(50 gallons of feed) showed 83% of the adsorbed hafnium in the sulfuric strip as 50 wt. % hafnium oxide.

After conversion to the tetrachloride, the enriched hafnium made available by the first process cycle was further concentrated in a second similar cycle to 90 wt. % hafnium oxide. The over-all yield for the entire operation averaged 70%. Further concentration of hafnium by adsorption would probably require a zirconium-selective adsorbent.

Acknowledgment.—The authors are indebted to Olaf A. Runquist and Wendell Van Horn of the spectrographic section of the Ames Laboratory, Atomic Energy Commission, for their coöperation in analyzing the many samples submitted in this investigation.

AMES, IOWA RECEIVED JUNE 11, 1951

NOTES

Carbohydrate Thioacetals. I. Lead Tetraacetate Oxidation of D-Arabinose Derivatives

BY S. B. BAKER

Sugar thioacetals are important intermediates in carbohydrate syntheses and the oxidation of these sulfur-containing derivatives by means of glycol-cleaving oxidants should yield valuable intermediates. However, divalent sulfur atoms readily oxidize to form sulfones.[1] Some work has been done[2,3] on the periodate and lead tetraacetate oxidations of sugar thioacetals. The relative position of a glycol group to a thioacetal group may have some effect on the mode of oxidation and the present paper shows that this apparently occurs with arabinose thioacetal derivatives.

Two derivatives of D-arabinose dibenzyl thioacetal were prepared to determine what effect the position of a glycol had on the mode of oxidation of a thioacetal by lead tetraacetate. The first derivative, 4,5-isopropylidene-D-arabinose dibenzyl thioacetal, on reaction with one molecular equivalent of lead tetraacetate was oxidized in the normal manner, as shown by the isolation of isopropylidene-D-glyceraldehyde in good yield. The second derivative, 2,3-dibenzoyl-D-arabinose dibenzyl thioacetal did not yield formaldehyde on reaction with one molecular equivalent of lead tetraacetate, because the oxidant was apparently consumed in the oxidation of a sulfur atom.[3] On addition of a second equivalent of oxidant, the latter was consumed and approximately one equivalent of formaldehyde was produced as determined by the formation and isolation of formaldimethone.

Thus it seems that oxidation of arabinose thioacetal derivatives containing a glycol group in different positions relative to the thioacetal group can follow two paths and the point of reaction is apparently dependent on these relative spacial positions of the two groups.

(1) W. A. Bonner and R. W. Drisko, THIS JOURNAL, **73**, 3699 (1951).

(2) B. H. Nicolet and L. A. Shinn, *ibid.*, **61**, 1615 (1939).

(3) C. F. Huebner, R. A. Pankratz and K. P. Link, *ibid.*, **72**, 4811 (1950).

Experimental

D-Arabinose Dibenzyl Thioacetal.—D-Arabinose (100 g.) was dissolved in cold concentrated hydrochloric acid (200 cc.). Benzyl mercaptan (200 cc.) was added and the mixture was vigorously agitated. After about 30 min. the mixture, which had become homogeneous with evolution of heat, began to cool and solidify. The hard reaction mixture was broken up, filtered and washed with water (6000 cc.), dilute ammonium hydroxide (400 cc.) and finally with water again. The crude air-dried material was recrystallized from 1-propanol–petroleum ether (3:1). The yield was 215 g. (80%) and melted at 148–149°; $[\alpha]^{22}D$ +18.3 (*c* 2.6, pyridine). Pacsu[4] reported a melting point of 144° and $[\alpha]^{20}D$ −18.86 for the L-isomer.

4,5-Isopropylidene-D-Arabinose Dibenzyl Thioacetal.—D-Arabinose dibenzyl thioacetal (70 g.) and anhydrous cupric sulfate (350 g.) were suspended in anhydrous acetone (1750 cc.) in a 5 l. round-bottomed flask. The mixture was vigorously agitated for 7 days on a shaking machine. The reaction mixture was filtered and the partially hydrated copper sulfate washed with chloroform. The filtrates were combined and concentrated to dryness at 50° *in vacuo*. The crystalline residue was dissolved in chloroform (100 cc.), the solution decolorized with charcoal and then filtered. The colorless filtrate was treated with low-boiling petroleum ether until turbid. Crystallization commenced immediately and the mixture was then cooled at −15° overnight for maximum crystallization; yield 70 g. (90%). A portion was twice recrystallized from boiling petroleum ether (65–110°) and dried at 65° *in vacuo*, melted at 100–100.5° and $[\alpha]^{24}D$ −56.5° (*c* 1.7, chloroform).

Anal. Calcd. for $C_{22}H_{28}S_2O_4$; C, 62.85; H, 6.66; S, 15.2. Found: C, 62.7; H, 6.9; S, 15.2.

Lead Tetraacetate Oxidation of 4,5-Isopropylidene-D-Arabinose Dibenzyl Thioacetal.—The presumed 4,5-isopropylidene derivative (6.07 g.) was dissolved in thoroughly dried benzene (150 cc.). Twice recrystallized lead tetraacetate (6.4 g., 1 mole) was added rapidly and the mixture was agitated for 30 min. with occasional cooling. The mixture was then allowed to stand for 2 hr. and a 1-ml. aliquot showed that all the lead tetraacetate was consumed. The mixture was filtered through a sintered glass filter and the filter washed well with two portions of anhydrous benzene (25 cc.). The combined filtrates were then distilled through a 30-cm. column to remove the benzene and the residue slowly distilled under reduced pressure. A fraction (1.6 g.) was obtained, boiling at 42–44° (13 mm.), $n^{21}D$ 1.4559; $[\alpha]^{22}D$ +68.1 (*c* 0.45, benzene). These constants were in agreement with those found by Baer and Fischer[5] for isopropylidene-L-glyceraldehyde except for the direction of rotation.

A fraction (0.5 g.) was dissolved in saturated 2,4-dinitrophenylhydrazine hydrochloride and the solution after stand-

(4) Pacsu and Tichanich, *Ber.*, **62**, 3008 (1929).

(5) E. Baer and H. O. L. Fischer, THIS JOURNAL, **61**, 764 (1939).

ing overnight deposited yellow needles. After recrystallization from 50% ethanol the melting point was 147–148°. The reported[5] melting point for the 2,4-dinitrophenylhydrazone of L-glyceraldehyde is 147–148°.

2,3-Dibenzoyl-4,5-Isopropylidene-D-Arabinose Dibenzyl Thioacetal.—4,5-Isopropylidene-D-arabinose dibenzyl thioacetal (86 g.) was dissolved in anhydrous pyridine (200 cc.) and after cooling to −15° benzoyl chloride (60 cc.) was added dropwise with stirring. The mixture was then allowed to stand at room temperature for 48 hours. The reaction mixture was added to ice water with stirring and after about 30 min. the sirupy product crystallized. The solid mass was broken up, filtered and washed with water to remove most of the pyridine. After air drying, the crude product was recrystallized from methanol in the presence of decolorizing charcoal. The material was recrystallized twice more from methanol with very little loss; yield 117 g. (91%), m.p. 103.5–104°; $[\alpha]^{22}D$ +81.5° (*c* 1.9, chloroform). *Anal.* Calcd. for $C_{36}H_{36}S_2O_6$: C, 68.82; H, 5.73; S, 10.19; benzoyl, 33.4. Found: C, 68.7; H, 5.9; S, 10.1; benzoyl, 33.2.

Monobenzoyl-D-Arabinose Dibenzyl Thioacetal.—2,3-Dibenzoyl-4,5-isopropylidene-D-arabinose dibenzoyl thioacetal (45 g.) was dissolved in ethanol (250 cc.). Dilute (5%) hydrochloric acid (70 cc.) was added and the solution heated on the steam-bath for one hour. The reaction mixture was cooled and neutralized with saturated sodium bicarbonate solution and the mixture concentrated under reduced pressure until viscous. Chloroform was added and the mixture warmed for a few minutes to hasten solution and then filtered. The chloroform solution was dried over anhydrous sodium sulfate, treated with charcoal, and then filtered. The colorless filtrate was concentrated to dryness and the viscous, colorless sirup triturated with hot ether. The sirup crystallized and after filtration and washing with ether it was recrystallized from absolute ethanol containing about 10% petroleum ether; yield was 25 g. (71%), m.p. 112–112.5°; $[\alpha]^{23}D$ −25.4° (*c* 2.1, chloroform). *Anal.* Calcd. for $C_{26}H_{28}S_2O_5$: S, 13.2. Found: S, 13.2.

A sample (0.5 g.) was heated on the steam-bath for 30 min. with 2% sodium hydroxide solution (40 cc.). The hot solution was filtered rapidly through a preheated funnel and a precipitate separated which was filtered and washed with water until the washings were neutral. After drying the product weighed 0.3 g. (79%), m.p. 147–148°. A mixed melting point determination with authentic D-arabinose dibenzyl thioacetal showed no depression.

2,3-Dibenzoyl-D-arabinose Dibenzyl Thioacetal.—2,3-Dibenzoyl-4,5-isopropylidene-D-arabinose dibenzyl thioacetal (50 g.) was heated on the steam-bath for one hour in 80% acetic acid (500 cc.). The solvent was removed under reduced pressure and the nearly colorless sirup dissolved in ether and the solution washed with saturated bicarbonate and then with water. The ethereal solution was then dried over anhydrous sodium sulfate in the presence of decolorizing charcoal. After filtration the solvent was removed and a perfectly colorless sirup was obtained that would not crystallize after three months. On prolonged standing in an evacuated desiccator over phosphorus pentoxide, the sirup became a colorless glass; yield was 44 g. (93%); $[\alpha]^{26}D$ +56.5° (*c* 1.7, chloroform). It was insoluble in water and soluble in all the usual organic solvents, including warm petroleum ether.

Anal. Calcd. for $C_{33}H_{32}S_2O_6$: C, 67.35; H, 5.44; S, 10.9; benzoyl, 35.7. Found: C, 67.2; H, 5.6; S, 10.9; benzoyl, 35.3.

A sample (0.5 g.) of 2,3-dibenzoyl-D-arabinose dibenzyl thioacetal was dissolved in anhydrous acetone (350 cc.) containing anhydrous cupric sulfate (15 g.) in suspension. The mixture was agitated for 5 days at room temperature, then filtered and the filter washed with dry acetone. The solvent was removed from the filtrate and the gummy residue triturated with a little methanol. Immediate crystallization occurred. The product was recrystallized from methanol. A mixed melting point determination with authentic 2,3-dibenzoyl-4,5-isopropylidene-D-arabinose dibenzyl thioacetal showed no depression.

Lead Tetraacetate Oxidation of 2,3-Dibenzoyl-D-Arabinose Dibenzyl Thioacetal.—Oxidation of a sample (0.2536 g.) of the above compound with 90 ml. of 0.048 *M* lead tetraacetate in glacial acetic acid, made up to 100 ml. with the same solvent showed that 0.09, 1.6, 1.9, 2.4, 2.9, 3.2, 4.4, 4.6 and 4.9 molecular equivalents of the oxidant were consumed in 1/12, 1/4, 3/4, 2, 3.5, 5.5, 24, 28.5 and 48 hours, respectively. The analytical results thus indicated that oxidation of the divalent sulfur atoms occurred.

In another experiment a sample of the above compound was oxidized in glacial acetic acid with one molecular equivalent of lead tetraacetate. The oxidant was consumed but formaldehyde could not be detected. Two molecular equivalents of lead tetraacetate were consumed with the formation of a high yield (93%) of formaldimethone. The authenticity of the latter compound was determined by a mixed melting point of 188–190°. The reported m.p. is 189–190°.

Acknowledgment.—The author wishes to acknowledge the kind financial assistance rendered by the Sugar Research Foundation, Inc. Thanks are due to Miss Anne Seath, of this Institute, for some of the microanalyses.

RESEARCH INSTITUTE
MONTREAL GENERAL HOSPITAL
3619 UNIVERSITY ST.
MONTREAL, CANADA RECEIVED SEPTEMBER 17, 1951

S-(*n*-Butyl)-homocysteine (Butionine)

BY ERNST D. BERGMANN

Ethionine is known to act as an antagonist to the utilization of methionine[1,2]; to some extent, it can be utilized by the living cell instead of the latter amino acid.[2,3] It seemed, therefore, interesting to study a higher homolog of ethionine, such as S-(*n*-butyl)-homocysteine (Butionine). This substance, however, proved to cause no response on the part of *Escherichia coli*.[2]

β-Butylthio-ethanol.—Butyl bromide (12 ml.) was added at 0° to a solution of 15.6 g. of β-thioethanol and 13 g. of potassium hydroxide in 65 ml. of alcohol. The mixture was refluxed for three hours and, after addition of water, extracted with ether; b.p. 118° (28 mm.); yield 17.5 g. (65%). This method is preferable to that of Whitner and Reid[4] who prepared the compound from ethylene chlorohydrin and butyl mercaptan (b.p. 92–93° (3 mm.)).

Anal. Calcd. for $C_6H_{14}OS$: S, 23.9. Found: S, 23.7.

β-Butylthioethyl Chloride.—At 0° with agitation, 17.5 g. of β-butylthioethanol was added to 10.5 ml. of phosphorus trichloride. After two hours, at room temperature, the upper layer was treated with ice-water and extracted with ether; b.p. 96° (26 mm.); yield 10.5 g. (54%) (literature,[4] b.p. 68° (6 mm.)).

Anal. Calcd. for $C_6H_{13}ClS$: Cl, 23.0. Found: Cl, 23.1, 23.2.

