NOTES

Identification of the Products of Thermal Exchange between Alkyl Iodides and Molecular Iodine by the "Wash Out" Carrier Technique[1]

By Richard G. Badger, Chester T. Chmiel and Robert H. Schuler

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Exchange between molecular iodine and the alkyl iodides has previously been observed to be induced both by light in the visible region[2] and thermally.[3] The thermal reaction proceeds at a very low rate at temperatures of approximately 75° and is readily measurable only at low iodine concentrations. Preliminary evidence points to the mechanism as probably being due to a rate controlling reaction of the type

$$\mathrm{RI} + \mathrm{I}\cdot \longrightarrow \mathrm{R}\cdot + \mathrm{I_2} \qquad (1)$$

followed by a quenching of the radicals with molecular radioiodine.[4]

$$\mathrm{R}\cdot + \mathrm{I_2}^* \longrightarrow \mathrm{RI}^* + \mathrm{I}\cdot \qquad (2)$$

Isolation of the alkyl iodides formed provides identification of the radicals produced and the use of radioiodine together with suitable carriers makes this identification feasible. Radioiodine has previously been employed for free radical detection in the photolysis of the alkyl iodides,[5] the radiolysis of alkyl iodides and hydrocarbons,[6] in the photodecomposition of methyl ethyl ketone and in studies of the decomposition of propyl radicals produced by the sodium flame reaction with propyl bromide.[7] The purpose of this investigation is to ascertain the nature of the products of thermal exchange between alkyl iodides and molecular iodine and to determine the extent of radical rupture and isomerization under the conditions in which they are formed in these exchange experiments.

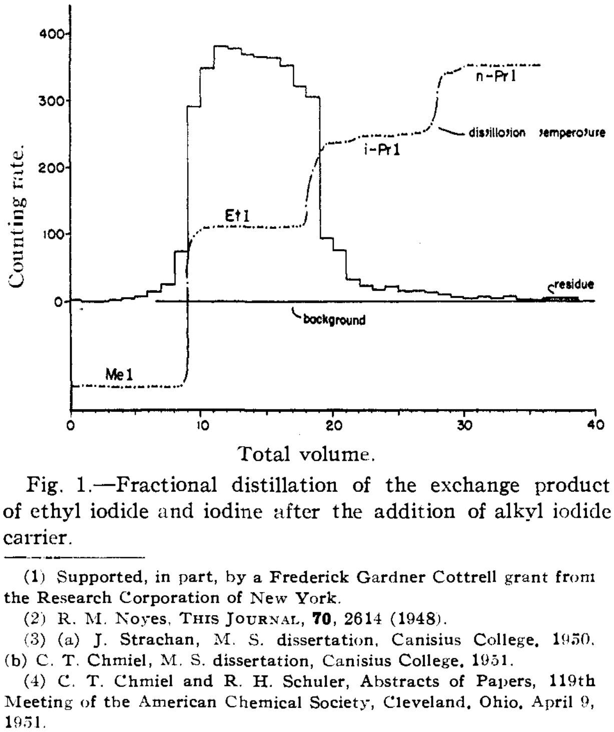

Fig. 1.—Fractional distillation of the exchange product of ethyl iodide and iodine after the addition of alkyl iodide carrier.

Preliminary investigations employed a fractionation procedure similar to that of Williams and Hamill.[6a] Ethyl iodide and iodine[8] were exchanged at 65°. The free iodine was extracted from the sample and 10 ml. each of methyl, *n*-propyl and isopropyl iodide carriers were added to 10 ml. of the exchange product. The mixture was fractionated using a 30-cm. Podbielniak heligrid packed column with one-cc. cuts of the distillate being taken. These were diluted to five ml. and counted. The activity, together with the boiling point, of each fraction is plotted in Fig. 1 as a function of the total volume distilled; with account being taken for any variation in the volume of the individual cuts. It is seen that the majority of the activity appears in the ethyl iodide fraction. No activity ($< 1\%$) is observed in the methyl iodide and the small amounts of activity ($< 4\%$) which do appear in the high boiling fractions probably result from contamination by incomplete fractionation or by physical hold-up in the column head. Three other experiments of this type gave similar results. This technique is extremely tedious to operate manually and somewhat less reliable if set up for automatic operation.[6b] It also suffers in that the alkyl iodides can only be recovered with difficulty should further work on any of the fractions be desirable.

A modified technique has been developed in which the major fraction of each cut is collected as a unit, counted, and contaminating activity washed out by the addition of suitable carriers followed by fractionation. This "Wash Out" technique essentially involves the preparation of a sample which is radiochemically pure although not necessarily pure in the chemical aspect. Small amounts of impurities in the separated samples, as long as they do not contain activity, will not affect the results to an appreciable extent.

Ethyl iodide (b.p. 71.8° (750 mm.), $n^{25}\mathrm{D}$ 1.5102), *n*-propyl iodide (b.p. 42.8° (100 mm.), $n^{25}\mathrm{D}$ 1.5030), and isopropyl iodide (b.p. 47.0° (178 mm.), $n^{25}\mathrm{D}$ 1.4961) were allowed to thermally exchange with added iodine after the samples had been degassed and sealed on a vacuum line. The iodine was extracted, the samples washed, carriers added and the mixture separated on the Podbielniak column. Where there was possibility of contamination, the sample obtained from the first distillation was refractionated after the addition of inactive material identical to that of the supposed contaminant (*e.g.*, in the case of isopropyl iodide following a highly active ethyl iodide fraction, ethyl iodide was added to carry any contamination).

The results of these latter investigations, given in Table I, indicate that thermal exchange of the alkyl iodides with molecular iodine results almost entirely in the formation of a radiochemical species chemically identical to the parent substance. The propyl radical appears to have a sufficient lifetime in the liquid phase to be able to diffuse, without appreciable decomposition or isomerization, to the iodine present (at a mole fraction of 10^{-4}). While a very small amount of decomposition to methyl radical does appear to take place at 95° in the case of the *n*-propyl radical, the isopropyl radical gives entirely negative results in this regard. It is possible for the propyl radical to decompose by reaction 3

$$\mathrm{CH_3{-}CH_2{-}CH_2}\cdot \longrightarrow \mathrm{CH_3}\cdot + \mathrm{CH_2{=}CH_2} \qquad (3)$$

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[1] Supported, in part, by a Frederick Gardner Cottrell grant from the Research Corporation of New York.

[2] R. M. Noyes, This Journal, **70**, 2614 (1948).

[3] (a) J. Strachan, M. S. dissertation, Canisius College, 1950. (b) C. T. Chmiel, M. S. dissertation, Canisius College, 1951.

[4] C. T. Chmiel and R. H. Schuler, Abstracts of Papers, 119th Meeting of the American Chemical Society, Cleveland, Ohio, April 9, 1951.

[5] W. H. Hamill and R. H. Schuler, This Journal, **73**, 3466 (1951).

[6] (a) R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **72**, 1857 (1950); (b) L. H. Gevantman and R. R. Williams, Jr., *J. Phys. Chem.*, **56**, 569 (1952).

[7] R. W. Durham, G. R. Martin and H. C. Sutton, *Nature*, **164**, 1052 (1949).

[8] Radioiodine ($\mathrm{I^{131}}$) prepared from samples obtained from the U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

while no analogous reaction path is open to the isopropyl radical. Although they give no data in regard to the lifetime of the radicals, Durham, Martin and Sutton[7] indicate a partial decomposition of propyl radical in the vapor phase at 400°.

TABLE I

PRODUCTS OF THE THERMAL EXCHANGE OF IODINE AND THE ALKYL IODIDES

Exchange, %	Total org. activity, c./m.	Per cent. activity as CH_3I	C_2H_5I	i-C_3H_7I	n-C_3H_7I	CH_2I_2
Ethyl iodide (75°, 0.024 M in I_2)						
71	885	0^b	>98	0^b	0^b	0^b
n-Propyl iodide (75°, 0.024 M in I_2)						
64	660	0^b	0^b	0^c	>98	..[a]
n-Propyl iodide (95°, 0.0008 M in I_2)						
71	5730	0.5	0.2	0.3	98.5	0.5
Isopropyl iodide (95°, 0.0023 M in I_2)						
98	14100	0.0^d	0.4	98.6	0.7	0.3

[a] No carrier methylene iodide added. [b] < 0.5%. [c] < 1%. [d] < 0.1%.

The results of Table I represent an upper limit to systematic errors that can affect the validity of the present separation methods. It is indicated that the reliability of results obtained by this method is better than a fraction of one per cent., or the limit of the activity measurements should this be higher. Detection of the formation of small amounts of radicals appears to be quite practicable especially in the case of methyl since methyl iodide is easily separated from the higher boiling components.

Further investigations are in progress utilizing the technique described above in studies of alkyl iodide systems.

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A New Synthesis of Aminomalonic Acid[1]

BY JAN H. R. BEAUJON AND WALTER H. HARTUNG

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Aminomalonic acid was first described in 1864, by Baeyer who prepared it by reduction of potassium oximinomalonate with sodium amalgam and water.[2] Ruhemann and Orton[3] synthesized aminomalonic acid from nitromalonamide by reducing the nitro group with sodium amalgam and water, and removing the amido groups by hydrolysis. Lütz,[4] in 1902, found that he could obtain aminomalonic acid by treating halogenated malonic acid with ammonia. Finally, in 1904, Piloty and Finckh[5] obtained aminomalonic acid by alkaline hydrolysis of uramil, 5-aminobarbituric acid.

In view of the known instability of malonic acids, it is doubtful that any of these methods yields aminomalonic acid in pure form. In most cases the reagents used are quite destructive and the decomposition products, mainly glycine, may be expected to contaminate the product.

The present synthesis employs diethyl carbobenzyloxyaminomalonate, an intermediate in the preparation of malonic acid analogs of α-amino acids.[6] The unsubstituted ester, hydrolyzed under conditions previously described,[6] gives good yields of the alkali salt of carbobenzyloxyaminomalonic acid, which, on catalytic hydrogenolysis in aqueous solution, gives the salts of aminomalonic acid.

Experimental

Potassium Carbobenzyloxyaminomalonate.—This compound was prepared by hydrolysis of 12.4 g. (0.04 mole) of diethyl carbobenzyloxyaminomalonate[6] in 50 ml. of a 20% solution of potassium hydroxide in 95% ethanol. A gummy precipitate, weighing more than 12.5 g. (calcd. for pure dipotassium salt, 12.6 g.), was formed on standing overnight. This precipitate, on attempted recrystallization from 80–90% ethanol, formed a slightly yellowish, oily material. On washing with 95% ethanol it became almost colorless, and after drying over phosphorus pentoxide it turned into a white, hygroscopic solid. *Anal.* Calcd. for $C_{11}H_9O_6NK_2$: N, 4.26. Found: N, 4.31, 4.43.

Potassium carbobenzyloxyaminomalonate could be acidified to produce carbobenzyloxyaminomalonic acid, m.p. 147–148° (uncor.), with evolution of gas. *Anal.* Calcd. for $C_{11}H_{11}O_6N$: N, 5.54. Found: N, 5.56, 5.51.

Monodecarboxylation of carbobenzyloxyaminomalonic acid by boiling with dilute hydrochloric acid yielded N-carbobenzyloxyglycine, m.p. 119–120° (uncor.), m.p. reported, 120°.[7] Although the analysis for the free acid is satisfactory, the visible evolution of gas on its formation suggests that it is more stable as a salt.

Monopotassium Carbobenzyloxyaminomalonate.—To a solution of 2.4 g. of KOH (0.041 mole) in 10 ml. of water was added with constant stirring 10.2 g. of carbobenzyloxyaminomalonic acid (0.04 mole). To the resulting clear solution was added with stirring commercial absolute ethanol until no further precipitate formed. The solid was removed, washed with 95% alcohol and recrystallized three times from 80–90% alcohol; obtained 7.1 g. of pure white crystals, 61.1%. *Anal.* Calcd. for $C_{11}H_{10}O_6NK$: N, 4.82. Found: N, 4.82, 4.85.

Monopotassium Aminomalonate.—A solution of 5.8 g. of monopotassium carbobenzyloxyaminomalonate (0.02 mole) in 50 ml. of distilled water was hydrogenated in the Parr apparatus in the presence of 2 g. of palladium–charcoal catalyst at an initial pressure of 4 atm. hydrogen; shaking was continued for an hour after the gage pressure became constant. The catalyst was removed and the solution concentrated under reduced pressure to 25 ml. and then poured into 150 ml. of boiling absolute ethanol and filtered. The solution, after standing for about a week, yielded large crystals, which were removed and recrystallized twice from 80–90% alcohol; yield 1.0 g., 32%. *Anal.* Calcd. for $C_3H_3O_4NK$: N, 8.91. Found: N, 8.92, 8.86.

Hydrogenation of dipotassium carbobenzyloxyaminomalonate under similar conditions, and isolation of the product as described above, also leads to the monopotassium aminomalonate, the carbon dioxide liberated during hydrogenolysis of the carbobenzyloxyl group accounting for the other potassium ion.

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[1] No. 13 in amino acid series. For No. 12 see J. H. R. Beaujon, W. R. Straughn, Jr., and W. H. Hartung, *J. Am. Pharm. Assoc.*, **41**, 581 (1952).

[2] A. Baeyer, *Ann.*, **131**, 291 (1864).

[3] S. Ruhemann and K. J. P. Orton, *J. Chem. Soc.*, **67**, 1002 (1895).

[4] O. Lütz, *Ber.*, **35**, 2549 (1902).

[5] O. Piloty and C. Finckh, *Ann.*, **333**, 71 (1904).

[6] J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc.*, **41**, 578 (1952).

[7] H. D. Carter, R. L. Frank and H. W. Johnston, *Org. Syntheses*, **23**, 13 (1943).

4-Nitrophthalimides. I. Derivatives of Alkyl Halides Giving a Saponification Equivalent[1]

BY JOHN H. BILLMAN AND R. VINCENT CASH

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Among the many derivatives suggested for the identification of alkyl halides are the N-alkyl-

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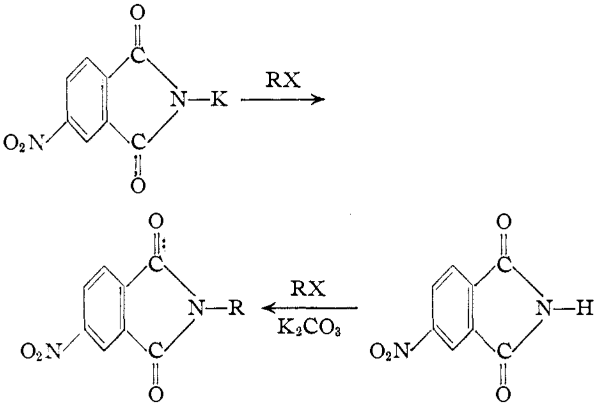
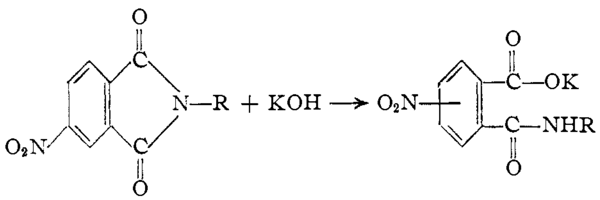
[1] From the Ph.D. Thesis of R. Vincent Cash, Indiana University, September, 1951.

phthalimides,[2] the N-alkyl-3-nitrophthalimides,[3] the N-alkyltetrachlorophthalimides[4] and the related N-alkylsaccharins.[5] In terms of suitability, each of these derivatives has certain limitations—the N-alkylphthalimides and the N-alkylsaccharins are rather low-melting and may separate as oils, the N-alkyl-3-nitrophthalimides and the N-alkyltetrachlorophthalimides give higher melting points but require 10 hours of heating for their preparation.

The possibility of the N-alkyl-4-nitrophthalimides as derivatives of alkyl halides has been investigated. The imides which we prepared may be obtained by the reaction of the proper alkyl halide with either potassium 4-nitrophthalimide or 4-nitrophthalimide and potassium carbonate. High yields are obtainable by either reaction, in dimethylformamide, according to the directions which follow. The latter reaction is more convenient since it obviates the preparation of potassium 4-nitrophthalimide. The alkyl bromide was employed for each of these preparations, unless otherwise indicated in the table.



It has been found that these imides lend themselves to the determination of saponification equivalents, since under mild conditions in the presence of a slight excess of dilute standard base the imide ring opens to form the salt of the related phthalamic acid. The saponification equivalent is determined by titration of the excess standard base with hydrochloric acid, using *m*-cresol purple as indicator. Phenolphthalein was found to be unsatisfactory.



For characterization purposes, the combination of melting point and saponification equivalent will usually clearly distinguish two of the imides in Table I even though either alone might not suffice.

TABLE I

N-ALKYL-4-NITROPHTHALIMIDES

N-Alkyl substituent	M.p.,[a] °C.	Yield,[b] %	Sapn. equiv. Calcd.	Sapn. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl[c]	177–178	87.5[d]	206.1	205.0		
Ethyl[e]	114–115	80.6	220.2	218.3		
Propyl[e]	102–102.5	75.0	234.2	233.6		
Isopropyl	133–134	21.6[f]			11.94	11.98
Butyl[e]	95–96	82.5	248.3	245.4		
Isobutyl	127–128	46.7[f]	248.3	248.6	11.28	11.42
Amyl[e]	95–96	77.8	262.3	261.3		
Isoamyl	118-119	81.7	262.3	260.2	10.68	10.54
Hexyl[e]	94.5-95.5	74.3	276.3	275.1		
3-Methyl-pentyl	95.5–96	93.4	276.3	264.5	10.13	10.34
2-Ethylbutyl	88–89	66.8	276.3	276.0	10.13	10.17
Heptyl[e]	92–93	73.8	290.3	290.4		
Octyl[e]	88.5–89.5	87.4	304.3	303.9		
2-Ethylhexyl	61.5–62	80.7	304.3	306.1	9.21	9.20
Nonyl[e]	88–88.2[g]					
Decyl[e]	87.5–88.5	84.0	332.4	331.3		
Undecyl	86.5–87.5	23.6			8.09	8.10
Dodecyl	85.5–86	21.6			7.78	7.68
Tetradecyl	86.5–87	72.3			7.21	7.14
Hexadecyl	91.5–92	82.8	416.6	414.7	6.73	7.03
Octadecyl	91.5–92.5	96.6			6.30	6.55
Allyl	105.5–106.5	79.2[f]	232.2	231.3	12.06	12.26
Benzyl[e]	164-165	73.4[f]	282.2	282.5		
p-Nitrobenzyl	163–164	79.4[f]			12.83	12.85
2-Phenylethyl	144–144.5	58.4	296.3	296.2	9.47	9.33
3-Phenylpropyl	110.5–111.5	81.5[f]	310.3	307.3	9.04	8.82

[a] All melting points corrected. [b] Yield after recrystallization based on 4-nitrophthalimide or potassium 4-nitrophthalimide. [c] M. T. Bogert and R. R. Renshaw, THIS JOURNAL, **30**, 1135 (1908), found m.p. 179–180°. [d] Prepared from methyl iodide. [e] A. F. Kirkpatrick, Ph.D. Thesis, Penn State Coll., 1943, p. 17. [f] Prepared from the alkyl chloride. [g] Not prepared, m.p. value of Kirkpatrick.

It was found that N-benzyl-3-nitrophthalimide, prepared from benzylamine, also gave a satisfactory saponification equivalent by our procedure. This suggests that the N-alkyl-3-nitrophthalimides derived from other primary amines[6] would permit the determination of a saponification equivalent in the same manner.

Experimental

N-Alkyl-4-nitrophthalimides.—In a 250-ml. round-bottomed flask was placed either 2.4 g. (0.104 mole) of potassium 4-nitrophthalimide or preferably 2.0 g. (0.104 mole) of 4-nitrophthalimide and 0.9 g. (0.065 mole) of anhydrous potassium carbonate. If the alkyl halide was not an iodide, 0.2 g. of potassium iodide was also included. Then 2–3 ml. (2 g. if a solid) of the dry alkyl halide and 20 ml. of dimethylformamide[7] were added. Under a reflux condenser bearing a drying tube, the mixture was heated at 135–145° for 1.25 hours. With low-boiling halides the temperature was raised slowly to this range. The flask was shaken occasionally. Some color appeared in the mixture, and if potassium carbonate were a reactant, carbon dioxide was evolved.

The cooled reaction mixture was poured into 100 ml. of cold water, using another 50 ml. of water to wash out the flask. After collecting the solid, it was washed with successive 40-ml. portions of water, 2% sodium hydroxide solution,[8] and water again. The dried crude product was recrystallized by dissolving it in a slight excess of 95% ethanol, filtering while hot, concentrating the solution somewhat, and adding water dropwise until the turbidity just disappeared.

Determination of the Saponification Equivalent.—An approximately 0.6-g. sample of pure N-alkyl-4-nitrophthal-

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[2] O. Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1923, p. 164.

[3] P. P. T. Sah and T. S. Ma, *Ber.*, **65B**, 1630 (1932): *Science Repts. Natl. Tsing Hua Univ.*, **2**, 147 (1933).

[4] C. F. H. Allen and R. V. V. Nicholls, THIS JOURNAL, **56**, 1409 (1934).

[5] L. L. Merritt, S. Levey and H. B. Cutter, *ibid.*, **61**, 15 (1939).

[6] J. W. Alexander and S. M. McElvain, *ibid.*, **60**, 2285 (1938).

[7] Dimethylformamide requires care in handling. Breathing of the vapor or contact of the liquid with the skin is to be avoided.

[8] The brief washing with base to remove 4-nitrophthalimide may be omitted with little sacrifice of product purity. Prolonged contact with base causes loss of product by saponification.

imide was weighed exactly on a tared watch glass and washed into a 250-ml. erlenmeyer flask with 12 ml. of 95% ethanol. From a buret, 25.00 ml. of standard potassium hydroxide (about 0.2 *N*) was added and the corked flask was warmed at 50° until the solid completely dissolved. When it had cooled to room temperature, the solution was diluted to a volume of about 100 ml. and four drops of 0.05% *m*-cresol purple indicator was added. The excess base was then titrated with standard hydrochloric acid (about 0.12 *N*), taking as the end-point, the first definite yellow (no purple) tint. The saponification equivalent of the N-alkyl-4-nitrophthalimide was computed in the same manner as that of an ester.

Two compounds gave unsatisfactory results by this procedure. The N-octadecyl-4-nitrophthalimide forms a rather insoluble, soapy potassium salt and complete solution was not attained. In the case of the N-(*p*-nitrobenzyl)-4-nitrophthalimide, the basic solution containing the salt displayed a yellow-brown color rather than purple when the indicator was added.

N-Benzyl-3-nitrophthalimide.—This compound was prepared from benzylamine and 3-nitrophthalic anhydride by the procedure of Alexander and McElvain.[6] Its saponification equivalent was determined by the above procedure as 280.6 (calcd., 282.2).

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Trifluoroacetyl Hypofluorite[1]

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For some time an investigation of the reactions of elementary fluorine with volatile carbon compounds containing oxygen has been under way in these laboratories. In the early stages of the work, the compound trifluoromethyl hypofluorite[2] was obtained by the fluorination of methanol or carbon monoxide. Later it was found that numerous organic compounds containing oxygen, such as ethanol, acetic acid, cyclohexanone, ethylene glycol and acetone, would react with fluorine, even by combustion, to produce trifluoromethyl hypofluorite as well as certain fluorinated hydrocarbons.

In another series of experiments fluorine was allowed to react at room temperature with various oxygen containing substances. In one case trifluoroacetic acid was placed in a platinum boat enclosed in a Teflon tube, and undiluted fluorine was passed over it. The reaction products which condensed in a trap cooled by liquid oxygen were found to be easily exploded by an electric spark. It was at once suspected that the explosive substance might be trifluoroacetyl hypofluorite formed by replacement of the hydrogen atom by fluorine. Attempts were then made to isolate and identify the compound. These efforts were discouraging. Sometimes no explosive product was obtained. At other times the substance exploded as the preparative reaction proceeded or while in the process of distillation. Several rather elaborate systems of glass apparatus were destroyed. Metallic systems were tried but the explosive compound was not obtained. Finally, the substance was prepared in a small amount as described below, and its molecular weight and composition were established.

The present article describes only exploratory experiments. There still remains a need for additional work in order that more properties of the substance may be known with precision.

Solutions believed to contain compounds of the formulas CF_3COOBr and CF_3COOI have been prepared by Henne and Zimmer[3] by the reaction of the free halogen with silver trifluoroacetate.

Materials.—Fluorine was used directly from cylinders obtained from the Pennsylvania Salt Manufacturing Co. Anhydrous trifluoroacetic acid was obtained from the Minnesota Mining and Manufacturing Co. Usually it was used just as it came from the manufacturer; for some experiments, however, the acid was distilled. The distillation appeared to have little effect upon the reaction of the acid with fluorine.

Experimental.—Figure 1 shows the equipment finally used for the preparation and identification of the compound. Inlets for controlled and measured streams of fluorine and nitrogen were provided as shown at the left of the figure. Bubblers A and B contained water and trifluoroacetic acid held at 20 and 0°, respectively. Trifluoroacetic acid vapor and water vapor were swept by streams of nitrogen into vessels C and D, where the reaction with fluorine occurred. The part of the system between boundaries F and G was composed of polyethylene bottles and tubing, Saran tubing and rubber stoppers. A glass tube served as the inlet for fluorine into bottle C. Bottles C and D were kept at room temperature. They had a combined volume of 1060 ml. Bottle E was held at −78° and was used as a trap to condense hydrogen fluoride, water vapor and unreacted trifluoroacetic acid from the gas stream. From it the gas passed through the glass system and out through stopcock X. Among the products condensed in the trap, W, which was cooled to −183° by liquid oxygen, were: CF_3COOF, CF_4, COF_2, CO_2 and SiF_4. The remainder of the glass system was used for refining the product and for taking samples. Before use, the system was carefully cleaned and dried. Stopcocks were lubricated with a greasy wax composed of polymers of chlorotrifluoroethylene. This highly essential material was obtained from the M. W. Kellogg Co. of Jersey City, N. J., and from the Halocarbon Products Corp. of North Bergen, N. J.

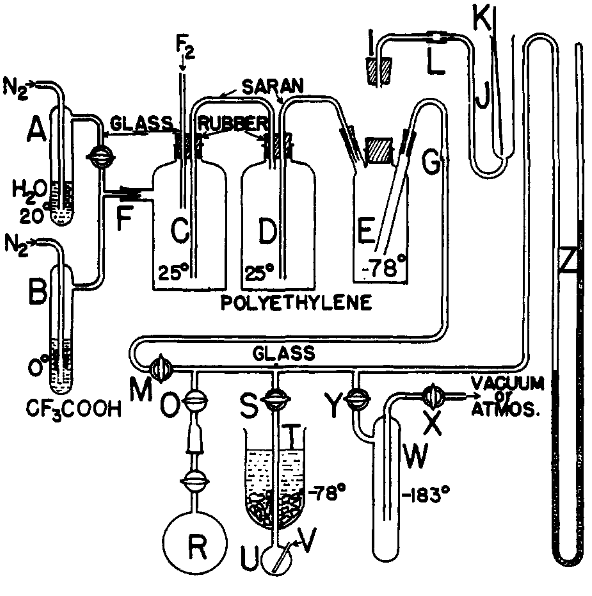

FIG. I.

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[1] This compound was mentioned in an article about the industrial production of fluorine chemicals at the Minnesota Mining and Manufacturing Co. [*Chem. Eng. News*, **29**, 4488 (1951)]. A letter to one of the authors from N. W. Taylor, Manager of the Fluorochemicals Department of that company states, "The story in Chemical and Engineering News referring to this type of product was due to a misunderstanding on the part of the editor. . . As far as 3M is concerned, you are the inventor of CF_3COOF."

