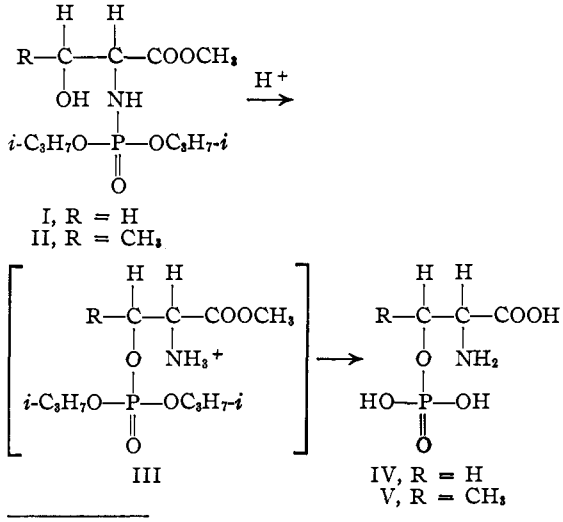
A Nitrogen-to-Oxygen Phosphoryl Migration: Preparation of *dl*-Serinephosphoric and Threoninephosphoric Acid

BY ROBERT E. PLAPINGER AND T. WAGNER-JAUREGG

RECEIVED JULY 10, 1953

Previous publications have dealt with the isolation of serinephosphoric acid from the acid hydrolysates of the diisopropylphosphoryl derivatives of chymotrypsin and purified cholinesterase.[1] In connection with these findings, it was advisable to determine whether O-phosphorylated hydroxyamino acids can be formed by migration of a phosphoryl group from nitrogen to oxygen.

It is a well established fact that certain N-acyl-1,2-aminoalcohols rearrange on treatment with mineral acid to the corresponding amine salt of the O-acyl-1,2-aminoalcohol.[2] We found that a similar transformation was accomplished easily with N-diisopropylphosphoryl derivatives of *dl*-serine, *dl*-threonine and ethanolamine.[3] These findings now provide a simple method for the preparation of both serinephosphoric and threoninephosphoric acids.[4] Treatment of N-diisopropylphosphoryl derivatives of *dl*-serine methyl ester (I) and *dl*-threonine methyl ester (II) with boiling aqueous hydrochloric acid gave *dl*-serinephosphoric (IV) and "threoninephosphoric acid" (V), respectively, the former in 25% yield and the latter[5] in 50% yield. Ethanolaminephosphoric acid was obtained similarly from its N-diisopropylphosphoryl derivative, in 18% yield.



I, R = H
II, R = CH_3

III

IV, R = H
V, R = CH_3

An unsuccessful attempt was made to isolate the intermediate III as the hydrochloride, by treatment of I or II with dry hydrogen chloride gas in either dioxane or absolute methanol. The product obtained in each case was a sirupy, ether-insoluble hydrochloride, which would not crystallize. In the case of the intermediate derived from N-diisopropylphosphoryl-*dl*-serine methyl ester, a small amount of *dl*-serine methyl ester hydrochloride was isolated. This indicated that some hydrolysis of the phosphoramide linkage had occurred. When I and II were first treated with dry hydrogen chloride gas, as described above, and then hydrolyzed with boiling aqueous hydrochloric acid, the yields of the corresponding phosphoramino acids (IV and V) were identical with those obtained by direct treatment of I and II with boiling aqueous hydrochloric acid.

An attempt to synthesize cysteine-phosphoric acid from N-diisopropylphosphoryl-1-(+)-cysteine methyl ester was unsuccessful.

Experimental

All melting points were taken on a Fisher–Johns block and are uncorrected.

N-Diisopropylphosphoryl Derivatives of *dl*-Serine, *dl*-Threonine and *l*-(+)-Cysteine Methyl Esters.—The serine and threonine derivatives were prepared from diisopropylphosphoryl chloride (DClP) and the appropriate amino acid ester by the procedure described earlier.[6] The serine derivative, which had been reported[6] as a sirup, has since been obtained in crystalline form, as a white waxy solid of m.p. 48–50°.

Anal. Calcd. for $C_{10}H_{22}O_6NP$: N, 4.94; P, 10.94. Found: N, 4.94; P, 11.0.

The cysteine derivative, which has not been previously characterized, was similarly prepared from DClP and *l*-(+)-cysteine methyl ester hydrochloride,[7] in the presence of 2 moles of triethylamine. This product was isolated as a viscous sirup, soluble in ether, benzene and chloroform, and insoluble in petroleum ether. It solidified when kept overnight in the ice-box, and softened at approximately 22°. This substance gave a positive test for a sulfhydryl group with alkaline sodium nitroprusside.

Anal. Calcd. for $C_{16}H_{32}O_6NPS$: N, 4.68; P, 10.35. Found: N, 4.70; P, 10.65.

Standard Van Slyke amino nitrogen determinations indicated the absence of free amino nitrogen in the above mentioned phosphoramides.

N-Diisopropylphosphorylethanolamine.—This substance was prepared from DClP and ethanolamine in the presence of triethylamine, using dry chloroform as a solvent. It boiled at 151° (0.8 mm.), decomposition setting in after about one-half of the material distilled, $n^{23}D$ 1.4400.

Anal. Calcd. for $C_8H_{20}O_4NP$: N, 6.2; P, 13.75. Found: N, 6.05; P, 13.85.

A standard Van Slyke amino nitrogen determination indicated the absence of free amino nitrogen in this compound.

Preparation of *dl*-Serinephosphoric, "Threoninephosphoric" and Ethanolaminephosphoric Acids.—Approximately 0.01 mole of N-diisopropylphosphoryl-amino acid ester or -ethanolamine was placed in a 100-cc. round-bottom flask containing 40 cc. of 5–7% hydrochloric acid. After refluxing for 6 hours, the solution was concentrated *in vacuo* to dryness. The oily residue was dissolved in water, and ethanol was added until turbidity was reached. The turbid solution was allowed to stand overnight, and the solid which precipitated was then separated from the mother liquor by centrifugation. This solid was washed several times with alcohol, then ether, and dried over phos-

(1) (a) N. K. Schaffer, S. C. May, Jr., and W. H. Summerson, *J. Biol. Chem.*, **202**, 67 (1953); (b) *Federation Proc.*, **12**, 264 (1953).