Diethyl (β-Butylthioethyl)-phthalimidomalonate.—An intimate mixture of 10.5 g. of β-butylthioethyl chloride and 25.6 g. of diethyl sodiophthalimidomalonate[5] was heated at 160° for six hours and then at 200° for 15 minutes. The mass was triturated with hot water and the oily reaction product extracted with ether; b.p. 265–270° (13 mm.); yield 12.6 g.

Anal. Calcd. for $C_{21}H_{27}NO_6S$: C, 60.0; H, 6.4; N, 3.3 S, 7.6. Found: C, 60.3; H, 6.6; N, 3.7; S, 7.6.

S-(*n*-Butyl)-homocysteine.—To the foregoing product in 12 ml. of alcohol, 33.6 ml. of 5 *N* sodium hydroxide was added. With evolution of heat, a salt crystallized out. The mass was heated on the water-bath for two hours, di-

(1) P. Siekevitz and D. M. Greenberg, *Federation Proc.*, **9**, 227 (1950); M. V. Simpson, E. Farber and H. Tarver, *J. Biol. Chem.*, **182**, 81 (1950); H. M. Dyer, *ibid.*, **124**, 519 (1938); J. A. Stekol and K. Weiss, *ibid.*, **179**, 1049 (1949).

(2) E. D. Bergmann, B. E. Volcani and R. Ben-Ishai, *ibid.*, in press (1952).

(3) S. A. Stekol, K. Weiss and S. Weiss, THIS JOURNAL, **72**, 2309 (1950).

(4) T. C. Whitner and E. E. Reid, *ibid.*, **43**, 636 (1921).

(5) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 384.

luted with 50 ml. of water, cooled at 0° and after neutralization with 2 *N* hydrochloric acid, precipitated by addition of 12 ml. of concentrated hydrochloric acid. After twelve hours, a resinous product had separated, which was freed from the supernatant liquid by decantation and heated on the steam-bath for 45 minutes with 120 ml. of 20% hydrochloric acid and for further two hours with 60 ml. of concentrated hydrochloric acid. The filtered solution was evaporated *in vacuo* to dryness and the residue taken up in 40 ml. of 50% alcohol. When pyridine was added to the solution, well-shaped needles separated which were recrystallized from water; m.p. 240° (dec.); yield 2.8 g. (21.4%, calculated on β-butylthioethyl chloride).

Anal. Calcd. for $C_8H_{17}NO_2S$: C, 50.3; H, 8.9; N, 7.3. Found: C, 50.4; H, 8.8; N, 7.1.[6]

Also **β-ethylthio-ethanol** can be produced by the above method more easily than by condensation of ethylene chlorohydrin with ethyl mercaptan[7]: to a solution of 82 g. of β-thioethanol and 4 g. of sodium hydroxide in 200 ml. of water, 154 g. of diethyl sulfate was added with stirring at 50°. The mixture was heated for six hours at 100° and extracted with ether; b.p. 99° (28 mm.); yield 71.5 g. (64%).

Anal. Calcd. for $C_4H_{10}OS$: S, 30.2. Found: S, 30.5.

(6) The amino-acid has been obtained by a different method, by E. Borek and H. Waelsch, *J. Biol. Chem.*, **147**, 135 (1949); *cf.* M. D. Armstrong and J. D. Lewis, *J. Org. Chem.*, **16**, 749 (1950).

(7) W. Steinkopf, J. Herold and J. Stoehr, *Ber.*, **53**, 1007 (1920).

DANIEL SIEFF RESEARCH INSTITUTE
WEIZMANN INSTITUTE OF SCIENCE
REHOVOTH, ISRAEL

RECEIVED JULY 12, 1951

Some Heterocyclic Secondary Amines[1]

BY W. K. DETWEILER[2] AND E. D. AMSTUTZ

Four unsymmetrically substituted heterocyclic secondary amines which involve the 2-pyridyl, 2-pyrimidyl and 2-thiazolyl radicals have been prepared as part of a program on the synthesis of basically substituted heterocyclic compounds containing the amidine structure. These compounds were prepared by the reaction of the sodium salt of a primary amine with an "active" heterocyclic halide. The sodium salt of the amine was employed since it has been established[3] that the ring nitrogen of 2-aminopyridine, for example, is capable of substitution *via* the imino form of the amine. The necessity of employing the sodium salt of the amine has been demonstrated during the course of this investigation.[4]

Although the method of synthesis employed appears to be straightforward, the actual preparation of pure samples of these amines has involved considerable difficulty. It has been impossible to develop one set of conditions which would satisfactorily lead to all the desired products. Thus the sodium salt of 2-aminopyridine reacted with 2-chlorothiazole in refluxing benzene to produce a 40% yield of 2-pyridyl-2′-thiazolylamine. Similarly, the sodium salt of aniline reacted with 2-chloropyrimidine to give a 22% yield of 2-anilinopyrimidine.[5] In contrast, the reaction of the sodium salt of 2-aminopyrimidine with 2-chlorothiazole in benzene led to no reaction; the same reactants in *p*-cymene produced an insoluble and infusible substance which probably arose from ring rupture. This latter reaction was successfully carried out in 9.5% yield by the direct reaction of the sodium salt of the amine with the heterocyclic halide. Correspondingly, the sodium salts of 2-aminopyrimidine and 2-aminopyridine did not produce 2-pyridyl-2′-pyrimidylamine when refluxed in benzene with 2-bromopyridine and 2-chloropyrimidine, respectively; however, the direct reaction of the sodium salt of 2-aminopyrimidine with 2-bromopyridine produced a 27% yield of 2-pyridyl-2′-pyrimidylamine.

Experimental[6]

Sodium Salts of 2-Aminopyrimidine and 2-Aminopyridine.—2-Aminopyrimidine (19.02 g., 0.2 mole) was added over a 10-minute period to a solution of sodium amide[7] (0.2 mole) in approximately 200 ml. of anhydrous liquid ammonia. After 2 additional hours of stirring, the solvent was evaporated, the gray-white sodium salt pulverized, extracted with two 100-ml. portions of anhydrous benzene and dried under vacuum over phosphorus pentoxide; yield 19 g. (85%).

The sodium salt of 2-aminopyridine was prepared in an analogous manner except for the extraction process which was omitted; this salt was dark blue in color.

2-Pyridyl-2′-thiazolylamine.—The sodium salt of 2-aminopyridine (35.9 g., 0.3 mole) was refluxed in 50 ml. of anhydrous benzene with stirring for one-half hour in order to ensure complete reaction. 2-Chlorothiazole[8] (30 g., 0.25 mole) in 40 ml. of anhydrous benzene was added over a 10-minute period to the warm suspension of the sodium salt while the reaction flask was being cooled in a cold water-bath. The reaction mixture was then stirred and heated at gentle reflux for 10 hours. The dark brown mixture was cooled and extracted with 250 ml. of a 1:1 mixture of concentrated hydrochloric acid and water. The acidic extract was cooled and adjusted to a *p*H 10 with 48% sodium hydroxide. The tan colored precipitate was filtered, washed with four 50-ml. portions of cold water and dried at 100°; yield 22 g., m.p. 191.8–193°. Recrystallization from 95% ethanol after treatment with charcoal gave 17.9 g. (40.3%) of light tan colored needles, m.p. 195.8–196.6°, sublimation at 15 mm. pressure and recrystallization from ethanol gave colorless needles which had essentially the same melting point as the discolored crystals. *Anal.* Calcd. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.72; S, 18.09. Found: C, 54.32; H, 4.18; N, 23.75; S, 17.95.

2-Pyridyl-2′-pyrimidylamine.—The sodium salt of 2-aminopyrimidine (22.65 g., 0.193 mole) and 2-bromopyridine[9] (30.6 g., 0.193 mole) were heated in an oil-bath at 150–170° for 45 minutes. The cooled reaction mixture was thoroughly extracted by shaking with several portions of cold water; the addition of a cold 1:1 mixture of ethanol and ether converted the sticky mixture into a light cream colored powder which was filtered, washed with ether and dried under vacuum over phosphorus pentoxide; yield 9.1 g. (27.2%), m.p. 149.6–151.7°. Recrystallization from ethanol gave light cream colored hexagonal plates, m.p. 149.3–152.1°; vacuum sublimation under 2 mm. pressure produced

(1) Abstracted, in part, from a thesis presented by W. K. Detweiler to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the Ph.D. degree, June, 1951.

(2) The Wm. S. Merrell Company Research Assistant in Organic Chemistry, 1948–1951.

(3) A. E. Tschitschibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54**, 814 (1921).

(4) The direct fusion of 2-chloropyrimidine with 2-aminopyridine for 42 hours at approximately 100° gave an ionic halogen compound which upon treatment with base liberated a substance which melted at 182–184°; in contrast, the reaction of the sodium salt of the amine with the same halide gave 2-pyridyl-2′-pyrimidylamine which melted at approximately 150–152°. The higher melting material was not investigated further but may have been an isomeric material formed by reaction of a ring nitrogen.

(5) This reaction was run in order to determine the stability of 2-chloropyrimidine in the presence of a sodium salt of an active primary amine.

(6) All melting points have been corrected for thermometer stem-emergence.

(7) Prepared according to T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(8) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343–358 (1945); *C. A.*, **40**, 4095.

(9) C. F. H. Allen and J. R. Thirtle, *Org. Syntheses*, **26**, 16 (1946).

colorless crystals, m.p. 150.2–152.1°. *Anal.* Calcd. for $C_9H_9N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.82; H, 4.68; N, 32.47.

2-Pyrimidyl-2′-thiazolylamine.—The sodium salt of 2-aminopyrimidine (22.18 g., 0.189 mole) and 2-chlorothiazole (22.58 g., 0.189 mole) were heated in an oil-bath at 95° for 2.75 hours when it became necessary to cool the reaction mixture in order to moderate an exothermic reaction which had developed; the reaction mixture was then heated for an additional 6 hours at 95°, cooled, suspended in 50 ml. of water and steam distilled (6 g. of 2-chlorothiazole was recovered). The residue from the steam distillation was filtered, washed with cold water and dried at 100°; yield 3.1 g. (9.5%), m.p. 209–211.8°. Cream colored crystals were obtained upon recrystallization from ethanol, m.p. 211–212.1°. Vacuum sublimation under 6 mm. pressure and recrystallization from ethanol gave colorless crystals, m.p. 212.1–212.6°. *Anal.* Calcd. for $C_7H_6N_4S$: C, 47.18; H, 3.39; N, 31.44; S, 17.99. Found: C, 47.22; H, 3.44; N, 31.44; S, 17.89.

2-Anilinopyrimidine.[10]—A mixture of aniline (3.26 g., 0.035 mole) and sodium amide (1.37 g., 0.035 mole) in 35 ml. of dry benzene was heated and stirred for 3.25 hours in an oil-bath at 92° under an atmosphere of nitrogen. 2-Chloropyrimidine (4 g., 0.035 mole) in 20 ml. of anhydrous benzene was added to the cooled reaction mixture. After the addition, this mixture was heated and stirred at gentle reflux for 4.5 hours, cooled and then steam distilled. The distillate was acidified with concentrated hydrochloric acid and shaken to extract the amine from the benzene portion of the distillate. A brown colored solid was precipitated from the acidic solution upon adjusting it to a *p*H 10; yield 2.7 g. Solution of this substance in boiling water and filtration from insoluble impurities produce 1.3 g. (22%) of colorless needles, m.p. 114.3–115.2°.

Acknowledgment.—We are grateful to the Wm. S. Merrell Company for the funds that made this research possible and for many helpful discussions in connection with this investigation.

(10) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **38**, 244 (1907), prepared this compound by the reduction of 4-chloro-2-anilinopyrimidine, m.p. 116°.

WM. H. CHANDLER CHEMISTRY LABORATORY
LEHIGH UNIVERSITY
BETHLEHEM, PENNA. RECEIVED JUNE 20, 1951

The Hydrolysis of Glucose-4-phosphate[1]

BY H. R. DURSCH AND F. J. REITHEL[2]

The mechanism by which galactose may be derived from glucose in biological systems is one which holds considerable interest. Robinson[3] suggested that D-glucose-4-phosphate, if present in nature, might be hydrolyzed at the C–O– bond at carbon number four with a resultant Walden inversion. This mechanism is referred to repeatedly, but it has never been tested directly. Cohn[4] has shown, using O^{18}, that hydrolysis of glucose-1-phosphate may occur at the C–O– bond or the –O–P bond depending on the catalyst used.

Experimental

The disodium and barium salts of D-glucose-4-phosphoric acid were prepared in this Laboratory.[5]

Acid Hydrolysis.—To 28 mg. of barium D-glucose-4-phosphate was added excess (2 ml. of 0.1 *N*) sulfuric acid. After barium sulfate was removed by centrifugation, the solution was maintained at 100° for 30 hours. The hydrolysis mixture was concentrated, extracted with pyridine[6] and chromatographed[7] (descending) on Whatman No. 1 paper, using *s*-collidine–water as a solvent. The spray used was that recommended by Trevelyan.[8] Well defined glucose spots were obtained, but no galactose spot was discernible. There was no difficulty in differentiating the spots due to the glucose and galactose standards.

Hydrolysis at *p*H 7.—A solution of 21.4 mg. of the disodium salt of glucose-4-phosphoric acid in 2.0 ml. of water was found to be at *p*H 7.2. After 42 hours heating at 100° in a stoppered tube 50% of the compound was hydrolyzed as evidenced by analysis for inorganic phosphate.[9] The solution was chromatographed as above and identical results were obtained.