[2] K. B. Kellogg and George H. Cady, THIS JOURNAL, **70**, 3986 (1948).

[3] A. L. Henne and W. F. Zimmer, *ibid.*, **73**, 1362 (1951).

Before starting a run, qualitative tests were made to see that the explosive product was being formed. To do this, the cap was removed from bottle E, and stopcock M was closed. Stopper I was inserted into the neck of bottle E and the gas was passed through the glass trap J, which was cooled at the bottom to −183°. After gas had passed for a measured time of four to eight minutes, tube J was disconnected at L and it was placed in an explosion shield made of sheet iron. Copper wire K was inserted as shown. After waiting for about 100 seconds to allow the product to vaporize, a spark producing "leak tester" was touched to wire K. If this caused a sharp explosion to occur, the apparatus was known to be producing the desired substance. The flow rates given below yielded enough material in four minutes to explode with a sharp report but not with enough energy to shatter the glass tube.

The role of water vapor in the reaction is not clear. Usually the product could be obtained without adding water. However, in the case of the last cylinder of fluorine used in the study, almost none of the explosive substance was formed unless water vapor was added.

The run which finally resulted in identification of the compound involved the following flow rates: F_2 from 0.97 to 0.83 g. per hour, trifluoroacetic acid at 2.1 g. per hour, water vapor at 0.1 g. per hour and nitrogen at 9.0 liters per hour. The reaction vessels were held at 25 ± 1° and the reaction was allowed to continue for three hours while the product was condensed in trap W. At the end of this time fluorine was swept from the system by a stream of dry nitrogen; then stopcock M was closed and the glass system was pumped out for about 10 minutes with a pump connected at X. After closing stopcock X, the product was distilled from trap W to the 10-ml. bulb U. Dry nitrogen at atmospheric pressure was then admitted to the glass apparatus and the system was left open to the atmosphere. Bulb U was then allowed to warm slowly to about −60°, being kept there by the near proximity of Dry Ice held in a suitable container, leaving only a few drops of liquid in the bulb. Stopcock S was then closed and gas was pumped from all of the glass system except bulb U. Stopcocks Y, O and M were closed and bulb U was immersed in a bath of acetone and solid carbon dioxide. Stopcock S was then opened and after a few seconds was closed. The pressure of gas in the system was measured on mercury manometer Z. An unsuccessful attempt was made to explode the gas in the system using the spark producing "leak tester" held outside the manometer tube at a point about 1 cm. above the mercury meniscus. The non-reacting gas was pumped from the system through stopcocks Y and X; then another sample of gas was allowed to escape from bulb U. With stopcock S closed another attempt was made to explode the gas in the line. The fourth trial of this sort and all succeeding trials resulted in explosions. This procedure removed impurities more volatile than trifluoroacetyl hypofluorite and finally resulted in what appeared to be the nearly pure compound being the gas escaping from bulb U. Repeated sampling of this sort showed the vapor pressure of the hypofluorite at −78.5° to be about 27 mm. When the gas at this pressure was exploded, the products had a pressure of about 57 mm. A 45.4 ml. (measured at 0°, 760 mm.) sample of the explosion product was found upon a rather crude analysis to contain about 13.5 ml. of COF_2, 12.6 ml. of CO_2, 15.3 ml. of CF_4 and 4.0 ml. of a mixture of gases remaining uncondensed when bulb R was cooled to −183°. When this uncondensed mixture was examined using the mass spectrometer it was found to contain CF_4, SiF_4, CO_2, O_2 and N_2. Some carbon monoxide may also have been present.

Two low pressure samples of the unexploded gas were collected in bulbs of the type shown at R. These samples had densities corresponding to molecular weights of 137 and 136 (theoretical for CF_3COOF = 132). The total fluorine content was found to be 57.0 ± 1.0% (theoretical 57.6%).

When the gas was allowed to stand at room temperature it decomposed slowly as shown by a gradual increase in pressure. Within a few hours the decomposition was complete.

Upon contact with a solution of potassium iodide the substance was found to explode. When diluted with much nitrogen it did not explode, but it did react rapidly liberation iodine.

When the reflux condenser T was cooled by solid carbon dioxide, and trifluoroacetyl hypofluorite was then boiled in bulb U under a pressure of one atmosphere, the temperature indicated by a thermocouple in well V was −21.5 ± 1°. This is an approximate value for the normal boiling point.

As far as could be told from the small samples observed, the substance was colorless. Its odor was irritating and similar to that of fluorine and the other compounds containing an –O–F bond.

The total weight of the purified compound obtained in the above run from 2.11 g. of trifluoroacetic acid was 0.33 g. Even though a part of the material was lost during the purification process, the total yield must have been less than 25% of theoretical.

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5-Benzyloxyindole

BY WERNER R. BOEHME[1]

RECEIVED JANUARY 5, 1953

The recent elucidation of structure[2] and synthesis[3,4] of 5-hydroxytryptamine, a naturally occurring vasoconstrictor substance of serum and tissue fluids,[5] has prompted the investigation of a more convenient preparation of 5-benzyloxyindole, an intermediate in two of the reported syntheses.[3] Burton and Stoves[6] have described the reduction and cyclization of 2-nitro-5-benzyloxyphenylpyruvic acid in the presence of ferrous hydroxide and alkali to yield 70% 5-benzyloxyindole-2-carboxylic acid. Decarboxylation in glycerol at 210° afforded a 24% yield of benzyloxyindole.

Application of the Japp–Klingemann reaction[7] with 4-benzyloxybenzenediazonium chloride and ethyl methylacetoacetate followed by cyclization of the phenylhydrazone in absolute ethanolic hydrogen chloride yielded 46–49% ethyl 5-benzyloxyindole-2-carboxylate. Alkaline saponification of the ester (84–95%) and decarboxylation of the resulting 5-benzyloxyindole-2-carboxylic acid gave 65% crystallized 5-benzyloxyindole.

Experimental[8]

4-Benzyloxyaniline.—To a solution of 23 g. (1 mole) of sodium in 1 l. of absolute ethanol was added 151 g. (1 mole) of 4-acetylaminophenol and 127 g. (1 mole) of benzyl chloride. The mixture was refluxed with stirring for 1.5 hr., about 750 ml. of solvent removed by distillation, and the residue poured into 2 l. of cold water. The 4-benzyloxyacetanilide which precipitated as fine almost colorless needles was filtered off and washed with water. The damp filter-cake was then refluxed for 15 hr. with a solution of 280 g. (5 moles) of potassium hydroxide in 2 l. of 90% ethanol. Most of the solvent was again removed by distillation. The residue partially crystallized on cooling. The crude product was taken up in ether and the extracts were dried superficially by filtration through a layer of anhydrous magnesium sulfate. Distillation yielded 167–170 g. (84–85%) of a

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[1] Ethicon Suture Laboratories, Inc., New Brunswick, N. J.

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[3] (a) K. E. Hamlin and F. E. Fischer, THIS JOURNAL, **73**, 5007 (1951); (b) M. E. Speeter, R. V. Heinzelmann and D. I. Weisblat, *ibid.*, **73**, 5514 (1951).

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[6] H. Burton and J. L. Stoves, *J. Chem. Soc.*, 1726 (1937).

[7] C. K. Hughes, *et al.*, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 475 (1938).

[8] Analyses by S. Alpert.

light yellow oil which solidified on cooling to large almost colorless rectangular plates, b.p. 161–164° (0.25 mm.), m.p. 51–53°. For analysis a sample was crystallized from hexane, m.p. 54–55° (lit. 56°).[9]

Ethyl 5-Benzyloxyindole-2-carboxylate.—4-Benzyloxyaniline (116 g., 0.583 mole) was dissolved in 250 ml. of boiling ethanol. The hydrochloride was precipitated in a finely divided form by the rapid addition with vigorous stirring of a solution of 233 ml. of concentrated hydrochloric acid in 360 ml. of water followed by the addition of 1 kg. of ice. A solution of 47.7 g. (0.68 mole) of sodium nitrite in 110 ml. of water was run in below the surface of the cream-colored slurry and stirring was continued until a clear solution resulted (*ca.* 20 min.).

Ethyl methylacetoacetate (92 g., 0.64 mole) was dissolved in 600 ml. of ethanol. To this solution was added 100 g. of potassium hydroxide dissolved in 100 ml. of water followed by 1 kg. of ice. The diazonium solution was then added in one portion with stirring. The red oil which separated was taken up in benzene, the benzene extracts dried superficially by filtration through anhydrous potassium carbonate, and the solvent removed under vacuum on the steam-bath. The crude red liquid phenylhydrazone was dissolved in 450 ml. of absolute ethanol and a rapid stream of dry hydrogen chloride was passed into the solution until a precipitate formed (*ca.* 20 min.). The introduction of hydrogen chloride was then continued for 10 min. longer. When the spontaneous exothermic reaction subsided (*ca.* 15 min.) the mixture was allowed to stand overnight in the refrigerator. The product was filtered off, washed with several small portions of ice-cold ethanol and then with water until the washings were substantially free of chloride ion. The air-dried yellow prisms weighed 110–117.5 g. (46–49%), m.p. 161–163°. A sample recrystallized from carbon tetrachloride for analysis melted at 162–164°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: N, 4.74. Found: N, 4.69, 4.75.

5-Benzyloxyindole-2-carboxylic Acid.—Ethyl 5-benzyloxyindole-2-carboxylate (117.5 g., 0.4 mole) was dissolved in 3 l. of boiling ethanol. With stirring a solution of 237 g. (3 moles) of potassium hydroxide in 400 ml. of water was added rapidly. Crystallization of the potassium salt began in a few minutes. The suspension was refluxed 1 hr., acidified with acetic acid, and poured into 10 l. of cold water. The solid was filtered off, washed well with water, and crystallized from aqueous acetic acid. The yield of light tan crystals was 89–101 g. (84–95%), m.p. 194.5–195.5° (dec.) (lit. m.p. 193–194°[10]).

5-Benzyloxyindole.—5-Benzyloxyindole-2-carboxylic acid (45.0 g., 0.169 mole) was heated for 1.5 hr. in a Claisen flask at a bath temperature of 210–220°. The dark brown melt was distilled in vacuum yielding 27.5 g. of an almost colorless liquid which solidified on cooling, b.p. 176–190° (0.1 mm.). Redistillation of the crude product (26.0 g., b.p. 182–188° (0.1 mm.), m.p. 81–86°) and crystallization from toluene–hexane gave 24.3 g. (65%) of fine colorless needles, m.p. 94–96° (lit. m.p. 96–97°[6]).

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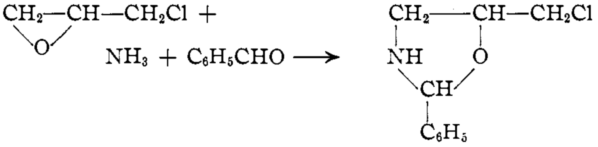
Improvements in the Synthesis of DL-Carnitine[1]

BY H. E. CARTER AND P. K. BHATTACHARYYA

RECEIVED FEBRUARY 11, 1953

In the course of studies on the biochemistry of (−)-carnitine (β-hydroxy-γ-butyrobetaine) we had occasion to synthesize a quantity of the racemic form. Several crystalline salts of DL-carnitine have been prepared but the substance itself has been obtained only as a hygroscopic gum. The present note describes the preparation of crystalline DL-carnitine by a modified procedure giving considerably better yields than those obtained by Bergmann, *et al.*[2] It was discovered that a key intermediate—2-phenyl-5-chloromethyloxazolidine—could be obtained in one step (instead of three) by the direct condensation of epichlorohydrin, ammonia and benzaldehyde (yield 70–80%).



Subsequent reactions leading to β-hydroxy-γ-aminobutyric acid were carried out as previously described.[2]

Methylation of β-hydroxy-γ-aminobutyric acid was effected by a slight modification of the procedure of Tomita[3] and the product was purified by extraction into phenol from an aqueous solution. This extraction procedure has been used to advantage in the isolation of (−)-carnitine from natural sources.[4] The yield of crystalline DL-carnitine in this step was 75–78% and the over-all yield was 20–25% (compared to the 5–7% yield obtained according to methods previously described). In view of the recent identification of (−)-carnitine as an essential growth factor for *Tenebrio molitor*[5] it seemed worthwhile to make available these modifications in the synthesis of DL-carnitine.

Experimental

2-Phenyl-5-chloromethyloxazolidine.—To a solution of 212 g. of benzaldehyde in 1000 ml. of ethanol was added with stirring 200 ml. of concentrated aqueous ammonium hydroxide (29% NH_3). This solution was stirred continually while 185 g. of epichlorhydrin was added in a thin stream. The reaction mixture warmed spontaneously to 40–45° over a 2-hour period. It was allowed to stand overnight at room temperature and was then heated on the steam-bath for 20 minutes to complete the reaction. The alcohol and ammonia were removed on the water pump and the residual yellow sirup was poured into 200 ml. of ice-water. The mixture was cooled in an ice-bath and stirred from time to time. Over a 4-hour period the entire mass solidified. The solid residue was filtered and sucked dry on the filter giving 345 g. of crude material. Recrystallization of this material from 4800 ml. of hot hexane gave 271 g. (69% yield) of pure 2-phenyl-5-chloromethyloxazolidine melting at 81–83°. The mother liquor was cooled overnight at −11° giving 42 g. of less pure material.

Conversion of β-Hydroxy-γ-aminobutyric Acid to DL-Carnitine.—A solution of 7 g. of methyl iodide in 50 ml. of methanol was added to a solution of 1.0 g. of β-hydroxy-γ-aminobutyric acid and 2.0 g. of potassium hydroxide in 5 ml. of water. The mixture was refluxed slowly under an efficient condenser for 36 hours (*p*H of solution about 5.5). The reaction mixture was evaporated to dryness on the water pump and the residue was dissolved in 50 ml. of water. The solution was extracted with three 50-ml. portions of phenol saturated with water. The three phenol extracts were washed countercurrently with two 50-ml. portions of water. The phenol extracts were then combined and poured into 450 ml. of ether in a separatory funnel. The aqueous layer was separated and the ether–phenol layer was washed with three 50-ml. portions of water. The combined aqueous extracts were washed with 450 ml. of ether and passed through a column containing 100 ml. of Amberlite IRA 45 in the hydroxyl phase. The column was washed with 500 ml. of

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[1] The authors are happy to acknoweldge a research grant from Merck and Co., Inc., in support of this work.

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distilled water and the combined percolates were evaporated to dryness under reduced pressure. The pale yellow crystalline residue consisted of essentially pure DL-carnitine (yield 1.05 g., 78%). This material can be recrystallized by dissolving it in 30 volumes of 60:40 acetone–ethanol, filtering from any insoluble material, and adding anhydrous acetone at 0° in successive 60-volume portions (total of 240 volumes). Each fraction is collected after 12–24 hours in the cold room. By this procedure the 1.05-g. sample above gave 0.81 g. of crystalline DL-carnitine (m.p. 194–196°) in 4 fractions (last two collected together). Pure DL-carnitine is a hygroscopic crystalline solid melting at 195–197° dec. (Found: C, 51.78; H, 9.36; N, 8.92.) The chloroaurate melts at 154–156° (Found: C, 16.9; H, 3.15; N, 2.77) and the reineckate melts at 146–147°.

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Hydrolysis of Some Flavonoid Rhamnoglucosides to Flavonoid Glucosides

BY DANIEL W. FOX, WILLIAM L. SAVAGE AND SIMON H. WENDER

RECEIVED DECEMBER 22, 1952

The rhamnoglucosides rutin, hesperidin and naringin are among the most readily available flavonoid compounds at present. The glucosides corresponding to the above three flavonoids are quercetin-3-glucoside (isoquercitrin), hesperetin-7-glucoside and naringenin-7-glucoside (prunin). These latter three compounds are desired for biological testing, and have not been readily available in the amounts needed. To our knowledge, partial hydrolysis of the rhamnoglucoside to remove the rhamnose and leave the glucose still attached to the flavonoid portion had not been successfully achieved. The present paper reports a method for accomplishing the hydrolyses in significant amount of rutin, hesperidin and naringin to the corresponding flavonoid glucosides. The method appears likely to be a general one for this type of compound.

Formic acid in cyclohexanol has been used for the hydrolysis. The hydrolysate containing a mixture of flavonoids has been separated chromatographically and the identity of each resulting pure flavonoid glucoside has been established.

Experimental

Hydrolysis of Rutin.—Rutin (S. B. Penick and Co., New York) was first purified by treatment with Magnesol[1] from methanol solution, and then by several recrystallizations from methanol. Although the highly purified rutin was used in these experiments, this additional purification is not necessary for routine preparation of isoquercitrin. Ten grams of the pure rutin was dissolved in 225 ml. of boiling cyclohexanol. Seventy-five ml. of formic acid (85–90%) was next added through the reflux condenser, the addition being performed as rapidly as possible without flooding. The mixture was then refluxed, with stirring, for approximately 10 hours at a temperature of 102–107°. Small samples were withdrawn at regular intervals and chromatographed on paper, usually using 15% acetic acid–water as the solvent system. One could thus follow the progress of the hydrolysis and estimate the relative amounts of isoquercitrin, quercetin and unhydrolyzed rutin present (R_f values in the 15% acetic acid are 0.45, 0.09 and 0.62, respectively). When the highly purified rutin is used, and the reaction is followed closely with paper chromatograms, isoquercitrin is detectable before the quercetin.

After about 10 hr. of hydrolysis, distillation of solvent was carried out *in vacuo* until practically no liquid came over. The volume of the mixture was made up to 600 ml. with anhydrous acetone and filtered through a 2.5 × 3 cm. column of Magnesol. The filtrate was then put on a 7 × 26 cm. column of Magnesol packed as an acetone slurry. When all of the flavonoids had been adsorbed, the top half of the column was colored. Several hundred ml. of anhydrous ethyl acetate was then passed through the column to displace the acetone and cyclohexanol. The column was next developed as a liquid chromatogram with wet ethyl acetate. A definite break occurred between the bulk of the quercetin and the glycosides, but sufficient quercetin still remained on the column to make detection of the glycoside zones almost impossible. The eluant was, therefore, collected in 200-ml. fractions. Small portions of each fraction were spotted on paper strips for chromatographic study. At the first appearance of isoquercitrin, the eluted fraction was saved and combined with all following fractions which showed isoquercitrin to be present. The combined solution of all the eluted fractions containing isoquercitrin was concentrated to 750 ml. by distillation and then rechromatographed on a fresh 3.5 × 20 cm. column of Magnesol packed as an anhydrous ethyl acetate slurry, and the column developed with an ethyl acetate–water solution. Four zones were detected on this column in both visible and ultraviolet light as elution proceeded. When the major portion of zone one, containing the quercetin, reached the bottom of the column, a faint zone, containing an unknown glycoside, was noted between this fastest moving pigment (quercetin) and the isoquercitrin which occupied the center portion of the column. Some unhydrolyzed rutin remained at the top of this column, but most of the rutin had been left on the preceding column. The major part of the center zone, containing the isoquercitrin, was eluted and the solvent removed *in vacuo*. Yellow solid isoquercitrin—yield approximately 760 mg.—was obtained.

For final purification, the isoquercitrin was recrystallized at least four times from boiling alcohol-water. The supernatant liquid was removed by decantation after centrifugation. A trace of an oily material could not be removed if regular filtration were used. The recrystallized isoquercitrin was dried at 110° for 1 hr. and gave a m.p. of 228°, uncor. On paper chromatograms, it showed no trace of quercetin or any other impurity, and its R_f values corresponded to those of authentic isoquercitrin isolated from plant sources.[2] The 3′,4′,5,7-tetramethoxy-3-hydroxyflavone was obtained according to the method of Shimokoriyama,[3] m.p. 195°. Hydrolysis of the prepared isoquercitrin yielded one sugar, glucose, which was identified by paper chromatography, and quercetin, which was identified by its R_f values, its m.p. 314–315°, and its pentaacetate, m.p. 194–195°.[4]

Hydrolysis of Hesperidin.—Five grams of hesperidin was dissolved in 250 ml. of boiling cyclohexanol (minimum solvent requirement) and 125 ml. of formic acid (85–90%) was added as rapidly as possible through the reflux condenser. The hydrolysis mixture was refluxed approximately 20 hr. and then distilled until the temperature reached 135°. Samples were withdrawn at 3-4-hr. intervals, and chromatographed on paper, using 15% acetic acid-water as the solvent system. R_f values in this system were 0.80 for hesperidin, 0.70 for hesperetin-7-glucoside, and 0.43 for hesperetin. From the paper chromatograms, no apparent improvement of yield resulted after about 15 hr., but the amount of aglycone increased, and the amount of hesperidin decreased.

The entire hydrolysis mixture was filtered through a 2.5 × 5 cm. column of Magnesol to remove decomposition material. On washing this column with dry acetone, the very dark material which had been adsorbed was removed. Only the initial filtrate was saved. A rough separation was effected on a 7.5 × 25 cm. column of Magnesol. The cyclohexanol solution was put on an acetone–Magnesol column; washed with dry ethyl acetate to displace the cyclohexanol; and finally developed as a liquid chromatogram with wet ethyl acetate. The entire column was white in ultraviolet light, but a slight break was detectable between the aglycone and the hesperetin-7-glucoside after considerable elution. The hesperidin moved very slowly and remained near the top of the column. The 7-glucoside fraction was concen-

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trated by distillation to 300 ml., and rechromatographed on a 3.7 × 25 cm. column of Magnesol packed from dry ethyl acetate. All three compounds, hesperidin, hesperetin and the hesperetin-7-glucoside were present on this column, but a relatively clean separation was possible. The central portion of the middle zone was collected as a separate fraction and taken to dryness under reduced pressure. The resulting solid—yield about 0.35 g.—was purified by four recrystallizations from alcohol. This sample had a m.p. of 206–207° uncor., and an optical rotation $[\alpha]^{27}\text{D}$ −51.8° in pyridine, which agree well with those reported for hesperetin-7-glucoside by Zemplén, *et al.*[5] On hydrolysis, the sugar was identified as glucose, with no trace of rhamnose detectable.

Hydrolysis of Naringin.—Five grams of naringin, 100 ml. of cyclohexanol and 50 ml. of formic acid were refluxed 20 hr. and then the solvent distilled off until the temperature reached 135°. The first detectable trace of naringenin-7-glucoside was found after 3 hr., and continued to increase relatively for about 15–20 hr. R_f values in 15% acetic acid were 0.80 for naringin; 0.75 for naringenin-7-glucoside; and 0.47 for naringenin. After hydrolysis, the volume of the remaining solution was doubled with acetone and filtered through a 1.5 × 3 cm. column of Magnesol. Filtration removed dark, flocculent material. The solution was then chromatographed on a 7 × 25 cm. column of Magnesol packed as an acetone slurry. When all of the reaction mixture had been adsorbed, a column volume of dry ethyl acetate was passed through to displace the cyclohexanol and then wet ethyl acetate was used to elute the liquid chromatogram. The column was too overloaded to permit detection of zones, but some fractionation was possible. The eluate was collected in fractions and microliter portions were spotted on paper. The first fractions contained mainly naringenin and were discarded. Elution was continued, and fractions containing naringenin-7-glucoside now appeared, and were collected, combined, concentrated to 200 ml. *in vacuo*, and rechromatographed on a 4.5 × 20 cm. column of Magnesol, packed this time with an ethyl acetate slurry. Some separation of the zones was detected under ultraviolet light, but a clear-cut separation was not achieved. The naringenin-7-glucoside fraction from this column was concentrated and again rechromatographed on a fresh 2.5 × 15 cm. column of Magnesol. A good separation between the leading naringenin and the central naringenin-7-glucoside was obtained in this case. A dark, narrow zone appeared at both the top and bottom of the central naringenin-7-glucoside zone. The dark zones were collected separately, and the center of the middle zone was taken as the naringenin-7-glucoside. After evaporation at reduced pressure, the resulting solid—yield about 0.40 g.—was recrystallized several times from methanol–water. The m.p. of the naringenin-7-glucoside was 225–226°, uncor., and no lowering occurred on admixture with a sample of authentic prunin. Mixed paper chromatograms of the prepared naringenin-7-glucoside with prunin showed no separation. R_f values for both were 0.84 in 60% acetic acid–water and 0.92 in the butyl alcohol–acetic acid–water system (4–1–5). The naringenin-7-glucoside and the prunin from the cherry tree[6] are thus identical. After hydrolysis, paper chromatography showed the presence of glucose, but no rhamnose, in the neutralized filtrate.

In preparing a sample of naringenin from naringin, using sulfuric acid, according to the method of Will,[7] paper chromatograms at the end of 2 hr. revealed the presence of some naringenin-7-glucoside. Thus, for naringin hydrolysis, there may be a possibility for using sulfuric instead of formic acid.

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The Synthesis and Alkaline Decomposition of γ-Aminopropylsulfuric Acid

BY HAROLD W. HEINE, RICHARD W. GREINER, MARJORIE A. BOOTE AND BETSY A. BROWN

RECEIVED OCTOBER 27, 1952

The preparation of γ-aminopropylsulfuric acid was undertaken in an effort to convert it into trimethylenimine. The sulfuric ester was first synthesized by Gabriel and Lauer[1] in unreported yields by treating γ-bromopropylamine with silver sulfate. Yields of 90% crude γ-aminopropylsulfuric acid were obtained in this Laboratory by the treatment of γ-aminopropanol with sulfuric acid.

The γ-aminopropylsulfuric acid was subjected to a flash distillation with excess base to give a small yield of impure trimethylenimine.

Experimental

γ-Aminopropylsulfuric Acid.—In a one-liter flask equipped with a stirring motor, thermometer and dropping funnel were placed 50 g. of water and 105 ml. of concentrated sulfuric acid. To this was added dropwise and with cooling a solution containing 150 g. (2 moles) of redistilled γ-aminopropanol and 75 g. of water. The dropping funnel was replaced by a condenser set for downward distillation and the mixture was distilled under slightly reduced pressure until the temperature of the reaction reached 190°. Approximately 140 ml. of water was collected. The mixture was allowed to cool and crystallization was induced by scratching the walls of the flask with a glass rod. The solid cake was then softened with 300 ml. of 95% ethanol, removed from the flask, ground with an additional 400 ml. of ethanol, filtered and dried. The crude γ-aminopropylsulfuric acid (278 g.) was then recrystallized from water. The once recrystallized product melted at 219–220°. Gabriel[1] reported a melting point of 221°. Further recrystallization gave a product which melted at 227–228°.

Anal.[2] Calcd. for $C_3H_9C_4NS$: N, 9.02; S, 20.66. Found: N, 8.84; S, 20.54.

Trimethylenimine.—The γ-aminopropylsulfuric acid (155 g.) was decomposed in an analogous fashion employed by Reeves[3] for the decomposition of β-aminoethylsulfuric acid. A fraction (1 g.) distilling at 66–69° was obtained. This corresponds to a 1.7% yield of trimethylenimine. The picrate of this fraction melted at 166° and the chloroplatinate at 201°. Gabriel[4] reported melting points for the picrate and chloroplatinate of trimethylenimine at 165° and 200–203°, respectively. The refractive index, however, of the 66–69° fraction was n^{25} 1.3450 which did not correspond to the value observed by Ruzicka[5] for trimethylenimine, *viz.*, $n^{25}\text{D}$ 1.4287. The product was considered moist and redried over anhydrous sodium sulfate and redistilled. The refractive index did not change. Further attempts of drying over solid potassium hydroxide and redistillation still gave the same value for the refractive index. A low-boiling fraction 47–64° and a high-boiling fraction 110–191° were also obtained but were not characterized.

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[1] S. Gabriel and W. E. Lauer, *Ber.*, **23**, 87 (1890).

[2] Analyses were made by Schwarzkopf Microanalytical Laboratory, Middle Village, N. Y.

[3] W. A. Reeves, G. L. Drake and C. Hoffpaur, THIS JOURNAL, **73**, 3522 (1951).