(2) Some recent papers are: A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947); L. H. Welsh, *ibid.*, **71**, 3500 (1949); G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950); E. E. van Tamelen, *ibid.*, **73**, 5773 (1951); D. F. Elliot, *Biochem. J.*, **50**, 542 (1952).

(3) Presumably the mechanism postulated by Welsh (see footnote 2) for acyl migrations of derivatives of ephedrine and ψ-ephedrine can be interpreted to be operative in these phosphoryl migrations.

(4) Our attempts to prepare these substances by the procedures of P. H. Levine and A. Schormuller, *J. Biol. Chem.*, **105**, 547 (1934), and R. H. A. Plimmer, *Biochem. J.*, **35**, 461 (1941), were unsatisfactory with respect to both purity and yield. R. E. Ferrel, H. S. Olcott and H. Fraenkel-Conrat, THIS JOURNAL, **70**, 2106 (1948), experienced similar difficulties.

(5) In the light of Welsh's work (see footnotes 2 and 3) this product could be *dl*-threoninephosphoric acid, *dl*-allothreoninephosphoric acid or a mixture of both of these substances. No attempt was made to determine the stereochemical uniformity of our preparation.

(6) T. Wagner-Jauregg, J. J. O'Neill and W. H. Summerson, THIS JOURNAL, **73**, 5202 (1951).

(7) Prepared from *l*-(+)-cysteine hydrochloride, absolute methanol and gaseous hydrogen chloride; m.p. 145°. *Anal.* Calcd. for $C_4H_{10}O_2NSCl$: N, 8.16. Found: N, 8.30.

phorus pentoxide. In order to induce precipitation, it was sometimes necessary to keep the turbid solution at −20° overnight. Addition of ether to the turbid solution often proved helpful. The alcohol and ether washings, when added to the original mother liquor, usually yielded additional amounts of the aminophosphoric acid.

N-Diisopropylphosphoryl-*dl*-serine methyl ester (4.0 g.) yielded 0.540 g. (21%) of **dl-serinephosphoric acid**,[8] melting at 166–167°. When the reflux time was reduced to 4 hours, *dl*-serinephosphoric acid was isolated in 26% yield.

Anal. Calcd. for $C_3H_8O_6NP$: C, 19.47; H, 4.36; N, 7.57; P, 16.74. Found: C, 19.4; H, 4.43; N, 7.45 (Van Slyke), 7.80 (Dumas); P, 16.6.

N-Diisopropyl-*dl*-threonine methyl ester (3.0 g.) yielded 1.04 g. (52%) of **threoninephosphoric acid**,[9] melting at 184°.

Anal. Calcd. for $C_4H_{10}O_6NP$: C, 24.13; H, 5.06; N, 7.04; P, 15.56. Found: C, 24.2; H, 5.30; N, 7.1 (Van Slyke), 7.0 (Dumas); P, 15.8.

N-Diisopropylphosphorylethanolamine (3.0 g.) yielded 350 mg. of **ethanolaminephosphoric acid** (18.6%), melting at 242°.[10]

Anal. Calcd. for $C_2H_8O_4NP$: C, 17.03; H, 5.72; N, 9.93; P, 21.96. Found: C, 16.8; H, 5.6; N, 9.55 (Van Slyke), 9.65 (Kjeldahl); P, 22.10.

Attempts were made to isolate the O-diisopropylphosphorylated esters of serine and threonine by treatment of the corresponding N-phosphorylated isomer, in either methanol or dioxane, with gaseous hydrogen chloride gas. When these attempts proved unsuccessful, the organic solvent was removed under vacuum and the residue hydrolyzed with boiling aqueous hydrochloric acid. The yields of phosphoroamino acids were identical with those obtained by direct treatment of the phosphoramide with boiling aqueous acid. N-Diisopropylphosphoryl-*l*-(+)-cysteine methyl ester yielded only cysteine hydrochloride when subjected to treatment with gaseous and then boiling aqueous hydrochloric acid.

Acknowledgment.—The authors wish to express their sincere appreciation to Pfc. Patrick Tetta, of this Branch, and to the Analytical Branch, Chemical and Radiological Laboratories, Army Chemical Center, Md., for the microanalyses of the compounds encountered in this investigation.

(8) R. H. A. Plimmer (see footnote 4), reports a m.p. of 165–166° for this substance.

(9) R. H. A. Plimmer (see footnote 4), reports a m.p. of 169° for *dl*-threoninephosphoric acid. However, his material is a monohydrate. C. H. de Verdier, *Nature*, **170**, 894 (1952), reports a m.p. of 194° for *l*-threoninephosphoric acid isolated from bovine casein.

(10) E. L. Outhouse, *Biochem. J.*, **31**, 1454 (1937), reports a m.p. of 244° for this compound.

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Some Pyrimidine Derivatives[1]

BY JOSEPH L. RABINOWITZ AND SAMUEL GURIN

RECEIVED JULY 10, 1953

During the course of an antimetabolite project to be reported elsewhere, several new pyrimidine derivatives were prepared. This note concerns their synthesis in addition to modifications or improvements in the preparation of a number of previously known substances.

Experimental[2]

(a) **Thymine-1-acetic Acid.**—To 12.6 g. (0.1 mole) of thymine and 9.6 g. (0.2 mole) of KOH in 75 ml. of H_2O was added slowly 7.85 g. (0.1 mole) of chloroacetic acid in 30 ml. of H_2O.[3] (The corresponding ester can be used with equal success.) The *p*H of the solution was adjusted to and kept at 10 by the dropwise addition of a KOH solution. After refluxing for two hours, the solution was cooled, and acidified to *p*H 2 by the addition of concd. HCl. The resulting precipitate was filtered, washed with a little cold water, dissolved in a saturated $KHCO_3$ solution and reprecipitated with HCl; crude yield 16 g. (*ca.* 85%); recrystallized *ca.* 50% yield, m.p. 260–261°.

Anal. Calcd. for $C_7H_8O_4N_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.64; H, 4.41; N, 15.21.