Acid Phosphatase Action.—The enzyme used was obtained by ammonium sulfate precipitation of potato press juice.[10] A sample of 20.6 mg. of disodium glucose-4-phosphate was dissolved in 2.0 ml. of water. To each volume of this solution used was added an equal volume of molar acetate buffer, *p*H 5.2, and an equal volume of purified phosphatase solution. Liberation of inorganic phosphate indicated 90% hydrolysis after 12 hours incubation at 37°. A chromatogram of the solution showed only a glucose spot.

Alkaline Phosphatase Action.—Essentially identical experiments were performed using Armour intestinal phosphatase as a catalyst at a *p*H of 8.0. Neither chromatography nor the colorimetric method of Dische,[11] *et al.*, indicated the presence of galactose in the hydrolysis mixtures.

Conclusion.—The above results do not suggest the idea that Walden inversion occurs during the hydrolysis of sugar phosphates and in this they agree with the work of Cohn.[4] The mechanism of cleavage will be further investigated with O^{18}.

(1) Work performed under Contract N6onr-218, Office of Naval Research.

(2) To whom inquiries concerning this article should be addressed.

(3) R. Robinson, *Nature*, **120**, 44 (1927).

(4) M. Cohn, *J. Biol. Chem.*, **180**, 771 (1949).

(5) F. J. Reithel and C. K. Claycomb, THIS JOURNAL, **71**, 3669 (1949).

(6) F. H. Malpress and A. B. Morrison, *Nature*, **164**, 963 (1949).

(7) S. M. Partridge and R. G. Westall, *Biochem. J.*, **42**, 238 (1948).

(8) W. E. Trevelyan, D. P. Proctor and J. S. Harrison, *Nature*, **166**, 444 (1950).

(9) C. H. Fiske and Y. SubbaRow, *J. Biol. Chem.*, **61**, 63 (1924).

(10) G. Schramm and H. Flammersfeld, *Naturwissenschaften*, **34**, 216 (1947).

(11) Z. Dische, L. B. Shettles and M. Osnos, *Arch. Biochem.*, **22**, 169 (1949).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OREGON
EUGENE, OREGON RECEIVED OCTOBER 2, 1951

The Reaction between Diazonium Fluoborates and Antimony Trichloride in Organic Solvents

BY G. O. DOAK, LEON D. FREEDMAN AND STELLA M. EFLAND

The present paper describes the reaction between antimony trichloride and diazonium fluoborates and is a continuation of our study of the reaction between the halides of certain elements and diazonium fluoborates in organic solvents. Under conditions similar to those employed with arsenic trichloride,[1] a mixture of arylstibonic and diarylstibinic acids was obtained. A number of attempts were made to separate the mixture of primary and secondary acids. Fractional crystallization of various derivatives of these acids was used, and it was found possible to obtain the pure secondary acids in low yields. However, analyses of the primary acids and m.ps. of the corresponding pyridinium chloroantimonates[2] indicated that the primary acids were invariably contaminated with small amounts of secondary acids.

The total yield as well as the ratio between the yields of the two acids varied with both the solvent

(1) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951).

(2) *Cf.* G. O. Doak and H. G. Steinman, *ibid.*, **68** 1987 (1946).

TABLE I

DIARYLSTIBINIC ACIDS AND PYRIDINIUM DIARYLCHLOROANTIMONATES

R_2SbO_2H	Yield, %	Formula	Sb analyses, % Calcd.	Found	Pyridinium diarylchloroantimonate formula	Sb analyses, % Calcd.	Found
C_6H_5-[a]	5	$C_{12}H_{11}O_2Sb$	39.41	39.45	$C_{17}H_{16}Cl_4NSb$	24.46	24.24
p-$CH_3C_6H_4-$[b]	8	$C_{14}H_{15}O_2Sb$	36.13	35.93	$C_{19}H_{20}Cl_4NSb$	23.15	22.88
m-ClC_6H_4-	6	$C_{12}H_9Cl_2O_2Sb$	32.22	32.19	$C_{17}H_{14}Cl_6NSb$	21.48	20.78
p-ClC_6H_4	12	$C_{12}H_9Cl_2O_2Sb$	32.22	32.30	$C_{17}H_{14}Cl_6NSb$	21.48	21.48
p-$O_2NC_6H_4-$[c]	20	$C_{12}H_9N_2O_6Sb$	30.52	30.40	$C_{17}H_{14}Cl_4N_2O_4Sb$	20.71	20.60

[a] Previously prepared by A. Michaelis and A. Reese, *Ann.*, **233**, 39 (1886), and other workers. [b] Previously prepared by A. E. Goddard and V. E. Yarsley, *J. Chem. Soc.*, 719 (1928). [c] Calcd.: N, 7.02. Found: N, 6.99.

and catalyst used. The results were generally comparable to those obtained with arsenic trichloride, except that the presence of water in the solvent did not materially increase the yields of stibinic acids. The best yield of arylstibonic acid was obtained by the use of absolute alcohol as the solvent and cuprous chloride as the catalyst; the yield of *p*-nitrobenzenestibonic acid was 65% under these conditions.[3] The best yield of diarylstibinic acid was obtained by the use of isopropyl or *t*-butyl alcohol and copper bronze.

Since it has been shown that the crystalline pyridinium arylchloroantimonates serve as useful derivatives for the characterization of primary stibonic acids,[2] the corresponding derivatives of the secondary acids were prepared and recrystallized. However, these compounds did not give sharp, reproducible m.ps.

Experimental

Antimony trichloride (0.1 mole) was dissolved in 100 ml. of the solvent and the solution added to 0.1 mole of the diazonium fluoride in a 2-necked flask. The subsequent procedure to the end of the steam distillation was similar to that used with arsenic trichloride.[1] After steam distillation the residual liquid in the flask was treated with 150 ml. of concentrated hydrochloric acid. A crystalline precipitate of the diarylstibine trichloride separated after several hours. This was removed by filtration and dissolved in 100 ml. of ethanol and 10 ml. of concentrated hydrochloric acid. The solution was treated with Darco and filtered. Ten ml. of pyridine reagent (*cf.* ref. 2) was added to the clear filtrate to precipitate the pyridinium chloroantimonate. The latter was then recrystallized from ethanol acidified with hydrochloric acid. The purified pyridinium salt was dissolved in 2% sodium hydroxide solution, and the clear solution acidified to congo red. The diarylstibinic acid which separated was thoroughly washed with water on a buchner funnel and air dried.

The filtrate, after removal of the diarylstibine trichloride, was treated with pyridine reagent in order to precipitate the pyridinium salt of the primary acid. This salt was then recrystallized and hydrolyzed by the procedure described in a previous paper.[2] Regardless of the solvent or catalyst used, the resulting arylstibonic acid was not analytically pure. Similar results were obtained when the ammonium chloroantimonate was used.

Table I lists the diarylstibinic acids and the corresponding pyridinium chloroantimonates prepared in this study. These results were obtained by the use of anhydrous isopropanol as the solvent and copper bronze as the catalyst. Athough previous workers have reported m.ps. for some diarylstibinic acids, the compounds listed in the present paper softened on heating but in no case was a sharp m.p. observed.

Acknowledgment.—The authors wish to thank Miss Sadie Herndon for performing the analyses incident to this research.

(3) The ratio between nitrogen and antimony in this sample was 1.11 after attempted purification.

VENEREAL DISEASE EXPERIMENTAL LABORATORY
U. S. PUBLIC HEALTH SERVICE
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NORTH CAROLINA

RECEIVED SEPTEMBER 17, 1951

The Synthesis of Ketones from Di-*t*-butyl Malonates

BY GUNTHER S. FONKEN[1] AND WILLIAM S. JOHNSON

Attempts to prepare ketones of the type $RCOCH_2R'$ by the acylation of diethyl alkylmalonates with acid chlorides, followed by hydrolysis and decarboxylation with acidic or alkaline reagents, have been almost uniformly unsuccessful, because the intermediary acylalkylmalonates preferentially undergo hydrolysis of the acyl–carbon bond to, in effect, reverse the process.[2] Bowman[3] has utilized the benzyl esters of alkylated malonic acids to circumvent this difficulty elegantly. The acylmalonic esters formed from these compounds were cleaved to ketones by catalytic hydrogenolysis followed by thermal decarboxylation.

In the present note we wish to report the use of *t*-butyl esters of malonic acids for the preparation of ketones.[4] Di-*t*-butyl malonate, prepared in 60% yield by the acid-catalyzed reaction between malonic acid and isobutylene, was alkylated with benzyl chloride, cyclohexyl bromide and *n*-octyl bromide to give the corresponding di-*t*-butyl alkylmalonates. Conversion of these compounds to the sodio derivatives by treatment with sodium hydride in an inert solvent, followed by reaction of the sodio compound with an acid chloride, gave oily di-*t*-butyl acylalkylmalonates which were not purified, but treated directly with *p*-toluenesulfonic acid in refluxing toluene or anhydrous acetic acid to effect cleavage of the carbo-*t*-butoxy groups to give isobutylene, carbon dioxide and the ketone. The following ketones have been prepared in this manner: phenyl β-phenylethyl ketone (70–85% yield from benzoyl chloride), *p*-nitrophenyl β-phenylethyl ketone (81% from *p*-nitrobenzoyl chloride), *o*-nitrophenyl β-phenylethyl ketone (71%

(1) Allied Chemical and Dye Corp. Fellow, 1950; Sterling-Winthrop Research Institute Fellow, 1950–1951. The Upjohn Co., Kalamazoo, Mich.

(2) See R. E. Bowman, *J. Chem. Soc.*, 322 (1950), for discussion and leading references. An exception is the case where R' = H; *i.e.*, the use of unsubstituted malonic esters gives good yields of methyl ketones. H. G. Walker and C. R. Hauser, THIS JOURNAL, **68**, 1386 (1946).

(3) R. E. Bowman, *J. Chem. Soc.*, 325 (1950).

(4) *Cf.* the preparation of keto esters by the use of *t*-butyl ethyl malonates, D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

from *o*-nitrobenzoyl chloride), styryl β-phenylethyl ketone (79% from cinnamoyl chloride), *n*-heptyl *n*-nonyl ketone (65% from capryloyl chloride), phenyl cyclohexylmethyl ketone (56%, as the 2,4-dinitrophenylhydrazone, from benzoyl chloride), *o*-tolyl β-phenylethyl ketone (70% from *o*-toluyl chloride), and *o*-tolyl cyclohexylmethyl ketone (56% from *o*-toluyl chloride).

The present method offers an advantage over the Bowman method[3] in that it is possible to prepare ketones with easily reducible groups. The two nitro ketones described above, for example, could not be prepared by the Bowman method, because the nitro groups would not be expected to survive the hydrogenation step. The styryl ketone is another case in point.

In order to test the steric limitations of the reaction an attempt was made to prepare mesityl β-phenylethyl ketone by the acylation of di-*t*-butyl benzylmalonate with mesitoyl chloride. It was found necessary to allow the acylation to proceed for 20 hours to bring about appreciable reaction. The intermediary di-*t*-butyl benzylmesitoylmalonate was isolated in crystalline form in 26% yield and was cleaved to mesityl β-phenylethyl ketone in 84% yield. Thus although the introduction of one hindering group appears to exert relatively little effect as shown in the preparation of *o*-tolyl β-phenylethyl ketone, a second hindering group results in a marked decrease in the rate and yield of the acylation step.

Experimental[5]

Di-*t*-butyl Malonate.—The following procedure is essentially that developed in these laboratories by McCloskey.[6] A mixture of 50.0 g. (0.48 mole) of malonic acid, 120 ml. (about 1.5 moles) of liquid isobutylene, 100 ml. of ether and 5 ml. of concentrated sulfuric acid was shaken in a pressure bottle until all of the malonic acid had dissolved (about 6 hours). The bottle was cooled to −10°, opened, and the contents were washed with a solution of 70 g. of sodium hydroxide in a mixture of 250 ml. of water and 250 g. of ice. The organic layer was separated, dried over anhydrous potassium carbonate, and distilled in equipment which had been previously washed with alkali. After removal of the ether, 62.0 g. (60%) of di-*t*-butyl malonate was collected at 112–115° (31 mm.), $n^{25}D$ 1.4172 (reported[7] b.p. 93° (10 mm.), $n^{20}D$ 1.4184).

Di-*t*-butyl Alkylmalonates.—Di-*t*-butyl benzylmalonate was prepared by adding a solution of 6.96 g. (0.055 mole) of benzyl chloride in 25 ml. of dry *t*-butyl alcohol to a solution of di-*t*-butyl sodiomalonate, prepared from 35.57 g. (0.165 mole) of di-*t*-butyl malonate and 2.54 g. (0.11 mole) of sodium hydride in 75 ml. of *t*-butyl alcohol, in a 200-ml. three-necked flask equipped with a glass stirrer, a dropping funnel, and a reflux condenser capped with an Ascarite drying tube. After stirring for 1.5 hours at about 65° the mixture was cooled and diluted with 350 ml. of water. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined extracts and organic layer were dried over anhydrous potassium carbonate. After removal of the ether and *t*-butyl alcohol by distillation at atmospheric pressure, a trace of magnesium oxide was added (to inhibit decomposition of the alkylmalonic ester) and the liquid was distilled in alkali-washed equipment. The first fraction consisted of 15.45 g. of di-*t*-butyl malonate, b.p. 50–58° (0.5 mm.), $n^{25}D$ 1.4171. After an intermediate fraction (3.45 g.) the **di-*t*-butyl benzylmalonate** distilled at 105–120° (0.5 mm.); yield 13.41 g. (80% based on benzyl chloride), $n^{25}D$ 1.4678. Redistillation afforded material, b.p. 115–117° (0.9 mm.), $n^{25}D$ 1.4682.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.56. Found: C, 70.54; H, 8.72.