[4] S. Gabriel and J. Weiner, *Ber.*, **21**, 2676 (1888).

[5] L. Ruzicka, G. Salomon and K. E. Meyer, *Helv. Chim. Acta*, **20**, 109 (1937).

Acknowledgment.—The authors are indebted to the American Cyanamid Company for the γ-aminopropanol used in this work.

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Isolation of Thymidine by Means of the Chromatopile

BY WILLIAM DRELL[1]

RECEIVED JANUARY 2, 1953

Methods have been described recently for the isolation of the desoxyribosides by means of alumina, cation exchange and anion exchange columns.[2-5] The convenient isolation of thymidine from an enzymatic hydrolysate of commercial desoxyribonucleic acid by butanol extraction followed by separation on a chromatopile[6] is reported below.

Sperm nucleic acid[7] (40 g.) was incubated with phosphatase from 240 ml. of calf intestinal mucosa glycerol extract by the method of Klein[8] for 16 hours. The weighed inorganic precipitate, removed by filtration, indicated about 50% hydrolysis (*cf.* Brown and Lythgoe[4]). The solution (2000 ml.) was exhaustively extracted with butanol saturated with water.[9] The remaining aqueous phase contained no ribosides, as determined by paper chromatography. The combined butanol extract was evaporated *in vacuo* to 200 ml., cooled overnight and filtered. The filtrate was evaporated to 35 ml. *in vacuo* and absorbed on double sheets of Whatman #1 filter paper, 12.5 cm. in diameter. After partially drying in air (3.5 hr.) the sheets were incorporated into a 500-sheet pile and developed for 35 hr. at 0° with 1-propanol:0.1 *N* H_2SO_4 (3:1). The thymidine fraction, located in sheets 250 to 375, was eluted with water, neutralized with hot saturated $Ba(OH)_2$ solution to *p*H 6.5 and evaporated *in vacuo* to a small volume. No crystals appeared on standing for three months. When seeded[10] the solution set to a crystalline mass within 30 seconds. The slightly wet crystalline precipitate (1.5 g.) was recrystallized twice from water, washed with ethanol and dried over P_2O_5; yield 0.9 g., m.p. 185–186°. The relative spectra agreed within experimental error with those reported by Hotchkiss,[11] $\lambda_{\text{max.}}$ (0.1 *N* HCl) 267 mμ, log ε 4.021, $\lambda_{\text{min.}}$ 235 mμ, log ε 3.355, $\lambda_{\text{max.}}$ (0.1 *N* NaOH) 266 mμ, log ε 3.942, $\lambda_{\text{min.}}$ 246 mμ, log ε 3.751, N_{260}[12] is 38.5.

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[1] University of California School of Medicine, Los Angeles 24, Calif.

[2] O. Schindler, *Helv. Chim. Acta*, **32**, 979 (1949).

[3] P. Reichard and B. Estborn, *Acta Scand. Chem.*, **4**, 1047 (1950).

[4] D. M. Brown and B. Lythgoe, *J. Chem. Soc.*, 1990 (1950).

[5] W. Andersen, C. A. Dekker and A. R. Todd, *ibid.*, 2721 (1952).

[6] H. K. Mitchell and F. A. Haskins, *Science*, **110**, 278 (1949).

[7] Dougherty Chem. Co., Richmond Hill, N. Y.

[8] W. Klein, *Z. physiol. Chem.*, **207**, 125 (1932); **255**, 82 (1938).

[9] The recently employed ethanol extraction procedure[5] may be less tedious.

[10] Seed crystals were obtained through the courtesy of Dr. M. S. Dunn of the University of California.

[11] R. D. Hotchkiss, *J. Biol. Chem.*, **175**, 315 (1948).

[12] N_{260} was defined by Hotchkiss[11] as the absorption of a neutral solution of thymidine (1 mg. per ml.) at 260 mμ. His reported value is 36.

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The Resolution of Parsidol

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RECEIVED JANUARY 14, 1953

Although differences in the pharmacological and physiological effects of the optical isomers of assorted natural products have been well-known for many years,[1] only relatively recently has much attention been given to resolution of synthetic drugs into their enantiomorphs. When the latter has been done it has frequently been found that one of the isomers is more active than the other,[2] although this is not always true.[3]

In order to make available for pharmacological and clinical evaluation both of the optical isomers we have effected a resolution of N-(2-diethylaminopropyl)-phenothiazine,[4] variously known as Parsidol, Lysivane, Ethopropazine, RP3356 and W-483, which has recently shown favorable results[5] in the treatment of Parkinsonism.

Resolution of the racemic base was accomplished with *d*-tartaric acid in *n*-propanol from which solvent the *d*-base *d*-bitartrate crystallized more readily than did the *l*-base *d*-bitartrate.

The pure diastereoisomeric bitartrates were converted to the enantiomorphic *d*- and *l*-bases and thence to the corresponding enantiomorphic hydrochlorides by usual methods. The optical rotation of the hydrochlorides was very small but it was verified that these were indeed the desired *d*- and *l*-salts by their conversion back to the free bases which had the same optical rotations as those obtained from the original *d*-bitartrate.

Pharmacology.—Comparative toxicity determinations of all the salts were made and statistically evaluated. Toxic symptoms following intravenous injection in mice were essentially the same for the *dl*-, *d*- and *l*-base hydrochlorides and for the *d*- and *l*-bitartrates: collapse, exophthalmus, apnea, convulsions and death. Surviving animals were depressed and the respiration was slow. In spite of the general depression, these animals were hyperreactive to minimal stimuli.

The intravenous dose which killed 50% of the mice (LD_{50}) was the same for the racemic and the optically active base hydrochlorides (36 mg./kg.), while the *d*- and *l*-base *d*-bitartrates were less toxic (62 and 54.5 mg./kg.). In terms of the free base, however, only the *d*-base *d*-bitartrate was significantly less toxic (see Table II).

Antagonism of nicotine-induced tremors in the rabbit[6] was used to estimate nicotinolytic activity.

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[1] References 3 and 4 on p. 662 and pp. 662–666 of G. L. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1949. Some further recent examples are: thyroxine, W. E. Griesbach, T. H. Kennedy and H. D. Purves, *Nature*, **160**, 192 (1947); arterenol, F. P. Luduena, E. Ananenko, O. H. Siegmund and L. C. Miller, *J. Pharmacol. Exptl. Therap.*, **95**, 155 (1949); chloramphenicol, J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., THIS JOURNAL, **71**, 2463 (1949).

[2] Amidone, C. C. Scott, E. B. Robbins and K. K. Chen, *J. Pharmacol. Exptl. Therap.*, **93**, 282 (1948); Dromoran, L. O. Randall and G. Lehmann, *ibid.*, **99**, 163 (1950); Amphetamine, D. F. Marsh and D. A. Herring, *ibid.*, **97**, 68 (1949); other pressor amines, G. M. Badger, *Nature*, **159**, 194 (1947); Lacophenetidide, K. Brand and R. Priesner, *Angew. Chem.*, **62**, 447 (1950); Nirvanol, H. Sobotka, U. S. Patent 1,861,458 (June 7, 1932) (*C. A.*, **26**, 4133 (1932)).

[3] Atabrine, F. A. Bacher, R. P. Buhs, J. C. Hetrick, W. Reiss and N. R. Trenner, THIS JOURNAL, **69**, 1534 (1947).

[4] P. Charpentier (to Société des Usines Chimiques, Rhône-Poulenc), United States Patent 2,526,118 (October 17, 1950); (*C. A.*, **45**, 2511 (1951)).

[5] W. H. Timberlake and R. S. Schwab, *New England J. Med.*, **247**, 98 (1952).

[6] D. Bovet and V. G. Longo, *J. Pharm. Exptl. Therap.*, **102**, 22 (1951).

Although these studies are limited, one can conclude from Table III that the *l*-base, either as the hydrochloride or as the bitartrate, has about twice the nicotinolytic activity of the *d*-base in the form of its corresponding salt.

TABLE I

SUMMARY OF PHYSICAL PROPERTIES OF RACEMIC AND OPTICALLY ACTIVE N-(2-DIETHYLAMINOPROPYL)-PHENOTHIAZINE AND ITS SALTS

Salt	M.p., °C.	$[\alpha]^{25}\text{D}$[a]
dl-Bitartrate	135–138	*ca.* +7 to +8°[b]
d-Bitartrate	156–158[c]	−4.6°[b]
l-Bitartrate dihydrate	93–95[d]	+19°[e]
dl-Base	Oil[f,g]	....
d-Base	Oil	+16.7°[h]
l-Base	Oil	−16.7°[h]
dl-Hydrochloride	220–225[g]	....
d-Hydrochloride	203–210[i,j]	+1°[k]
l-Hydrochloride	203–210[i,l]	−1°[k]

[a] All rotations observed in a one decimeter tube. [b] 8% in distilled water. [c] *Anal.* Calcd. for $C_{19}H_{24}N_2S{\cdot}C_4H_6O_6$: C, 59.72; H, 6.54. Found: C, 59.53; H, 6.38. [d] *Anal.* Calcd. for $C_{19}H_{24}N_2S{\cdot}C_4H_6O_6{\cdot}2H_2O$: C, 55.42; H, 6.82. Found: C, 55.49; H, 6.65. [e] 1% in distilled water. [f] Solidified on standing at room temperature. [g] Prepared and analyzed by P. Charpentier and R. Ducrot, *Compt. rend.*, **232**, 415 (1951). [h] 4% in ethanol. [i] Could be raised to 206–210° by repeated recrystallizations from isopropyl alcohol. [j] *Anal.* Calcd. for $C_{19}H_{24}N_2S{\cdot}HCl$: N, 8.04; Cl, 10.16. Found: N, 8.02; Cl, 9.94. [k] 6% in ethanol. [l] *Anal.* Calcd. for $C_{19}H_{24}N_2S{\cdot}HCl$: N, 8.04; Cl, 10.16. Found: N, 7.78; Cl, 9.92.

TABLE II

SUMMARY OF INTRAVENOUS LD_{50} DETERMINATIONS IN MICE OF RACEMIC AND OPTICALLY ACTIVE N-(2-DIETHYLAMINOPROPYL)-PHENOTHIAZINE SALTS

Salt	LD_{50} (mg./kg.)[a] Salt	Calcd. as free base	Limits of error, %
dl-Base hydrochloride	36	32	95–105
d-Base hydrochloride	36	32	90–111
l-Base hydrochloride	35.5	32	88–114
d-Base *d*-bitartrate	62	42	93–108
l-Base *d*-bitartrate	54.5	34	93–108

[a] All solutions were made in physiological saline and were injected at the same rate (0.4 cc./20 g. mouse/10 sec.) by the same worker.

TABLE III

PROTECTION AGAINST NICOTINE-INDUCED TREMORS IN THE RABBIT BY INTRAVENOUS RACEMIC AND OPTICALLY ACTIVE N-(2-DIETHYLAMINOPROPYL)-PHENOTHIAZINE SALTS

Salt	Dose, mg./kg. Salt	Calcd. as free base	No. of animals, protected/no. injected
None	0	0	0/37
dl-Base hydrochloride	2.5	2.24	4/10
	5.0	4.47	9/10
d-Base hydrochloride	2.5	2.24	3/5
	5.0	4.47	5/5
l-Base hydrochloride	1.25	1.12	2/10
	2.5	2.24	5/5
	5.0	4.47	4/5
d-Base *d*-bitartrate	2.5	1.68	1/5
	5.0	3.37	5/5
l-Base *d*-bitartrate	1.79	1.12	4/10
	2.5	1.56	5/5
	5.0	3.13	5/5

We wish to acknowledge the technical assistance of Mr. Heino A. Luts. Microanalyses were carried out by or under the supervision of Dr. F. A. Buehler.

Experimental[7]

***dl*-N-(2-Diethylaminopropyl)-phenothiazine.**—The base was prepared from the corresponding purified hydrochloride, obtained essentially by the procedure of Charpentier,[4] by dissolving the latter in water, basifying the aqueous solution and extracting the resultant oil with ether. Removal of the ether gave the base in quantitative yield.

Resolution of *dl*-N-(2-Diethylaminopropyl)-phenothiazine.—The racemic base (25.0 g., 0.08 mole) and *d*-tartaric acid (12.0 g., 0.08 mole) were dissolved in 300 ml. of warm (50°) *n*-propanol and the solution was allowed to cool slowly. Crystallization was induced by scratching. After remaining 1.5 hours at room temperature the crystals were filtered off and dried *in vacuo*. There was obtained about 13 g. (70%) of partially resolved *d*-base *d*-bitartrate, $[\alpha]^{25}\text{D}$ +1°, m.p. 149–151°. The impure *d*-base *d*-bitartrate was purified by three recrystallizations from *n*-propanol. There was obtained 5.9 g. (45%) of pure material, $[\alpha]^{25}\text{D}$ −4.6°.

The filtrate from which the impure *d*-base *d*-bitartrate had been removed was allowed to stand for 24–36 hours more at room temperature (25–30°), and deposited crystals that were rich in *l*-base *d*-bitartrate. The crystals were filtered off and dried; they weighed 12 to 15 g. (65–80%) and had $[\alpha]^{25}\text{D}$ +14 to +16°. This material could not be purified by recrystallization from *n*-propanol but it was found that the sparingly soluble *l*-base *d*-bitartrate dihydrate could be readily obtained by several recrystallizations of the crude material from water. The pure *l*-base *d*-bitartrate dihydrate obtained from the crude material by recrystallization from three parts of water weighed about 5.4 g. (40%), $[\alpha]^{25}\text{D}$ +19°, m.p. 93–95°.

***d*- and *l*-N-(2-Diethylaminopropyl)-phenothiazine.**—Each pure *d*-bitartrate was dissolved in water and the solution was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the ether removed *in vacuo* leaving the optically active bases as oils. The *d*-bitartrate having $[\alpha]^{25}\text{D}$ −4.6° gave a base having $[\alpha]^{25}\text{D}$ +16.7° and the *d*-bitartrate having $[\alpha]^{25}\text{D}$ +19° gave a base having $[\alpha]^{25}\text{D}$ −16.7°.

***d*- and *l*-N-(2-Diethylaminopropyl)-phenothiazine Hydrochloride.**—The optically active bases were dissolved in ether (5% solution) and dry hydrogen chloride passed in until no more precipitate formed. The precipitates were filtered, washed with ether and dried *in vacuo*. The *d*- and *l*-hydrochlorides, $[\alpha]^{25}\text{D}$ +1 and −1°, respectively, m.p. 203–210°, were obtained in quantitative yield. Samples of these hydrochlorides were converted back to the free bases in the usual manner; these bases had $[\alpha]^{25}\text{D}$ +16.7 and −16.7°, respectively.

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(7) Melting points are uncorrected.

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The Preparation of Some Trialkyltin-lithium Compounds

BY HENRY GILMAN AND SANDERS D. ROSENBERG

RECEIVED NOVEMBER 20, 1952

In a previous publication[1] from this Laboratory the preparation of triphenyltin-lithium from stannous chloride and three equivalents of phenyllithium was described. In order to ascertain if aromatic groups bonded to the tin atom were necessary for the formation of complexes of this type and investigate the possibility of preparing alkylorganotin compounds by means of similar

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(1) H. Gilman and S. D. Rosenberg, THIS JOURNAL, **74**, 531 (1952). See also G. Wittig, F. J. Meyer and G. Lange, *Ann.*, **571**, 167 (1951); G. Wittig, *Angew. Chem.*, **62**, 231 (1950).

complexes, reactions have been carried out between stannous chloride and some alkyllithium compounds, and the results are reported herein.

In 1858, Wanklyn[2] tried unsuccessfully to prepare ethylsodium by the reaction of diethylzinc with sodium metal. Much later, Hein[3] showed that ethylsodium and diethylzinc form a stable complex metal alkyl, triethylzinc-sodium. Hein demonstrated that ethylsodium, a non-conductor, will conduct an electric current when diethylzinc is used as solvent, and that on electrolysis sodium ion migrates to the cathode and triethylzinc complex ion migrates to the anode. These findings support the idea that, in attempting to prepare ethylsodium from diethylzinc and sodium, Wanklyn[2] had actually prepared the first reported complex metal alkyl, triethylzinc-sodium. More recently, it has been reported[4] that an attempt to prepare diethylstrontium by the action of strontium metal on diethylzinc actually resulted in the preparation of a complex involving one molecule of diethylstrontium and one molecule of diethylzinc.

$$\mathrm{Sr} + 2(\mathrm{C_2H_5})_2\mathrm{Zn} \longrightarrow (\mathrm{C_2H_5})_2\mathrm{Sr}\cdot(\mathrm{C_2H_5})_2\mathrm{Zn} + \mathrm{Zn}$$

Schlesinger and Brown[5] reported the preparation of trimethylethylboronlithium, and Hurd[6] described tetramethylaluminum-lithium, tetramethylboron-lithium and tetramethylzinc-dilithium. In each case the complex metal alkyl was formed by treating the methylorganometallic compound with an ether solution of the appropriate alkyllithium compound.

It was found in this Laboratory that it is not necessary to prepare the dialkyltin compound separately, and then treat it with the alkyllithium compound to form the complex metal alkyl. As before,[1] tri-*n*-butyltin-lithium was prepared directly by treating finely ground, anhydrous stannous chloride with three equivalents of *n*-butyllithium in the cold. Similarly, triethyltin-lithium was

$$3\mathrm{RLi} + \mathrm{SnCl_2} \longrightarrow \mathrm{R_3SnLi} + 2\mathrm{LiCl}$$

prepared by treating stannous chloride with ethyllithium. In the addition of *n*-butyllithium to stannous chloride, Color Test I[7] became positive[8] when exactly two equivalents of RLi had been added, but color test II,[9] for very reactive organometallic compounds, remained negative until exactly three equivalents of RLi had been added. The Color Test results were not quite the same in the formation of triethyltin–lithium. As before, Color Test I became positive at the two-equivalents point,[8] but Color Test II became positive when 2.5 equivalents of ethyllithium had been added. This latter result is similar to that obtained in the preparation of triphenyllead-lithium from lead chloride and three equivalents of phenyllithium.[10]

Tri-*n*-butyltin-lithium has been treated with *n*-butyl iodide and iodobenzene to form tetra-*n*-butyltin and tri-*n*-butylphenyltin, respectively; triethyltin-lithium and ethyl bromide gave tetraethyltin in good yield.

$$\mathrm{R_3SnLi} + \mathrm{R'X} \longrightarrow \mathrm{R_3SnR'} + \mathrm{LiX}$$

Experimental

Tri-*n*-butyltin-lithium.—To a well-stirred suspension of 8.54 g. (0.045 mole) of finely ground, anhydrous stannous chloride in 100 ml. of ether maintained at −10°, was added, dropwise, 0.135 mole (3 equivalents) of *n*-butyllithium in 150 ml. of ether. When one equivalent (0.045 mole, 50 ml.) had been added, the reaction mixture was orange-colored; with two equivalents (0.09 mole, 100 ml.) the color was deep red; with three equivalents (0.135 mole, 150 ml.) the color was deep brown. Color Test I[7] was negative until two equivalents (100 ml.) of *n*-butyllithium were added; Color Test II[9] was negative until three equivalents (150 ml.) were added.

Tetra-*n*-butyltin.—To 0.045 mole of tri-*n*-butyltin-lithium was added 9.1 g. (0.0495, 10% excess 0.045, mole) of *n*-butyl iodide. The deep brown color of the reaction mixture immediately changed to bright yellow. The mixture was refluxed for 3 hours and hydrolyzed by pouring it into a saturated ammonium chloride solution. The layers were separated, and the ether layer dried over sodium sulfate. The ether was removed by distillation from a water-bath leaving about 15 ml. of a water-like liquid. The liquid was distilled under reduced pressure to yield 8.2 g. (52.5%) of tetra-*n*-butyltin, b.p. 127° (1.7 mm.),[11] n^{20}_{D} 1.4727.[12] The compound gave a positive qualitative test for tin.[13]

Run 2.—This run was carried out exactly as the first. The yield of tetra-*n*-butyltin was 7.0 g. (44.9%), b.p. 130° (2.0 mm.), n^{20}_{D} 1.4729.

Tri-*n*-butylphenyltin.—To 0.10 mole of tri-*n*-butyltin-lithium was added 20.4 g. (0.10 mole) of iodobenzene in 30 ml. of ether. The reaction mixture was refluxed for 24 hours and hydrolyzed as above. Removal of the ether yielded a water-like liquid which was distilled under reduced pressure. Two fractions were collected: Fraction I distilled at 70–87° (0.1 mm.), weighed 10.0 g., n^{20}_{D} 1.4780. Fraction II distilled at 94–110° (0.1 mm.), weighed 15.4 g., n^{20}_{D} 1.5094. Fraction II was redistilled under reduced pressure to yield a forerun distilling at 108–136° (0.6 mm.) and 10.1 g. (27.6%) of tri-*n*-butylphenyltin, b.p. 139° (0.6 mm.), n^{20}_{D} 1.5155. The forerun was combined with Fraction I which was then redistilled under reduced pressure to yield 7.2 g. (27.8%) of tetra-*n*-butyltin, b.p. 109° (0.5 mm.), n^{20}_{D} 1.4731.[12] Both compounds gave a positive qualitative test for tin.[13]

Anal. Calcd. for $\mathrm{C_{18}H_{32}Sn}$: Sn, 32.33. Found: Sn, 32.37.

Triethyltin-lithium.—To a well-stirred suspension of 8.54 g. (0.045 mole) of finely ground, anhydrous stannous chloride in 100 ml. of ether maintained at −10°, was added dropwise 0.135 mole (3 equivalents) of ethyllithium in 162 ml. of ether. When one equivalent (0.045 mole, 54 ml.) had been added, the reaction mixture was deep orange-colored; with two equivalents (0.09 mole, 108 ml.) the color was very deep red; with three equivalents (0.135 mole, 162 ml.) the color was very deep red. Color Test I was negative until two equivalents (108 ml.) of ethyllithium were added; Color Test II was negative until 2.5 equivalents (135 ml.) were added.

Ethyl Bromide; Tetraethyltin.—To 0.045 mole of triethyltin-lithium was added 10.0 g. (0.09 mole, 100% excess 0.045 mole) of ethyl bromide. The very deep red color of the reaction mixture immediately changed to dark gray.

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[2] J. A. Wanklyn, *Ann.*, **107**, 125 (1858); 111, 234 (1859); **140**, 211 (1866).

[3] F. Hein, *Z. Elektrochem.*, **28**, 469 (1922); *Z. anorg. Chem.*, **141**, 161 (1924); **158**, 159 (1926); *Z. physik. Chem.*, **151A**, 24 (1930).

[4] H. Gilman, R. N. Meals, G. O'Donnell and L. Woods, THIS JOURNAL, **65**, 268 (1943).

[5] H. I. Schlesinger and H. C. Brown, *ibid.*, **62**, 3429 (1940); see also A. E. Finholt, A. C. Bond and H. I. Schlesinger, *ibid.*, **69**, 1199 (1947).

[6] D. T. Hurd, *J. Org. Chem.*, **13**, 711 (1948).

[7] H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

[8] Color Test I at this point was not the usual dark green color but was remindful of the blue of Michler hydrol. In contrast with this, triphenyltin-lithium does not give a positive Color Test I.

[9] H. Gilman and J. Swiss, THIS JOURNAL, **62**, 1847 (1940).

[10] H. Gilman, L. Summers and R. W. Leeper, *J. Org. Chem.*, **17**, 630 (1952).

[11] All boiling points are uncorrected.

[12] W. J. Jones and co-workers, *J. Chem. Soc.*, 39 (1935), report n^{20}_{D} 1.4730 for tetra-*n*-butyltin.

[13] H. Gilman and T. N. Goreau, *J. Org. Chem.*, **17**, 1470 (1952).

The mixture was stirred overnight and hydrolyzed. Removal of the ether yielded a water-like liquid which was distilled to yield 7.3 g. (68.6%) of tetraethyltin, b.p. 178.5°, $n^{20}\text{D}$ 1.4691.[14] The compound gave a positive qualitative test for tin.[13]

Run 2.—This run was carried out exactly as the first. The yield of tetraethyltin was 7.7 g. (72.6%), b.p. 177°, $n^{20}\text{D}$ 1.4691.

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[14] L. L. Gershbein and V. N. Ipatieff, This Journal, **74**, 1540 (1952), report $n^{20}\text{D}$ 1.4693 for tetraethyltin.

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Formation of Tetraphenylsilane from Reactions Involving Triphenylsilylpotassium

BY HENRY GILMAN AND T. C. WU

RECEIVED JANUARY 26, 1953

It has been shown that triphenylsilylpotassium adds to unsaturated linkages such as the carbon–carbon double bond of *trans*-stilbene.[1] Studies

$$(C_6H_5)_3SiK + C_6H_5CH{=}CHC_6H_5 \longrightarrow (C_6H_5)_3SiCH(C_6H_5)CH(C_6H_5)K$$

of the extension of the addition reaction to the acetylenic linkage showed that good yields of tetraphenylsilane were obtained. Thus, the reaction of triphenylsilylpotassium with phenylacetylene gave tetraphenylsilane as the major product.[2] Similarly, tolane reacts with triphenylsilylpotassium to give tetraphenylsilane in a lower yield. The high yield of tetraphenylsilane from the phenylacetylene reaction suggested the possible significance of the acidic hydrogen although we observed tetraphenylsilane was also formed from reactions involving triphenylsilylpotassium and some other compounds.[3] We have examined the reactions of triphenylsilylpotassium with phenylcarbinols and obtained high yields of tetraphenylsilane in all cases. It was interesting to observe that triphenylsilanol also gave a high yield of tetraphenylsilane. Whether tetraphenylsilane was formed by disproportionation in these reactions is not known. The course of these reactions is being examined with compounds containing other functional groups as well as compounds containing substituted aryl groups, like the *m*-tolyl group.

Incidental to the studies of the reaction of triphenylsilylpotassium with triphenylcarbinol we observed that triphenylcarbinol does not depress the melting point of triphenylsilanol. The similarities between these two compounds rendered the separation of a mixture of them very difficult. It has been found that by treating a mixture of triphenylcarbinol and triphenylsilanol with formic acid the carbinol was reduced to triphenylmethane,[4] whereas the silanol was converted into hexaphenyldisiloxane.[5]

$$(C_6H_5)_3COH + HCOOH \longrightarrow (C_6H_5)_3CH$$

$$(C_6H_5)_3SiOH + HCOOH \longrightarrow (C_6H_5)_3SiOSi(C_6H_5)_3$$

The resulting hydrocarbon and the silicon compound were separated by recrystallization.

Experimental[6]

Reaction of Triphenylsilylpotassium with Phenylacetylene.—A triphenylsilylpotassium suspension in ether prepared from 5.2 g. (0.01 mole) of hexaphenyldisilane followed by amalgamation according to the recent directions[7] was added rapidly to 1 g. (0.01 mole) of phenylacetylene dissolved in 20 ml. of ether. There was a slight heating effect accompanied by a slight change in color during the addition. The reaction mixture was stirred at room temperature for 30 hours. At the end of this period Color Test I[8] was still positive. Water was added to the reaction mixture and the latter was stirred and filtered. There was obtained 3.5 g. of light gray solid melting at 230°. This solid was extracted with benzene and filtered hot in order to remove a trace of gray residue. The filtrate yielded 2.8 g. (83%[9]) of colorless shining crystals melting at 233–235°; a mixed melting point with an authentic sample of tetraphenylsilane showed no depression. The ether solution of the hydrolyzed mixture was separated, dried over sodium sulfate, and distilled. The oily solid residue was recrystallized from a mixed solvent of benzene and petroleum ether (b.p. 60–70°) to give 0.5 g. of triphenylsilanol (mixed m.p.) melting at 149–151°.