(b) **1,3-Diethylthymine.**—To 13 g. (*ca.* 0.1 mole) of thymine in a solution of 10 g. of NaOH in 60 ml. of water, was added dropwise 30 ml. of ethyl sulfate.[4] The solution was stirred at room temperature for one hour, then kept stirring for another hour just below its boiling temperature. After cooling, the solution was extracted several times with $CHCl_3$; after drying the $CHCl_3$ with $MgSO_4$, it was filtered and evaporated to dryness. The resulting 1,3-diethylthymine can be recrystallized from petroleum–ethyl ether, m.p. 56–57°, b.p. 140–143° (7 mm.), yield 6.5 to 7.8 g. (*ca.* 40%).

Anal. Calcd. for $C_9H_{14}O_2N_2$: C, 59.31; H, 7.74; N, 15.37. Found: C, 58.99; H, 7.61; N, 15.27.

(c) **2,4-Diethoxy-5-nitro-6-methylpyrimidine.**—To a cold mixture consisting of 15 ml. of red fuming nitric acid (d. 1.5) and 15 ml. of concd. H_2SO_4 was added slowly 2.5 g. (0.02 mole) of **2,4-diethoxy-6-methylpyrimidine**.[12] The solution was kept at 80° for one hour, then poured onto cracked ice. The mixture was first neutralized with KOH, then acidified to *p*H 2 with HCl. The solution was chilled, filtered and the precipitate washed with cold water, the residue was extracted with 50 ml. of ether, decolorized with charcoal and treated with 50 ml. of MeOH. The ether was removed by warming on a water-bath and the remaining solution treated with cold water to faint turbidity. The suspension was chilled, and fine yellow needles collected. The compound sublimes, m.p. 88°, yield 2.7 g. (*ca.* 60%).

Anal. Calcd. for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.76; N, 18.49. Found: C, 47.93; H, 5.71; N, 18.53.

(d) **2,4-Diethoxy-5-nitropyrimidine.**—Twenty-five grams (0.15 *M*) of 2,4-diethoxypyrimidine[5] was added dropwise to a mixture of 150 ml. of red fuming nitric and 150 ml. of concd. sulfuric acids (prepared by slow addition of chilled sulfuric to chilled nitric). After standing for one hour at room temperature, the solution was placed in warm water (60°) and stirred. The temperature was maintained at 60° for one hour. The solution was then cooled to room temperature and decomposed cautiously with 500 g. of cracked ice. After removal of the first crop by filtration, additional material was recovered from the filtrate by neutralization with concd. KOH to *p*H 7.5 followed by the addition of NaCl and chilling.

All of the precipitated material was combined, dissolved in hot absolute EtOH and decolorized with charcoal. Fine, pale yellow needles were obtained after chilling, m.p. 45°, yield 9.5–11 g. (*ca.* 30%).

Anal. Calcd. for $C_8H_{11}O_4N_3$: C, 45.06; H, 5.20; N, 19.71. Found: C, 44.96; H, 5.21; N, 19.64.

(e) **4-Methoxy-1,6-dimethyl-2-pyrimidone.**—To a mixture of 3 g. of 2,4-dimethoxy-6-methylpyrimidine[6] and 2.1 ml. of methyl iodide a few drops of pyridine were added; after 24 hr. at room temperature a solid deposited. The solid was recrystallized from hot alcohol by the addition of absolute ether, yield 95%, m.p. 112.5°.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.52; H, 6.54; N, 18.18. Found: C, 54.70; H, 6.55; N, 17.96. Upon hydrolysis with HCl 1,6-dimethyluracil was obtained.

(f) **1,3-Diethyl-6-methyluracil.**[7]—A more convenient method of preparation involved the addition of 45 ml. of

(1) Supported by a grant of the Cancer Institute of the National Institutes of Health.

(2) All melting points are uncorrected. We wish to thank the Organic Research Laboratory of Sharp and Dohme, Inc., for most of the analyses reported in this paper.

(3) H. L. Wheeler and L. M. Liddle, THIS JOURNAL, **30**, 1152 (1908).

(4) P. A. Levene, L. W. Bass and H. S. Simms, *J. Biol. Chem.*, **70**, 229 (1926).

(5) G. E. Hilbert and T. B. Johnson, THIS JOURNAL, **52**, 2004 (1930).

(6) S. Gabriel and J. Colman, *Ber.*, **32**, 2921 (1899).

(7) J. Hoffmann, *Ann.*, **253**, 68 (1889); M. Hagen, *ibid.*, **244**, 8 (1888); O. Heobel and R. Behrend, *ibid.*, **353**, 246 (1907); O. Buchendorff, *ibid.*, **385**, 314 (1911).

ethyl sulfate to a mixture of 20 g. of 6-methyluracil and 17 g. of sodium hydroxide in 100 ml. of H_2O.[4] After 3 hr. of vigorous stirring, the solution was extracted with chloroform, dried over $MgSO_4$, filtered and the chloroform then distilled off, yield 75%, m.p. 52°. The m.p. of a mixture of material prepared by this method and Behrend's method was unchanged.

(g) 1,5-Dimethyl-4-ethoxy-2-pyrimidone.[8]—The addition of a few drops of pyridine to a solution containing an excess of methyl iodide with 2,4-diethoxypyrimidine,[5] improves the yield materially.

(h) 1-Ethyl-4-ethoxy-2-pyrimidone.[9]—Slightly better yields were obtained by the addition of a few drops of pyridine to a solution containing an excess of ethyl iodide with 2,4-diethoxypyrimidine. The reaction is complete after 24 hours instead of 7 days.

(i) 1-Tetraacetyl-β-D-glucosido-2-oxy-4-ethoxy-1,2-dihydropyrimidine.[10]—An improvement in the reported yield of this compound was obtained when a molecular equivalent of pyridine was added to an equimolecular mixture of 1-bromo-tetraacetyl-D-glucose with 2,4-diethoxypyrimidine[5] in chloroform. The yield is increased from 20 to 50% (calculated from the pyrimidine). The bromoacetylglucose need not be recrystallized when this method is used. The intermediate pyrimidium salt of bromoacetylglucose[11] can be isolated when this reaction is carried out in the presence of chloroform and pyridine.