Di-*t*-butyl cyclohexylmalonate was prepared similarly from 18.5 g. (0.113 mole) of cyclohexyl bromide, 49.1 g. (0.227 mole) of di-*t*-butyl malonate and 5 g. of sodium hydride. An alkylation time of 63 hours at 90° gave 25.7 g. (76.5% yield based on cyclohexyl bromide) of di-*t*-butyl cyclohexylmalonate, b.p. 100–102° (0.1 mm.), $n^{25}D$ 1.4422. Shorter alkylation times gave much lower yields.

Anal. Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.51; H, 10.19.

The preparation of di-*t*-butyl ***n*-octylmalonate** in the same way from 9.7 g. (0.05 mole) of *n*-octyl bromide, 21.6 g. (0.1 mole) of di-*t*-butyl malonate, and 1.8 g. (0.075 mole) of sodium hydride (alkylation time 48 hours) gave 11.7 g. (71% yield based on octyl bromide) of redistilled diester, b.p. 113–115° (0.5 mm.), $n^{25}D$ 1.4284.

Anal. Calcd. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.43; H, 11.22.

Preparation of Ketones.—The following description of the preparation of phenyl β-phenylethyl ketone serves as an example of the general method. The other ketones were prepared similarly, except that in the preparations of styryl β-phenylethyl ketone and *n*-heptyl *n*-nonyl ketone the acylations were allowed to proceed for 2 minutes rather than one hour. In these cases the longer acylation time led to intractable oily products.

To a solution of 1.22 g. (0.004 mole) of di-*t*-butyl benzylmalonate in 25 ml. of dry benzene in a 200-ml. three-necked flask equipped with a glass stirrer (rubber slip-seal) and a reflux condenser capped with an Ascarite drying-tube was added 0.15 g. (0.006 mole) of sodium hydride. The mixture was stirred gently and heated at about 80° until gas evolution stopped (about 2.5 hours), and a solution of 0.56 g. (0.004 mole) of benzoyl chloride in 10 ml. of benzene was added. Heating and stirring were continued for one hour, the mixture was cooled to room temperature, and the excess sodium hydride was destroyed by the addition of 0.35 g. (0.002 mole) of anhydrous *p*-toluenesulfonic acid.[8] The salts were removed by filtration and washed with a little benzene. Evaporation of the benzene solution left a clear yellow oil which was refluxed for one hour with 0.1 g. of anhydrous *p*-toluenesulfonic acid in 25 ml. of glacial acetic acid containing about 2% acetic anhydride by volume. The reaction was followed by means of a constant-pressure eudiometer, and was found to be complete after 45 minutes, 83.5% of the theoretical amount of gas being evolved. The pale-brown solution was poured over crushed ice, neutralized by the addition of 5% sodium hydroxide solution, and the white crystalline precipitate of phenyl β-phenylethyl ketone was recovered by filtration. After drying, it weighed 0.67 g. (80% yield), m.p. 68.3–70.3°. On recrystallization from ethanol the m.p. was raised to 70–72° and was undepressed on admixture with authentic phenyl β-phenylethyl ketone. The semicarbazone melted at 144–144.8° (reported m.p. 143°,[9] 144°[10]). The **2,4-dinitrophenylhydrazone** crystallized from benzene–ethanol in clusters of stocky orange needles, m.p. 186.6–187.2° (reported,[11] 166°).

Anal. Calcd. for $C_{21}H_{18}O_4N_4$: C, 64.61; H, 4.65. Found: C, 64.65; H, 4.64.

Treatment of the sodio derivative from 1.20 g. of di-*t*-butyl benzylmalonate and 0.15 g. of sodium hydride with 0.75 g. (0.004 mole) of *p*-nitrobenzoyl chloride followed by decomposition as described above gave 0.83 g. (81% yield) of ***p*-nitrophenyl β-phenylethyl ketone**, m.p. 69–73°. Recrystallization from ethanol gave colorless plates, m.p. 74.5–75°.

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58, H, 5.13. Found: C, 70.58; H, 4.98.

The 2,4-dinitrophenylhydrazone crystallized from benzene in the form of orange micro crystals, m.p. 235.9–236.7°.

(5) All melting points are corrected.

(6) A. L. McCloskey, Ph.D. Dissertation, University of Wisconsin, 1951.

(7) H. J. Backer and J. D. H. Homan, *Rec. trav. chim.*, **58**, 1048 (1939).

(8) K. H. Slotta and W. Franke, *Ber.*, **63**, 678 (1930).

(9) S. Jacobson and B. Ghosh, *J. Chem. Soc.*, 959 (1915).

(10) T. S. Stevens, *et al.*, *ibid.*, 3193 (1928); C. W. Shoppee, *ibid.*, 2567 (1928).

(11) J. F. J. Dippy and R. H. Lewis, *Rec. trav. chim.*, **56**, 1000 (1937).

Anal. Calcd. for $C_{21}H_{17}O_6N_5$: C, 57.93; H, 3.94. Found: C, 57.93; H, 3.75.

Treatment of the sodio derivative from 2.44 g. of di-*t*-butyl benzylmalonate and 0.29 g. of sodium hydride with 1.50 g. (0.008 mole) of *o*-nitrobenzoyl chloride as described above gave 1.44 g. (71% yield) of crude *o*-nitrophenyl β-phenylethyl ketone. Purification of the oil was effected by distillation (b.p. 163.5–166° (0.5 mm.) with some decomposition) followed by chromatography on alumina. The ketone was eluted by benzene and was then evaporatively distilled at 85–95° (0.02–0.04 mm.); $n^{25}D$ 1.5833.

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13. Found: C, 70.03; H, 4.90.

Treatment of the sodio derivative from 1.22 g. of di-*t*-butyl benzylmalonate and 0.15 g. of sodium hydride with 0.67 g. (0.004 mole) of cinnamoyl chloride as described above gave 0.75 g. (79% yield) of **styryl β-phenylethyl ketone**, m.p. 49–52°. Recrystallization from petroleum ether (b.p. 90–100°) raised the m.p. to 52.5–53.8° (reported 53°,[12] 53–54°[13]).

Treatment of the sodio derivative from 1.32 g. of di-*t*-butyl *n*-octylmalonate and 0.15 g. of sodium hydride with 0.65 g. (0.004 mole) of capryloyl chloride as described above gave after crystallization from methanol 0.59 g. of ***n*-heptyl *n*-nonyl ketone**, m.p. 40.8–41.6° (reported,[8] 42°). A second crop amounting to 0.07 g., m.p. 37–39.5°, was obtained, raising the yield to 65%. The hydantoin, 5-heptyl-5-nonylhydantoin, prepared from the ketone by the procedure of Henze and Speer,[14] crystallized from methanol in clusters of white needles, m.p. 116.5–117.2° (reported,[8] 123°).

Anal. Calcd. for $C_{19}H_{36}O_2N_2$: N, 8.64. Found: N, 8.41.

Treatment of the sodio derivative from 1.20 g. of di-*t*-butyl cyclohexylmalonate and 0.15 g. of sodium hydride with 0.56 g. (0.004 mole) of benzoyl chloride as described above afforded an oil which was converted to the **2,4-dinitrophenylhydrazone of phenyl cyclohexylmethyl ketone**. The crude derivative, m.p. 145–150°, was obtained in 56% yield. Recrystallization from benzene–petroleum ether raised the m.p. to 148.3–148.6°.

Anal. Calcd. for $C_{20}H_{22}O_4N_4$: N, 14.65. Found: N, 15.00.

Treatment of the sodio derivative from 2.44 g. of di-*t*-butyl benzylmalonate and 0.29 g. of sodium hydride with 1.24 g. (0.008 mole) of *o*-toluyl chloride as described above gave ***o*-tolyl β-phenylethyl ketone**[15] in 70% yield. The product was purified by evaporative distillation at 125–130° (0.05 mm.), $n^{25}D$ 1.5720.

Anal. Calcd. for $C_{18}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.26; H, 7.36.

Treatment of the sodio derivative from 14.95 g. of di-*t*-butyl cyclohexylmalonate and 1.6 g. of sodium hydride with 7.75 g. (0.05 mole) of *o*-toluyl chloride as described above afforded 6.02 g. (56% yield) of ***o*-tolyl cyclohexylmethyl ketone**, b.p. 126–130° (0.5 mm.), $n^{25}D$ 1.5278. An analytical sample was obtained by redistillation; b.p. 109.5–110° (0.04 mm.), $n^{25}D$ 1.5290.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.16; H, 9.06.

An attempt to prepare the 2,4-dinitrophenylhydrazone of this ketone was unsuccessful.

Di-*t*-butyl Benzylmesitoylmalonate.—The sodio derivative from 4.88 g. (0.016 mole) of di-*t*-butyl benzylmalonate and 0.6 g. (0.025 mole) of sodium hydride, was heated at 80° in 150 ml. of benzene with 2.92 g. (0.016 mole) of freshly distilled mesitoyl chloride for 20 hours. The gelatinous precipitate was removed by filtration and evaporation of the filtrate under reduced pressure gave a brown oil which was dissolved in petroleum ether (b.p. 90–100°) and chromatographed on activated alumina. Development with petroleum ether eluted a small amount (1.33 g.) of a yellow oil. Further development with a 10% solution of chloroform in petroleum ether yielded from the least strongly adsorbed fraction, after extrusion of the column and elution with chloroform, a crystalline product contaminated with traces of oil. The oil was washed from the crystals with a small amount of cold petroleum ether (b.p. 40–60°) to yield 1.86 g. (26%) of almost pure di-*t*-butyl benzylmesitoylmalonate, m.p. 104.5–107.5°. Three recrystallizations from petroleum ether (b.p. 90–100°) gave glistening white crystals, m.p. 106.8–107.6°.

Anal. Calcd. for $C_{28}H_{36}O_5$: C, 74.31; H, 8.02. Found: C, 74.39; H, 7.98.

Mesityl β-Phenylethyl Ketone.—A solution of 4.60 g. (0.01 mole) of di-*t*-butyl benzylmesitoylmalonate in 35 ml. of propionic acid containing a trace of anhydrous *p*-toluenesulfonic acid was refluxed for about ten hours, and 95% of the calculated amount of gas was evolved. The reaction mixture was worked up as described above to yield 2.13 g. (84% yield) of mesityl β-phenylethyl ketone, b.p. 140–141° (0.05 mm.), $n^{25}D$ 1.5547 (reported[16] b.p. 167–169° (1.5 mm.), $n^{25}D$ 1.5520.)

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.98. Found: C, 85.42; H, 7.99.

(12) C. Harries, *Ann.*, **330**, 185 (1904).
(13) C. Paal, *Ber.*, **45**, 2221 (1912).
(14) H. R. Henze and R. J. Speer, THIS JOURNAL, **64**, 522 (1942).
(15) *Cf.* Mailhe, *Bull. Soc. Chim.*, [4] **15**, 324 (1914).
(16) J. M. Sprague and H. Adkins, THIS JOURNAL, **56**, 2669 (1934).

LABORATORY OF ORGANIC CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN
RECEIVED OCTOBER 1, 1951

On the Infrared Spectrometry of N^{15}-Labeled Phthalyl Glycine Ethyl Ester

BY FELIX FRIEDBERG AND LAWRENCE M. MARSHALL

The analysis of deuterium-containing compounds by means of infrared spectrometry has been described recently.[1,2] In the course of a study on the spectra–structure correlation in simple peptides, we observed, that phthalyl glycine ethyl ester labeled with N^{15} exhibited a characteristic shift of its spectrum to the right in the region, from 1430 to 1350 cm.$^{-1}$ if compared to the N^{14} control (see graph).

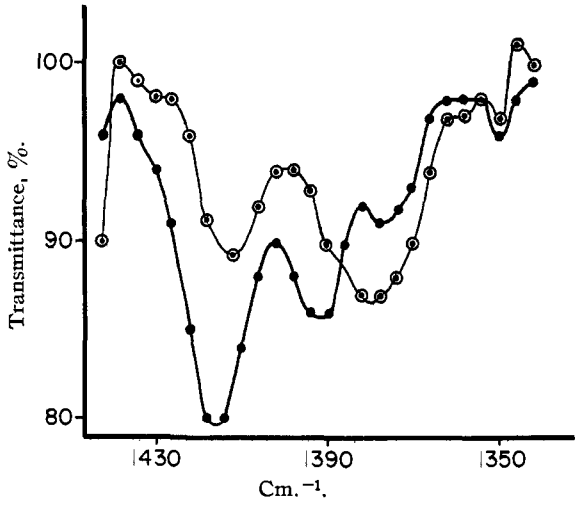


Fig. 1.—Absorption for 5 mg. of phthalyl glycine ethyl ester dissolved in 1 ml. of CCl_4, examined at one-half maximum gain: ●, N^{14} containing compound; ⊙, N^{15} containing compound.

Hence, especially in physiological investigations, infrared spectrometry may be of value in the detection and identification of compounds labeled with N^{15}.

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF MEDICINE
HOWARD UNIVERSITY
WASHINGTON, D. C.
RECEIVED OCTOBER 11, 1951

(1) C. M. Herget and J. D. Hardy, *Proc. Amer. Phys. Soc.* (Washington Meeting), 1938.
(2) F. Halverson, *Rev. Mod. Phys.*, **19**, 87 (1947).

β-Isopropylmercapto-L-alanine and Derivatives

BY OSCAR GAWRON AND JOHN A. LIEB[1]

β-Isopropylmercapto-L-alanine, its methyl ester hydrochloride and its N-tosyl and N-cinnamoyl derivatives have been synthesized by the following procedures.