In another experiment involving the same quantities of reactants the phenylacetylene was added to the triphenylsilylpotassium suspension. After 22 hours of stirring at room temperature the reaction mixture was carbonated with Dry Ice–ether slurry. Following the attainment of room temperature the carbonation mixture was hydrolyzed with dilute hydrochloric acid. There was separated 3.1 g. of light gray solid melting from 228–234°. This was recrystallized twice from benzene to yield 1.6 g. (48%[9]) of tetraphenylsilane. Some impure tetraphenylsilane was recovered from the mother liquor. The ethereal solution from the hydrolysis mixture was extracted with dilute alkali. Some white solid was separated upon the acidification of the alkaline extract. This was dissolved in ether from which 0.8 g. of light brown solid residue was obtained by evaporation. This solid was recrystallized from benzene to give colorless shining prisms melting at 134–136°; a mixed melting point with phenylpropiolic acid showed no depression. The purified acid weighed 0.5 g. (34%).

Reaction of Triphenylsilylpotassium with Tolane.—One and eight-tenths grams (0.01 mole) of tolane in 30 ml. of ether was added to 0.02 mole of a triphenylsilylpotassium suspension in ether without amalgamation over a period of 5 minutes. No appreciable amount of heat was evolved while the reaction mixture became very dark brown during the period of addition. The resulting mixture was stirred at room temperature for 24 hours. The black mixture thus formed was hydrolyzed with water and filtered by suction. There was collected 1.6 g. of solid melting to a turbid mass at 190°. This was recrystallized from benzene. The first crop separated as a fine white powder melting from 325–340°. Evaporation of the mother liquor to a small volume yielded 0.7 g. of colorless crystals melting from 225–230°. One recrystallization from benzene gave 0.5 g. (15%[9]) of tetraphenylsilane (mixed m.p.) melting at 233–235°. Evaporation of the ethereal solution from the hydrolysis mixture resulted in a glue-like residue. Attempts to purify it by crystallization and by chromatographic separation were unsuccessful.

Reaction of Triphenylsilylpotassium with Triphenylcarbinol.—A triphenylsilylpotassium suspension was prepared by cleaving 5.2 g. (0.01 mole) of hexaphenyldisilane with sodium–potassium alloy in ether. The excess alloy was removed by amalgamation and the triphenylsilylpotassium

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[1] H. Gilman and T. C. Wu, This Journal, **75**, 234 (1953).

[2] From one reaction between phenylacetylene and triphenylsilylpotassium, followed by carbonation, there was isolated phenylpropiolic acid as well as tetraphenylsilane.

[3] For example, reaction of triphenylsilylpotassium with diphenyl sulfoxide also gives tetraphenylsilane.

[4] A. Kovache, *Ann. chim.*, **10**, 184 (1918).

[5] Unpublished studies by H. W. Melvin.

[6] All melting points are uncorrected.

[7] H. Gilman and T. C. Wu, *J. Org. Chem.*, in press; H. Gilman and T. C. Wu, This Journal, **73**, 4031 (1951); H. Gilman, T. C. Wu, H. A. Hartzfeld, G. A. Guter, A. G. Smith, J. J. Goodman and S. H. Eidt, *ibid.*, **74**, 561 (1952).

[8] H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

[9] The percentage yield was calculated on the assumption that from an initial mole of hexaphenyldisilane there is obtained 1 mole of tetraphenylsilane.

suspension was transferred to another flask filled with nitrogen. To this there was added 2.6 g. (0.01 mole) of triphenylcarbinol dissolved in 50 ml. of ether. Very little heat was evolved during the addition while the reaction mixture became slightly deeper in color. After 48 hours of stirring at room temperature Color Test I[8] was still positive. Water was added to the mixture and it was filtered to separate 1.8 g. of cream-colored solid melting from 230–235°. This crude product was dissolved in hot benzene and filtered to remove a trace of gray specks. From the filtrate there was obtained 1.6 g. (48%[9]) of pure tetraphenylsilane (mixed m.p.) melting at 234–235°. The ethereal solution from the hydrolysis mixture was separated and dried over sodium sulfate. Evaporation of the solvent left 5.5 g. of a colorless solid residue melting from 145–151°. This was dissolved in hot petroleum ether (b.p. 60–70°) and allowed to cool. The first fraction of 0.2 g. of white solid melting at 225° was shown to be impure tetraphenylsilane after recrystallization. The petroleum ether solution was concentrated to give 2.7 g. of colorless crystals melting at 149–151°. It was suspected that this material might be a mixture of triphenylcarbinol and triphenylsilanol. A prepared mixture of about equal parts of triphenylcarbinol (m.p. 160–162°) and triphenylsilanol (m.p. 150–151°) melted at 151–153°. After some preliminary studies the reaction products were separated in the following manner.

The mixture of reaction products was refluxed in formic acid (Baker and Adamson, 98–100%) for 15 hours. Some colorless crystals were formed. The resulting mixture was diluted with 4 volumes of water and filtered. The solid residue (2.3 g.) was dissolved in petroleum ether (b.p. 60–70°) to give 0.5 g. of lustrous plates melting at 227–229°; a mixed melting point with hexaphenyldisiloxane showed no depression. This quantity corresponded to 10% of triphenylsilanol (presumably from the hydrolysis of excess triphenylsilylpotassium) originally present in the mixture of triphenylcarbinol and triphenylsilanol. The mother liquor after the removal of hexaphenyldisiloxane was evaporated to yield 1.6 g. of white crystals melting at 90–92°; a mixed melting point with an authentic sample of triphenylmethane was not depressed. The amount of triphenylmethane thus obtained was equivalent to 66% recovery of the triphenylcarbinol.

Reaction of Triphenylsilylpotassium with Benzohydrol.—The procedure used in this reaction was exactly the same as that described in the previous section except that 0.01 mole of benzohydrol was used instead of triphenylcarbinol. Following hydrolysis there was obtained, by filtration, 3.0 g. of crude tetraphenylsilane. This was purified as described above and 2.7 g. (80%[9]) of pure tetraphenylsilane (mixed m.p.) was isolated. From the ethereal solution 2.8 g. of white solid melting at 67–69° was obtained by recrystallization. Analyses of this product showed that it contained 3.0–3.5% of silicon. Melting point studies also pointed out that the presence of triphenylsilanol does not depress appreciably the melting point of benzohydrol. However, no attempt was made to separate this mixture.

Reaction of Triphenylsilylpotassium with Benzyl Alcohol.—Using exactly the same procedure described in the reaction with triphenylcarbinol except that 0.01 mole of benzyl alcohol was used instead of triphenylcarbinol, there was obtained 2.6 g. of crude and 2.3 g. (68%[9]) of pure tetraphenylsilane (mixed m.p.) melting at 234–235°. The ethereal solution was worked up as usual to give 1.0 g. (18%) of triphenylsilanol (mixed m.p.). Evaporation of the mother liquor resulted in an oil.

Reaction of Triphenylsilylpotassium with Triphenylsilanol.—The procedure used in this reaction was also the same as that for the triphenylcarbinol except that 0.01 mole of triphenylsilanol was used instead of triphenylcarbinol. Following hydrolysis there was obtained 3.2 g. of an insoluble solid melting at 232–235°. Recrystallization of this crude product gave 2.9 g. (86%[9]) of tetraphenylsilane (mixed m.p.) melting at 234–235°. The solid obtained from the ethereal solution was recrystallized twice from petroleum ether (b.p. 60–70°) to yield 3.2 g. of pure triphenylsilanol (mixed m.p.) melting at 150–151°. It was believed that part of the triphenylsilanol was the starting material and the rest came from the hydrolysis of triphenylsilylpotassium.

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16α-Methoxy-5-pregnen-3β-ol-20-one

BY DAVID GOULD, FRED GRUEN AND E. B. HERSHBERG

RECEIVED DECEMBER 19, 1952

Recently Mattox[1] reported the isolation of 16α-methoxy-5-pregnen-3β-ol-20-one acetate obtained by the action of methanolic hydrogen chloride on 5,16-pregnadien-3β-ol-20-one followed by acetylation of the product. Fukushima and Gallagher[2] isolated the same substance after saponifying pregnadienolone acetate in methanol and acetylating the crude product. Since we had previously isolated the unacetylated 16α-methoxy-5-pregnen-3β-ol-20-one by use of the Freudenberg[3] conditions, we are giving our results on this work.

During our studies on the acid hydrolysis of cortisone acetate, we isolated a product for which one possible structure was a 16,21-dimethoxypregnetrione.[1,4] In order to investigate whether the addition of methanol to the Δ^{16}-20-keto system would proceed by acid catalysis, we treated pregnadienolone in methanol with acetyl chloride and obtained a product having an E-value of 72 at 239 mμ, corresponding to the presence of about 25% of the original α,β-unsaturated ketone. The major product, 16α-methoxy-5-pregnen-3β-ol-20-one was separated by chromatography in about 35% yield, and was found to be identical with that obtained upon treatment of pregnadienolone acetate with methanolic alkali.

Treatment of the methoxypregnenolone with boiling acetic anhydride did not split out methanol, but only gave the known 3-acetate.[2] Cleavage was successful, however, when acetic anhydride catalyzed with hydrochloric acid was used, and it was possible to isolate 5,16-pregnadien-3β-ol-20-one acetate from the mixture.

Experimental[5]

16α-Methoxy-5-pregnen-3β-ol-20-one from 5,16-Pregnadien-3β-ol-20-one.—5,16-Pregnadien-3β-ol-20-one (2.0 g.) was dissolved in 160 ml. of abs. methanol and cautiously treated with 4 ml. of acetyl chloride (equiv. to 1% HCl). The mixture was allowed to stand 18 hours at room temperature. A solution of 5 g. of sodium acetate in 500 ml. of water was added and the precipitate which formed was collected by suction and washed with water. It weighed 2.1 g., m.p. 125–128°, E 72 (239 mμ in 95% ethanol).

One gram of the material was dissolved in benzene and chromatographed on 25 g. of Florisil as follows (100 ml. fractions):

Fraction	Eluant	Wt., mg.	M.p., °C.	$E^{1\%}_{1\,\mathrm{cm}}$	Product
1–4	Hexane	Neg.			
5–14	3:1 Hexane–C_6H_6	235	180–195	200	Pregnadienolone
15–22	1:1 Hexane–C_6H_6	50	150–180	150	Mixture
23–37	Benzene	360	144–154	22	16-Methoxy-pregnenolone
38–48	1% MeOH in C_6H_5	320	Oil		

Upon crystallization from methanol, fractions 23–37 gave 16α-methoxy-5-pregnen-3β-ol-20-one, m.p. 151–153°, $[\alpha]^{25}\mathrm{D}$ −23.9° (EtOH). *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.51; H, 10.00. The ratio to re-

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(1) V. R. Mattox, THIS JOURNAL, **74**, 4340 (1952).

(2) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951).

(3) K. Freudenberg and W. Jakob, *Ber.*, **74**, 1001 (1941).

(4) D. Gould and E. B. Hershberg, in press.

(5) All melting points are corrected. $E^{1\%}_{1\,\mathrm{cm}} = (l/cd) \log I_0/I$; $\epsilon = \mathrm{M.W.} \times E/10$. Analyses and optical data obtained by the Microanalytical Department of these laboratories.

covered starting material taking account of the purity of fractions 5–14 was about 2:1.

The same product was obtained[6] when 50 g. of 5,16-pregnadien-3β-ol-20-one acetate was saponified by refluxing for 6 hours in 1200 ml. of methanol with 20 g. of potassium hydroxide in 50 ml. of water. The water-precipitated product was dissolved in chloroform, the solution was washed neutral with water, dried and evaporated. The residue was recrystallized twice from ethyl acetate to give 16α-methoxy-5-pregnen-3β-ol-20-one, m.p. 151–152°, $[\alpha]^{24}\text{D}$ −24.4° (EtOH), no absorption between 220 and 300 mμ. *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.40; H, 9.53.

5,16-Pregnadien-3β-ol-20-one Acetate from 16α-Methoxy-5-pregnen-3β-ol-20-one.—When 16-methoxypregnenolone was refluxed one hour with acetic anhydride, the product was not that of dehydration, but was the known 16α-methoxy-5-pregnen-3β-ol-20-one acetate, m.p. 154–156°, $[\alpha]^{23}\text{D}$ −27.1° (EtOH).[2]

A sample of 5 g. of 16-methoxypregnenolone was dissolved in 20 ml. of acetic anhydride and treated with 2 ml. of concd. hydrochloric acid. The mixture was refluxed 20 minutes and chilled. There was obtained upon cooling 0.8 g. of crystalline 5,16-pregnadien-3β-ol-20-one acetate, m.p. 169–172°, m.p. mixed with authentic material, 171–174°, ε 9100 (234 mμ in *i*-octane).

From the mother liquor, there was obtained a low melting product which gave on crystallization from isopropyl alcohol 16α-methoxy-5-pregnen-3β-ol-20-one acetate, m.p. 153–155°.

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(6) We are indebted to T. Clayton and J. R. Confroy for permission to report these experimental data.

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A New Synthesis of Carnosine[1]

BY HARRY KROLL[2,3] AND HENRY HOBERMAN

RECEIVED DECEMBER 20, 1952

The use of N-phthalylamino acids as coupling agents in the syntheses of peptides has been studied by several groups of investigators.[4] The peptides prepared by this method include di- and tripeptides of the simple amino acids, as well as several peptides containing cysteine, glutamic acid and aspartic acid. There has been no reported use of this procedure for the preparation of peptides containing histidine.[5]

In a continuation of a previous investigation on the metabolism of β-alanine,[6] it was considered desirable to evaluate methods for the synthesis of carnosine labeled with N^{15} in the β-alanine portion of the molecule. An examination of the methods[7] available for the preparation of this interesting peptide indicated that the procedures were either too involved or that the yields were too low.

The phthalyl method for the preparation of carnosine was investigated since N-phthalyl-β-alanine could be prepared in good yields from phthalimide and methyl acrylate. N-Phthalyl-β-alanyl chloride was prepared by the method of Sheehan and Frank,[4b] but the direct coupling of the acid chloride with L-histidine in aqueous dioxane in the presence of magnesium oxide was unsuccessful. It was found that the N-phthalyl-β-alanyl chloride underwent a very rapid hydrolysis in aqueous solution. N-Phthalylcarnosine methyl ester was obtained by the direct condensation of either the acid chloride or the azide with L-histidine methyl ester in chloroform. However, difficulties were encountered in converting the methyl ester to phthalylcarnosine by both acid and mild alkaline saponification. The latter procedure yielded the phthalamic acid derivative of carnosine.

N-Phthalylcarnosine was obtained by treating the azide with the sodium salt of L-histidine in 50% dioxane. Removal of the phthalyl group was accomplished by the method of Sheehan and Frank[4b] which resulted in the isolation of carnosine hydrochloride as an amorphous solid. Treatment of N-phthalylcarnosine with phenylhydrazine by the method of Shuman and Boissonnas[4d] gave carnosine directly in moderate yields.

Experimental

Phthalyl-β-alanyl Chloride.—Phthalyl-β-alanine was converted to the acid chloride by the procedure described by Sheehan and Frank[4b] for the preparation of phthalylglycyl chloride. The compound was obtained in 85–90% yields, m.p. 102–103°.

Phthalyl-β-alanyl Azide.—A solution of 2.40 g. (0.01 mole) of phthalyl-β-alanyl chloride was dissolved in 25 ml. of cold acetone, and the solution mixed with 0.07 g. of sodium azide dissolved in 2 ml. of water. The reaction mixture was agitated for five minutes while the flask was immersed in an ice-bath. A white oil separated initially which gradually solidified after about ten minutes. The solid material was obtained by filtration, and dried *in vacuo* over phosphorus pentoxide. The crude material weighed 2.1 g., and decomposed explosively at 89–90°.

Phthalylcarnosine Methyl Ester.—A solution of histidine methyl ester in 25 ml. of chloroform was prepared from 2.42 g. (0.01 mole) of histidine methyl ester dihydrochloride by the method of Fischer and Cone.[8] To the chloroform solution was added 2.4 g. (0.01 mole) of phthalyl-β-alanyl azide, and the solution was allowed to stand overnight at room temperature. A white crystalline solid weighing 2.2 g. was obtained. The product was recrystallized from water, m.p. 193–194°.

Anal. Calcd. for $C_{18}H_{18}O_5N_4$: N, 15.1. Found: N, 14.9.

Phthalylcarnosine.—Histidine hydrochloride monohydrate, 1.05 g. (0.005 mole), was dissolved in 9.9 ml. of 1.02 *N* sodium hydroxide. The phthalyl-β-alanyl azide, 1.2 g. (0.005 mole), was dissolved in 25 ml. of dioxane, and the resulting solution poured into the aqueous histidine solution. The mixture was allowed to stand in the refrigerator overnight. The reaction mixture was neutralized with 4.7 ml. of 0.994 *N* sulfuric acid. The resulting mixture was filtered from a small amount of insoluble material, and concentrated to dryness at 50° under reduced pressure. The residue was extracted with three 25-ml. portions of boiling methanol, and the combined filtrates were placed in the refrigerator. A white crystalline solid was obtained weighing 0.7 g., m.p. 225–230°, dec. Recrystallization from methanol containing a trace of water brought about no change in the decomposition point.

Anal. Calcd. for $C_{17}H_{16}O_5N_4$: N, 15.68; neut. equiv., 357. Found: N, 15.55; neut. equiv., 357.

Carnosine (Method A).—The procedure used for the removal of the phthalyl group is identical with that described by Sheehan and Frank.[4b] Phthalylcarnosine, 3.56 g. (0.01 mole) was dispersed in 20 ml. of 95% ethyl alcohol, and 25 ml. of 1 *M* hydrazine hydrate in 95% ethyl alcohol was

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(1) Presented before the Division of Biological Chemistry, A. C. S. Meeting, Atlantic City, N. J., 1952.

(2) American Cancer Society Research Fellow.

(3) Alrose Chemical Co., Providence, R. I.

(4) (a) F. E. King and D. A. Kidd, *J. Chem. Soc.*, 3315 (1949); (b) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **71**, 1856 (1949); (c) W. Grassmann and F. Shulte-Uebbing, *Ber.*, **83**, 244 (1950); (d) I. Shuman and R. A. Boissonnas, *Nature*, **169**, 154 (1952).

(5) A private communication from Dr. R. A. Turner has disclosed the synthesis of carnosine from phthalylcarnosine.

(6) J. Graf and H. Hoberman, *J. Biol. Chem.*, **186**, 369 (1950).

(7) (a) R. H. Sifferd and V. du Vigneaud, *ibid.*, **108**, 753 (1935); (b) G. Barger and F. Tutin, *Biochem. J.*, **12**, 408 (1918); (c) L. Baumann and J. Ingvaldsen, *J. Biol. Chem.*, **35**, 263 (1918).

(8) E. Fischer and L. H. Cone, *Ann.*, **363**, 107 (1908).

added. The mixture was heated at reflux for one hour, and the reaction mixture concentrated to dryness. The residue was taken up in 50 ml. of 1.2 *M* hydrochloric acid and heated on a water-bath at 40–50° for 15 minutes. The mixture was concentrated to dryness under reduced pressure in a water-bath at 50°. The residue was dispersed in 30 ml. of water, and the insoluble phthalylhydrazide removed by filtration. The aqueous solution, on dilution with 75 ml. of 95% ethyl alcohol, precipitated 2.9 g. of carnosine hydrochloride as an amorphous, hygroscopic solid. It was converted to carnosine by passing an aqueous solution of the hydrochloride through an ion exchange column containing Deacidite. The aqueous eluate was concentrated to dryness and the residue was recrystallized from aqueous alcohol to give 0.6 g. of carnosine.

Anal. Calcd. for $C_9H_{14}O_3N_4$: N, 24.7. Found: N, 24.5.

(**Method** B).—The procedure was a modification of that described by Shuman and Boissonnas.[4d] To 1.78 g. of phthalylcarnosine (0.005 mole), there was added 25 ml. of 95% ethyl alcohol, 0.5 g. of triethylamine and 1.55 g. of phenylhydrazine. The mixture was refluxed for three hours on a water-bath. At the completion of the heating period, the clear yellow solution was cooled, and acidified with 1 g. of glacial acetic acid, and the mixture poured into 80 ml. of methyl ethyl ketone. An amorphous precipitate was obtained which was dissolved in 5 ml. of water and reprecipitated by the addition of 75 ml. of 95% ethyl alcohol. The dried product weighed 0.63 g., and after recrystallization from aqueous ethyl alcohol, 0.41 g. of carnosine was obtained.

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Stereochemistry of 1,4-Addition. II. The Bromination of Butadiene

BY KURT MISLOW

RECEIVED NOVEMBER 28, 1952

A recent paper[1] reports the 1,4-adduct of bromine and butadiene, 1,4-dibromo-2-butene (m.p. 53°), to have the *cis* configuration. This claim rests on the observed Raman frequency of 1655 cm.$^{-1}$, associated with *cis*-ethylenic double bonds,[2] and is the basis for the assumption that butadiene enters into reaction with bromine in the "bent" or s-*cis* form.

It has been shown that a frontal transition state cannot be of any appreciable importance in the 1,4-addition of chlorine to butadiene[3]; the implied claim that this argument does not apply in the case of bromine addition would therefore be of considerable interest. The following observations may however be marshaled as convincing evidence in favor of the identity of 1,4-dibromo-2-butene (m.p. 53°), I, with *trans*-1,4-dibromo-2-butene. (a) The infrared spectrum of I exhibits a pronounced and characteristic[4] *trans* peak near 10.3 μ, absent in the saturated analog.[5]

(b) Lithium aluminum hydride reduction of I affords *trans*-2-butene, as evidenced by conversion to *meso*-2,3-dibromobutane.[6] The present author has repeated this experiment and obtained *meso*-2,3-dibromobutane, b.p. 46° (14 mm.), $n^{25}\text{D}$ 1.5088 (repd.[7] $n^{25}\text{D}$ 1.5091).

(c) The dipole moment of I, 1.63 *D*, is similar to that of *trans*-1,4-dibromo-2,3-dimethyl-2-butene, 1.72 *D*, but smaller than that of the *cis*-isomer 2.49 *D*.[8]

(d) A *cis*-1,4-dibromo-2-butene (II), prepared from authentic *cis*-2-butene-1,4-diol,[9] differs from I in a manner characteristic[4a] of the relative properties of *cis* and *trans* isomers. Thus, the melting point of I is higher than that of II, II is thermally unstable with respect to I, and I and II give different 1,2,3,4-tetrabromobutanes, m.p. 116 and 39°, respectively.

The evidence here adduced compels us to maintain that as yet no satisfactory experimental basis exists for the view of frontal attack in the 1,4-addition of halogen to butadienes.[10] Equally, the tetrabromides, m.p. 116 and 39°, must be assigned the *meso* and racemic configurations, respectively, the claim[1] to the contrary notwithstanding.

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[1] Ya. M. Slobodin and S. A. Zaboev, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*, *U. S. S. R.*), **22**, 603 (1952).

[2] *E. g.*, N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

[3] K. Mislow and H. M. Hellman, THIS JOURNAL, **73**, 244 (1951).

[4] *E.g.* (a) L. Crombie, *Quart. Revs.*, **6**, 101 (1952); (b) L. Crombie, *J. Chem. Soc.*, 2997 (1952); (c) F. Sondheimer, THIS JOURNAL, **74**, 4040 (1952); (d) K. Mislow, *ibid.*, **74**, 5155 (1952).

[5] A Baird Model B instrument with 0.1-mm. cells was employed. In this connection, the assistance afforded by correspondence with Dr. Ralph Nusbaum and his staff, Spectroscopy Section, Atomic Energy Project, U. C. L. A., Los Angeles, Calif., is gratefully acknowledged.

[6] L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

[7] R. T. Dillon, W. G. Young and H. J. Lucas, *ibid.*, **52**, 1953 (1930).

[8] O. J. Sweeting and J. R. Johnson, *ibid.*, **68**, 1057 (1946).

[9] A. Valette, *Ann. chim.*, [12] **3**, 644 (1948).

[10] Some recent developments pertaining to this concept as originally expressed (ref. 3): the 1,4-addition of sulfur dioxide to terminally substituted butadienes involves the s-*cis* form of butadiene (O. Grummitt and J. Splitter, THIS JOURNAL, **74**, 3924 (1952)); halonium ions can be incorporated in a stable symmetrical 5-membered ring as part of a diphenyl system (R. B. Sandin and A. S. Hay, *ibid.*, **74**, 274 (1952)); the argentation constants of monoargentated *cis*-1,2-diiodoethylene and o-diiodobenzene are indicative of the existence of symmetrical 5-membered onium rings (L. J. Andrews and R. M. Keefer, *ibid.*, **73**, 5733 (1951)).

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D-Glucuronolactone Isonicotinyl Hydrazone

BY PETER P. T. SAH

RECEIVED OCTOBER 1, 1952

D-Glucuronolactone isonicotinyl hydrazone, a new compound with comparatively low toxicity and very high antitubercular activity *in vitro* as well as *in vivo*,[1] may be prepared easily by the following procedure.

D-Glucuronolactone (Eastman Kodak Co., 88 g.) was placed in a 3-l. round-bottomed flask and covered with 1.5 liters of methyl alcohol (acetone-free). The mixture was boiled gently on the steam-bath for 10 minutes when a clear solution was obtained. To the hot solution, isonicotinic acid hydrazide (Pfizer, 70 g.) was added all at once. The mixture was boiled vigorously for 10 minutes and the clear solution filtered without suction through a piece of lens paper into a 2-l. erlenmeyer flask. After standing for 24 hours at room temperature, the beautiful crystals (white rods and narrow plates) were filtered off with suction, washed with a small amount of methyl alcohol, and sucked completely to dryness. The product was dried in a vacuum desiccator for 3 days; yield 148 g. The product thus ob-

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[1] Biological tests were performed by W. B. Sutton of the Lilly Research Laboratories, Indianapolis, Indiana, and the results later confirmed by Dr. E. G. Roberts of Stanford University School of Medicine. The new drug is now undergoing clinical trial. Results will be reported elsewhere.

tained is already very pure. It may be recrystallized from a large amount of methyl or ethyl alcohol (absolute). The recrystallized product showed the same physical properties as the unrecrystallized.

D-Glucuronolactone isonicotinyl hydrazone thus prepared is in the form of white plates and rods from methyl alcohol or needles from absolute ethyl alcohol. On heating, it charred and decomposed with foaming between 150 and 160° without any sharp melting point. The decomposition point depends on the rate of heating and the type of apparatus used. The new compound is very soluble in water from which it cannot be recrystallized. It is practically insoluble in cold methyl or ethyl alcohol but slightly soluble in these boiling solvents (100 cc. of methyl alcohol dissolves about 1.2 g. of the product at 66°).

Anal. Calcd. for $C_{12}H_{13}O_6N_3$: C, 48.79; H, 4.45; N, 14.24. Found: C, 48.58, 48.63; H, 4.33, 4.29; N, 14.51, 14.48.

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On Salt Effects and the Temperature Coefficients of Solubility of Benzoic and Phenylacetic Acids in Aqueous Solutions

BY MARTIN A. PAUL

RECEIVED NOVEMBER 14, 1952

Recent publications call attention to the anomalous effect of temperature on the solubility of benzoic acid in water and in aqueous salt solutions.[1,2] The anomalies may be briefly summarized as follows.

(1) The solubility s_0 in water fails to satisfy a linear relationship between log s_0 and $1/T$, such as would be expected of an ideal dilute solution if the heat of solution were not exceptionally temperature sensitive; it increases instead at a much more accelerated rate with increasing temperature.[3]

(2) The solubility s in aqueous salt solutions for a particular salt fails to satisfy the Setschenow equation

$$\log (s_0/s) = K'm_s \qquad (1)$$

Instead, the parameter K' called for by this equation, which is quite generally satisfied by slightly soluble non-electrolytes, shows a tendency to decrease in magnitude with increasing concentration m_s of the electrolyte, this tendency being more marked at higher than at lower temperatures.