(j) 1-Tetraacetylglucosido-4-ethoxy-6-methyl-2-pyrimidone or 2-Tetraacetylglucosido-4-ethoxy-6-methylpyrimidine.—A thick oil was obtained when 9 g. (0.02 mole) of 2,4-diethoxy-6-methyluracil[12] and 9 g. (0.02 mole) of 1-bromotetraacetylglucose were kept in a sealed tube at 65° for four days. The resulting oil was filtered, treated with 30 ml. of ether and chilled for one day. A heavy white crystalline precipitate was filtered and twice recrystallized from EtOH–H_2O using Norite; m.p. 166°, yield 2.9 to 3.2 g. (*ca.* 32%), $[\alpha]^{26}D$ +119.7 (*c*, 0.5 in C.P. chloroform). Similar results have been reported recently by Newmark and Goodman.[13]

Anal. Calcd. for $C_{12}H_{28}O_{11}N_2$: C, 52.06; H, 5.82; N, 5.78. Found: C, 51.96; H, 5.75; N, 5.78–5.71.

(8) W. Schmidt-Nickels and T. B. Johnson, THIS JOURNAL, **52**, 4511 (1930).

(9) G. E. Hilbert, *ibid.*, **59**, 330 (1937).

(10) G. E. Hilbert and E. F. Jansen, *ibid.*, **58**, 60 (1936).

(11) E. Fisher and K. Raske, *Ber.*, **43**, 1751 (1910).

(12) B.p. 235°, $n^{23}D$ 1.4853. *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.31; H, 7.74; N, 15.37. Found: C, 59.08; H, 7.62; N, 15.30. The compound was prepared before R. Andrisano's work in *Boll. sci. Faculta chim. ind., univ. Bologna*, **5**, 52 (1944); **5**, 56 (1947), became available.

(13) P. Newmark and I. Goodman, A. C. S. 122nd Meeting, 1952, abstract of Papers, 44C.

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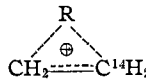
Rearrangement in the Reaction of C^{14}-Labeled *n*-Propylamine (1-Aminopropane-1-C^{14}) with Nitrous Acid[1]

BY JOHN D. ROBERTS[2] AND MARTIN HALMANN[3]

RECEIVED JUNE 24, 1953

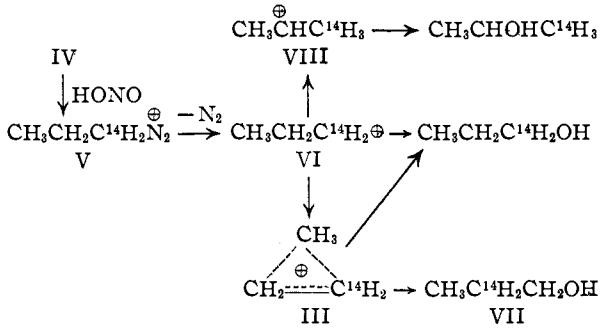
Ethylamine-1-C^{14} on treatment with aqueous nitrous acid has been shown[4] to yield, besides ethylene, a mixture of 98.5% of ethanol-1-C^{14} and 1.5% of ethanol-2-C^{14}. It was concluded that if the ethyl cation is an important intermediate in the reaction of ethylamine with nitrous acid it reacts with water considerably more rapidly than it is converted to the ethyleneprotonium ion (I). Much more rearrangement is found with 2-phenylethylamine-1-C^{14} with nitrous acid and about 56% of the 2-phenylethanol formed appears to result from a symmetrical intermediate such as II.[5]



I, R = H
II, R = C_6H_5
III, R = CH_3

Alkyl-bridged cations analogous to III ("ethylenealkonium" ions) have been proposed[6] to account for a wide variety of rearrangement reactions of alkyl derivatives but there are very few data which indicate the degree of stability of such ions relative to the isomeric classical carbonium ions like R–$CH_2CH_2^{\oplus}$.

In the present research, the tendency of the *n*-propyl cation to be converted to III was tested in the reaction of 1-propylamine-1-C^{14} (IV) with nitrous acid. The reaction is complicated by elimination and rearrangement to 2-propyl derivatives,[7] but if III is formed from the *n*-propyldiazonium ion (V) or cation VI the 1-propanol obtained from IV should contain at least some 1-propanol-2-C^{14} (VII). A possible reaction sequence for propanol formation is given below in which, for simplicity, it has been assumed that all of the cation isomerization processes are irreversible[8] and further that all of the propanol is formed by carbonium ion processes. The validity of the latter assumption has been discussed before.[4,5]



The following reactions were carried out in the present investigation. The substances represented by formulas in bold-face type were analyzed for radioactive carbon. The degradation procedure was checked for rearrangement as indicated by a blank experiment on authentic 1-propanol-1-C^{14}. The results are presented in Table I. The 1-propanol from the amine–nitrous acid reaction was found to contain 8.5% of isotope-position rearrangement product such as would be expected from hav-

(1) Supported in part by the program of research of the U. S. Atomic Energy Commission.

(2) Gates and Crellin Laboratories, California Institute of Technology, Pasadena 4, Calif.

(3) Foreign Students Summer Project, Massachusetts Institute of Technology, 1952. The Weizmann Institute of Science, Rehovoth, Israel.

(4) J. D. Roberts and J. A. Yancey, THIS JOURNAL, **74**, 5943 (1952).

(5) J. D. Roberts and C. M. Regan, *ibid.*, **75**, 2069 (1953).

(6) (a) A number of references have been given previously[4,5]; (b) D. P. Stevenson, C. D. Wagner, O. Beeck and J. W. Otvos, *ibid.*, **74**, 3269 (1952).

(7) A. Siersch, *Ann.*, **144**, 137 (1867); F. C. Whitmore and R. S. Thorpe, THIS JOURNAL, **63**, 1118 (1941).

(8) The assumption only becomes important to the qualitative interpretation of the tracer results if VI and VIII are in rapid equilibrium, which event is unlikely since 2-propylamine with nitrous acid gives no 1-propanol and, in other processes, primary and secondary cations do not appear to be at all readily interconvertible; *cf.* J. D. Roberts, R. E. McMahon and J. S. Hine, *ibid.*, **72**, 4237 (1950).

ing 17% of the 1-propanol originating from III[9] and 83% by way of VI.