β-Isopropylmercapto-L-alanine.[2]—To 20 g. (0.0833 mole) of cystine in 600 ml. of liquid ammonia in a 3-necked flask bearing a Dry Ice–acetone condenser and cooled in a Dry Ice–acetone-bath, 8.1 g. (0.35 gram-atom) of sodium was added slowly and with vigorous stirring. After completion of the reduction,[3] 20.9 g. (0.17 mole) of isopropyl bromide (the chloride does not react) was added in one portion. Stirring and cooling were then continued for 2 hours, after which time the cooling bath and condenser were removed and the ammonia allowed to evaporate (approx. 3 hours) with the stirrer in operation. Residual ammonia was removed by evacuation (water-pump) at 50°. The white residue was taken up in 150 ml. of water and extracted with 50 ml. of ether. Acidification of the aqueous solution with dilute hydrochloric acid to a *p*H of 4.5, followed by filtration, washing with cold water, and drying in a desiccator yielded 20 g. (72%) of crude product, m.p. 202–205°. The crude was recrystallized by dissolving in 300 ml. of boiling water, filtering, vacuum concentrating to one-half the volume and cooling in the refrigerator; yield, 8.5 g. of material melting at 223–224°.[4] Stoll and Seebeck[2] report 237–239°.

Anal. Calcd. for $C_6H_{13}O_2NS$: N, 8.6. Found: N, 8.5.

β-Isopropylmercapto-L-alanine Methyl Ester Hydrochloride.—The crude residue (after removal of the ammonia) from the isopropylation (above) of 24 g. (0.1 mole) of cystine was dissolved in 200 ml. of water. Concentrated hydrochloric acid was then added to excess, the precipitated β-isopropylmercapto-L-alanine redissolving. The acid solution was then concentrated *in vacuo* and the residue was dried *in vacuo* at 70°. The dry residue was then extracted with two 150-ml. portions of hot methanol and the combined methanol extracts after saturation with dry hydrogen chloride were allowed to stand overnight at room temperature. The methanol was then removed *in vacuo*, 300 ml. of fresh methanol added and the esterification procedure was repeated. After standing overnight the product was filtered off, washed with cold methanol and dried *in vacuo;* yield 20 g. (50%), m.p. 144–145°.

Anal. Calcd. for $C_7H_{16}O_2NSCl$: Cl, 16.6. Found: Cl, 16.4.

β-Isopropylmercapto-N-(*p*-tosyl)-L-alanine.—Essentially the procedure of Woolley[5] for the tosylation of amino acids was employed. To 3.3 g. (0.02 mole) of β-isopropylmercapto-L-alanine dissolved in 20 ml. of 2 *N* sodium hydroxide, 4.0 g. (0.021 mole) of *p*-toluenesulfonyl chloride was added in one portion. The mixture was shaken vigorously, and intermittently heated in a water-bath at 70° for 20 minutes. At the end of this period the reaction mixture was cooled under the tap, extracted once with 15 ml. of ether, filtered and the filtrate made acid to congo red with concentrated hydrochloric acid. The crude product after filtration, washing with water and drying in a desiccator weighed 3.0 g. (47%) and melted at 84–86°. After three recrystallizations from alcohol–water, 0.8 g. of analytically pure material, m.p. 116.5–117°, was obtained.

Anal. Calcd. for $C_{13}H_{19}O_9NS_2$: S, 20.3. Found: S, 20.3.

β-Isopropylmercapto-N-cinnamoyl-L-alanine.—To 3.6 g. (0.022 mole) of β-isopropylmercapto-L-alanine in 44 ml. of 1 *N* sodium hydroxide, 3.7 g. (0.023 mole) of cinnamoyl chloride was added in one portion. The reaction mixture was then vigorously shaken for 10 minutes, at the end of which time the exothermic reaction was complete. Following filtration and acidification of the filtrate, 5.1 g. (80%) of crude, air-dried product, m.p. 142–148°, was obtained. Recrystallization from alcohol–water gave pure material, m.p. 159–160°.

Anal. Calcd. for $C_{15}H_{19}O_3NS$: N, 4.8. Found: N, 4.7.

DEPARTMENT OF CHEMISTRY
DUQUESNE UNIVERSITY
PITTSBURGH, PENNSYLVANIA

RECEIVED SEPTEMBER 26, 1951

(1) Abstracted in part from a thesis submitted by J. A. Lieb in partial fulfillment of the requirements for the Master's degree.

(2) During the course of this work A. Stoll and E. Seebeck (*Helv. Chim. Acta*, **32**, 866 (1949)) synthesized this compound in unreported yield by treating cysteine with isopropyl bromide in aqueous alcohol containing sodium hydroxide.

(3) V. du Vigneaud, L. F. Audrieth and H. S. Loring, THIS JOURNAL, **52**, 4500 (1930).

(4) Capillary melting points are uncorrected.

(5) D. W. Woolley, *J. Biol. Chem.*, **172**, 71 (1948).

The Reaction of Brom Phenol Blue with Amino Acids and Peptides[1]

BY IRVING I. GESCHWIND AND CHOH HAO LI

Brom phenol blue affords a sensitive indication of the presence of proteins in paper electrophoresis.[2,3] The paper is dipped in a 0.1–1% solution of the dye in ethanol saturated with $HgCl_2$. Rinsing of the strip in water, with or without prior fixation, allows the removal of excess dye, leaving the protein-containing areas a green-blue color.

In the course of experiments designed to demonstrate the mutual presence of peptides and proteins on paper chromatograms, it was discovered that certain natural and synthetic peptides and amino acids gave false positive tests for the presence of proteins under these conditions. A systematic study was then instituted, which revealed the findings reported below.

Among the naturally occurring amino acids (cysteine alone was not employed in this study) only histidine gave a definite positive reaction which could be accented by quickly passing the paper strip through ammonia vapor, in which case a deep blue color was obtained. Methionine gave a slightly positive reaction, and tryptophan a weak one. Histamine gave a reaction similar to that of histidine. Of all the peptides (28 were used, in all) only glutathione (GSH) and leucyl-histidine gave positive reactions. The former was the only cysteine-containing peptide, and the latter the only histidine peptide, used in this study. Glutathione gave a red-brown color with the dye, whereas the histidine peptide gave a green color.

In another series of experiments it was found that, if the chromatograms were treated very quickly with NH_3 vapor prior to the application of the dye, after the final washing with water, arginine, histidine, lysine and histamine showed up as royal blue spots on a light blue background. None of the other amino acids, with the exception of aspartic and glutamic acids, could be detected. These latter two could be detected by bright white areas left on the blue background.

The basic reaction of the amino acids and peptides would seem to depend upon the insolubility in the final rinsing process of the mercury complexes formed. Thus, after treatment with the dye, rinsing, and drying, spraying the paper with ninhydrin revealed none of the other amino acids originally present. That combination with the dye *per se*, was not involved, was shown by experiments in

(1) This work was supported in part by a grant from the Rockefeller Foundation.

(2) E. L. Durrum, THIS JOURNAL, **72**, 2943 (1950).

(3) H. D. Cremer and A. Tiselius, *Biochem. Z.*, **320**, 273 (1950).

which only histidine could be demonstrated by the dye, or by the ninhydrin, after the paper had been dipped in alcohol saturated with $HgCl_2$ (containing no dye), washed and dried. Nor is solubility in the alcohol involved, since almost all the amino acids are visible early in the rinsing process, only to be washed out eventually by the water.

In order to visualize all the amino acids along with histidine, it has been found practical to first spray the papers with ninhydrin, and, after development of the color, to apply the dye. In this way, all the amino acids and peptides may still be located. After this dual treatment, histidine and leucyl-histidine gave dark-brown areas which were changed to blue by NH_3 vapor, whereas histamine was green. All the other acids were salmon or pink in color.

The sensitivity of the dye reaction is less than that of the ninhydrin reaction with histidine. However, a combination of these two reactions offers a specific, sensitive test for histidine and its peptides.

The reaction with brom phenol blue has been used in conjunction with paper chromatographic and electrophoretic runs. The dye reaction with paper chromatograms obtained with partial hydrolysates of proteins is more revealing than that obtained with ninhydrin. Thus, some areas of peptide-containing material gave a blue color even though the ninhydrin reaction was negative.

Experimental

Brom phenol blue was made up as a 0.1% solution in 95% ethanol saturated with mercuric chloride. Ninhydrin was employed as a 0.1% solution in 95% ethanol. The latter solution was used as a spray, while the former was used as a spray (caution!) or as a dip. Color development with ninhydrin was carried out in a 70° oven.

Whatman No. 1 paper was used exclusively in these experiments. Later experiments have shown that Whatman No. 52 is preferable, for its greater tenacity is advantageous during the rinsing process. The amino acids and glutathione were obtained from commercial sources. The following peptides were used.[4,5] G–A, G–L, G–ϕ, G–Tyr, G–S, G–Asp, GSH, G–G–G, G–L–G, G–L–L, A–G, A–A, A–S, L–G, L–H, L–Sarc, L–L, L–Glut, L–Asp, L–G–L, S–A, S–S, S–G, S–A–Glut, S–G–L, S–G–Glut, Prol–ϕ, and V–G.

The paper chromatograms of amino acids and peptides were developed according to a standard procedure[6] in the following solvents: collidine–lutidine–H_2O (1:1:2), phenol–H_2O, and butanol–acetic acid–H_2O (4:1:5). The peptides were developed additionally in 2 N NH_3–lutidine (1:1). Phenol–H_2O together with one of the other solvent systems was used for two-dimensional chromatography. With the basic solvents employed, it was necessary first to remove the solvent before attempting to stain with the dye. This was accomplished by one of two procedures. In the first, the paper was placed in a long cylinder into which ether had been poured, and the solvents were removed from the paper by repeated extraction with fresh ether. The second procedure involved placing the paper in a drying oven, through which a stream of warm air was continually blown. After 1 to 2 days, the paper was removed and placed in a vacuum desiccator over H_2SO_4. Usually, these procedures were sufficient to remove most of the basic volatile solvents, which otherwise gave the paper a dark blue background with the dye. When neither of these procedures was completely effective, it was found useful to repeat as often as needed, after the addition of the dye, the process of passing the paper through HCl fumes and the subsequent rinsing in water.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA RECEIVED SEPTEMBER 4, 1951

(4) We are indebted to Prof. H. O. L. Fischer for the gift of peptides from the Emil Fischer collection, and to Dr. J. I. Harris for the serine peptides.

(5) G, glycine; A, alanine; L, leucine; ϕ, phenylalanine; Tyr, tyrosine; S, serine; Asp, aspartic acid; H, histidine; Sarc, sarcosine; Glut, glutamic acid; Prol, proline; and V, valine; GSH is glutathione.

(6) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

Calculated Values for the Solubility Product Constants of the Metallic Sulfides

BY J. REX GOATES, MARVIN B. GORDON AND NEAL D. FAUX

Recent determinations of the second ionization constant of H_2S[1,2] (K_{2H_2S}) show that the standard free energy of formation of the sulfide ion ($\Delta F_f^\circ{}_{S^-}$) is considerably lower than it was previously thought to be. When the value of K_{2H_2S} given by Konopik and Leberl[2] (7.9×10^{-14} at 20°) is corrected to 25° by means of heat content data from reference 3, one obtains $K_{2H_2S} = 1.2 \times 10^{-13}$. Use of this value for K_{2H_2S} and 3.01 kcal.[3] for $\Delta F_f^\circ{}_{HS^-}$ gives $\Delta F_f^\circ{}_{S^-} = 20.64$ kcal. at 25°. This figure is 2.7 kcal. lower than the value calculated from Knox's[4] work, which has been used in previous calculations of solubility product constants of the metallic sulfides, and hence makes necessary a recalculation of these constants. The correction in the $\Delta F_f^\circ{}_{S^-}$ together with smaller changes made in the last few years in the free energy data of the metallic sulfides and metallic ions produce changes of approximately two orders of magnitude in the values of the solubility product constants. The K_{sp} values given in the table below have been calculated from free energy data by means of the relationship $\Delta F^\circ = -RT \ln K_{sp}$, in which ΔF° is the value of the standard free energy change of the reaction $M_2S_{(S)} \rightleftarrows 2M^+_{(aq)} + S^{=}_{(aq)}$ or the corresponding equation when the metallic ions are di- or trivalent. The data in Table I are for the crystalline forms that are stable at 25°.

Three values for the solubility product constant of Bi_2S_3 may be found in the literature: 1×10^{-91}, 1.6×10^{-72} and 7.1×10^{-61}. The first value is found in the tables of Bruner and Zawadski[5] and was calculated from electrochemical data taken by I. Bernfeld[6] on the cell Bi, $Bi_2S_3 | S^{--} ||$ calomel reference electrode, the Bi, $Bi_2S_3 | S^{--}$ half-cell reaction for which was assumed to be $2Bi + 3S^{--} \rightleftarrows Bi_2S_3 + 6e$. In 1931, Kolthoff[7] recalculated Bernfeld's data to get the value of 1.6×10^{-72}(?), which has been very widely quoted (minus his question mark) in both texts and source books.

Inasmuch as Bernfeld's work was old (1898), we repeated his experiments and obtained consistent reproducible voltages near those reported by him. The value of the solubility product constant calculated from these data is near 10^{-72}, but the value of the $\Delta F_f^\circ{}_{Bi_2S_3}$ that corresponds to the e.m.f. data is the unreasonable value of 1 kcal., indicating that the reaction taking place in the cell is not the one postulated by the earlier investigators. Hence,

(1) H. Kubli, *Helv. Chim. Acta*, **29**, 1962 (1946).