(3) The total effect of a given salt on the solubility, whether it salts-out or salts-in the benzoic acid, appears to increase markedly with increasing temperature, in contrast with the rather slight decrease in the salt effect normally observed for other slightly soluble non-electrolytes.

Similar anomalies are shown by phenylacetic acid,[1] with the further anomaly that if one assumes both phenylacetic and benzoic acids to be ideal solutes, then the effects of salts on their respective solubilities appear to differ in magnitude rather more than one would expect in view of their close similarity in molecular size and structure.

These anomalies receive a consistent explanation, as pointed out by Long and McDevit,[4] if one supposes that the solute is not an ideal solute, but deviates from Henry's law in the sense that its activity coefficient with respect to the infinitely dilute solution decreases with increasing concentration. It then "salts-in" itself, so to speak, at the increased concentrations normally accompanying the higher temperatures; the apparent effects of electrolytes on the solubility are thereby enhanced, because any appreciable change in the solute's concentration normally associated with the presence of the electrolyte is accompanied by a further change in the same direction as a result of the changing self interaction. It should be noted that deviation from Henry's law is a natural consequence of failure of the solute to follow Raoult's law, that is, failure of its activity to decrease in exact proportion to its mole fraction over the entire composition range.[5] The only special point at issue is whether such deviations can indeed become significant at the solute concentrations attained in the cases here under consideration.

By making certain simplifying assumptions, we may in fact use the deviation of the temperature coefficient of solubility from ideal-dilute-solution behavior in the pure solvent (as would be embodied by a linear relationship between log s_0 and $1/T$) to calculate a self-interaction parameter for the solute. Such a parameter, k_i', is defined by the first term in a series expansion of log γ' as a function of the molality, m_i

$$\log \gamma' = k_i'm_i \qquad (2)$$

where γ' represents the molal activity coefficient referred to infinite dilution in the pure solvent, water.[6] Let us assume that such an expression can be made to fit the data over the concentration ranges of interest (up to about 0.3 m in the case of benzoic acid and 0.7 m in the case of phenylacetic acid), and that furthermore we may neglect the variation of ΔH, the enthalpy of solution at infinite dilution, with temperature. Then from the thermodynamic equation

$$\frac{\mathrm{d} \ln (s_0\gamma')}{\mathrm{d}T} = \frac{\Delta H}{RT^2} \qquad (3)$$

it follows that

$$\log s_0 + k_i's_0 = -\frac{\Delta H}{2.303RT} + C \qquad (4)$$

where s_0 represents the molal solubility at absolute temperature T and C is an integration constant.

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[1] T. J. Morrison, *Trans. Faraday Soc.*, **40**, 43 (1944).

[2] J. O'M. Bockris, J. Bowler-Reed and J. A. Kitchener, *ibid.*, **47**, 184 (1951).

[3] See ref. 2, where the empirical equation, $\ln s_0 = A + 0.0357\,T$, is given for the molal solubility between 25 and 85° in water containing 0.01 m sodium benzoate to repress ionization. If benzoic acid were an ideal solute, the implied enthalpy of solution would have the form $0.0357\,RT^2$, corresponding to a heat capacity difference between solute in infinitely dilute solution and in the pure crystalline state of magnitude 0.142 T cal./mole deg. While the heat capacity of crystalline benzoic acid is 42.5 and that of the pure liquid, 63.2 cal./mole deg. (at the melting point, from data quoted in the "International Critical Tables"), it seems likely that the partial molal heat capacity in dilute aqueous solution is much closer to that of the crystalline solid, since the comparatively high value for the pure liquid no doubt corresponds with extensive dimerization undergoing decrease with rising temperature.

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

[5] This is made clear in the discussion and diagram given by J. H. Hildebrand and R. L. Scott, "The Solubility of Nonelectrolytes," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1950, p. 12.

[6] See ref. 4; primes will be used to distinguish symbols based on moles per kilogram of water as concentration measure from corresponding symbols used by Long and McDevit based on moles per liter of solution. The "solvent" in the present instance is actually a 0.01 m aqueous solution of sodium benzoate or sodium phenylacetate, respectively.

From a plot of the quantity ($\log s_0 + \Delta H/2.303RT$) *vs.* s_0, it should be possible to derive the value of k_i' as the negative of the slope of the resulting curve, the plot being linear if in addition to the conditions previously assumed, it turns out that k_i' itself is practically constant with temperature. Such a plot for benzoic acid, with ΔH = 6500 cal./mole,[7] is presented in Fig. 1, based on the solubility data of Morrison[1] and of Ward and Cooper.[8] One sees that between 25° (the lowest temperature included) and 85°, the plot is indeed quite linear, the two highest points, at 88.3 and 88.6°, respectively, showing a trend away from linearity.

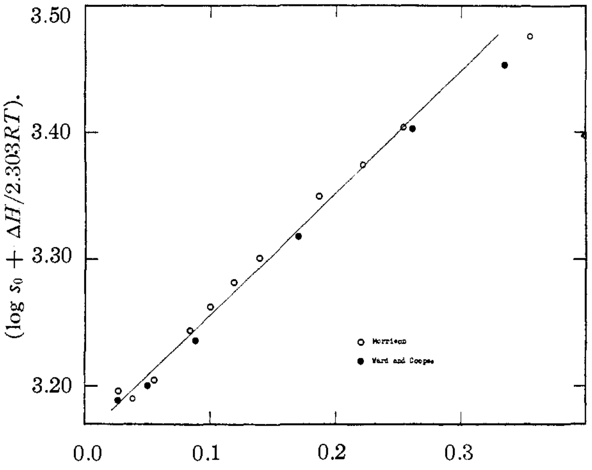

Fig. 1.—(Log s_0 + $\Delta H/2.303\ RT$) *vs.* s_0 for benzoic acid in water: ○, Morrison; ●, Ward and Cooper.

From the slope of the linear relationship indicated by Fig. 1, we obtain a value of the self-interaction parameter k_i' for benzoic acid of about -0.96. This value may seem rather large as compared for example with the value of -0.25 for mandelic acid derived by McDevit and Long (using a different principle),[9] but independent evidence is available from boiling point elevation data reported by Peddle and Turner.[10] These authors, working with benzoic acid concentrations in the range 0.5–0.6 *m*, discovered enormous deviations from ideal behavior, such as to lead them in fact to the conclusion that the solute was practically completely associated into dimeric molecules. This conclusion is at variance with the essentially ideal behavior actually shown by benzoic acid in dilute aqueous solutions toward ionization equilibria and partition with other non-aqueous liquid phases; if extensive dimerization existed in 0.5 *m* solutions, the law of mass action would call for a still appreciable degree of association even in 0.01 *m* solutions, quite contrary to experience. But while the boiling point elevation data cannot be fitted precisely by means of a simple linear equation such as eq. (2) representing the deviation from ideality, yet the indicated activity coefficients do have magnitudes consistent with k_i' values of order -0.9. By contrast, the behavior of mandelic acid is almost ideal.[10]

When ΔH values are lacking, as seems to be the case for phenylacetic acid, we may still fit a three-constant equation of the form

$$\log s_0 = -k_i's_0 - (A/T) + C \qquad (5)$$

to the solubility data; the best value so found for the constant A then represents the mean value of $\Delta H/2.303R$ over the given temperature range, assuming of course that eq. (2) correctly represents the form of the deviation from ideal behavior. Applying this method to Morrison's solubility data for phenylacetic acid,[1] we find for the solid, which melts under water at 47°, that from just three experimental points (at 25, 35 and 45°), $k_i' = -0.59$ and ΔH = 5520 cal./mole; it is noteworthy that even over such a short interval of temperature, log s_0 itself departs significantly from linearity as a function of $1/T$. From six experimental points for the liquid ranging between 41 and 87°, we obtain by the method of least squares, $k_i' = -0.57$ and ΔH = 1745 cal./mole. The agreement between the k_i' values indicated by the two sets of data is excellent, and Fig. 2, in which ($\log s_0 - 0.58s_0$) is plotted against $1/T$ for both solid and liquid, shows how well eq. (5) fits the data with k_i' assigned the average value, -0.58. It is gratifying to note that boiling point elevation data for this compound in aqueous solutions at concentrations

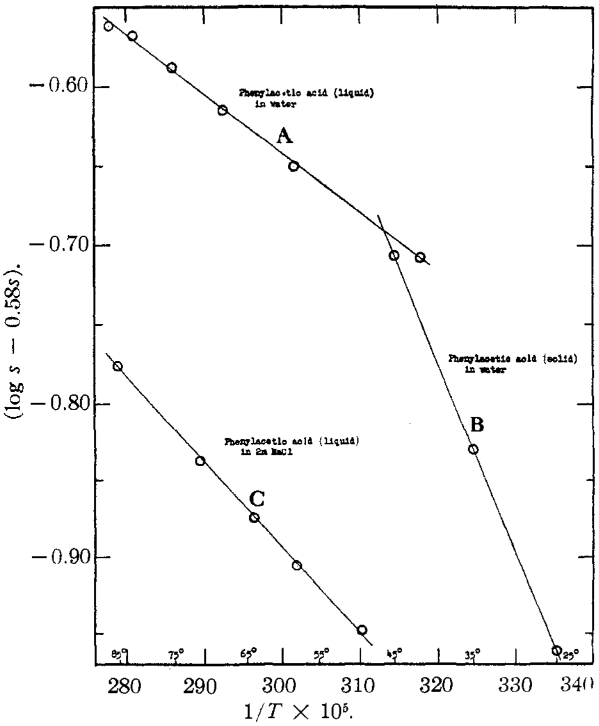

Fig. 2.—(Log s − 0.58s) *vs.* $1/T$ for phenylacetic acid: A, phenylacetic acid (liquid) in water; B, phenylacetic acid (solid) in water; C, phenylacetic acid (liquid) in 2 *m* NaCl.

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[7] "International Critical Tables," from direct calorimetric investigation at 20° by M. Berthelot.

[8] H. L. Ward and S. S. Cooper, *J. Phys. Chem.*, **34**, 1484 (1930). These data in pure water, after correction for ionization, are in substantial agreement with those of Morrison in 0.01 *m* sodium benzoate solutions; the data in ref. 2 are in agreement at the lower temperatures, but deviate in the direction of lower solubilities at the higher temperatures.

[9] W. F. McDevit and F. A. Long, This Journal, **74**, 1090 (1952).

[10] C. J. Peddle and W. E. S. Turner, *J. Chem. Soc.*, **99**, 685 (1911); the data were corrected by the authors for the slight but not insignificant volatility of the solute.

between 0.4 and 0.7 m are consistent with a k_i' value of order -0.6,[10] though as in the case of benzoic acid, it is not possible to fit the data exactly by means of a linear deviation function such as is described by eq. (2). The difference between the indicated ΔH values for solid and liquid agrees quite well with the latent heat of fusion of pure phenylacetic acid, 3890 cal./mole, derived from its cryoscopic constant at the normal melting point.[11]

These results have an important bearing on the interpretation of salt effects. For benzoic acid, the solubility at 25° is sufficiently low (0.027 mole/kg. H_2O) so that self interaction cannot be very influential at that temperature, the indicated value of the molal activity coefficient in the saturated aqueous solution being 0.94. For phenylacetic acid, the value of 0.84 (corresponding with solubility of 0.130 mole/kg. H_2O) deviates sufficiently from unity, however, to cast doubt on the applicability of the Setschenow equation, eq. (1), or at least on the interpretation of K' in that equation as the true salting-out parameter for the electrolyte. For both benzoic and phenylacetic acids, self interaction must have a profound effect on the temperature coefficients of salt effects, as is indeed indicated by the abnormal increase previously mentioned in the apparent effects of salts on the solubilities at the higher temperatures.[1,2]

Long and McDevit[4] have shown that in cases of this kind, one may often represent the activity coefficient of the non-electrolyte in the form

$$\log \gamma' = k_i' m_i + k_s' m_s \qquad (6)$$

where k_s' represents the true salting-out parameter for the electrolyte, while the other symbols have the same significance as before. In this generalization of eq. (2), it is assumed essentially that k_i' and k_s' are independent of each other, or what amounts to the same thing, that terms involving $m_i m_s$ as well as terms involving higher powers of m_i and m_s in the series expansion of $\log \gamma'$ may be neglected. It follows that in the saturated solutions

$$(\log s_0 + k_i' s_0) - (\log s + k_i' s) = k_s' m_s \qquad (7)$$

If k_i' has been established, one may readily apply this equation to evaluate k_s' from solubility data.

Applying eq. (7) to Morrison's solubility data for benzoic and phenylacetic acids,[1] using the k_i' values previously derived, one obtains k_s' values for different electrolytes which are indeed quite independent of the electrolyte's concentration. This is shown by the data for phenylacetic acid in NaCl solutions plotted in Fig. 3. It should be recalled that a plot of $\log (s_0/s)$ itself against m_s, as suggested by eq. (1), is definitely not linear, particularly at the higher temperatures. Figure 2 shows how well $(\log s + k_i' s)$ for a particular salt concentration conforms to a straight line when plotted against $1/T$; the negative of the slope in this case, multiplied by $2.303R$, evidently represents the enthalpy of solution at infinite dilution in the salt solution of given concentration. The data for benzoic acid in solutions of NaCl, the only electrolyte for which Morrison reports more than one salt concentration for this solute, do not conform so well at 25° to the linear form (7) as his data for phenylacetic acid, but the indicated experimental error is of order ±0.02 unit in $\log s$;[12] at higher temperatures, where the higher solubilities reduce the relative experimental error, eq. (7) appears to give an entirely satisfactory account of the data.

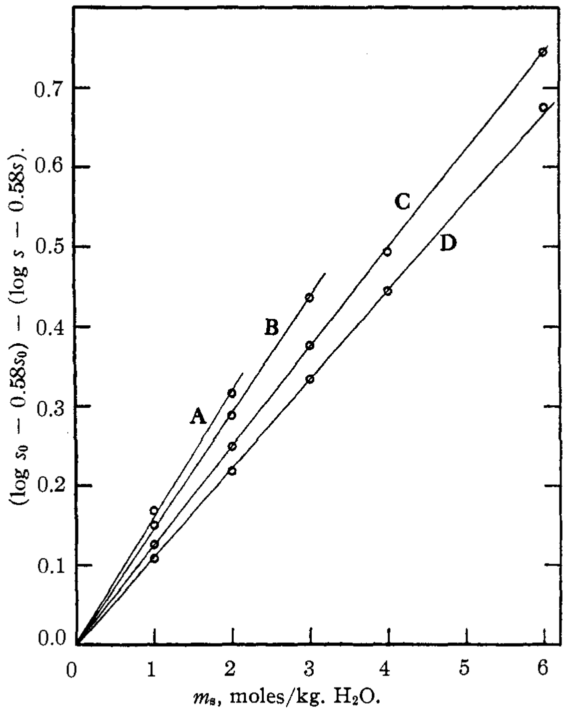

Fig. 3.—$(\log s_0 - 0.58s_0) - (\log s - 0.58s)$ vs. m_s for phenylacetic acid in aqueous NaCl solutions: A, 25°; B, 45°; C, 65°; D, 85°.

Table I summarizes average k_s' values so derived for the electrolytes studied by Morrison.[1] One sees that with the possible exception of KNO_3,

TABLE I

SALTING-OUT PARAMETER, k_s', AT t, °C.

Salt	25	35	45	55	65	75	85
			Benzoic acid				
NaCl	0.160	0.151	0.143	0.135	0.129	0.122	0.116
KCl	.123	.117	.112	.106	.102	.097	.092
NH_4Cl	.098	.087	.076	.066	.057	.047	.039
KNO_3	.011	.017	.023	.029	.034	.039	.043
			Phenylacetic acid				
NaCl	0.162	0.151	0.143	0.133	0.124	0.117	0.110
KCl	...	...	.103	.097	.091	.087	.081
$NaNO_3$	...	...	.058	.054	.050	.047	.043
KNO_3	...	...	.026	.027	.027	.026	.026

for which the salt effects are very small and therefore subject to large relative error, the salting-out parameters show what appears to be the normal gradual decrease with increasing temperature. One sees furthermore that there is little difference between the salting-out parameters for the two nonelectrolytes. While the data of Bockris, Bowler-Reed and Kitchener for the salting-in of benzoic acid by tetraethylammonium iodide[2] are not given in sufficient detail to permit calculation, there appears to be no doubt that self interaction is sufficient to account for the marked increase they observed in the apparent effect of the salt between

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(11) "International Critical Tables."

(12) The data of other authors at this temperature, however, apparently conform quite well with the Setschenow equation, eq. (1); for references, see ref. 4.

60 and 85° as compared with the much smaller increase between 25 and 50°.

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A New Synthesis of *n*-Heptafluoropropyl Grignard Reagent

BY O. R. PIERCE, A. F. MEINERS AND E. T. MCBEE

RECEIVED FEBRUARY 6, 1953

The synthesis and reactions of *n*-heptafluoropropylmagnesium iodide have been reported in recent literature,[1-3] and in all cases the Grignard reagent was prepared by reaction of 1-iodoheptafluoropropane with magnesium metal. In this Laboratory, a Grignard reagent has been prepared in good yield from this iodide by reaction with phenylmagnesium bromide in diethyl ether at 0–10°. The reagent obtained was found to give a normal addition reaction with acetone in high yield, employing simultaneous addition of the phenyl Grignard reagent and acetone to a solution of the iodide. A study of the scope of this rather unusual Grignard exchange reaction is in progress.

Experimental

In a typical experiment, a 3-necked round bottom flask was equipped with a mercury-sealed Hershberg stirrer and two closed circuit addition funnels. A mercury bubble counter and Dry Ice-cooled vapor traps were attached to one of the addition funnels and dry nitrogen was introduced through the other. The flask was flamed with a Bunsen burner and, on cooling, 59.2 g. (0.2 mole) of 1-iodoheptafluoropropane in 250 ml. of anhydrous ether was added to the flask. The flask and contents were then cooled by means of an ice-water bath. Into one of the addition funnels was placed 110 ml. of 1.88 *M* phenylmagnesium bromide (0.207 mole) in ether, and into the other was placed 17.4 g. (0.3 mole) of acetone (commercial grade, 99%) in an equal volume of anhydrous ether. The Grignard reagent and the acetone were then added simultaneously to the ether solution of 1-iodoheptafluoropropane. A white flocculent precipitate formed as soon as a few drops had been added. The addition was conducted over a period of four hours and the reaction mixture was stirred at ice-bath temperatures for an additional eight hours. The reaction mixture was then light yellow in color and contained a considerable quantity of the white flocculent material. No escaping gas was observed and no material condensed in the vapor trap.

The reaction mixture was then hydrolyzed with 300 ml. of ice-cold 10% sulfuric acid. The solid completely dissolved and the mixture was separated into two sharply divided portions. The ether layer was separated and washed once with water. The water layer was extracted three times with ether and the ether portions were combined and dried with Drierite. The ether was distilled through a short column (14 mm. barrel, stainless steel, "heli-pak" packing) and the residue was rectified through the same column. After a short forerun (2–3 cc.), 29.6 g. of 3,3,4,4,5,5,5-heptafluoro-2-methyl-2-pentanol[1-3] boiling at 107–108° was obtained, representing a 65% yield based on the 1-iodoheptafluoropropane. Also, 33.8 g. of iodobenzene was formed, which raises to 83% the accounting of the 1-iodoheptafluoropropane.

Acknowledgment.—The authors wish to express their appreciation to the Westinghouse Electric Corporation for support of this work.

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(1) O. R. Pierce and M. Levine, THIS JOURNAL, **73**, 1254 (1951).

(2) A. L. Henne and W. Francis, private communication.

(3) R. N. Haszeldine, *J. Chem. Soc.*, 3423 (1952).

The Fluoroplatinates. I. Lanthanum, Cerium, Praseodymium and Neodymium Fluoroplatinates

BY THEODORE P. PERROS[1] AND CHARLES R. NAESER

RECEIVED JANUARY 9, 1953

During the investigation of the effect of fluorine on certain rare earth fluorides, the reaction between fluorine, platinum and a rare earth fluoride was noted. The product was determined to be the fluorine analog of the chloroplatinates, namely, a fluoroplatinate. This is the first of a series of papers dealing with the preparation and properties of compounds containing the fluoroplatinate ion.

Of the platinum complexes having the general formula $(PtX_6)^{-2}$ in which X is a halogen, a number of compounds have been prepared which contain either chlorine, bromine or iodine as X. With regard to fluorine, there is only one original reference citing the preparation and properties of a compound containing the complex $(PtF_6)^{-2}$. This is the work of Schlesinger and Tapley[2] who prepared K_2PtF_6. This compound was formed by heating finely divided platinum with $3KF{\cdot}HF{\cdot}PbF_4$ in a platinum boat. Their efforts to prepare other fluoroplatinic salts were unsuccessful.

In this investigation the fluoroplatinates of lanthanum, cerium, praseodymium and neodymium were prepared and some of their physical properties determined. The rare earth fluoroplatinates were prepared by treating an intimate mixture of platinum and the respective fluoride with elemental fluorine at 525°.

Experimental Methods and Materials

Rare Earth Fluorides.—The rare earth oxides from which the rare earth fluorides were prepared, were a part of the Welsbach collection. Only trace amounts of the neighboring rare earth elements were found in each respective rare earth oxide. The rare earth trifluorides were prepared by precipitation from rare earth chloride solutions with hydrofluoric acid. Absolute alcohol was used to wash the precipitates.

Platinum.—The platinum foil from which the platinum boats were fashioned was 0.0015 inch thick. The boat had the dimensions 4.8 cm. × 1.0 cm. × 0.7 cm.

Fluorine.—Fluorine was prepared by the electrolysis of molten potassium bifluoride. The fluorine generator was constructed according to the description given by Von Wartenburg.[3] The anode was made of carbon.

Reaction Tube.—Fluorination was carried out in a nickel tube, 14″ in length, 7/8″ inside diameter and 1/8″ in thickness. During the runs, the tube was heated in a calibrated electric combustion furnace. The connections between the nickel tube and the fluorine inlet consisted of plaster of Paris stoppers.

The Rare Earth Fluoroplatinates.—All samples were prepared by identical procedures. A rare earth fluoride was spread evenly in a thin layer on the bottom of a platinum boat. Several strips of platinum foil were placed lengthwise on top of the layer of salts, and then covered with another thin layer of the rare earth fluoride. This process was repeated until the capacity of the boat had been reached. The sample was then placed in the reaction tube. While the tube was being heated to 525°, the system was flushed with dry air. The sample was fluorinated for five hours. In each instance, after the completion of a run, the platinum foil had disappeared in the formation of the fluoroplatinate. The rare earth fluoroplatinates are soluble in water and thus

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[1] Abstracted from a portion of the thesis submitted by Theodore P. Perros in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) H. Schlesinger and M. Tapley, THIS JOURNAL, **46**, 276 (1924).

(3) H. Von Wartenburg, *Z. anorg. allgem. Chem.*, **244**, 277 (1940).

were easily separated from the residual, unreacted, insoluble rare earth fluorides.

Solubility.—The solubilities of the rare earth fluoroplatinates were determined approximately by measuring the least amount of water necessary to dissolve a weighed sample of the salt at a temperature of 30°.

Density.—The densities were determined at 30° with a 1-ml. pycnometer using toluene as the displacement liquid.

Absorption Spectra.—For each compound the absorption spectrum was measured with a model DU Beckman spectrophotometer using matched 1-cm. cells.

Analyses.—The compounds were analyzed according to the accepted analytical procedures. Each of the rare earth elements was determined by precipitation as the oxalate. After filtration of the precipitate, it was titrated with standard permanganate solution. Platinum was determined by reduction of the fluoroplatinate ion with hydrazine. Fluorine was determined gravimetrically as lead fluochloride. The results are summarized in Table I.

TABLE I

ANALYTICAL DATA

Compound	Rare earth, % Calcd.	Rare earth, % Found	Platinum, % Calcd.	Platinum, % Found	Fluoride, % Calcd.	Fluoride, % Found
$La_2(PtF_6)_3$	23.05	22.93	48.58	48.47	28.37	28.22
$Pr_2(PtF_6)_3$	23.30	23.16	48.43	48.12	28.27	28.01
$Nd_2(PtF_6)_3$	23.72	23.45	48.16	48.00	28.12	27.90

Discussion

The fluoroplatinate of cerium was the only one which could not be isolated. This was to be expected, since tetravalent cerium was produced by the action of fluorine. The addition of water to the cerium product resulted in the immediate but gradually complete hydrolysis of the salt. The addition of oxalic acid to a fresh solution of the cerium fluoroplatinate precipitated all of the cerium at once, leaving the fluoroplatinate ion in solution.

The presence of this ion was established by (a) its precipitation as potassium fluoroplatinate through the addition of potassium fluoride and (b) the subsequent analysis of this precipitate. The alkali fluoroplatinates will be the subject of a future paper.

The aqueous solution of lanthanum fluoroplatinate has a pale yellow color. Since lanthanum ions are colorless, this color may be attributed to the fluoroplatinate ion. The absorption spectrum of this compound revealed two characteristic peaks of the fluoroplatinate ion at 273 and 308 mμ. These appeared in all subsequent absorption spectra measurements of other fluoroplatinate compounds.

The color of praseodymium fluoroplatinate is yellow-green, whereas that of neodymium is lavender. In the absorption spectra of these two compounds, the bands characteristic of praseodymium and neodymium as well as those of the fluoroplatinate ions are evident.

The solubilities and densities of the rare earth fluoroplatinates are given in Table II.

TABLE II

Fluoroplatinates	Density	Solubility/100 g. of H_2O
Lanthanum	2.63	7.5
Praseodymium	2.64	7.1
Neodymium	2.66	6.6

Acknowledgment.—Part of this investigation was performed under the terms of a contract with the AEC, Washington, D. C.

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Kinetics of Chlorine Replacement by Ethylate Ion in Ethanol Solutions of Symmetrical Trichlorobenzene[1]

BY THOR R. RUBIN AND A. A. BROOKS[2]

RECEIVED FEBRUARY 4, 1953

Previous work on the replacement of aromatic halogen by basic ions indicates the reactions are of second order.[3–5]

Some of the above studies[6–12] involve aromatic compounds which are subject to reduction in anhydrous alcohol solution, particularly at temperatures greater than 70°.

In a preliminary study Holleman[13] showed that symmetrical 1,3,5-trichlorobenzene reacts reasonably rapidly with base in methanol solution without forming large amounts of phenols.

The present results are concerned with the replacement of halogen in 1,3,5-trichlorobenzene by ethylate ion in anhydrous ethanol.

The replacement process of halogen by ethylate on the benzene ring forms under certain conditions several reaction products two of which were identified. One was 3,5-dichlorophenetole (compound A of Table I) the other was 3,5-diethoxychlorobenzene (compound B of Table I).

These compounds were recovered from a relatively large amount of a reaction mixture consisting initially of excess sodium ethylate, 1,3,5-trichlorobenzene and anhydrous ethanol which was kept at 170° in a glass lined bomb for 50 hours under nitrogen. The amount of 3,5-diethoxychlorobenzene recovered was about 15% of the amount of

TABLE I

PROPERTIES OF THE REACTION PRODUCTS AND THEIR DERIVATIVES

	Compound A	3,5-Dichlorophenetole[a]	Compound B	3,5-Diethoxychlorobenzene[b]
B.p., °C. (mm.)	92 (4) 106 (8)	... ...	111 (4) 116 (8)	....
$n^{20}D$	1.5405	...	1.5225	....
Analysis, % C	50.20 50.15	50.28	60.49 60.56	59.85
Analysis, % H	4.88 4.52	4.22	6.71 6.82	6.53
Phenol dev., m.p., °C.	64.4–65.5	68	114.0–116.5	117
Benzoate dev., m.p., °C.	56.8–57.4	55	....	....
Hydrate dev.	....	...	Formed in moist benzene	Insoluble in benzene

[a] E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 217. [b] *Ibid.*, pp. 340.