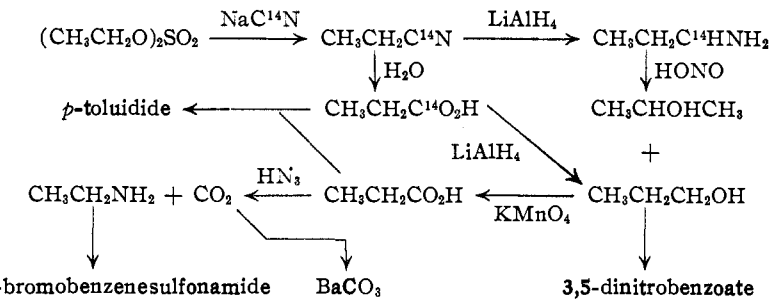


TABLE I

RADIOACTIVITY DETERMINATIONS

Reaction		1-Aminopropane-1-C14 + nitrous acid	Degradation of 1-propanol-1-C14
C14-Activities,[a] mc. per millimole × 10^8	1-Propanol[b]	139	.....
	Propionic acid[c]	142 ± 4[f]	11380
	Barium carbonate[d]	127 ± 2[f]	11070
	N-Ethyl-p-bromobenzenesulfonamide	12 ± 1[f]	16
	Rearrangement,[e] %	8.5 ± 1	0.15

[a] Measured by the procedure of O. K. Neville, THIS JOURNAL, **70**, 3051 (1948), using a vibrating reed electrometer (Applied Physics Corp.). Corrected for background. [b] Assayed as the 3,5-dinitrobenzoate. [c] Assayed as the *p*-toluidide. [d] Since the barium carbonate samples are particularly subject to contamination their activities are only considered to be useful as a qualitative check on the other activities. [e] % rearrangement = activity of N-ethyl-*p*-bromobenzenesulfonamide/activity of *p*-toluidide × 100. [f] Average of four to five different combustions with standard deviations.

It is clear that rather more rearrangement (8.5%) occurs in the process of forming 1-propanol through the reaction of 1-propylamine with nitrous acid than in the corresponding reaction (1.5%) with ethylamine.[4] The results probably reflect a greater stability of III compared to I under similar reaction conditions. This amounts to saying that the intrinsic migratory aptitude of methyl is likely to be greater than that of hydrogen in circumstances where the degree of substitution of the methylene groups of the intermediates (I or III) is the same.

Experimental

Propionitrile-1-C14.—Ethyl sulfate (66 ml.) was added dropwise to a solution of 25 g. of sodium cyanide[10] containing 1 mc. of C14 in 50 ml. of water and 50 ml. of ethylene glycol at 35°. The mixture was allowed to stand overnight and the low-boiling material was distilled out. The distillate was diluted with 20 ml. of 18 *N* sulfuric acid, the upper layer separated, dried over calcium chloride and distilled. The yield of propionitrile-1-C14 was 12.1 g. (44%), b.p. 94–97°.

1-Propyl-1-C14-ammonium Perchlorate.— The procedure was based on that of Amundsen and Nelson.[11] Propionitrile-1-C14 (12.1 g.) dissolved in 30 ml. of ether was added dropwise with stirring to 9 g. of lithium aluminum hydride in 300 ml. of dry ether in a flask cooled in ice-water. After 3 hours, 8 ml. of water, 6 ml. of 20% sodium hydroxide solution and 25 ml. more of water were added successively. The mixture was distilled and the distillate collected in a flask containing 20 ml. of 70% perchloric acid. The volatile material was removed at 30–35° under reduced pressure and the residual perchlorate salt recrystallized from *n*-hexyl alcohol by adding *n*-heptane. The yield of 1-propyl-1-C14-ammonium perchlorate was 11 g. (31%), m.p. 167°.

***n*-Propylamine–Nitrous Acid Reaction.**—To a stirred solution at 25° of 22.5 g. of 1-propyl-1-C14-ammonium perchlorate in 20 ml. of 35% perchloric acid was added dropwise over 2 hours 21 g. of sodium nitrite dissolved in 30 ml. of water. The solution was then distilled until 25 ml. of distillate was collected. The distillate was acidified with hydrochloric acid and redistilled to remove any excess amine. Potassium fluoride was added to the distillate to salt out the organic products which were then separated and diluted with 2.0 ml. of 1-propanol as a carrier. The products were fractionated through a Podbielniak Micro Column and yielded, besides 3.4 g. (41%) of 2-propanol with b.p. 80–84°, 0.76 g. of pure 1-propanol, b.p. 95–96°. The 1-propanol was diluted with 20 g. of carrier 1-propanol for the degradation reactions. Part of the 1-propanol was converted to the 3,5-dinitrobenzoate, m.p. 73°, for radioactive assay.

Degradation Procedure.—A stirred solution of 20 g. of labeled propanol in 300 ml. of water containing 30 ml. of concd. sulfuric acid was cooled to 5° with an ice-bath and 54 g. of potassium permanganate added in small portions at a rate slow enough to keep the temperature below 15°. The mixture was stirred for 1.5 hours, after which time sulfur dioxide was passed in until the manganese dioxide dissolved. The solution was extracted continuously with ether for 10 hours. The extract was dried with sodium sulfate and distilled. The yield of propionic acid, b.p. 135.5–139.5°, was 8.1 g. (42%). The product was assayed as the *p*-toluidide, m.p. 124°.

A mixture of 1.44 g. of labeled propionic acid, 5 ml. of chloroform and 3 ml. of concd. sulfuric acid was stirred magnetically at 45–55° in a 200-ml. flask equipped with a dropping funnel and gas inlet and outlet tubes while a stream of carbon dioxide-free nitrogen was passed through. The outlet was connected to two absorption flasks containing 0.07 *N* barium hydroxide solution. The nitrogen flow was stopped and 35 ml. of a solution of 1.2 *N* hydrazoic acid in chloroform added over 70 minutes. After two additional hours at 50°, nitrogen was passed through to sweep out the balance of the carbon dioxide. The barium carbonate precipitate in the absorption flasks was filtered, washed with boiling water and acetone, then dried at 120°. The yield was 2.8 g. (73%). The material in the reaction flask was cooled with ice, cautiously basified with 5% sodium hydroxide solution and stirred with a solution of 2 g. of *p*-bromobenzenesulfonyl chloride in 5 ml. of chloroform. After 2 hours, the mixture was acidified with concd. hydrochloric acid, the chloroform layer separated, dried over sodium sulfate and evaporated to dryness. The residue was dissolved in 5% sodium hydroxide solution, the crude N-ethyl *p*-bromobenzenesulfonamide precipitated with hydrochloric acid, dried and crystallized from a benzene–*n*-hexane mixture. The yield was 1.4 g. (30%), m.p. 80.5°.