(2) N. Konopik and O. Leberl, *Monatsh.*, **80**, 781 (1949).

(3) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine and I. Jaffe, *Natl. Bur. Standards Circ.*, 500 (1950).

(4) Knox, *Trans. Faraday Soc.*, **4**, 29 (1908).

(5) L. Bruner and J. Zawadski, *Anorg. Chem.*, [2] **67**, 454 (1910).

(6) I. Bernfeld, *Z. physik. Chem.*, **25**, 46 (1898).

(7) I. M. Kolthoff, *J. Phys. Chem.*, **35**, 2712 (1931).

TABLE I

SOLUBILITY PRODUCT CONSTANTS OF 16 METALLIC SULFIDES AT 25° AND THE DATA[a] USED IN THEIR CALCULATIONS

Compound	$\Delta F_f°$, kcal. Metallic sulfide	Metallic ion	K_{sp}
PbS	−22.15	− 5.81	8×10^{-28}
Tl_2S	−21.0[b]	− 7.755	7×10^{-20}
ZnS	−47.4	−35.184	8×10^{-25}
CdS	−33.6	−18.58	7×10^{-27}
HgS	−10.22[c]	39.38	3×10^{-52}
Cu_2S	−20.6	12.0	1×10^{-48}
CuS	−11.7	15.53	8×10^{-36}
Ag_2S	− 9.56[d]	18.430	7×10^{-50}
NiS	−18.8[b]	−11.1	2×10^{-21}
CoS	−21.8[b]	−12.3	8×10^{-23}
Co_2S_3	−47.6[b]	29.6	10^{-124}
FeS	−23.32	−20.30	5×10^{-18}
MnS	−47.6[b]	−53.4	1×10^{-11}
Ce_2S_3	−293.0[b]	−170.5	6×10^{-11}
La_2S_3	−301.2[b]	−172.9	2×10^{-13}
Bi_2S_3	−39.4	15	10^{-96}

[a] Except where otherwise noted the free energy data are from F. D. Rossini, *et al.*, *Natl. Bur. Stds. Circ.*, 500 (1950). [b] Calculated from heat content data taken from reference "a" and estimates of entropy made by the method recently proposed by W. M. Latimer, THIS JOURNAL, **73**, 1480 (1951). [c] J. R. Goates, A. G. Cole and E. L. Gray, *ibid.*, **73**, 3596 (1951). [d] J. R. Goates, A. G. Cole , E. L. Gray and Neal D. Faux, *ibid.*, **73**, 707 (1951).

the values of 1×10^{-91} and 1.6×10^{-72}(?) should certainly be discarded.

The value of 7.1×10^{-61} was reported by A. F. Kapustinsky and I. A. Makolkin[8] and was supposed to have been calculated from the $\Delta F_f°_{Bi_2S_3}$ given by Kelley (−39.14 kcal.).[9] It appears, however, that an error was made in these calculations, for the $\Delta F_f°_{Bi^{+++}}$ which corresponds to Kapustinsky and Makolkin's solubility product constant value is the unreasonable value of −9.5 kcal.

The value given in the table was calculated from the $\Delta F_f°_{Bi_2S_3}$ given by the Bureau of Standards[3] and a value for the $\Delta F_f°_{Bi^{+++}}$ that was calculated from data reported by Feitknecht.[10] There is some question as to the accuracy of this last value, but it appears reasonable, and since its effect on the solubility product constant is much less than that of the sulfide ion, the value of the solubility product constant given seems to be a reasonable approximation.

(8) A. F. Kapustinsky and I. A. Makolkin, *Acta Physiochim., U. R. S. S.*, **10**, 259 (1939).
(9) K. K. Kelley, *U. S. Bur. of Mines, Bul.* 406, 63 (1937).
(10) W. Feitknecht, *Helv. Chim. Acta*, **16**, 1307 (1933).

DEPARTMENT OF CHEMISTRY
BRIGHAM YOUNG UNIVERSITY
PROVO, UTAH
RECEIVED OCTOBER 22, 1951

The Chlorination of Diisopropyl Ether at Low Temperatures[1,2]

BY GEORGE E. HALL AND ICLÂL SIREL

The chlorination of diethyl ether at −20° or lower yields α,α'-dichlorodiethyl ether rather than the α,β-dichlorodiethyl ether obtained at higher temperatures.[3] The present investigation was made to determine whether this low temperature orientation to the α-position is also found with diisopropyl ether. Chlorination of diisopropyl ether under the conditions used with diethyl ether gave no more than traces of α-chlorinated ethers, as determined by hydrolysis of the products and Volhard chloride determinations. The chlorination mixture distilled over a wide range and fractional distillation, both at atmospheric and reduced pressures, failed to give sharp fractions. 1,3-Dichloropropanone was the only substance isolated. This product indicates a cleavage during chlorination not found with diethyl ether.

Henry's method,[4] using isopropyl alcohol and acetone, failed to give α-chlorodiisopropyl ether, desired for comparison with the chlorination products.

Experimental

Chlorination of Diisopropyl Ether.—Seventy-two grams (0.710 mole) of purified[5] anhydrous diisopropyl ether were placed in a Pyrex flask fitted with a thermometer, mechanical stirrer and gas inlet tube and protected from moisture. The flask was immersed in a Dry Ice–acetone-bath and irradiated with a 275-watt reflector sun lamp at a distance of 30 cm. Dry chlorine was slowly passed into the ether at −20 to −25° until 53.0 g. (0.746 mole) had been absorbed, requiring 8.5 hours. Gases escaped as the reaction mixture warmed to room temperature, leaving a net gain of 30.8 g. Distillation and redistillation under reduced pressure gave 12.0 g. of material boiling at 83–88° (33 mm.) which solidified in the ice-box. Repeated crystallization from chloroform gave colorless needles with the following properties: m.p. 42.0–43.0° (cor.); b.p. 172–172.5°; n_D^{25} 1.4773; volatile at room temperature; lachrymatory; soluble water, alcohol, ether; reduces Fehling solution. These properties are in agreement with those reported for 1,3-dichloropropanone.[6]

Anal. Calcd. for $C_3H_4Cl_2O$: C, 28.35; H, 3.18; Cl, 55.91; mol. wt., 127.0. Found: C, 28.56; H, 3.18; Cl, 55.40; mol. wt.,[7] 128.4.

(3) G. E. Hall and F. M. Ubertini, *J. Org. Chem.*, **15**, 715 (1950).
(4) L. Henry, *Bull. acad. roy. Belg.*, [3] **25**, 439 (1893); *Ber.*, **26**, Referate, 933 (1893).
(5) A. I. Vogel, *J. Chem. Soc.*, 618 (1948).
(6) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 91.
(7) Cryoscopic method, *dl*-camphor solvent.

MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MASS.
RECEIVED SEPTEMBER 19, 1951

The Preparation and Spectrophotometric Estimation of 2-Amino-7-hydroxyfluorene[1]

BY HELMUT R. GUTMANN

The preparation and properties of 2-amino-7-hydroxyfluorene are of considerable interest since this phenolamine is a likely intermediate in the metabolism of the carcinogen 2-aminofluorene.

The synthesis of this compound from 2-amino-7-nitrofluorene was first reported by Bielschowsky.[2] 2-Amino-7-hydroxyfluorene melting at 271° was obtained in unrecorded yield. Goulden and Kon[3] prepared 2-amino-7-hydroxyfluorene starting with 2-aminofluorenone.

(1) This investigation was supported by Research Grant C-1066 from the National Cancer Institute of National Institutes of Health, Public Health Service.
(2) F. Bielschowsky, *Biochem. J.*, **39**, 287 (1945).
(3) F. Goulden and G. Kon, *J. Chem. Soc.*, 930 (1945).

The present method simplifies the existing procedures by utilizing the readily available 2,7-diaminofluorene dihydrochloride as the starting material.[4] 2-Amino-7-hydroxyfluorene, m.p. 265–268°, was obtained in yields ranging from 24–37%.

The quantitative estimation of the compound in solution or in biological materials may be based on the measurement of the red dye which is formed when 2-amino-7-hydroxyfluorene is diazotized and coupled with sodium 2-naphthol-3,6-disulfonate (R-salt). The dye absorbs maximally at a wave length of 530 mμ (Fig. 1). The molar extinction coefficient at 530 mμ is 34,300. The spectrophotometric measurement of the dye under the conditions described in the experimental part permits the detection of as little as 5 micrograms of 2-amino-7-hydroxyfluorene. Beer's law is followed with quantities of 2-amino-7-hydroxyfluorene ranging from 5–80 micrograms. The great sensitivity of of the method makes it particularly suited for the estimation of the compound in metabolic studies.

Experimental

2-Acetylaminofluorene-7-diazonium Chloride.—Thirteen grams of 2,7-diaminofluorene dihydrochloride[4] (0.049 mole) was dissolved in 300 ml. of distilled water with slight warming and filtered. After the solution had attained room temperature 5.6 ml. of freshly distilled acetic anhydride (0.060 mole) was added dropwise with vigorous stirring. After the addition of the acetic anhydride had been completed, stirring was continued for one hour. The 2-amino-7-acetylaminofluorene hydrochloride which had precipitated was filtered with suction and washed with 400 ml. of distilled water. The washed product was dried in air for 12 hours and used without further purification in the next step of the synthesis. All of the material was mixed in small succeeding portions in a Waring blendor with 500 ml. of 0.18 *M* hydrochloric acid and the mixture transferred to a 1-l. beaker. To the rapidly stirred suspension there was added 1.95 g. of sodium nitrite (0.028 mole) in 30 ml. of distilled water. After the suspension had been stirred for 2 hours it was warmed to 60° and filtered with suction. The residue on the filter was washed with 145 ml. of distilled water. The filtrate was made 80% saturated with 200 g. of sodium chloride. After standing at 5° for 12 hours the fine, reddish-brown precipitate was filtered with suction and washed with cold 50% saturated sodium chloride solution. The use of hard filter paper (Whatman No. 52) facilitates the quantitative collection of the compound. The material was recrystallized by dissolving it in methanol (90 ml./g.) and adding sufficient ether (100 ml./g.) to cause incipient precipitation. After standing at 5° for 1 hour the precipitate was filtered with suction and dried over calcium chloride. Additional material was obtained from the mother liquor after standing at 5° for 12 hours. After it had been collected with suction the product was added to the material which had been obtained previously. The compound weighed 3 g. and melted at 143–145°. Ray and Peters[5] report a melting point of 146° for this compound.

2-Amino-7-hydroxyfluorene.—A solution of 1.7 g. of 2-acetylaminofluorene-7-diazonium chloride (0.0062 mole) in 150 ml. of distilled water was added dropwise to 300 ml. of boiling 3 *M* hydrochloric acid in the course of 1.5 hours. Nitrogen was passed through the solution during the hydrolysis. The hot solution was filtered and the filtrate cooled in an ice-bath. The solution was neutralized with concentrated ammonium hydroxide. The very fine gray precipitate was collected with suction on hard filter paper (Whatman No. 52) and dried *in vacuo* over calcium chloride. There was obtained 0.65 g. of material which melted at 258–263° (with decomposition). The compound was recrystallized from 30 ml. of refluxing absolute ethanol. After standing in the refrigerator for 12 hours the gray, crystalline powder was collected and washed with cold ethanol and ether; m.p. 265–268° (with decomposition).

(4) S. Schulman, *J. Org. Chem.*, **14**, 382 (1949).

(5) F. E. Ray and J. H. Peters, *Brit. J. of Cancer*, in press.

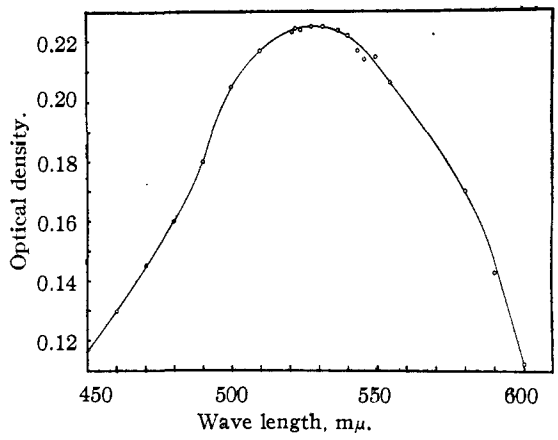


Fig. 1.

Anal. Calcd. for $C_{18}H_{11}ON$: N, 7.11. Found: N, 7.19.

The compound was soluble in acetone, amyl acetate and glacial acetic acid. It darkened quickly on standing in contact with air.

Measurement of the Absorption Spectrum of the Sodium Salt of 7-Hydroxyfluorenyl-2-azo-2′-naphthol-3′,6′-disulfonic Acid.—To 0.0678 mg. of 2-amino-7-hydroxyfluorene in 2 ml. of 4.5 *M* glacial acetic acid and 0.3 ml. of concentrated hydrochloric acid there was added 1 ml. of 0.029 *M* sodium nitrite. The mixture was shaken and, after 1 minute, it was added to 10 ml. of 0.031 *M* sodium 2-naphthol-3,6-disulfonate in 5 *M* aqueous ammonium hydroxide. The solution was cooled to room temperature, 5 ml. of acetone was added and the absorption spectrum of the red dye determined with a Beckman model DU spectrophotometer (Fig. 1).

Acknowledgment.—The author is indebted to Dr. F. E. Ray of the Cancer Research Laboratory for valuable discussion and criticism.

CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA RECEIVED SEPTEMBER 21, 1951

O-*p*-Toluenesulfonyl-L-tyrosine, Its N-Acetyl and N-Benzoyl Derivatives

BY ERNEST L. JACKSON

O-*p*-Toluenesulfonyl-L-tyrosine was reported by Fischer[1] as having m.p. 218° (cor., dec.) and $[\alpha]^{20}D$ −4.6° in *N* hydrochloric acid (*c* 6.5). Fischer expressed doubt of the optical purity of the compound, which he prepared by the reaction of hydriodic acid and phosphonium iodide with O,N-di-*p*-toluenesulfonyl-L-tyrosine.

Hydrolysis of the pure methyl ester of O-*p*-toluenesulfonyl-N-acetyl-L-tyrosine with a mixture of hydrochloric and acetic acids yields O-*p*-toluenesulfonyl-L-tyrosine showing m.p. 213–214° (uncor., dec.) and $[\alpha]^{20}D$ +9.0° in *N* hydrochloric acid (*c* 0.42) or +9.5° (*c* 3.16). The rapid separation of crystals from a 6.5% solution of the compound in *N* hydrochloric acid at 20° prevented the determination of the rotation at this concentration. The methyl ester of O-*p*-toluenesulfonyl-N-acetyl-L-tyrosine was prepared by the reaction of *p*-toluenesulfonyl chloride in alkaline acetone solution with the methyl ester of N-acetyl-L-tyrosine, which resulted from acetylation of the known methyl ester of L-tyrosine. Acetylation and benzoylation of O-*p*-toluenesulfonyl-L-tyrosine

(1) E. Fischer, *Ber.*, **48**, 100 (1915).

yielded, respectively, the crystalline N-acetyl and N-benzoyl derivatives.

Experimental

N-Acetyl-L-tyrosine Methyl Ester.—Fifteen grams of the methyl ester[2] of L-tyrosine was acetylated by Fischer's[3] method with mechanical stirring and the use of 7.6 g. of acetyl chloride, 800 cc. of absolute chloroform, 9 g. of anhydrous sodium carbonate and 60 cc. of water. At the end of the reaction the suspended solid was collected on a filter, washed with chloroform and extracted with 400 cc. of hot ethyl acetate in several portions. The ethyl acetate solution upon concentration deposited in two crops 16.6 g. or 91% of nearly pure product. The chloroform solution yielded a small amount of product. The compound was purified by recrystallization from ethyl acetate as colorless, rod-shaped prisms which, after being dried overnight in an evacuated desiccator over calcium chloride, were usually in a solvated state and melted at 118–120°. Sometimes the crystals were almost solvent-free and melted near 135°. Drying at 100° *in vacuo* yielded solvent-free crystals; m.p. 136–137° (uncor.); $[\alpha]^{20}D$ +29.7° in methanol (*c* 0.41).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.91. Found: C, 60.56; H, 6.38; N, 5.88.

O-*p*-Toluenesulfonyl-N-acetyl-L-tyrosine Methyl Ester.—A solution of 8.8 g. of methyl ester of N-acetyl-L-tyrosine and 7.4 g. of *p*-toluenesulfonyl chloride in 185 cc. of acetone, after being mixed with 37 cc. of *N* sodium hydroxide solution, was refluxed for one hour and then concentrated at 25° *in vacuo* to 50 cc. The sirupy product was separated from the aqueous solution, which was extracted thoroughly with chloroform. The sirup was combined with the chloroform extract; the solution was extracted with 10% sodium carbonate solution, washed with water and dried over sodium sulfate. After removal of the solvent *in vacuo*, the thick sirup was crystallized as colorless needles from ethyl acetate–petroleum ether (b.p. 30–75°); yield 10.4 g. or 72%; m.p. 90–91° (cor.); $[\alpha]^{20}D$ +15.5° in methanol (*c* 0.8). Samples for analysis and rotation were dried in an evacuated desiccator over calcium chloride.

Anal. Calcd. for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; S, 8.19. Found: C, 58.36; H, 5.38; N, 3.59; S, 8.11.

O-*p*-Toluenesulfonyl-L-tyrosine.—A solution of 5.7 g. of pure methyl ester of O-*p*-toluenesulfonyl-N-acetyl-L-tyrosine in a mixture of 100 cc. of glacial acetic acid and 100 cc. of 38% hydrochloric acid was refluxed for two hours. The solution was cooled, mixed with 850 cc. of water and neutralized to litmus paper with ammonium hydroxide. The precipitated crystals were collected on a filter and washed with water; air-dried; yield 4.7 g. Recrystallized from water as colorless needles and dried at 79° *in vacuo*, it melted at 213–214° (uncor., dec.); $[\alpha]^{20}D$ +9.0° in *N* hydrochloric acid (*c* 0.42) or +9.5° (*c*, 3.16).

Anal. Calcd. for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.02; H, 5.13; N, 4.14; S, 9.49.

O-*p*-Toluenesulfonyl-N-acetyl-L-tyrosine.—The acetylation of 2.3 g. of O-*p*-toluenesulfonyl-L-tyrosine was carried out according to Fischer,[3] using 0.7 g. of acetyl chloride, 100 cc. of absolute chloroform, 1.2 g. of anhydrous sodium carbonate and 8 cc. of water. The solvent was removed at 25–30° *in vacuo*. A filtered solution of the residual oil in 20 cc. of water was made slightly acid (litmus paper) by addition of hydrochloric acid which precipitated 0.8 g. of starting compound. The addition of more acid to the filtrate precipitated a sirup. The decanted aqueous layer was extracted with two 10-cc. portions of ethyl acetate which, after being combined with an ethyl acetate solution of the sirup, deposited at 25° 0.1 g. of starting compound. After removal of the solvent at 25° the sirup was stirred with 2% hydrochloric acid to yield 1.2 g. of crystals. The compound crystallized, slowly the first time, as rosettes of colorless short blades from its solution in ethyl acetate–petroleum ether; m.p. 134–135° (uncor.); $[\alpha]^{20}D$ +29.4° in methanol (*c* 0.83).

Anal. Calcd. for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. Found: C, 57.38; H, 5.00; N, 3.79; S, 8.31.

(2) E. Fischer and W. Schrauth, *Ann.*, **354**, 34 (1907).

(3) E. Fischer, *Ber.*, **37**, 2495 (1904).

O-*p*-Toluenesulfonyl-N-benzoyl-L-tyrosine.—O-*p*-Toluenesulfonyl-L-tyrosine (1.5 g.) was benzoylated by the method of Fischer,[4] using 1.9 g. of benzoyl chloride, 3 g. of sodium bicarbonate and 40 cc. of water. After the crystalline product had been extracted thoroughly with petroleum ether, it was recrystallized as colorless, hexagonal plates from acetone–petroleum ether; yield 0.9 g.; m.p. 194–195° (uncor.); $[\alpha]^{20}D$ −1.3° (*c* 2.61) in water containing 1.1 molecular equivalents of sodium hydroxide.

Anal. Calcd. for $C_{23}H_{21}NO_6S$: C, 62.85; H, 4.82; N, 3.19; S, 7.30. Found: C, 63.02; H, 5.10; N, 3.12; S, 7.39.

Acknowledgment.—Indebtedness is expressed to Dr. W. C. Alford, Mrs. Evelyn G. Peake and Miss Paula M. Parisius for microanalyses.

(4) E. Fischer, *ibid.*, **32**, 2454 (1899).

NATIONAL INSTITUTE OF ARTHRITIS & METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY
BETHESDA 14, MARYLAND RECEIVED SEPTEMBER 12, 1951

Some N-(β-Substituted Ethyl)-N,N-dibenzylamines

BY IRVING ALLAN KAYE AND HERMAN HORN

The importance of the dibenzylamino residue as a contributor to the activity of Dibenamine[1] [N-(2-chloroethyl)-dibenzylamine] hydrochloride, a compound commercially available as a potent and specific adrenergic blocking agent,[2] suggested the preparation of several N,N-dibenzyl-N′-aralkyl-N′-heterocyclic-ethylenediamines for pharmacological screening tests. The products, structurally related to several histamine antagonists on the market,[3] were prepared by alkylating an N-aralkyl-N-heterocyclicamine with 2-dibenzylaminoethyl chloride hydrochloride in the presence of lithium amide. The benzohydryl ether of 2-dibenzylaminoethanol (an analog of Benadryl[4]),

$$\text{R—NH—CH}_2\text{R}' + \text{LiNH}_2 + (\text{C}_6\text{H}_5\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{Cl}\cdot\text{HCl} \longrightarrow \text{R—N(CH}_2\text{R}')\text{—CH}_2\text{CH}_2\text{N(CH}_2\text{C}_6\text{H}_5)_2$$

R = 2-pyridyl, 2-pyrimidyl, 2-thiazolyl, or 2-lepidyl

R′ = phenyl, *p*-methoxyphenyl or *p*-chlorophenyl

also synthesized, was obtained by heating the benzohydryl ether of ethylene chlorohydrin with dibenzylamine.

$$(\text{C}_6\text{H}_5)_2\text{CHOCH}_2\text{CH}_2\text{Cl} + 2(\text{C}_6\text{H}_5\text{CH}_2)_2\text{NH} \longrightarrow (\text{C}_6\text{H}_5)_2\text{CHO—CH}_2\text{CH}_2\text{N(CH}_2\text{C}_6\text{H}_5)_2 + (\text{C}_6\text{H}_5\text{CH}_2)_2\text{NH}\cdot\text{HCl}$$

Three of the products, N,N-dibenzyl-N′-(benzyl and *p*-chlorobenzyl)-N′-(2-pyridyl)-ethylenediamines and N,N-dibenzyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine, tested against histamine using the isolated guinea pig ileum strip, showed less than 0.1% of the activity of Pyribenzamine.[5a,6] None of these compounds showed any evidence of

(1) Trademark of Smith, Kline and French Laboratories.

(2) W. S. Gump and E. J. Nikawitz, THIS JOURNAL, **72**, 1309 (1950); J. F. Kerwin, T. F. Herdegen, R. Y. Heisler and G. E. Ullyot, *ibid.*, **72**, 940 (1950).

(3) B. Idson, *Chem. Revs.*, **47**, 377 (1950).

(4) Trademark of Parke Davis & Co.

(5) The authors wish to thank (a) Dr. Harold Blumberg and Mr. Eric Meyer of Endo Products, Inc., and (b) Dr. C. Chester Stock of The Sloan-Kettering Institute for Cancer Research for this information.

(6) "Pyribenzamine" is the trademark of Ciba Pharmaceutical Products, Inc., for N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine.

TABLE I

N,N-DIBENZYL-N'-ARALKYL-N'-SUBSTITUTED ETHYLENEDIAMINES $RN(CH_2R')CH_2CH_2N(CH_2C_6H_5)_2$

R[a]	R	B.p., °C.	B.p., Mm.	Yield, %	$n^{25}D$	Nitrogen, % Formula	Calcd.	Found
C_5H_4N	C_6H_5	200–204	0.05	95	1.6082	$C_{28}H_{29}N_3$	10.33	10.47
C_5H_4N	$C_6H_5(OCH_3)(4)$[b]	234–236	.10	76	1.6059	$C_{29}H_{31}N_3O$	9.60	9.55
C_5H_4N	$C_6H_4Cl(4)$[c]	212–213	.08	78	1.6118	$C_{28}H_{28}ClN_3$	9.51	9.45
$C_4H_3N_2$	$C_6H_4(OCH_3)(4)$	210–212	.01	27	1.6021	$C_{28}H_{30}N_4O$	12.77	12.79
$C_{10}H_8N$	$C_6H_5Cl(4)$	164–165.5[d]		83		$C_{33}H_{32}ClN_3\cdot 2HCl$	7.26	7.15
C_3H_2NS	C_6H_5	216–219	0.05	68	1.6100	$C_{26}H_{27}N_3S$	10.16	9.93

[a] C_5H_4N, $C_4H_3N_2$, $C_{10}H_8N$, C_3H_2NS are 2-pyridyl, 2-pyrimidyl, 2-lepidyl and 2-thiazolyl, respectively. [b] The picrate melted at 119.5–120° after two recrystallizations from methanol. Calcd. for $C_{29}H_{31}N_3O\cdot 2C_6H_3N_3O_7$: N, 12.61. Found: N, 12.20. [c] The picrate, recrystallized twice from methanol, melted at 149–150°. *Anal.* Calcd. for $C_{28}H_{28}ClN_3\cdot 2C_6H_3N_3O_7$: N, 14.01. Found: N, 13.80. [d] Melting point of dihydrochloride after three recrystallizations from isopropyl alcohol.

ability to retard the growth of sarcoma 180 in mice.[5b]

Experimental[7]

Intermediates.—2-Dibenzylaminoethyl chloride hydrochloride, prepared in 85% yield by the procedure of Gump and Nikawitz,[8] melted at 187–189° after one recrystallization from isopropyl alcohol. Although this is below the reported melting point (194–195°), the product gave a satisfactory analysis (Calcd. for $C_{16}H_{19}Cl_2N$: Cl, 23.94. Found: Cl, 24.00) and was used successfully in the condensation reactions. The 2-(benzyl, *p*-methoxybenzyl and *p*-chlorobenzyl) - aminopyridines,[8] 2 - (*p* - methoxybenzyl)-aminopyrimidine,[8] 2-(*p*-chlorobenzyl)-aminolepidine[9] and 2-benzylaminothiazole[10] were described in other publications.

Benzohydryl Ether of 2-Dibenzylaminoethanol.—A mixture of 24.7 g. (0.1 mole) of the benzohydryl ether of ethylenechlorohydrin[11] and 39.4 g. (0.2 mole) of dibenzylamine was heated at a bath temperature of 150–155° for 36 hours. Ether was added to the cooled melt and the dibenzylamine hydrochloride was removed by filtration and washed well with ether. To the filtrate was added ethereal hydrogen chloride to maximum precipitation. The crude salt was separated by filtration and washed with ether. After air-drying, it weighed 31.2 g. (71%) and melted at 185–187°. After two recrystallizations from acetone, the melting point remained constant at 186–187°.