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[1] Taken from the dissertation submitted by A. A. Brooks, in partial fulfillment of the requirements for the degree of Doctor of Philosophy at The Ohio State University.

[2] Kimbereley Fellow 1948–1949.

[3] P. K. Lulofs, *Rec. trav. chim.*, **20**, 292 (1901).

[4] E. A. Kryuger and M. S. Bednova, *J. Gen. Chem.* (*U.S.S.R.*), **3**, 67 (1933).

[5] W. J. DeMooy, *Rec. trav. chim.*, **35**, 5 (1915).

[6] S. J. Riklis, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 825(1945).

[7] S. J. Riklis, *ibid.*, **17**, 1511 (1947).

[8] C. W. L. Bevan, *J. Chem. Soc.*, 2340 (1951).

[9] J. Miller, *ibid.*, 3350 (1952).

[10] A. V. Blom, *Helv. Chim. Acta*, **4**, 287, 510, 1029 (1921).

[11] H. S. Fry and J. L. Cameron, THIS JOURNAL, **49**, 864 (1927).

[12] H. S. Fry and P. E. Bowman, *ibid.*, **52**, 1531 (1930).

[13] A. F. Holleman, *Rec. trav. chim.*, **37**, 195 (1918).

3,5-dichlorophenetole recovered. The properties of the 3,5-dichlorophenetole and 3,5-diethoxychlorobenzene and those of certain of their derivatives are summarized in Table I.

Similar experiments with solutions containing an excess 1,3,5-trichlorobenzene over sodium ethylate in ethanol yielded 3,5-dichlorophenetole only, in detectable amounts. Thus it would appear that the replacement process consists of stepwise reactions the first step being the reaction in which 3,5-dichlorophenetole was formed.

The kinetics for the first step replacement reaction at various temperatures are given in Table II. The rate constants were calculated under the assumption that the reaction is first order each in ethylate ion and in 1,3,5-trichlorobenzene. The constants at any one temperature agree to within 1% of one another even when the reaction was run to 90% completion.

TABLE II

SUMMARY OF KINETIC DATA

$T = 161.92 \pm 0.01,°\ d = 0.6312,\ a = 0.1043$

t, min.	H^+, ml.	k
0	10.44	
140	8.86	11.69
285	7.62	11.43
480	6.27	11.47
645	5.38	11.45
870	4.49	11.21
1201	3.33	11.60
1515	2.61	11.60

TABLE III

SUMMARY OF THE RESULTS

k_{cor} is the average k corrected for density changes of the alcohol. The average deviations are of the order of 1%.

Run	T, °C.	a, M	b, M	$k_{cor} \times 10^3$
I	149.42	0.1043	0.0522	5.37
II	161.92	.1043	.0522	14.3
III	169.6	.1000	.0464	26.6
IV	174.32	.1043	.0522	36.1
V	185.57	.1043	.0522	78.4
VI	186.69	.1043	.0522	85.4

The slope corresponding to d ln k_{cor}/d($1/T$) for the first replacement reaction corresponds to an activation energy of 28,650 ± 300 cal./mole where k_{cor} is the rate constant and T is the absolute temperature.

The rate of halogen replacement of 1,3,5-trichlorobenzene by ethylate is about twice as fast as the similar replacement by methylate.[13]

No rearrangement products were found for this reaction in agreement with the work of Ogata and Okano[14] who studied aromatic ether interchange reactions.

Thus a mechanism which involves simple direct expulsion of chlorine from the aromatic compound by the incoming basic ion is consistent with the kinetic data of this work.[15]

Experimental

Preparation of Reactants.—1,3,5-Trichlorobenzene was prepared by deamination of 2,4,6-trichloroaniline by the method of Jackson and Lamar.[16] The 2,4,6-trichloroaniline was obtained from Eastman Kodak Company or for several samples prepared by the chlorination of aniline by the method of Chattaway and Irving.[17]

The purity of the 1,3,5-trichlorobenzene was determined in terms of a freezing point curve obtained with a platinum resistance thermometer. The freezing point obtained by calculating the freezing point depression when half the material had solidified was 62.79°. Assuming that the entropy of fusion is 5 cal. per degree mole, the amount of solid-insoluble, liquid-soluble impurity was 0.08 mole per cent. Commercial absolute ethyl alcohol was purified by a variation of the method of Danner and Hildebrand[18] using anhydrous oxalic acid instead of sulfuric acid. The alcohol was dried twice by the method of Smith[19] using diethyl phthalate and stored under pressurized nitrogen.

Sodium was prepared by pipetting clean molten C.P. sodium (Merck and Co.) under kerosene into test-tubes which were stored under dry kerosene. The sodium used to make sodium ethylate solutions was further purified by melting in vacuum and flowing it into glass tubes which were then sealed until used.

Apparatus.—The thermostat was a well-stirred, oil-filled 41-liter thermos bottle. The power delivered to the bath was controlled by a phase-shifting, proportional, electronic thermoregulator patterned after one by Tarnopol.[20] The thermostat when covered, could be maintained at a preset temperature to within 0.02°. The temperatures were measured by a platinum resistance thermometer which had been calibrated by the Bureau of Standards. The standard resistance thermometer used together with a Rubicon-Mueller Bridge gave temperatures accurate to 0.01°. The reaction tubes made of Pyrex glass, were of about 10-ml. capacity. Each tube was provided with a small neck which was sealed shut after the sample solution had been introduced.

A stock solution of sodium ethylate was made under dry, oxygen-free nitrogen from the dry ethyl alcohol and purified sodium. 1,3,5-Trichlorobenzene was accurately weighed into a tared volumetric flask, stock sodium ethylate solution was added and then enough dry alcohol to fill the flask to the mark. After mixing, approximately six milliliters of the solution was pipetted into each of several clean, dry tubes which were then sealed. All of the above procedure was performed under dry oxygen-free nitrogen. The sealed tubes were then placed in the thermostat at the appropriate temperature for a measured interval of time and then rapidly cooled in kerosene. The original solution and the solution from the sample tubes were titrated under nitrogen by pipetting samples from each solution into separate solutions containing a known amount of standard acid present in excess, and back titrating with a standardized barium hydroxide solution. All end-points were determined by means of a Beckman pH meter.

Calculations.—The second-order rate constant, k, was calculated from the relation

$$k = \frac{1}{t(b-a)} \ln \frac{a}{b}\frac{(b-x)}{(a-x)}$$

where t is the time in minutes, a and b are the initial concentrations of 1,3,5-trichlorobenzene and ethylate ion and x is the concentration in moles per liter of the products present at the time t. The rate constants are corrected for the thermal expansion of the solution, by using the temperature–density data for pure alcohol.

Identification of Products.—Both A and B were prepared by allowing excess ethylate to react with 1,3,5-trichlorobenzene for a long period of time. A typical reaction was carried out by mixing an alcoholic solution which was 0.50 M in sodium ethylate and 0.43 M in 1,3,5-trichlorobenzene. This mixture was kept for 50 hours at 170° in a glass-lined, stainless steel bomb. The total phenolic residues of this reaction were less than 0.7%. The actual 3,5-dichlorophenol present must have been far less than this, since its characteristic strong odor was not distinguishable. The two compounds were found to be aromatic ethers. They were separated by fractional distillation. Compound B was

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[14] Y. Ogata and M. Okano, THIS JOURNAL, **71**, 3211, 3212 (1949).

[15] E. D. Hughes, *Quarterly Review*, **5**, 245 (1951).

[16] C. L. Jackson and W. R. Lamar, *Am. Chem. J.*, **18**, 664 (1896).

[17] F. E. Chattaway and H. Irving, *J. Chem. Soc.*, 142 (1933).

[18] P. S. Danner and J. H. Hildebrand, THIS JOURNAL, **44**, 2824 (1922).

[19] E. L. Smith, *J. Chem. Soc.*, 1288 (1927).

[20] L. Tarnopol, *Rev. Sci. Instruments*, **12**, 367 (1941).

found to be present to the extent of about 10 to 20% of the amount of A formed.

The properties of 3,5-dichlorophenetole and 3,5-diethoxychlorobenzene, the expected products of the reaction, have not been previously given. For identification compounds A and B were cleaved with solid, anhydrous $AlCl_3$ to give the corresponding phenols. The benzoate of the phenol from compound A and the hydrate of the phenol from compound B were prepared. Table I summarizes the properties of compound A, compound B, 3,5-dichlorophenetole, 3,5-diethoxychlorobenzene and their indicated derivatives.

Since the carbon analyses for compound B are high it would appear that other products also were formed in small amounts; these were not identified. It seems clear that the compounds given are the major ones and the properties of 3,5-dichlorophenetole are fairly well defined.

Kinetic Results.—The kinetic studies data of the reaction are given in Table II where T is the temperature of the reaction in degrees centigrade, d is the density of alcohol at the temperature T, t is the time in minutes, ml. H^+ is the volume in milliliters of standard (0.02503 N) acid used in the titration, k is the calculated second-order rate constant in liter mole min.

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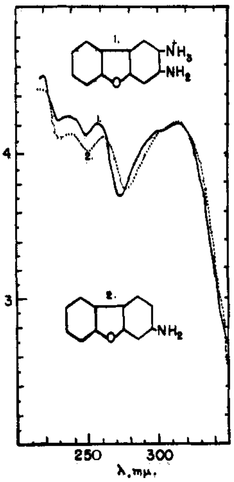
Absorption Spectra and Basicity of 2,3-Diaminodibenzofuran[1]

By Eugene Sawicki and F. E. Ray

Received November 20, 1952

In connection with an extensive investigation in this Laboratory on the chemical and physical properties of the aromatic carcinogens, it was of interest to determine the basicity of 2,3-diaminodibenzofuran as compared to 3-aminodibenzofuran. In the latter compound the amino group is in the extended para position as it is in all the known biphenylene carcinogens.[2,3] In Fig. 1, the monoprotonated derivative of the diamine is shown to have a spectra similar to that of 3-aminodibenzofuran. This means that the 2-amino group in the diamine is the more basic group. This is not unexpected, for the resonance effect of the oxygen atom would have a base-strengthening effect on this group. Consistent with this is the fact that 3-aminodibenzofuran has a pK_a of 3.3 while the diamine has a pK_a of 4.1. The diprotonated derivative of 2,3-diaminodibenzofuran, Fig. 2, curve 1, and the protonated derivative of 3-aminodibenzofuran, Fig. 3, curve 1, are shown to be spectrally similar to dibenzofuran, Fig. 2, curve 2, Comparison of these spectra with that of the diamine in Fig. 3, curve 2, emphasizes the remarkable changes caused by salt formation. In Fig. 4 are shown the typical curves obtained in the determination of the dissociation constant.



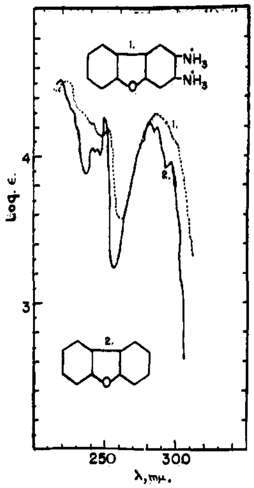
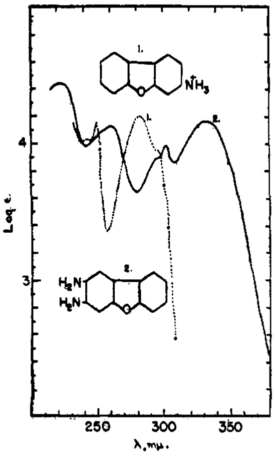


Fig. 1.—(1) 2,3-Diaminodibenzofuran in 50% ethanolic 0.08 N HCl; (2) 3-aminodibenzofuran in 95% ethanol.
Fig. 2.—(1) 2,3-Diaminodibenzofuran in 50% ethanolic 6 N HCl; (2) dibenzofuran in 95% ethanol.



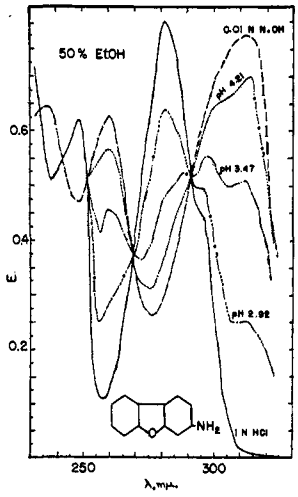


Fig. 3.—(1) 3-Aminodibenzofuran in 50% ethanolic 1 N HCl; (2) 2,3-diaminodibenzofuran in 95% ethanol.
Fig. 4.—3-Aminodibenzofuran in 50% ethanol.

Experimental

Dibenzofuran, m.p. 83–84°, gave an ultraviolet spectrum showing λ_{max} 218, 241, 244, 249, 280, 286 and 296 mμ and log ε 4.51, 4.04, 4.04, 4.26, 4.22, 4.19 and 3.95, respectively. Shoulders occurred at *ca.* 227, 275 and 300 mμ and log ε 4.31, 4.09 and 3.65. This agrees substantially with values reported in the literature.[4]

3-Aminodibenzofuran, m.p. 99°, was prepared by the procedure of Gilman and Avakian.[5] The ultraviolet spectrum showed λ_{max} 217–218, 237–238, 261 and 313 mμ and log ε 4.44, 4.13, 4.11 and 4.22, respectively. A shoulder occurred at 302–303 mμ and log ε 4.15.

2,3-Diaminodibenzofuran, m.p. 166°, was prepared by the procedure of Gilman, *et al.*[6] The ultraviolet spectrum showed λ_{max} 222–223, 259, 302 and 333 mμ and log ε 4.44, 4.12, 3.99 and 4.16, respectively. A shoulder occurred at 295–296 mμ and log ε 3.90.

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[1] This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

[2] E. Miller, J. Miller, R. Sandin and R. Brown, *Cancer Research*, **9**, 504 (1949).

[3] J. A. Miller, E. C. Miller, R. B. Sandin and H. P. Rusch, *ibid.*, **12**, 283 (1952).

[4] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Curve No. 337.

[5] H. Gilman and S. Avakian, This Journal, **68**, 580 (1946).

[6] H. Gilman, G. E. Brown, W. G. Bywater and W. H. Kirkpatrick, *ibid.*, **56**, 2473 (1934).

Procedure.—All absorption spectra were measured by means of a Beckman model DU spectrophotometer and 1-cm. silica cells at 26 ± 1°. In the determination of the ionization constants the spectra of buffered solutions were measured in "50%" aqueous ethanol (100 ml. of the solution contained 50 ml. of water; remainder of the solution consisted of 95% ethanol). The concentration of all compounds was 5×10^{-5} M. The ionization constants were calculated[7] by the equation $pK_a = pH_m + \log (E_B - E_m/E_m - E_{BH^+})$ where E_B, E_{BH^+} are the optical densities of base and salt and E_m is the optical density of a mixture of base and salt at an intermediate pH_m fairly close to the value of the pK_a of the compound.

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(7) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2106 (1935).

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The Preparation of S-Succinyl Coenzyme A[1]

BY ERIC J. SIMON[2] AND DAVID SHEMIN

RECEIVED FEBRUARY 27, 1953

We have previously concluded that a succinyl derivative is a precursor of protoporphyrin.[3] This succinyl intermediate may be identical with S-succinylcoenzyme A. We have found that this compound is readily formed by succinylating coenzyme A with succinic anhydride, as shown by the disappearance of the sulfhydryl group (nitroprusside reaction),[4] the formation of a hydroxamic acid,[5] and an increased light absorption of 232 mμ.[6] When the product is warmed for a few minutes on a steam-bath, the sulfhydryl group reappears, the reaction with hydroxylamine no longer occurs and there is a decreased light absorption at 232 mμ. Also, this synthetic preparation behaved as succinyl-coenzyme A in enzymatic systems.[7]

Thirty-five mg. of a coenzyme A preparation (Pabst) was dissolved in 30 ml. of ice cold water. To this solution 3 mg. of succinic anhydride was added, followed by sodium bicarbonate until the pH was 7–7.5. The mixture was kept in an ice-bath and shaken frequently. The reaction appeared to be completed within 30 minutes at which time over 90% of the sulfhydryl groups had disappeared. At 0° the succinyl coenzyme A is stable at pH 7–7.5 for several hours, at room temperature it is half hydrolyzed in about 1–2 hours, as measured by the nitroprusside and hydroxamic acid methods. However, at pH 1, at room temperature, the succinyl coenzyme is much more stable than at neutrality. The hydroxamic acid test was carried out on the formed succinyl coenzyme A after the complete hydrolysis of any unreacted succinic anhydride.

Succinyl coenzyme A has previously been enzymatically prepared from α-ketoglutarate.[8,9] Acetic anhydride has been used for the synthesis of acetyl-coenzyme A.[10] This anhydride method may be applicable for the preparation of other acyl coenzyme A derivatives.

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[1] This work was supported by grants from the National Institutes of Health, United States Public Health Service, from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council, and from the Rockefeller Foundation.

[2] Aided by a fellowship from the National Foundation of Infantile Paralysis. Present address: Payne Whitney Clinic, Cornell Medical College, New York, N. Y.

(3) (a) D. Shemin and J. Wittenberg, *J. Biol. Chem.*, **192**, 315 (1951); (b) D. Shemin and S. Kumin, *ibid.*, **198**, 827 (1952).

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(5) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

(6) E. R. Stadtman, 122d Meeting, Am. Chem. Soc., Atlantic City, N. J., Sept 1952, Abs. 32C.

(7) We are indebted to S. Kaufman, C. Gilvarg, M. J. Coon and J. R. Stern for these enzymatic experiments.

(8) D. R. Sanadi and J. W. Littlefield, *Science*, **116**, 327 (1952).

(9) H. Beinert, 122d Meeting, Am. Chem. Soc., Atlantic City, N. J., Sept. 1952, Abs. 34C.

(10) I. B. Wilson, THIS JOURNAL, **74**, 3205 (1952).

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On Some Partial Molal Volumes of Gases in Solution[1]

BY RICHARD H. SCHUMM AND OLIVER L. I. BROWN[2]

RECEIVED JANUARY 3, 1953

This note reports measurements of the partial molal volumes of carbon tetrafluoride and methane in some non-polar solvents at 27.0°.

Carbon tetrafluoride, obtained from the Minnesota Mining and Manufacturing Company, was led through a Dry Ice trap. Methane, Research Grade from the Phillips Petroleum Company, had been analyzed by mass spectrometer as 99.7% pure. Benzene was obtained thiophene-free or was freed of thiophene by washing with sulfuric acid, sodium carbonate and water, and dried over calcium chloride. Reagent grade (A.C.S.) carbon tetrachloride was used without further purification. *n*-Hexane, *n*-heptane and "isooctane" (2,2,4-trimethylpentane) from the Phillips Petroleum Company were all of 99 mole per cent. purity.

The apparatus and procedure were essentially the same as those of Horiuti[3] and of Gjaldbaek and Hildebrand.[4] The volume of the bulb was approximately 150 cc. The capillary stems had a capacity of about 8.5 cu. mm. per cm. Two dilatometers were used during each run; gas was dissolved in one and the other was used as a blank to correct for small temperature variations in the bath. Compression of the solution by the increased head of mercury in the capillaries was avoided by pulling a sufficient vacuum in one capillary to return the mercury in the other capillary to its original height.

To check the procedure against that of Horiuti and of Gjalbaek and Hildebrand the partial molal volume of methane in benzene was determined at 25.0°. Values of 53.51 and 51.22 cc. per mole were found, which agree well with Horiuti's value of 52.0 and Gjaldbaek and Hildebrand's value of 52.5 cc. per mole. The results of the measurements are summarized in Table I. It will be noted that the value determined for methane in *n*-hexane at 27° differs considerably from the value of 60.0 cc. per mole at 25° found by Gjaldbaek and Hildebrand and that it does not vary in the direction to be expected from the two-degree temperature difference. Horiuti found that the partial molal volume of methane in carbon tetrachloride increased 6.8% in going from 0 to 25°.

As shown by Gjaldbaek and Hildebrand, the partial molal volumes of methane, ethane and nitrogen decrease consistently with increasing solubility parameter of the solvent except for solutions in carbon disulfide. This exception they attribute to the effect of differences in the size and shape of the component molecules. However, if the data for these gases, as given here and in

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[1] This note is based on the Master's Thesis of R. H. Schumm, 1952.

[2] Department of Chemistry, Connecticut College, New London, Conn.

(3) J. Horiuti, *Sci. Papers, Inst. Phys. Chem. Res., Tokyo*, **17**, 125 (1931).

(4) J. Chr. Gjaldbaek and J. H. Hildebrand, THIS JOURNAL, **72**, 1077 (1950).

TABLE 1

PARTIAL MOLAL VOLUMES OF GASES

Gas	Solvent	Temp., °C.	Gas absorbed vol., Mmole	Cu. mm.	$\bar{v}_2$	Mean $\bar{v}_2$
CH_4	*n*-Hexane	27.0	0.6679	38.28	57.32	
			.5639	31.78	56.35	56.83
CH_4	*n*-Heptane	27.0	.9498	52.82	55.61	
			.9032	49.67	54.99	55.43
			.7582	42.22	55.69	
CH_4	Isoöctane	27.0	.9149	52.83	57.74	
			.8844	48.86	55.25	
			.9829	55.79	56.75	56.60
			.8062	45.69	56.67	
CF_4	Benzene	26.8	.3822	31.72	82.98	
			.3868	32.37	83.70	83.24
CF_4	CCl_4	26.9	.5453	43.44	79.65	
				46.85	79.78	79.72
CF_4	*n*-Heptane	27.0	.5436	47.25	86.92	
			.4983	42.82	85.93	86.43
CF_4	Isoöctane	27.0	.5738	48.94	85.30	
			.5726	48.93	85.44	85.37

Table II of their paper, are plotted against the solubility parameters of the solvents, it will be seen that the data are fairly well fitted by curves of parabolic shapes with minima at a solubility parameter of about 9. The data given in this paper for carbon tetrafluoride exhibit no regular variation, possibly because of the small range of solubility parameters investigated.

It is reasonable to expect a minimum in the partial molal volume of a gas. The partial molal volume of a solute increases with the change of volume on mixing, which is given by[5]

$$\Delta V^M = \beta_0 \Delta E_V^M$$

where β_0 is the compressibility of the isolated components and ΔE_V^M is the change of internal energy on mixing at constant volume. ΔE_V^M is directly related to the absolute difference in solubility parameters of the components[5]

$$\Delta E^M = (N_1 V_1 + N_2 V_2)(\delta_1 - \delta_2)^2 \phi_1 \phi_2$$

where N denotes the number of moles of a component, and ϕ its volume fraction. It follows, therefore, that the partial molal volume should exhibit a parabolic dependence on the solvent solubility parameter and show a minimum where the solubility parameters of the components are equal. The minimum for nitrogen, on the basis of three points,[4] seems to occur at a solvent solubility parameter of about 9, whereas Gjaldbaek and Hildebrand,[6] on the basis of solubility data, assign a solubility parameter of 5.2 to nitrogen gas at 25°.

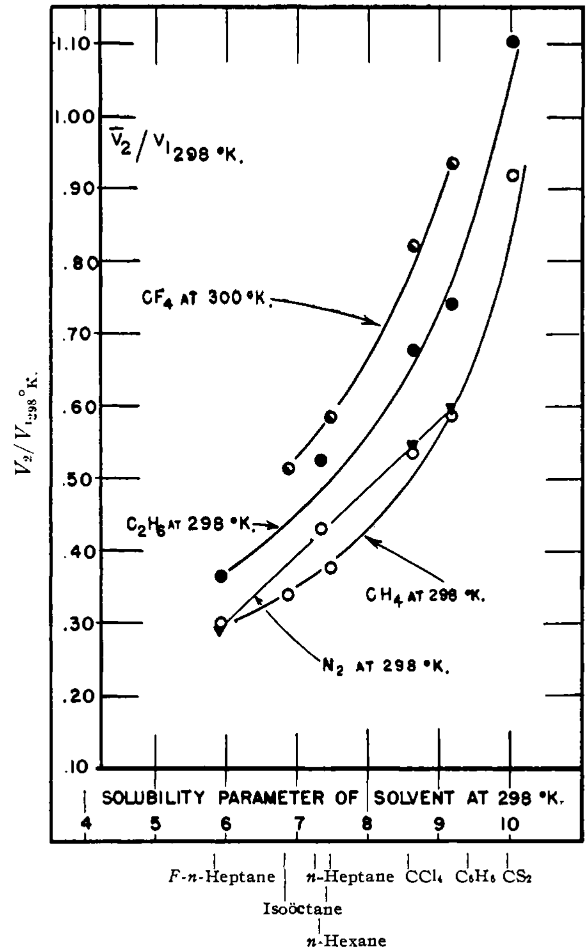

Fig. 1.

Figure 1 is a plot of the ratio of the partial molal volume of the solute to the molal volume of the solvent against the solubility parameter of the solvent. All the data conform well to smooth curves. This is especially noteworthy in the case of carbon tetrafluoride inasmuch as a plot of the partial molal volume of carbon tetrafluoride against the solvent solubility parameter exhibits a very irregular variation. This plot may be useful in predicting partial molal volumes in other solvents, yielding values of $\bar{v}_2$ which can be used in correlating the solubility of these gases by the equation[6]

$$-\log x_2 = -\log a_2 + \log(\bar{v}_2/v_1) + 0.434(1 - \bar{v}_2/v_1) + \bar{v}_2(\delta_1 - \delta_2)^2/4.575T$$

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Action of Carbon Tetrachloride on Silica Gel

BY ROGER K. TAYLOR

RECEIVED JANUARY 24, 1953

Rao and Rao[1] report that CCl_4 vapor reacts with the retained water in activated silica gel, at a rate appreciable at 110° and moderately rapid at 300°, to form $COCl_2$ and HCl. They further report that the gel firmly retains about 10% by weight of HCl.

Work in our laboratory in general confirms these observations, with the additional indication that at the higher temperatures a portion of the CCl_4 is hydrolyzed all the way to CO_2. Silica gel exposed for 24 hours at 275° to CCl_4 vapor, and then held at this temperature in a current of dry air until no fur-

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[5] J. H. Hildebrand and R. L. Scott, "Solubility of Non-electrolytes," third edition, Reinhold Pub. Corp., New York, N. Y., 1950, pp. 139, 129.

[6] J. Chr. Gjaldbaek and J. H. Hildebrand, THIS JOURNAL, 71, 3147 (1949).

[1] J. R. A. Rao and B. S. Rao, *J. Indian Chem. Soc.*, 12, 322 (1935).

ther HCl was evolved, was found to contain somewhat above 12% Cl.

Reyerson and Bemmels[2] show that the adsorption of hydrogen chloride on silica gel is normal in magnitude, reversible and decreases with elevation of temperature. It follows that Rao and Rao are in error in considering the Cl retained after CCl_4 treatment to be present as HCl. Rather, the product must be regarded as of the nature of an oxychloride of silicon with chlorine chemically bound to silicon, since HCl as such would not remain in the gel under the conditions of the preparation.

(2) L. H. Reyerson and C. Bemmels, *J. Phys. Chem.*, **46**, 35 (1942).

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Reversible Bleaching of Chlorophyll by Metallic Salts

BY W. F. WATSON

RECEIVED JANUARY 3, 1953

The interaction of chlorophyll with metallic salts possessing oxidizing and reducing properties is of importance in considering the participation of chlorophyll in oxidation–reduction systems. Addition of an oxidizing salt to an alcoholic or acetone solution of chlorophyll a or b causes bleaching to a straw yellow color within one or two seconds. Immediate subsequent addition of a reducing salt causes a reversion to green. The reversible reaction

$$\text{Chlorophyll} \underset{\text{reducing salt}}{\overset{\text{oxidizing salt}}{\rightleftarrows}} \text{“oxychlorophyll”} \qquad (1)$$

has been proposed, where "oxychlorophyll" is merely the designation of the unstable bleached form of chlorophyll.[1] The reversibility of (1) has not received complete credence among biochemists as the absorption spectra of the regenerated green solutions were significantly different from the initial spectra in some cases where regeneration of chlorophyll was claimed.