The degradation procedure was checked in the following way. 1-Propionitrile-1-C14 (see above) was hydrolyzed with 90% sulfuric acid to propionic-1-C14 acid in 67% yield. The acid was reduced with lithium aluminum hydride to give a 50% yield of 1-propanol-1-C14. The above degradation was then carried through on the 1-propanol-1-C14 and, as may be seen from the data given in Table I, a negligible fraction of the activity of the N-propionyl-*p*-toluidide was found in the N-ethyl-*p*-bromobenzenesulfonamide.

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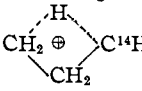
FOR NUCLEAR SCIENCE AND ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

(9) It is possible that some or all of the rearranged 1-propanol might arise from an intermediate such as  Such intermediates may be important in special sterically favorable conditions; J. D. Roberts and C. C. Lee, *ibid.*, **73**, 5009 (1951), J. D. Roberts and J. A. Yancey, *ibid.*, **75**, 3165 (1953), but are rendered unlikely with alkyl derivatives by the finding[4] that the presumably more stable ion I does not seem to play a very important role in the reaction of ethylamine with nitrous acid.

(10) The radioactive sodium cyanide was obtained from Tracerlab, Inc., Boston, Mass., on allocation from the U. S. Atomic Energy Commission.

(11) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 282 (1951).

The Alpha Phase of Some Sodium 1-Alkanesulfonates

BY L. A. WILCOX AND E. C. LINGAFELTER

RECEIVED JULY 17, 1953

X-Ray crystallographic data for the alpha phase of some sodium 1-alkanesulfonates containing even numbers of carbon atoms (from 8 to 18) have been reported previously.[1] Alpha phase crystals for the compounds containing odd numbers of carbon atoms (from 7 to 15) have now been obtained. This paper presents the data for the odd compounds and compares them with the even compounds.

Experimental

The sodium 1-alkanesulfonates were prepared by the action of aqueous sodium sulfite on the appropriate *n*-alkyl bromides,[2] and were purified by recrystallization from 95% ethanol.

Alpha phase crystals were obtained by cooling hot saturated solutions of the sulfonates in 95% alcohol. In the case of the C_{13} and C_{15} compounds, alpha phase crystals were also obtained by slow evaporation of aqueous solutions at 30–35°, sometimes associated with beta or epsilon crystals.

The hydration of the alpha phase crystals was determined for the C_{11} and C_{13} compounds with the apparatus described by Lingafelter, Jensen and Markham.[3] The values obtained are 0.126 and 0.124 mole of water per mole sulfonate, indicating $RSO_3Na \cdot {}^1/_8H_2O$, as was found for the even compounds. In the run on the C_{11} compound, after all of the water had been removed, the sample was cooled to 95° (*i.e.*, below the transition temperature), and 0.130 mole of water per mole sulfonate was taken up, while X-ray powder patterns showed reconversion to the alpha phase.

The monoclinic crystals show the same habit as previously observed for the even compounds, thin, tabular on (001), somewhat elongated in the *a* direction, and outlined by (01*l*) and (11*l*).

The X-ray data were obtained from rotation, equi-inclination Weissenberg, and precession photographs, using CuKα radiation (λ = 1.5418 Å.). The rotation and Weissenberg cameras were calibrated with NaCl.

The dimensions of the unit cells are given in Table I in which the values for both the odd and even compounds are included for comparison. The values chosen for β are not in conformance with the convention of choosing β as near as possible to 90°, but were chosen to give a unit cell whose *c* axis is probably closest to the actual direction of the paraffin chains. The basis for this choice will be discussed below.

TABLE I

UNIT CELL DIMENSIONS OF ALPHA-$RSO_3Na \cdot {}^1/_8H_2O$

Substance	a_0, Å.	b_0, Å.	c_0, Å.	β
$C_7H_{15}SO_3Na$	16.88	10.18	55.22	115°36′
$C_8H_{17}SO_3Na$	16.89	10.19	61.19	117°21′
$C_9H_{19}SO_3Na$	16.86	10.13	65.53	115°02′
$C_{10}H_{21}SO_3Na$	16.84	10.17	71.51	116°27′
$C_{11}H_{23}SO_3Na$	16.81	10.09	75.63	114°38′
$C_{12}H_{25}SO_3Na$	16.80	10.14	81.99	116°14′
$C_{13}H_{27}SO_3Na$	16.76	10.04	86.10	114°40′
$C_{14}H_{29}SO_3Na$	16.78	10.08	92.26	115°59′
$C_{15}H_{31}SO_3Na$	16.77	10.07	96.33	114°21′
$C_{16}H_{33}SO_3Na$	16.78	10.07	102.51	115°34′
$C_{18}H_{37}SO_3Na$	16.76	10.07	112.78	115°23′

Densities were determined by the flotation method using 1,4-dioxane and carbon tetrachloride. The unit cells contain 32 molecules of $RSO_3Na \cdot {}^1/_8H_2O$, with calculated and observed densities agreeing in all cases to better than 0.9%.

With the unit cells chosen as indicated in Table I, the extinctions of *hkl* for $k + l$ odd and *h*0*l* for *h* (or *l*) odd indicate the space groups Aa (C_s^4) or A2/a (C_{2h}^6) for the odd compounds, while Ia(C_s^4) or I2/a(C_{2h}^6) is indicated for the even compounds by the extinctions of *hkl* for $h + k + l$ odd and *h*0*l* for *h* (or *l*) odd.

Discussion

The angle of tilt of the chain direction from the normal to the (001) plane can be estimated from the ratio of the increase in d_{001} (Δd), between homologs to the expected increase in chain length. A comparison of d_{001} values from reported paraffin-chain compounds in which the tilt is zero gives an average value for the increase in chain length of 1.275 Å. per carbon atom. Since Δd is constant throughout the homologous series, with no significant difference between the odds and the evens, the average Δd has been calculated by a least squares treatment, assuming d_{001} to be a linear function of the number of carbon atoms. This gave Δd = 4.739 Å. Thus the tilt is 21° 40′ (*i.e.*, $\cos^{-1}[4.739/(4)(1.275)]$).