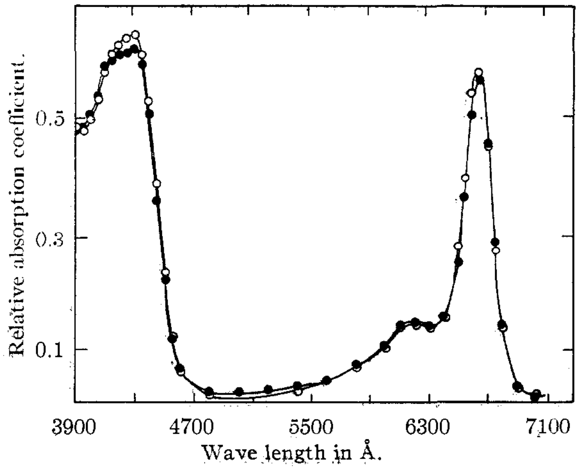

Fig. 1.—Regeneration of the spectrum of non-allomerized chlorophyll a: —●—, 5 × 10^{-6} m. chlorophyll a in methanol; —○—, after bleaching with ferric chloride and regeneration by cuprous chloride.

The data now presented confirm that chlorophyll undergoes a reversible reaction of type (1) within the accuracy of modern spectrophotometric methods, after allowance for a small amount of allomerized chlorophyll also produced. The reversion to green on addition of sodium chloride or standing exposed to air is not regeneration of chlorophyll but formation of allomerized chlorophyll. The reversion of color by hydroquinone is by production of yet another green compound.

Experimental Methods and Materials.—Chlorophylls a and b were prepared by a modification of Zscheile and Comar's method.[2] Purified chlorophyll was kept in ether at −10° in the dark till required, and then transferred to methanol by evaporating and condensing on a vacuum apparatus with avoidance of complete drying-off of solvent. Spectral measurements were made using conventional 1-cm. cells in a Beckman spectrophotometer. Methanolic solutions of salts were added directly to chlorophyll solutions in the Beckman holder from syringes.

Experimental Results and Discussion.—The spectrum after bleaching by ferric chloride and regeneration by cuprous chloride is illustrated in Fig. 1. Apart from the small increase in the main violet maximum and reduction in the minor violet maximum, typical of allomerization,[3] the chlorophyll was almost quantitatively regenerated. A chlorophyll solution left at room temperature till partially allomerized also underwent regeneration of spectrum except for slight further allomerization. The sensitivity of the bleached compound to traces of water was confirmed[1]; water of hydration of 10^{-5} mole/l. ferric chloride caused a marked loss of chlorophyll a on regeneration.

The bleached solution returned to green on standing. However, the spectrum was characteristic of allomerized chlorophyll.[3] (Figure 5 of the original paper[1] shows that the spectra of allomerized chlorophyll was also observed, though its spectrum at that time had not been independently characterized.) This removes the main, and recognized,[1] anomaly of reversion on standing.

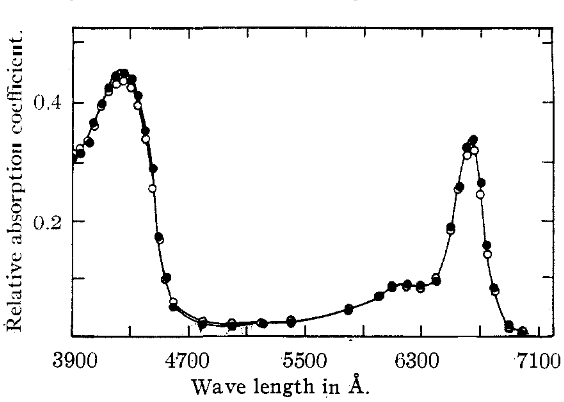

Fig. 2.—Regeneration of the spectrum of partially-allomerized chlorophyll a: —○—, partially-allomerized chlorophyll a in methanol; —●—, after bleaching with ferric chloride and regeneration by cuprous chloride.

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(1) E. Rabinowitch and J. Weiss, *Proc. Roy. Soc.* (*London*), **A162**, 2511 (1937).

(2) R. Livingston, D. Sickel and A. Uchiyama, *J. Phys. Colloid Chem.*, **51**, 777 (1947).

(3) E. I. Rabinowitch, "Photosynthesis," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 613.

There is as yet no complete confirmation that the bleached compound is an oxidation product of chlorophyll. An alternative explanation is that complex formation with Fe^{+++} occurs.[4] The interpretation of the bleaching as formation of an intermediate oxidation product is supported by a similar transitory bleaching by bromine and iodine and the production of allomerized chlorophyll on allowing the ferric salt to react without reversion. The effect of non-oxidizing salts[4] is probably similar to the acceleration of allomerization by lanthanum chloride[3]; dissolved oxygen was necessary and again an initial partial bleaching was observed.

This investigation was sponsored by the O.N.R. (Contract NR-ori-212 for the year 1948) at the University of Minnesota.

(4) M. S. Ashkinazi, T. S. Glikman and B. J. Dain, *Compt. rend. Acad. Sci., U. R. S. S.*, **73**, 743 (1950).

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The Origin of 3,5-Cycloandrostan-6β-ol-17-one (i-Androsten-6β-ol-17-one) in Urinary Extracts

By Sylvia Teich, Jean Rogers, Seymour Lieberman, Lewis L. Engel and John W. Davis

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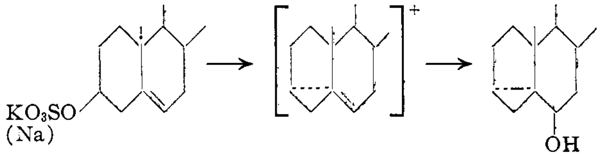
In 1948 Dingemanse, Huis in't Veld and Hartogh-Katz[1] reported the isolation from human urine of a new 17-ketosteroid, $C_{19}H_{28}O_2$, m.p. 140.5–141°, which shortly thereafter was identified[2–4] as 3,5-cycloandrostan-6β-ol-17-one (III).[5] Because III was readily converted even at room temperature by aqueous hydrochloric acid into 3-chloro-Δ^5-androsten-17-one (IV) and dehydroisoandrosterone (V), it was concluded[2] that the i-steroid was in fact the precursor of these familiar urinary products. III was isolated from urine only when neutral urine heated on a steam-bath was extracted continuously with benzene, a procedure which was postulated[6] to cause the hydrolysis of a "certain conjugate" of III without effecting its subsequent conversion to IV or V. The failure of previous workers to isolate any i-steroid was ascribed to the use of methods which involved acid hydrolysis either at room or elevated temperatures.[2]



I II III

This paper reports the conversion of sodium and potassium dehydroisoandrosterone sulfate (I) to 3,5-cycloandrostan-6β-ol-17-one (III) using the conditions employed by Dingemanse, *et al.*,[1,6] for the isolation of III from urine, *i.e.*, heating a neutral aqueous solution covered with a layer of benzene and also by refluxing solutions buffered at various *p*H values under toluene. Since I has been isolated from urine[7] and is the most important known urinary conjugate of dehydroisoandrosterone, its conversion to III can satisfactorily account for all the observed results without postulating that the i-steroid is a naturally occurring urinary metabolite which serves as a precursor of dehydroisoandrosterone. The equivocal manner by which III was isolated from urine leaves the existence of the i-steroid as a genuine steroid metabolite in doubt.[8]

The potassium dehydroisoandrosterone sulfate employed in our experiments was prepared[9] by the the action of pyridine–sulfur trioxide[10] on dehydroisoandrosterone. To ensure that the product of this reaction was indeed the 3-sulfate of the normal steroid and not the 6-sulfate of the i-compound resort has been taken to the Method of Molecular Rotation Differences.[11] Earlier data indicate that a sulfate group makes only a small negative contribution to the M_D value. Thus, the $\Delta M_D(\text{M–O–SO}_2\text{O–})$ calculated from sodium cholestan-3β-ol sulfate (M_D +81)[9] and cholestan-3β-ol (M_D +113) is −32, and that calculated from sodium cholestan-3α-ol sulfate (M_D +74)[9] and cholestan-3α-ol (M_D +132) is −58. It seems certain, therefore, that the sulfate group in I is at C_3 since the $\Delta M_D(\text{M–O–SO}_2\text{O–})$ calculated from potassium dehydroisoandrosterone sulfate (M_D +28) and dehydroisoandrosterone (M_D +29) is −1. On the other hand, the M_D of the 6-sulfate of the i-steroid (III) would be expected to be a large positive value, only slightly less positive than that of the M_D of the corresponding alcohol (+351).

The hydrolysis of steroid sulfates has been studied under a variety of conditions and the results can be summarized as follows:

At *room temperature* the sulfates can be cleaved under acidic conditions and this has been shown[9] to involve the splitting of the S–O bond of the sulfate, affording the alcohol with retention of configuration.

When *elevated temperatures* are employed, the C–O bond of the sulfate ester linkage may dissociate to give a resonating hybrid (II), such as described by

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(1) E. Dingemanse, L. G. Huis in't Veld and S. Hartogh-Katz, *Nature*, **161**, 848 (1948).

(2) E. Dingemanse, L. G. Huis in't Veld and S. Hartogh-Katz, *ibid.*, **162**, 492 (1948).

(3) D. H. R. Barton and W. Klyne, *ibid.*, **162**, 494 (1948).

(4) E. Dingemanse and L. G. Huis in't Veld, *J. Biol. Chem.*, **195**, 827 (1952).

(5) It has been postulated on theoretical and molecular rotation considerations that the i-steroids formed by rearrangement of the 3-tosylates have a 6β-configuration; ((a) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948); C. W. Shoppee, *Bull. soc. chim.*, **18**, 120 (1951)). In a recent comprehensive review of the stereochemistry and mechanism of this rearrangement convincing chemical evidence (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952)) has been presented which further substantiates this assignment. Based on reactions whose stereochemical course has not been clearly elucidated, Wallis and co-workers ((c) A. F. Wagner, N. E. Wolff and E. S. Wallis, *J. Org. Chem.*, **17**, 529 (1952)) have assigned the opposite configuration to the i-steroid.

(6) E. Dingemanse, L. G. Huis in't Veld and S. Hartogh-Katz, *J. Clin. Endocrin. and Metab.*, **12**, 66 (1952).

(7) P. Munson, T. F. Gallagher and F. C. Koch, *J. Biol. Chem.*, **152**, 67 (1944).

(8) H. L. Mason and W. W. Engstrom (*Physiol. Rev.*, **30**, 321 (1950)) have already called attention to this and have suggested that the procedure used for extraction might be responsible for the conversion of I to III.

(9) S. Lieberman, L. B. Hariton and D. K. Fukushima, This Journal, **70**, 1427 (1948).

(10) A. E. Sobel and P. E. Spoerri, *ibid.*, **63**, 1259 (1941).

(11) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948).

Shoppee[12] and Winstein and Adams.[13] The driving force[14] for such a dissociation is provided by the participation of the 5,6-double bond as a neighboring group, and results in centers of low electron density at C_3 and C_6. When heat is applied, *under neutral conditions*, and continuous extraction with benzene, the thermodynamically less stable but more rapidly formed i-androstenolone results from the attack of the solvent, water, on II at C_6. The continuous removal of the i-steroid into the organic phase makes possible its isolation and may increase the extent to which it is formed.

When *elevated temperatures and hydrochloric acid* are employed for the cleavage of the sulfates, two other types of products can be isolated in addition to dehydroisoandrosterone itself; the 3-chloro compound[15] which would result from an attack of chloride ion on II and the diene[16] which would result from the loss of a proton from II, an elimination reaction which is known to be favored by elevated temperatures.[17] Whether the dehydroisoandrosterone is formed from the sulfate by cleavage of the S–O bond, by rearrangement of an intermediate i-derivative or by attack of the solvent, water, on II at C_3 cannot now be decided.

When a solution of sodium dehydroisoandrosterone sulfate[18] was heated to boiling under toluene at *p*H 1.2, and at *p*H 3.2 (0.1 *M* phthalate buffer) and the reaction product subjected to countercurrent distribution, dehydroisoandrosterone was the only product recognized. However, at *p*H 4.7 (0.1 *M* acetate buffer) equal amounts of dehydroisoandrosterone and 3,5-cycloandrostanolone were realized. These latter conditions were recommended by Bitman and Cohen[19] as suitable for the hydrolysis of Δ^5-3β-stenol sulfates without concomitant production of transformation products of dehydration and halide formation. The present data indicate that another type of artifact may be introduced under these conditions. At *p*H 6.8 (0.1 *M* phosphate buffer) the yield of the i-steroid was more than twice that of dehydroisoandrosterone (Table I).

TABLE 1

THE EFFECT OF HYDROGEN ION CONCENTRATION ON THE HYDROLYSIS OF DEHYDROISOANDROSTERONE SULFATE

			Dehydroisoandrosterone			3,5-Cycloandrostanolone		
Buffer	*p*H	Reflux time, min.	Mg.	Yield, %	K^a	Mg.	Yield, %	K^a
HCl	1.2	15	3.7	42	0.62[b]			
Phthalate	3.2	50	5.3	60	.67			
Acetate	4.7	240	3.0	34	.50	3.1	35	1.22[c]
Phosphate	6.8	360	2.5	28	.62	6.3	71	1.64

[a] Partition coefficient in cyclohexane/50% MeOH–50% H_2O. [b] Average K = 0.60. The previously determined value for the pure compound was 0.62. [c] The previously determined value for the pure compound was 1.7.

From these considerations it is obvious that a change in any of the reaction conditions, such as temperature, acidity, nature of the anions present, and time can alter the character and the ratio of the products isolated and any conclusions concerning urinary steroid metabolites must take into account the nature of the hydrolytic procedure.

Experimental

The Conversion of Potassium Dehydroisoandrosterone Sulfate (I) to 3,5-Cycloandrostan-6β-ol-17-one (III).—One hundred milligrams of potassium dehydroisoandrosterone sulfate (m.p. 218–220°, $[\alpha]^{19}\text{D}$ +6.9 ± 2° (10.25 mg. in 2 cc. of a 1:3 propylene glycol–ethanol mixture); *Anal.* Calcd. for $C_{19}H_{27}O_5SK$: S, 7.88. Found: S, 8.13) was suspended in 90 cc. of water. The solution was brought to neutrality (glass electrode) with a few drops of 5% sodium carbonate solution and then covered with 30 cc. of benzene. The mixture was heated under reflux on a steam-bath with stirring for 5 hours. The benzene layer was separated, dried over sodium sulfate and evaporated to dryness leaving a crystalline product weighing 35 mg. (theoretical, 71 mg.). A second 5-hour heating with an additional 30 cc. of benzene resulted in a colorless crystalline product weighing 28 mg. These fractions were recrystallized once from ligroin (b.p. 90°)–ether and melted at 135–139°, $[\alpha]^{23}\text{D}$ +111 ± 2° (9.21 mg. in 2 cc. of chloroform), reported[3] m.p. of 3,5-cycloandrostan-6β-ol-17-one 139–140°, $[\alpha]\text{D}$ +122° (ethanol). On admixture with dehydroisoandrosterone (m.p. 145°, $[\alpha]\text{D}$ +11°), it melted at 96–104°.

Ten milligrams of the crystalline material was acetylated at room temperature with 0.1 cc. of acetic anhydride and 0.1 cc. of pyridine. The acetylated product, obtained by evaporation of the acetic anhydride and pyridine was purified by chromatography on silica gel. The acetate, eluted with ether–ligroin (1:3), was recrystallized once from acetone–ligroin (b.p. 30°) and melted at 110–113°. When mixed with an authentic sample of 3,5-cycloandrostan-6β-ol-17-one acetate (m.p. 115–116°), generously made available to us by Dr. W. Klyne, the sample melted at 113–116°. The infrared spectra[20] of the two samples were indistinguishable.

A third period of heating with 30 cc. of benzene gave 10 mg. of a brownish semi-crystalline residue. This material as well as the mother liquor from the recrystallization of the first two fractions was examined for absorption in the ultraviolet between 235 and 250 mμ. No absorption characteristic of $\Delta^{3,5}$-androstadien-17-one (maximum at 240 mμ) was observed.

An effort was made to determine whether small amounts of dehydroisoandrosterone were also formed by this procedure. The unacetylated fractions above were combined and carefully chromatographed on silica gel. The infrared spectrum of each eluate was determined. Only i-androstenolone could be detected; the characteristic spectrum of dehydroisoandrosterone was not observed.

Hydrolysis of Sodium Dehydroisoandrosterone Sulfate in Buffer Solutions.—Sodium dehydroisoandrosterone sulfate (12 mg.) was dissolved in 100-ml. portions of 0.1 *M* buffer solution of the required *p*H and refluxed under a layer of 25 ml. of toluene. After cooling, the toluene was removed and the aqueous solution was washed with four 20-ml. portions of ether which was added to the toluene solution. After washing with sodium bicarbonate solution and distilled water the organic phase was taken to dryness under reduced pressure. The residue was dissolved in 50% aqueous methanol (pre-equilibrated with cyclohexane) and transferred to a stainless steel 25-tube Craig counter-current distribution apparatus.[21] After 24 transfers had been accomplished, the contents of the tubes were removed and the solvents removed by evaporation from the frozen state. The residues were then analyzed for ketosteroids by the Zimmermann reaction[22,23] and the theoretical distribution curves calculated by the graphical method of Slaunwhite.[24] The contents of selected

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(12) C. W. Shoppee, *J. Chem. Soc.*, 1147 (1946). For further elaboration of the intimate details of the mechanism see ref. 5b.

(13) S. Winstein and R. Adams, This Journal, **70**, 838 (1948).

(14) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

(15) A. Butenandt and H. Dannenbaum, *Z. physiol. Chem.*, **229**, 192 (1934).

(16) H. Burrows, J. W. Cook, E. M. F. Roe and F. L. Warren, *Biochem. J.*, **31**, 950 (1937).

(17) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(18) Prepared by the method of Levi, Holden and Bromley, This Journal, **71**, 3844 (1949), and generously supplied by Ciba Pharmaceutical Products, Inc.

(19) J. Bitman and S. L. Cohen, *J. Biol. Chem.*, **191**, 35 (1951).

(20) A Perkin–Elmer model 12C infrared spectrometer was used.

(21) L. C. Craig and H. O. Post, *Anal. Chem.*, **21**, 500 (1949).

(22) I. T. Nathanson and H. Wilson, *Endocrinology*, **33**, 189 (1943).

(23) H. Wilson and I. T. Nathanson, *ibid.*, **37**, 208 (1945).

(24) W. R. Slaunwhite, Jr., *Anal. Chem.*, **23**, 687 (1951).

tubes were also examined by infrared spectroscopy to confirm the identities of the materials present.[25]

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[25] The Perkin–Elmer Model 21 double beam infrared spectrophotometer was used.

[26] This work undertaken independently and simultaneously in the Columbia and Harvard laboratories is published here jointly.

[27] This work was supported in part by gifts from the Squibb Institute for Medical Research and the Damon Runyon Memorial Fund.

[28] This is publication 782 of the Cancer Commission of Harvard University. This work was supported in part by an Institutional Grant from the American Cancer Society, Inc., to the Massachusetts General Hospital and in part by a grant from the National Cancer Institute (U. S. Public Health Service).

The Preparation of β-Ketosulfonyl Chlorides[1]

BY WILLIAM E. TRUCE AND CALVIN W. VRIESEN[2]

RECEIVED JANUARY 7, 1953

The conversion of a β-ketosulfonic acid or its salt to the corresponding sulfonyl chloride does not appear to have been reported previously. The action of chlorosulfonic acid on acetophenone produced the 2,ω-disulfonyl chloride, while acetophenone-4-sulfonic acid with chlorosulfonic acid probably formed the 4,ω-disulfonyl chloride.[3] Treatment of sodium ω-acetophenonesulfonate with the same reagent resulted in the 2,ω-disulfonyl chloride.[3] The preparation of γ- and δ-ketosulfonyl chlorides has been accomplished by conventional methods.[4,5]

When sodium ω-acetophenonesulfonate[6] was treated with phosphorus pentachloride or phosphorus oxychloride, charring occurred. The free sulfonic acid was then prepared by a modification of the procedure of Truce and Alfieri.[6] Separate portions were immediately treated with phosphorus pentachloride, thionyl chloride, or phosphorus oxychloride, but charring occurred in all cases. However, treatment of the acid with phosphorus trichloride,[7] resulted in the formation of ω-acetophenonesulfonyl chloride. The sulfonyl chloride was found to be too unstable to be submitted for analysis; it was necessary to prepare the sulfonamide for that purpose. The instability of the free acid and the sulfonyl chloride is probably due in part to the activity of the methylene group.[8] The activity of the methylene group is further demonstrated by the fact that the ester, ethyl ω-acetophenonesulfonate, can be dissolved in dilute aqueous sodium hydroxide and can be recovered by the addition of acid.

Attempts to reduce the sulfonyl chloride to ω-acetophenonesulfinic acid by conventional methods failed. Friedel–Crafts reactions with the sulfonyl chloride were unsuccessful due to the decomposition of that substance with the evolution of sulfur dioxide.

In an attempt to obtain a more stable β-ketosulfonyl chloride, isobutyrophenone-α-sulfonyl chloride was synthesized. Isobutyrophenone-α-sulfonic acid was prepared by the dioxane-sulfotrioxide method, and the sulfonyl chloride was prepared by means of phosphorus trichloride. These two substances were found to be much more stable than the analogous derivatives of acetophenone, *e.g.*, isobutyrophenone-α-sulfonic acid has been stored in a paraffin sealed bottle for a year with little apparent change. Despite its greater stability, attempts to reduce the sulfonyl chloride to the sulfinic acid and to carry out Friedel–Crafts reactions with it met with failure.

Experimental[9]

ω-Acetophenonesulfonyl Chloride.—Acetophenone (159 g., 1.34 moles) was added to 1.34 moles of the dioxane sulfotrioxide reagent[6] in 400 ml. of ethylene chloride. The reaction mixture was cooled with an ice-bath, whereupon the sulfonic acid separated out. The product was removed by filtration and placed in a vacuum desiccator for three hours. A portion of the acid was recrystallized twice from ethyl acetate; m.p. 75–78°, lit.[8,10] 73–75°, 77–78°. The crude acid and 361 g. (2.62 moles) of phosphorus trichloride were heated on the steam table under gentle reflux for 14 hours. The excess phosphorus trichloride was removed at a water aspirator and the product was recrystallized from chloroform; conversion 122 g. (42% of theory), m.p. 87.5–88.2°.

Dry ammonia was passed into an ether solution of ω-acetophenonesulfonyl chloride until the ammonia odor persisted. The resulting product was recrystallized from ethanol; m.p. 158–159°.

Anal. Calcd. for $C_8H_9O_3NS$: N, 7.04. Found: N, 7.02.

Thirteen grams (0.060 mole) of ω-acetophenonesulfonyl chloride was dissolved in 46 g. (1.0 mole) of absolute ethanol. Heat was liberated and after an hour the solution was cooled with an ice-bath, whereupon crystals of the product separated out; conversion 9.0 g. (64% of theory), m.p. 44.5–45.5° after recrystallization from petroleum ether. The neutral equivalent was obtained by titrating an alcoholic solution of the ester with standard aqueous sodium hydroxide solution to a phenolphthalein end-point; calcd. 228; found, 229 and 227.

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.29. Found: C, 52.88; H, 5.29.

Isobutyrophenone-α-sulfonyl Chloride.—Using the same procedure as previously described, 84 g. (0.57 mole) of isobutyrophenone (b.p. 217–220° (746 mm.)) was converted to 81 g. (63% of theory) of isobutyrophenone-α-sulfonic acid. A portion of the acid was recrystallized from ethyl acetate and melted at 69.5–72.0°.

Isobutyrophenone-α-sulfonic acid (51 g., 0.22 mole) and 21 g. (0.15 mole) of phosphorus trichloride were heated on a steam-bath overnight. The reaction mixture was decomposed with ice water and extracted with chloroform. After drying over sodium sulfate, chloroform was removed by distillation and the resultant yellow oil was taken up in boiling petroleum ether. White needles separated out; weight 25 g. (44% of theory), m.p. 40.0–41.5°.

Anal. Calcd. for $C_{10}H_{11}ClO_3S$: C, 48.64; H, 4.49. Found: C, 48.75; H, 4.42.

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[1] An abstract of a portion of a thesis submitted by Calvin W. Vriesen to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1952.

[2] Purdue Research Foundation Fellow.

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[10] W. von E. Doering and F. M. Beringer, THIS JOURNAL, **71**, 2221 (1949).

Evidence for α-Sulfonation in the Reaction of Palmitic Acid with Sulfur Trioxide[1]

By J. K. Weil, L. P. Witnauer and A. J. Stirton

Received November 24, 1952

The reaction of sulfur trioxide or chlorosulfonic acid with the lower molecular weight normal saturated fatty acids has been reported to give sulfonation at the α-carbon atom,[2-4] Hemilian[2a] prepared a sulfobutyric acid from chlorosulfonic acid and butyric acid. Comparison of physical form, degree of hydration and solubility of several salts with those from the reaction of ammonium sulfite with ethyl α-bromobutyrate and ethyl β-chlorobutyrate showed α-sulfonation. A sulfopropionic acid, apparently the product of direct sulfonation, has been resolved into optical antipodes, proving α- rather than β-substitution.[5] Further evidence[6] for α- rather than β- or γ-sulfonation exists in the values for the solubility of the barium sulfobutyrates (α-isomer, 7.11% at 16°; β-isomer, 22.7% at 29.8°), the melting point of the acid aniline salt (α-isomer, 175°; β-isomer, 162°) and the molecular rotation of the neutral barium salts (*d*,α-isomer, −32.2°; *d*-β-isomer +18.5°). The mechanism of the α-sulfonation of the lower fatty acids has been discussed recently.[7]

α-Sulfonation has been assumed[8] but has not been established in the case of the higher fatty acids. We present data here, based on X-ray diffraction patterns, on the structure of disodium sulfopalmitate prepared from liquid sulfur trioxide and palmitic acid. This compound and some of its homologs have been shown to have detergent properties.[9] The evidence for α-sulfonation involves the Hell–Volhard–Zelinskiĭ reaction, which has been shown by Hell and Jordanoff to give only α-bromination. The bromine atom of ethyl α-bromopalmitate was replaced by CN, and the hydrolysis and decarboxylation products were identified.[10] Still further evidence for α-bromination is in the fact that fatty acids which have no α-hydrogen atom cannot be brominated[11] and that bromopalmitic acid can be hydrolyzed and oxidized to pentadecanoic acid.[12]

As a reference standard, sodium α-sulfopalmitic acid was prepared from α-bromopalmitamide by the Strecker reaction[13] and from α-bromopalmitic acid by conversion to α-mercaptopalmitic acid and oxidation. The latter method was preferred. Although both the monosodium and disodium salts formed well-defined crystalline platelets, X-ray diffraction patterns of salts prepared by direct sulfonation and by indirect methods could not be compared because the diffraction lines were relatively few and somewhat diffuse. Reaction of sodium sulfopalmitic acid with phosphorus pentabromide and ammonia gave bromopalmitamide, which was suitable for X-ray comparison.

The decomposition of secondary alkyl sulfonyl halides to the corresponding halide has been reported,[2a,14] but it is not a well-known reaction. α-Bromopalmitic acid was converted to the mercaptan, oxidized to the sulfonic acid, and then allowed to react with phosphorus pentabromide and ammonia as shown by the equations

$$C_{14}H_{29}CHBrCO_2H \xrightarrow[2,\ NaOH]{1,\ SC(NH_2)_2}$$

$$C_{14}H_{29}CHSHCO_2Na \xrightarrow[Na_2CO_3]{Br_2} C_{14}H_{29}CH(SO_3Na)CO_2Na$$

$$C_{14}H_{29}CH(SO_3Na)CO_2H \xrightarrow{PBr_5} C_{14}H_{29}CHBrCOBr \xrightarrow{NH_3} C_{14}H_{29}CHBrCONH_2$$

Table I presents the chemical analyses and melting points for bromopalmitamide samples obtained by (A) α-bromination, (B) sulfonation of palmitic acid to form sodium sulfopalmitic acid and reaction with phosphorus pentabromide and ammonia, and (C) α-bromination, conversion to mercaptan, oxidation to sodium α-sulfopalmitic acid and reaction with phosphorus pentabromide and ammonia. The small amount of impurity indicated by the lower bromine content of sample (C) had no effect on the X-ray pattern. The melting points of a mixture of A with B, B with C, and A with C showed no depression.

TABLE I

ANALYSES AND MELTING POINTS OF BROMOPALMITAMIDES

	A Hell–Volhard–Zelinskiĭ reaction	B Sulfonated palmitic acid + PBr_5 + NH_3	C Oxidation of sodium α-mercaptopalmitate + PBr_5 + NH_3	Calculated for $C_{16}H_{32}BrNO$
Nitrogen	4.04	4.16	4.11	4.19
Bromine	24.07	23.95	23.21	23.90
Carbon	57.20	57.40	57.91	57.48
Hydrogen	9.47	9.43	9.83	9.64
Melting point, °C.	84.6–84.9	82.7–83.7	83.9–84.6	85[a] 88[b]

[a] G. Ponzio, *Gazz. chim. ital.*, **41**, I, 781 (1911). [b] See text footnote 13.

Table II shows the interplanar spacings and relative intensities of the three compounds. The structure is the same within the limits of experimental error. Although the structure might not change with the position of the bromine atom along the chain, a marked change in the relative intensities of some of the diffraction lines would be expected, as was observed in the case of the isomeric dihydroxy fatty acids.[15] However, comparison of

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[1] From one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. This paper was presented at the 5th meeting-in-miniature of the Philadelphia section, American Chemical Society, January 29, 1953.

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[6] H. J. Backer and A. Bloemen, *ibid.*, **45**, 100, 110 (1926).

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[13] T. N. Mehta and D. M. Trivedi, *Melliand Textilber.*, **21**, 288 (1940).

[14] M. H. Gold and L. J. Druker, *J. Org. Chem.*, **16**, 1510 (1951).

[15] E. S. Lutton, W. F. Huber, A. J. Mabis and C. B. Stewart, This Journal, **73**, 5206 (1951).

the relative intensities of diffraction lines of the three substances showed no differences. The three bromopalmitamides are therefore identical. The sulfonation of palmitic acid with sulfur trioxide appears to be as specific as the Hell–Volhard–Zelinskiĭ reaction. Only monosubstitution seems to occur and only at the α-carbon atom.

Experimental[16]

α-Bromopalmitic Acid and Amide.—α-Bromopalmitoyl bromide was prepared as described by Hell and Jordanoff.[17] Bromine was added to a mixture of palmitic acid (neut. equiv. 257.7, m.p. 61.0–61.3°) and red phosphorus over a period of one hour. The mixture was heated from 40 to 95° for five hours.

α-Bromopalmitoyl bromide was hydrolyzed with ice to give α-bromopalmitic acid. After purification by two crystallizations from acetone and three crystallizations from petroleum ether, the yield was 85%, m.p. 49.4–49.8°.

Anal. Calcd. for $C_{16}H_{31}O_2Br$: neut. equiv., 335.3. Found: neut. equiv., 336.4.

α-Bromopalmitamide was prepared by pouring α-bromopalmitoyl bromide into an excess of aqueous ammonia and ice. It was purified by three crystallizations from alcohol and one crystallization from petroleum ether to give a 50% yield. Table I, Column A, lists the chemical analyses and melting points.

α-Mercaptopalmitic Acid.—The method of Nicolet and Bate[18] was followed in preparing α-mercaptopalmitic acid from α-bromopalmitic acid without purification of the tetradecyl pseudothiohydantoin. Three crystallizations from 95% ethanol gave the required α-mercaptopalmitic acid in a 47% yield based on α-bromopalmitic acid, m.p. 71.6–71.8°.

Anal. Calcd. for $C_{16}H_{32}O_2S$: neut. equiv., 288.5. Found: neut. equiv., 289.3.

TABLE II

DIFFRACTION PATTERNS OF BROMOPALMITAMIDES

A Hell–Volhard–Zelinskii reaction		B Sulfonated palmitic acid + PBr_5 + NH_8		C Oxidation of Na α-mercaptopalmitate + PBr_5 + NH_3	
I, obsd.	*d*, Å.	*I*, obsd.	*d*, Å.	*I*, obsd.	*d*, Å.
M	15.5	M	15.7	M	15.6
W^{++}	10.30	W^{++}	10.35	W^{++}	10.32
M^{-}	7.71	M^{-}	7.73	M^{-}	7.74
W^{+++}	6.18	W^{+++}	6.21	W^{+++}	6.20
W^{-}	5.73	W^{-}	5.73	W^{-}	5.73
M	5.13	M	5.16	M	5.17
W^{-}	4.58	W^{-}	4.60	W^{-}	4.58
W^{++}	4.41	W^{++}	4.43	W^{++}	4.42
S^{-}	4.16	S^{-}	4.17	S^{-}	4.17
W	4.03	W	4.03	W	4.02
M^{++}	3.77	M^{++}	3.78	M^{++}	3.79
W^{++}	3.67	W^{++}	3.67	W^{++}	3.68
W	3.44	W	3.44	W	3.44
W^{+}	3.35	W^{+}	3.35	W^{+}	3.35
W^{+++}	3.15	W^{+++}	3.16	W^{+++}	3.16
W	3.07	W	3.06	W	3.07
W^{+}	2.90	W^{+}	2.91	W^{+}	2.90
W^{-}	2.82	W^{-}	2.83	W^{-}	2.82
W^{+}	2.67	W^{+}	2.67	W^{+}	2.67
W	2.60	W	2.61	W	2.60
W	2.48	W	2.49	W	2.49
W	2.43	W	2.43	W	2.43
W^{+++}	2.26	W^{+++}	2.26	W^{+++}	2.26

Sodium α-Sulfopalmitic Acid from Sodium α-Mercaptopalmitate.—The oxidation was a modification of the method of Levene, Mori and Mikeska.[19] Sodium α-mercaptopalmitate was treated with sodium hypobromite in an aqueous solution buffered with excess sodium carbonate. After being acidified to form the monosodium salt, it was purified by two crystallizations from water and one extraction with hot acetone; the yield was 43%.

Anal. Calcd. for $C_{16}H_{31}O_5SNa$: S, 8.95; neut. equiv., 358.5. Found: S, 8.98; neut. equiv., 358.1.

Direct Sulfonation of Palmitic Acid.—A 60% excess of sulfur trioxide was added slowly to palmitic acid in tetrachloroethylene.[9] The product was neutralized to form the monosodium salt, twice extracted with hot acetone and crystallized from water four times, giving a 61% yield. Yields of 80–90% of the monosodium salt of monosulfonated palmitic or stearic acid can be obtained with less rigorous purification.

Anal. Calcd. for $C_{16}H_{31}O_5SNa$: S, 8.95; neut. equiv., 358.5. Found: S, 8.92; neut. equiv., 358.9.

Bromopalmitamide from Sodium Sulfopalmitic Acid.—Phosphorus pentabromide, 0.10 mole, freshly prepared from phosphorus tribromide and bromine,[20] was intimately mixed with 0.04 mole of sodium sulfopalmitic acid and warmed on the steam-bath for two hours. The resultant viscous liquid was stirred into 60 ml. of 29% aqueous ammonia and 200 g. of cracked ice. The crude product was purified by two crystallizations from 95% ethanol and one crystallization from petroleum ether. The yield of purified product was 40%. Table I lists the chemical analyses and the melting points of bromopalmitamides made by the reaction of phosphorus pentabromide and ammonia with sulfonated palmitic acid (B), and from the mercaptan oxidation product (C).

X-Ray Technique.—The X-ray diffraction patterns were recorded with a powder camera of 14.32 cm. diameter; CuKα radiation, λ = 1.5405 Å. was used. Specimens were prepared for the camera by passing a finely ground sample on a glass slide and cutting from it a narrow section 0.3 mm. thick. Table II reports interplanar spacings and relative diffraction intensities for α-bromopalmitamide prepared by the three methods.

Acknowledgment.—The authors are indebted to Jacqueline N. Weitzel, for assistance in the X-ray measurements, to Raymond G. Bistline, Jr., for assistance in the organic preparations and to Frances J. Strolle and Ruth B. Kelly for the microanalyses.

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[16] All melting points corrected.

[17] C. Hell and C. Jordanoff, *Ber.*, **24**, 936 (1891).

[18] B. H. Nicolet and L. F. Bate, THIS JOURNAL, **49**, 2064 (1927).

[19] P. A. Levene, T. Mori and L. A. Mikeska, *J. Biol. Chem.*, **75**, 337 (1927).

[20] H. S. Booth and C. G. Seegmiller, "Inorganic Syntheses," Vol. II, 1st ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 151.

Studies on the Mucohalic Acids. III. The Chlorobromo Acids. Mechanism of Formation of the Mucohalic Acids

BY HARRY H. WASSERMAN, FRANK M. PRECOPIO AND TIEN-CHUAN LIU

RECEIVED JANUARY 8, 1953

In the course of investigations on halogenated furoic acids, Hill and Jackson[1] reported that a mucohalic acid, $C_4H_2BrClO_3$ (I), containing both bromine and chlorine atoms could be formed by the action of excess aqueous bromine on what was considered to be 3-chloro-2-furoic acid. Vander Wal[2] later showed that Hill's chlorofuroic acid was actually the 4-chloro-isomer but the "mucochlorobromic" acid derivable therefrom was never completely characterized. Our interest in replacement reactions involving the halogens of the mucohalic acids and esters has led us to study this product.

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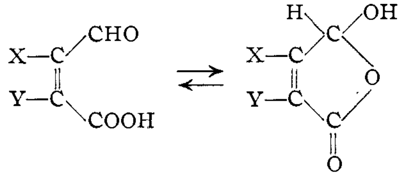
[1] H. B. Hill and O. R. Jackson, *Am. Chem. J.*, **12**, 37 (1890).

[2] R. J. Vander Wal, *Iowa State Coll. J. Sci.*, **11**, 128 (1936).

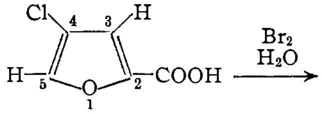
We have prepared "mucochlorobromic" acid following Hill's detailed procedure[1] as modified by Vander Wal,[3] and have shown, as outlined below, that it is α-bromo-β-chloro-β-formylacrylic acid (I, X = Cl, Y = Br).

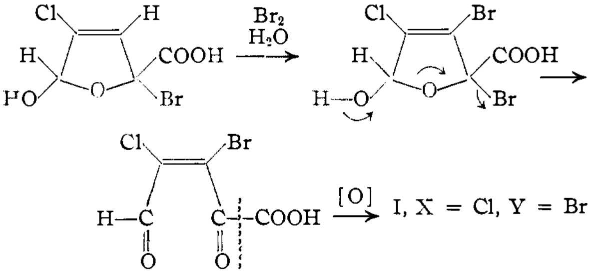


I

Treatment of Hill's "mucochlorobromic" acid with aqueous potassium phenylate yielded mucophenoxychloric acid (I, X = Cl, Y = OC_6H_5) identical with the product derived by the action of phenol and alkali on mucochloric acid (I, X = Y = Cl). That the halogen *α to the carboxyl group* was replaced by a phenoxy group in this reaction as originally postulated by Hill and Stevens[4] was verified by conversion of mucophenoxychloric acid to the known mucoxychloric acid system (I, X = Cl, Y = OH) through mild barium hydroxide hydrolysis. The barium salt isolated from this reaction was identical with known barium mucoxychlorate[8] $BaC_4HO_4Cl \cdot H_2O$, as shown by comparison of the infrared spectra of the two salts, and by conversion of each to the same monoanilino derivative,[5] $C_{10}H_8O_3NCl$. The above replacement reactions clearly establish the structure of Hill's "mucochlorobromic" acid as I, X = Cl, Y = Br, and are in accord with the recent findings of E. Kuh who has prepared an isomeric α,β-dihalo-β-formylacrylic acid to which he has assigned the structure I, X = Br, Y = Cl.[6] In agreement with this assignment we have found that Kuh's chlorobromo acid was transformed, by the action of aqueous potassium phenylate, into mucophenoxybromic acid (I, X = Br, Y = OC_6H_5) identical with the product similarly derived from mucobromic acid (I, X = Y = Br). In both of the latter conversions the halogen undergoing replacement must have been α to the carboxyl group.

The formation of α-bromo-β-chloro-β-formylacrylic acid by the bromination of 4-chloro-2-furoic acid, is good evidence for the fact that in the reaction of 2-furoic acids with aqueous halogens whereby the mucohalic acids are produced, the newly formed aldehyde group must have originated at C-5. The above conversion may have taken place by a process such as that depicted below, involving in successive steps, 1,4-addition of HOBr to the furan ring, replacement of hydrogen, ring opening, and then oxidative cleavage of the α-keto acid.





Experimental

Hydrolysis of Chlorobromo Acids.—The hydrolysis of the chlorobromo acids with aqueous potassium phenylate was accomplished according to the general procedure outlined by Hill and Stevens[4] as later modified by Sawyer.[7]

Barium Mucoxychlorate from Mucophenoxychloric Acid.—A stirred suspension of mucophenoxychloric acid, 7.0 g. (0.031 mole), in 300 ml. of water, was cooled in ice to 0°, and 9.75 g. of powdered $Ba(OH)_2 \cdot 8H_2O$ was added over a period of 1.5 hours while the temperature was maintained between 0 and 5°. The cloudy yellow solution was filtered while cold and an equal volume of 95% ethyl alcohol was added to the clear solution. After cooling in an ice–salt mixture for a short time, barium mucoxychlorate precipitated in its characteristic microcrystalline form[8]; yield 2.5 g. Infrared absorption spectra of this barium salt and of the authentic barium mucoxychlorate were almost identical. The action of aniline hydrochloride on this barium salt yielded an anil which was found to be identical in every respect with mucoxychloric acid anil.

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[3] R. J. Vander Wal, doctoral dissertation, Iowa State College (1936).

[4] H. B. Hill and E. K. Stevens, *Am. Chem. J.*, **6**, 187 (1884).

[5] H. B. Hill and A. W. Palmer, *ibid.*, **9**, 147 (1887).

[6] E. Kuh, private communication, U. S. Patent 2,588,852. We are indebted to Dr. Kuh of American Cyanamid Co. for a sample of his chlorobromo acid.

[7] H. F. Sawyer, *Proc. Am. Acad. Arts Sci.*, **29**, 242 (1894).

[8] H. H. Wasserman and F. M. Precopio, This Journal, **74**, 326 (1952).

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t-Butyl Sulfone

By J. Eliot Woodbridge

Received November 10, 1952

A sulfone in which all alpha hydrogen atoms have been replaced by alkyl groups has been prepared. This compound has not been reported previously. Attempts to isolate it may have been unsuccessful as it sublimes readily above 80° and decomposes at temperatures somewhat above 120°.

The method of preparation was as follows: 10 ml. of 30% hydrogen peroxide was added slowly with stirring to 8.15 g. (0.046 mole) of *t*-butyl sulfide[1] and 10 ml. of glacial acetic acid, the temperature being kept between 70 and 80° by means of an ice-bath. The sulfide was oxidized by the first equivalent of the hydrogen peroxide rapidly and by the second slowly. After 45 minutes, the solution was cooled and sufficient 5 *N* sodium hydroxide was added to neutralize the mixture. Sodium bisulfite, 5 g., was added to destroy any remaining peroxide, and the solution was cooled to room temperature and extracted four times with 50-ml. portions of ethyl ether. The ether was evaporated until crude colorless crystals appeared, after which the mixture was dissolved in 60 ml. of 50% ethanol, washed with 5.0 ml. of pentane, and allowed to crystallize in an ice-bath. The yield was 3.75 g., m.p. 127–128°.[2] The mother liquor was evaporated to 24 ml., and cooled to obtain 1.78 g. of additional material. The total yield was 5.53 g. or 55.8%.

Anal. Calcd. for $C_8H_{18}O_2S$: C, 53.9; H, 10.2; O, 18.0; S, 18.0; mol. wt., 178.28. Found: C, 54.2; H, 10.3; O, 17.6; S, 17.5; mol. wt. (mass spectrometer), 178.

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[1] Prepared by procedure of Edward A. Fehnel and Marvin Carmack, This Journal, **71**, 84 (1949).

[2] Sufficient material should be used, and the temperature should be raised fairly rapidly to avoid complete sublimation. There appears to be a transition point at 100 to 105°.

The presence of sulfone and *t*-butyl groups was indicated by infrared. The compound decomposed on heating to give sulfur dioxide and isobutylene.[3]

SOLUBILITIES

Solvent	Temp., °C.	Solubility, g./100 ml.
Water	20, 50, 80	1.08, 1.54, 3.18
0.1 *N* HCl	20	1.03
0.1 *N* NaOH	20	0.95
n-Pentane	20	0.82
Diethyl ether	20	5.61
Ethanol	20	16.1

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(3) The compound decomposes or builds up vapor pressure suddenly on heating in the combustion tubes, and mixtures with oxygen were several times obtained which ignited and ruined the analysis. The oxygen analysis was made by the Unterzaucher method.

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A Rapid Method for Fractionating Crude Rare Earth Ores into Mixtures Greatly Enriched with Regard to Particular Rare Earths

BY E. J. WHEELWRIGHT AND F. H. SPEDDING

RECEIVED FEBRUARY 6, 1953

It has been found in this Laboratory that efficiency of producing very pure rare earth oxides by ion-exchange methods can be greatly increased if the crude rare earth mixtures, as leached from the ores, can be first rapidly fractionated into several fractions, enriched in specific rare earths. Normally, the rare earth oxide, as obtained from the ore, consists of from 10 to 14 individual rare earths and rare earth-like elements. Some of these are present in very small amounts and some such as cerium, lanthanum, neodymium and yttrium may represent up to 50% of the total mixture, depending upon the ore involved. When the rare earth mixture is dissolved and adsorbed on the ion-exchange columns, these elements then occupy the major part of the resin band and require considerable time to elute. If the bulk of these less desirable elements can be removed by a preliminary, rapid fractionation, the efficiency of production of the pure heavy rare earths by ion-exchange methods can be increased many fold.

The older type fractionations are usually very slow and laborious. However, Schwarzenbach and Freitag,[1] Marsh,[2] Beck,[3] Vickery[4] and others, have pointed out that the rare earths do form very tight complexes with chelating agents such as Versene (ethylenediaminetetraacetic acid) and Marsh[2] and Vickery[4] have shown that fractionations using these complexes are more rapid than the older methods. However, their methods are still laborious and give smaller enrichments than might be desired. Recent determinations of the equilibrium constants of the rare earth–Versene complexes by Vickery[4] and by Wheelwright, Spedding and Schwarzenbach[5] show that the apparent equilibrium constants, determined at fixed ionic strength, differ by a factor of 10^5 across the rare earth series. It should therefore be possible to take advantage of this fact in effecting a rapid fractionation of the mixed rare earths. The purpose of this note is to indicate one of the ways in which this can be accomplished.

Most of the methods for separating the rare earths by ion-exchange columns, for example, the citrate elution as developed by this Laboratory,[6] depend upon an adsorption of a band of rare earths on the resin and the subsequent elution of this band down the column in a manner roughly analogous to chromotography. However, a much more rapid process could be effected if the ion-exchange columns were used—in a manner analogous to water-softening—to differentially adsorb one rare earth or group of rare earths and allow the others to pass through without being appreciably adsorbed. This technique has been tried by Fitch and Russell,[7] using other chelating agents, but the enrichments obtained have not been great enough to be entirely satisfactory for a preliminary separation to precede the citrate separation to obtain pure rare earths.

Our present process consists essentially of complexing part of the rare earths in a mixture with Versene, then separating the complexed rare earth ions from the uncomplexed ions by passing the solution through an ion-exchange column. The complexed ions pass through the column while the uncomplexed ions are adsorbed on the resin. Care must be taken that the capacity of the resin is such that it is capable of adsorbing all of the uncomplexed rare earths. The rare earth–Versene stability constants range from $10^{14.72}$ for La to $10^{19.65}$ for Lu, with Y appearing in the series between Tb and Dy. Since the rare earth mixture we used in this experiment contained about 60% Y, 15% heavy rare earths and 25% light rare earths, it was decided to complex the heavy rare earths Lu to Dy, make the initial separation with an ion-exchange column, and then remove the Y and the lighter rare earths from the column by passing successive solutions, containing a predetermined amount of Versene, through the column. While this experiment was performed with the resin in a column, it might be more desirable to place the resin in a tank, adsorb the rare earth mixture on the resin, and then intimately mix it with successive fixed amounts of Versene. The complexed rare earths could be removed by draining or filtering, and of course an equilibration period of about 24 hours should be allowed for each solution. We are continuing this work and it is obvious that the conditions can be greatly improved. However, the preliminary experiments were so promising and efficient that we felt that they should be reported at this time. This can best be illustrated by giving the procedure and data for one of our runs.

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(1) G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1503 (1951).

(2) J. K. Marsh, *J. Chem. Soc.*, 1819 (1950); 3057 (1951).

(3) G. Beck, *Helv. Chim. Acta*, **29**, 357 (1946); *Mikrochemie ver. Mikrochim. Acta*, **33**, 344 (1948).

(4) R. C. Vickery, *J. Chem. Soc.*, 1101 (1950); 2058 (1950); 1817 (1951).

(5) E. J. Wheelwright, F. H. Spedding and G. Schwarzenbach, in press.

(6) F. H. Spedding, E. I. Fulmer, J. E. Powell and T. A. Butler, THIS JOURNAL, **72**, 2354 (1950); F. H. Spedding, E. I. Fulmer, J. E. Powell, T. A. Butler and I. S. Yaffe, *ibid.*, **73**, 4840 (1951). Also see earlier papers.

(7) F. T. Fitch and D. S. Russell, *Can. J. Chem.*, **29**, 363 (1951); *Anal. Chem.*, **23**, 1469 (1951).

Procedure

A neutral solution containing 312 g. of mixed rare earths weighed as oxide, was obtained by dissolving a known larger amount of the rare earth material in a limited amount of hydrochloric acid and recovering the undissolved rare earth. A previously prepared solution of diammonium dihydrogen versenate, containing the theoretical amount of Versene required to complex the heavy rare earths in the mixture, and adjusted to a *p*H of 10, was then added to the rare earth solution, and the combined solution diluted to 90 liters. After equilibrating for 24 hours, the *p*H of the solution was adjusted to 4.5 with a little hydrochloric acid. Following a second 24-hour equilibration period, this solution was passed rapidly through a short bed of Dowex-50, and the column washed free of complexed rare earths with a few liters of distilled water. The rare earth material remaining on the resin was removed fractionally by pouring four successive predetermined amounts of Versene solution, which had been adjusted to a *p*H of 9.5, through the column at a slow flow rate, taking 24 hours for each fraction, so as to let the liquid remain in contact with the resin long enough to approach equilibrium conditions.

Results and Discussion

To obtain an analysis of the five fractions, 20 g. of oxide from each fraction was adsorbed on standard, small ion-exchange columns and eluted with citric acid according to our usual procedure for obtaining pure rare earths. This spread the fractions out into 20 to 30 secondary fractions, each of which contained only two to four rare earths. These secondary fractions could then be analyzed spectrographically and spectrophotometrically without running into the interferences which would occur in a direct analysis of the larger fractions. Also, much better material balances could be obtained. The results are presented in Table I.

It will be noticed that under these very preliminary conditions, which are almost certainly far from optimum, most of the heavy rare earths are concentrated away from the light rare earths and from most of the yttrium. Such a preliminary separation will permit us to add five times as much heavy rare earths on the ion-exchange columns as we could previously and therefore step up our production of these pure rare earths accordingly.

TABLE I

RARE EARTH OXIDES RECOVERED IN ONE RUN ON GADOLINITE ORE (GRAMS)

Elements	Sample I	Sample II	Sample III	Sample IV	Sample V	Total
Lu	1.67	...	...	...	...	1.67
Yb	14.02	1.69	...	...	...	15.71
Tm	1.55	1.22	...	...	...	2.77
Er	5.58	9.83	...	...	...	15.41
Ho	1.04	3.57	0.25	...	...	4.86
Dy	2.15	11.17	9.04	0.30	...	22.66
Tb	0.06	0.13	0.10	0.75	0.69	1.73
Gd	...	...	...	7.37	5.80	13.17
Sm	...	...	...	3.87	5.42	9.29
Nd	...	...	...	3.75	7.45	11.20
Pr	...	...	...	0.37	0.68	1.05
Ce	...	...	...	.81	2.27	3.08
La	...	...	...	.81	2.27	3.08
Y	13.81	65.17	72.80	25.80	13.22	190.80
Total	39.88	92.78	82.19	43.83	37.80	296.48

At the present time, we are studying the possibility of greatly improving this process by investigating such variables as a higher temperature to approach the various equilibria more rapidly, and utilizing more concentrated solutions to increase the yields.

CONTRIBUTION NO. 212 FROM THE INSTITUTE FOR
ATOMIC RESEARCH AND DEPARTMENT OF CHEMISTRY
AMES LABORATORY OF THE ATOMIC ENERGY COMMISSION
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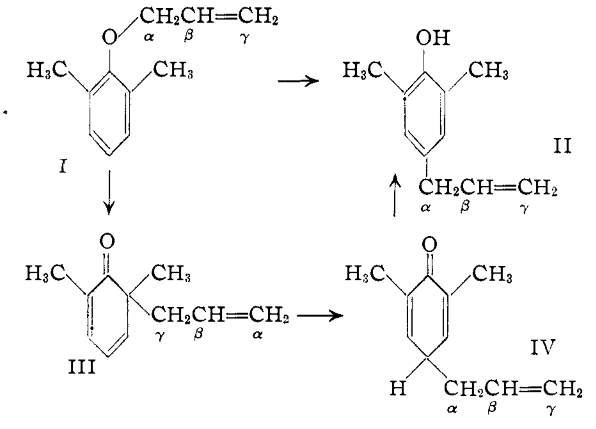
COMMUNICATIONS TO THE EDITOR

THE MECHANISM OF THE *PARA*-CLAISEN REARRANGEMENT

Sir:

Consideration of the literature[1-6] dealing with the *para*-Claisen rearrangement, of which the change I → II is an example, led us to suspect the intermediate formation of isomeric cyclohexadienones, *e.g.*, III and IV. Since III is a type which should readily participate in Diels–Alder additions, it was hoped that this substance, if present in the reaction mixture, might be trapped when the rearrangement was conducted in the presence of some suitable dienophile.



Allyl 2,6-dimethylphenyl ether, in a solution of maleic anhydride, was heated (200° for 2.5 hours, CO_2 atm.) and the acidic reaction products separated. One of these, m.p. 143 3–143.6°, obtained

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(1) O. Mumm, *et al.*, *Ber.*, **70**, 2214 (1937); **72**, 100 (1939); **72**, 1523 (1939).

(2) D. S. Tarbell and J. F. Kincaid, THIS JOURNAL, **62**, 728 (1940).

(3) C. D. Hurd and M. A. Pollack, *J. Org. Chem.*, **3**, 550 (1939).

(4) E. R. Alexander and R. W. Kluiber, THIS JOURNAL, **73**, 4304 (1951).

(5) D. S. Tarbell, chapter in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 1.

(6) H. B. Watson, *Ann. Repts. Chem. Soc.*, 206 (1930).