Since this calculation indicates a constant tilt of 21° 40′ it seems reasonable to choose the values of β given in Table I, since none of the other possible choices give values of (β − 90°) which are as constant through the series or as near to 21° 40′. The difference between 21° 40′ (the angle of tilt of the chains) and 25° 34′ (the average value of β − 90°) is readily explained by the assumption that, although the several chains in a given crystal are parallel, successive chains in the *c*-direction are not co-linear, there being a shift in the *a* direction between successive chains to permit efficient packing of the chain-ends.

This explanation is corroborated by the fact that β − 90° is approaching the value of the tilt as the chain length increases, due to the fact that the effect of the shift in the *a*-direction has a smaller effect on β, the greater the length of the unit cell in the *c*-direction.

The relation between tilt, β, and the shift at the chain ends can be treated quantitatively as follows. Let τ = actual tilt of chains; Δa = shift at the chain ends (total effect per unit cell). Then

$$d_{001} \tan\left(\beta - \frac{\pi}{2}\right) = d_{001} \tan \tau + \Delta a$$

$$\Delta a = d_{001}\left[\tan\left(\beta - \frac{\pi}{2}\right) - \tan \tau\right]$$

Using this equation, values of Δa for the several members of the series have been calculated for various assumptions of τ until a value of τ was found which gave a constant Δa for all members. This calculation gave a constant $\Delta a \cong 2.86$ Å. for τ = 22° 45′ for the odds and $\Delta a \cong 4.96$ Å. for τ = 23° for the evens. These two values of the tilt are certainly equal within the accuracy of the calculation and the difference of ~1° between this value and the tilt calculated from Δd_{001} is probably less than experimental uncertainties.

Thus it appears that the odd and even members of the homologous series of sodium 1-alkanesulfonates have the same tilt, ~22°, the only difference in their structures being in the displacement between successive layers of the structure.

The great similarity of the structures of the odd

(1) L. H. Jensen and E. C. Lingafelter, THIS JOURNAL, **66**, 1946 (1944). In this article the alpha phase was erroneously reported to be $RSO_3Na \cdot {}^1/_4H_2O$ instead of $RSO_3Na \cdot {}^1/_8H_2O$. *Cf.* ref. 3 below.

(2) R. M. Reed and H. V. Tartar, THIS JOURNAL, **57**, 570 (1935).

(3) E. C. Lingafelter, L. H. Jensen and A. E. Markham, *J. Phys. Chem.*, **57**, 428 (1953).

and even compounds is also evident from a comparison of the distribution of diffraction intensity in reciprocal space, all members of the series showing regions of relatively high intensity in the same positions.

The effective cross-sections of the paraffin chains normal to their chain direction, calculated from $1/8a_0b_0 \cos \tau$, have an average value of 19.6 Å.^{2}, and show a slight decrease with increasing chain length.

The average molar volume increment is found to be 29.6 cm.^{3}/CH_2/mole.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON

Densities and Thermal Expansion Coefficients of Several Organofluoro Compounds

BY GENE P. RUTLEDGE AND WILLIAM T. SMITH, JR.

RECEIVED JUNE 29, 1953

The densities of several liquid organofluoro compounds were determined (see Table I) in an attempt to find some liquid having an exceptionally high thermal expansion coefficient for an industrial application. The expansion coefficient, α, is defined as $(d_1 - d_2)/d_2(T_2 - T_1)$ where d_1 is the density at the lower temperature, T_1 and d_2 the density at T_2. Published density measurements[1] on perfluoro-*n*-heptane and perfluoro-1,3,5-trimethylcyclohexane indicate that large values of α might be expected for fluorine compounds.

All of the liquids used were purified by distillation. Calibrated, Sprengel type, Pyrex glass pycnometers having ground glass caps and an approximate capacity of 11 ml. were used. Agitation of the thermostatic fluid, 18 liters of mineral oil, was accomplished by two turbine pumps which brought the oil from the bottom of the lagged metal vessel to the surface. A De Khotinsky thermoregulator which activated a Fisher–Surfass electronic relay afforded temperature control of $\pm 0.02°$. The temperatures were measured using National Bureau of Standards thermometers. The average value of two density measurements was taken. From the precision of the temperature control, the accuracy of the weighing (± 0.1 mg.) and the agreement obtained for duplicate samples, it is estimated that the coefficients are accurate to $\pm 1\%$ for a 10° range.

A comparison of the expansion coefficients of the fluorinated compounds (Table I) with values calculated from density measurements[2] on the corresponding unfluorinated compounds reveals, in general, that the coefficients are greater for the fluorinated compounds. For example, α-fluoroanisole has a coefficient 2% greater than anisole over the same temperature range. For α-fluoronaphthalene the coefficient is 3% greater than for naphthalene; *p*-fluorobromobenzene, 2% greater than bromobenzene and benzotrifluoride, 12% greater than toluene. Toluene and *p*-fluorotoluene have nearly identical coefficients.

Ethyl acetate has a high expansion coefficient, typical of esters. Ethyl difluoroacetate has an even higher coefficient and ethyl trifluoroacetate has a coefficient that is 31% greater than that of the

TABLE I

DENSITIES AND THERMAL EXPANSION COEFFICIENTS OF ORGANOFLUORO COMPOUNDS AT VARIOUS TEMPERATURES

Temp., °C.	Ethyl difluoroacetate	Ethyl trifluoroacetate	Benzotrifluoride	1,1,1-Trifluoro-2,3,3-trichloropropene	1,1-Difluoro-3,3-dichloropropene-2	*p*-Fluorotoluene	*p*-Fluorobromobenzene	α-Fluoronaphthalene	α-Fluoroanisole
	Density, g./ml.								
30.00	1.1600	1.1670	1.1762	1.5940	1.4401	0.9869	1.5859	1.1256	1.1054
40.00	1.1446	1.1466	1.1621	1.5753	1.4248	.9763	1.5710	1.1168	1.0948
50.00	1.1287	1.1260	1.1478	1.5549	1.4069				
60.00	1.1125		1.1353	1.5336	1.3881	.9548	1.5413	1.0995	1.0734
70.00	1.0958		1.1184	1.5117	1.3692				
80.00	1.0790		1.1033	1.4905	1.3503	.9329	1.5114	1.0821	1.0514
100.00						.9102	1.4803	1.0649	1.0297
120.00							1.4490	1.0464	1.0061
140.00							1.4167	1.0284	0.9824
160.00								1.0091	
Temp. range, °C.	Thermal expansion coefficient, α, $\times 10^5$								
30– 40	135	178	121	119	108	108	94	79	97
40– 50	141	183	124	131	127				
50– 60	145		129	139	135				
40– 60						113	96	78	100
60– 70	152		133	145	138				
70– 80	157		137	142	140				
60– 80						118	99	80	104
80–100						125	105	81	106
100–120							108	88	117
120–140							114	88	121
140–160								96	

(1) A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.*, **39**, 375 (1947).

(2) "Annual Tables of Physical Constants," Sec. 301 (C), American Committee of Annual Tables, National Research Council, Princeton, New Jersey (1941).

difluoroacetate. In general, it appears that an increase in the extent of fluorination of an organic compound results in an increase in thermal expansion coefficient.

Acknowledgment.—This work was carried out under a grant established at the University of Tennessee as the Fulton Fellowship by the Fulton–Sylphon Company of Knoxville, Tennessee.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TENNESSEE
KNOXVILLE, TENN.

Decomposition of Nitrogen Pentoxide in the Presence of Nitric Oxide. IV. Effect of Noble Gases

BY DAVID J. WILSON AND HAROLD S. JOHNSTON

RECEIVED JUNE 22, 1953

The rate of the reaction $N_2O_5 + NO \rightarrow 3NO_2$ has been shown by Smith and Daniels[1] and by Mills and Johnston[2] to be that of an elementary unimolecular reaction. At around 0.1 mm. pressure in a 22-liter flask, the reaction is homogeneous and definitely within the second-order region.[3] The low-concentration second-order rate constants of a series of gases have been reported.[4]

Using the 22-liter bulb, and the same method of interpreting the data as was used previously,[3,4] we have determined the low-concentration second-order rate constants of the noble gases and carbon tetrachloride. Reactant pressures were each about 0.08 mm., and foreign gas pressures ranged from 3 to 0.02 mm. Experimental results are given in Table I.

TABLE I

EXPERIMENTAL RESULTS

M gas	No. of points	Intercept, sec.$^{-1}$	Low concn. second-order rate constant, cc. mole^{-1} sec.$^{-1}$ × 10^5 Value	Standard error	Ratio to pure N_2O_5
He	27	0.0132	2.80	0.26	0.124
Ne	17	.0129	2.02	.32	.090
Kr	26	.0119	3.57	.23	.159
Xe	11	.0134	3.30	.95	.147
CCl_4	30	.0130	12.4	1.3	.551

As shown previously, the activating efficiency function of the state i above the critical energy, a_{Mi}, can be written as $a_{Mi} = b_{Mi}P_i$, that is, the relative activating efficiency is also the relative deactivating efficiency. The function b_{Mi} is further factored, $b_{Mi} = b_M f_{Mi}$, where b_M is the kinetic collision constant

$$b_M = N_0\left[8\pi RT\left(\frac{1}{M_1}+\frac{1}{M_2}\right)\right]^{1/2}\left(\frac{\sigma_1+\sigma_2}{2}\right)^2 \quad (1)$$

where N_0 is Avogadro's number; σ_1 and σ_2, the collision diameters of the colliding particles; M_1 and M_2, the molecular weights of the colliding particles; and R and T have their usual meaning. The function f_{Mi} is the efficiency factor for deactivation which in general may be a function of each state i and a different function for each foreign gas M.

If the collision constant can be calculated by 1, then the relative efficiencies with b_M factored out give the ratios $\overline{(f_M)}/\overline{(f_1)}$, where 1 stands for nitrogen pentoxide, and the bar indicates an average with respect to P_i over the excited states. If deactivation occurred at every collision or if f_{Mi} depended on the quantum states i of the reactant molecule only but not on the identity of the foreign gas M, this ratio would be unity every time. It is not. (See Table II. This table includes data calculated from reference 4.)

TABLE II

EFFICIENCY AND RELATIVE EFFICIENCY

M gas	Mol. wt.	Collision diameter, Å.	Low concn. rate const./kinetic collision const., $\overline{(f_M)} \times 10^{10}$	$\overline{(f_M)}/\overline{(f_1)}$
He	4	2.18[a]	6.02	0.0650
Ne	20	2.59[a]	7.95	.0855
A	40	3.64[a]	14.3	.154
Kr	83.8	4.16[a]	19.3	.208
Xe	131.3	4.85[a]	17.5	.189
N_2	28	3.75[a]	21.2	.228
NO	30	3.75	27.9	.300
CO_2	44	4.59[a]	35.9	.387
CCl_4	154	5.46	62.5	.673
SF_6	146	4.52	41.2	.443
N_2O_5	108	6.00	93.0	1.000

[a] From E. H. Kennard, "Kinetic Theory of Gases," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 149.

Furthermore, it is impossible to adjust the collision diameters of either nitrogen pentoxide or of the various M gases to obtain ratios $\overline{(f_M)}/\overline{(f_1)}$ that are equal to unity. For the molecular weights are accurately known, and the ratio, $(2\sigma_{N_2O_5}/\sigma_{N_2O_5} + \sigma_M)^2$, can never be greater than 4, which is not sufficiently large to account for the observed relative efficiencies of the noble gases and nitrogen. Thus, the efficiency function f_{Mi} does differ markedly from one gas to another. (These results do not answer the question as to whether or how the efficiency function varies over the states i of the reactant molecule.)

Relative efficiency increases slowly with molecular weight through at least krypton for the noble gases. It increases at constant molecular weight as one goes from noble gases to diatomic or polyatomic gases, and nitrogen pentoxide is much more efficient than anything else we have yet used. A study of the relative efficiencies of diatomic and polar gases is now in progress.

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DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD, CAL.

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