Anal. Calcd. for $C_{29}H_{29}NO\cdot HCl$: N, 3.16; Cl, 7.99. Found: N, 3.10; Cl, 7.78.

N,N-Dibenzyl-N'-aralkyl-N'-(2-pyridyl, 2-Pyrimidyl, 2-Lepidyl and 2-Thiazolyl)-ethylenediamines.—A mixture of 0.05 mole of the secondary amine, 17.8 g. (0.06 mole) of 2-dibenzylaminoethyl chloride hydrochloride, 3.1 g. (0.12 mole) of 90% lithium amide and 100 ml. of benzene (previously dried over calcium hydride) was refluxed for 24 hours. The reaction mixture was filtered while still hot and the insoluble material washed well with benzene. After removing the solvent from the filtrate, the oil which remained was distilled *in vacuo*.

In the condensation with 2-(*p*-methoxybenzyl)-aminopyrimidine by this method, about one-half of the reactants were recovered and a non-distillable substance obtained. Modifying the procedure by adding the 2-dibenzylaminoethyl chloride hydrochloride to a mixture of lithium amide, the 2-pyrimidylamine and benzene, which had been refluxed for 24 hours, and refluxing for an additional 24 hours, gave the desired product in low yield.

N,N-Dibenzyl-N'-(*p*-chlorobenzyl)-N'-(2-lepidyl)-ethylenediamine was isolated and purified as its water-insoluble hydrochloride. The remaining products failed to form crystalline salts other than picrates, which were prepared from two of the bases. Results are summarized in Table I.

Acknowledgment.—The authors gratefully acknowledge the support (in part) of this work by Endo Products, Inc.

DEPARTMENT OF CHEMISTRY
BROOKLYN COLLEGE
BROOKLYN 10, N. Y. RECEIVED SEPTEMBER 24, 1951

(7) Melting points are corrected; boiling points are not.
(8) I. A. Kaye and I. C. Kogon, *Rec. trav. chim.*, in press.
(9) I. A. Kaye, THIS JOURNAL, **71**, 2322 (1949).
(10) I. A. Kaye and C. L. Parris, *ibid.*, in press.
(11) I. A. Kaye, *ibid.*, **73**, 5468 (1951).

A Convenient Method for Fluorinating Certain Chlorocarbons with Antimony Trifluoride

BY H. DEAN MALLORY

A number of methods are available for fluorinating chlorocarbons through the use of anhydrous hydrogen fluoride or elementary fluorine at some stage in the process; however, the amount of equipment necessary to handle these compounds is sometimes prohibitive in the small laboratory. The process described in this note requires no special apparatus, and when applicable is capable of yielding high purity fluorocarbons. It was developed specifically for the preparation of methylfluoroform[1] from methylchloroform although it is well adapted to the preparation of difluorodichloromethane from carbon tetrachloride, or difluorochloromethane from chloroform. Large scale production of the latter two compounds has been reported[2] by Booth and Bixby using the same starting materials as used here although the procedures differ. This process is applicable if the final product is: (a) gaseous at room temperature or slightly above and (b) the most highly fluorinated compound obtainable with antimony trifluoride. The final product will contain on the order of 95% of the highest fluoride. An exception is noted with ethylidene fluoride; it is easily formed from CH_3CHCl_2 but is then quickly decomposed to tar by the fluorinating mixture and the yields approach zero after three seconds contact. This process will give 25% yields[3] of CH_3CHF_2 if the reaction gases are collected after the first stage but no CH_3CHClF was ever isolated. Whalley[4] has obtained 40% yields of the monofluoride with a $HF–SnCl_4$ process.

Experimental Details

The apparatus is shown in Fig. 1 and consists of a flask with a separatory funnel for adding antimony pentachloride, a water jacketed glass column reactor, sodium hydroxide scrubber, drying tube and a Dry Ice–acetone trap. The initial reaction between chlorocarbon and SbF_3 catalyzed by a few drops of $SbCl_5$, occurs in the flask containing the calculated amount of reactants. The gas products from this stage consist of materials boiling near room temperature but which are incompletely reacted; the amount of ultimate product present may be 30% or less. Flow of gas from the flask to the column reactor is controlled by adding $SbCl_5$

(1) Reported in the author's Ph.D. thesis, The State University of Iowa, Iowa City, Iowa, February, 1950.
(2) A. S. Booth and E. May Bixby, *Ind. Eng. Chem.*, **24**, 637 (1932).
(3) About that reported for a similar process by Albert L. Henne and Mary W. Renoll, THIS JOURNAL, **58**, 889 (1936).
(4) Wm. B. Whalley (to Imperial Chemical Industries, Ltd.), U. S. Patent 2,452,975, Nov. 2, 1948.

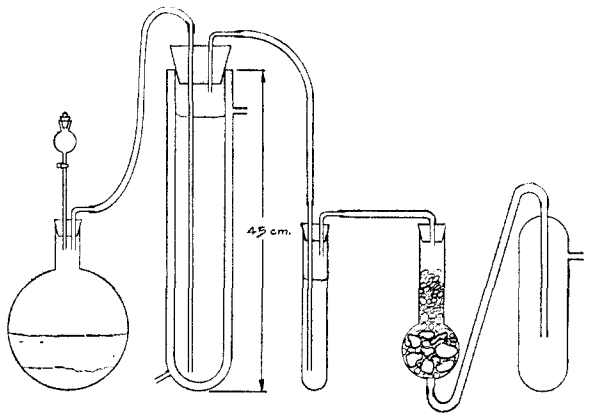


Fig. 1.—Fluorinating system.

dropwise from the separatory funnel until reaction begins, then cooling the flask in ice water as needed. Gas products enter the column and pass up through the fluorinating mixture composed of SbF_3 and $SbCl_5$ in the ratio of about 60 g. to 200 ml., respectively. A large excess of $SbCl_5$ is necessary to keep the mixture fluid and may be recovered after the reaction. Transit time for a gas bubble is from 2 to 4 seconds depending on the temperature and consequent fluidity of the mixture. A freshly prepared fluorinating mixture requires a column temperature between 25 and 35° for efficient reaction; at these temperatures much solid material is present which may clog the gas inlet. After a few ml. of product have been condensed in the cold trap, the operating temperature may be raised to 45°, where no solids are present, without impairing efficiency. If the reaction is begun at the higher temperature, especially with CH_3CCl_3, much of it is decomposed. Progress of the reaction may be easily followed by bleeding off a small amount of the gas and measuring its density with a gas density balance.[5]

(5) J. D. Edwards, Technological Paper No. 89, U. S. Bureau of Standards.

U. S. NAVAL ORDNANCE LABORATORY
WHITE OAK, SILVER SPRING, MD.

RECEIVED OCTOBER 5, 1951

Synthesis of Nitriles in Ethylene Glycol[1]

BY RICHARD N. LEWIS AND PETER V. SUSI

Low-boiling nitriles cannot be made from alkyl halides and sodium cyanine in aqueous alcohol because of the difficulty of isolating the products from the solvent. However, other solvents which dissolve appreciable amounts of sodium cyanide can be used. Thus, ethylene glycol has been used in the preparation of 5-hexenonitrile from 5-bromo-1-pentene,[2] and its monoalkyl ethers, as well as tetrahydrofurfuryl alcohol, have been used in the preparation of succinonitrile and adiponitrile.[3]

There are relatively few examples in the literature of the formation of secondary cyanides by displacement reactions, and none at all of tertiary cyanides. Low yields in these reactions are commonly attributed to olefin formation,[4] but there have been no quantitative studies to bear this out.

Several of the solvents tried were found to be quite unsatisfactory. *n*-Butyl bromide was largely unchanged after a 40-hour reflux with sodium cyanide in *n*-butyl cellosolve or nitrobenzene. *t*-Butyl chloride in *t*-butyl alcohol gave a high yield of isobutylene. *t*-Butyl bromide in hydrogen cyanide gave a little olefin along with unidentifiable material, although the sodium cyanide dissolved in the hydrogen cyanide to the extent of 0.54 g. per 100 cc. *t*-Butyl bromide in cold saturated aqueous sodium cyanide gave only a black tar.

Ethylene glycol proved to be a much more suitable solvent, even though it is not miscible with the alkyl halides. Table I shows the results of experiments with several primary, secondary and tertiary halides. In all runs there is some loss in the form of undistillable black residues. Other than this, the main side-reaction is the formation of glycol monoalkyl ethers (solvolysis); olefins are a relatively minor product.

The reactions with the primary halides were particularly gratifying. Valeronitrile, for instance, was prepared in 90% yield after one hour of reflux, and was readily separated from the reaction mixture by distillation. The best yield reported in aqueous alcohol after 25–30 hours of reflux and a careful, 10-hour distillation is 80%.[5] Butyronitrile has been made in aqueous alcohol, but not isolated.[6]

TABLE I

REACTION OF ALKYL HALIDES WITH SODIUM CYANIDE

Alkyl halide	Initial temp., °C.	Reaction time, hr.	Yield, % Nitrile	Ether	Olefin
n-BuBr	101	1	90		
n-PrBr	72	1	92		
i-PrBr	60	24	39		
i-PrBr[a]	60	15	39	16	7
s-BuBr[a]	92	4	28	Low	
s-BuCl	68	22	No reaction		
t-BuBr[a]	73	3[b]	Low	44	
t-BuCl	50	6	Low	41	
t-BuCl[a]	46	6	10[c]	27	18

[a] Sulfuric acid added. [b] Reaction seemed to be complete in one hour. [c] Impurities may reduce this to about 5%.

TABLE II

IDENTIFICATION OF PRODUCTS

Compound	Property	Observed	Reported	Reference
n-BuCN	B.p.	138–142°	140.75°	*a*
n-PrCN	B.p.	116–119°	117.28°	*a*
i-PrCN	B.p.	103–104°	103.7°	*a*
	$n^{20}D$	1.3728	1.37348	*a*
s-BuCN	B.p.	124–126°	125.4°	*a*
	$n^{30}D$	1.3857	1.38562	*a*
t-BuCN	B.p.	100–107°	103.5°[b]	*b*
	$n^{20}D$	1.3809	1.3792	*b*
i-PrOR[c]	B.p.	142.5–143°	144°	*d*
t-BuOR[c]	B.p.	153–154°	153°	*e*

[a] J. Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier Publishing Company, Inc., New York, N. Y., 1950, pp. 531–541. [b] Boiling point at 738 mm., F. C. Whitmore, C. I. Noll and V. C. Meunier, THIS JOURNAL, 61, 683 (1939). [c] R = $-CH_2CH_2OH$. [d] L. H. Cretcher and W. H. Pittenger, THIS JOURNAL, 46, 1503 (1924). [e] T. W. Evans and K. R. Edlund, *Ind. Eng. Chem.*, 28, 1186 (1936).

(1) From the M.S. thesis of Peter V. Susi, September, 1951.

(2) F. B. LaForge, N. Green and W. A. Gersdorff, THIS JOURNAL, 70, 3707 (1948).

(3) A. O. Rogers, U. S. Patent 2,415,261, Feb. 4, 1947.

(4) D. T. Mowry, *Chem. Revs.*, 42, 189 (1948).

(5) R. Adams and C. S. Marvel, THIS JOURNAL, 42, 310 (1920).

(6) K. W. Rosenmund, K. Luxat and W. Tiedemann, *Ber.*, 56, 1950 (1923).

Although the yields of secondary cyanides are only fair, the fact that they can be easily obtained in a single step may make the reaction useful. Isobutyronitrile, for instance, cannot be made in aqueous alcohol, and is difficult to make by indirect methods. It is doubtful whether this method of preparing *t*-butyl cyanide (pivalonitrile) is practical.

In a few runs part of the excess sodium cyanide was neutralized with sulfuric acid in an attempt to reduce the over-all alkalinity. This reduced the proportion of glycol ether in the product; the effect was small, however, and it was concluded that the alkoxide ion, $HOCH_2CH_2O^-$, which might have been present in the unbuffered solution, was not directly responsible for ether formation.

Experimental

The alkyl halides and ethylene glycol were redistilled before use. The sodium cyanide was Baker Analyzed, 98% minimum.

The general procedure was to mix 150 cc. of ethylene glycol, 0.5 mole of the alkyl halide and 0.55 mole of sodium cyanide in a 500-cc. three-necked flask, and to heat under reflux with constant stirring until the end of the reaction. The initial temperature, measured by a thermometer in the vapor, was always close to the boiling point of the halide, and the end of the reaction was marked by a rapid rise in temperature to a constant value as the last of the halide was used up. In a few runs 0.1 mole of sulfuric acid and an additional 0.2 mole of sodium cyanide were added before heating. In the reaction with *n*-butyl bromide it was observed that the heat of reaction was sufficient to maintain spontaneous reflux at the start.

The liquid products were distilled from the reaction mixture through a three-ball Snyder column. Where further purification of the nitriles was required they were washed with 4 *N* hydrochloric acid, 10% sodium bicarbonate and water, dried and redistilled through a 9-inch or 18-inch packed column. Their properties are listed in Table II. The odor revealed that traces of isocyanide were still present in all cases.

In the runs in which olefin was determined the evolved gases were passed through soda-lime to remove hydrogen cyanide, and condensed in a trap at −80°. The olefins were then converted to the dibromides by passing them into a sodium tribromide solution, prepared from 70 g. of sodium bromide, 112 g. of bromine and 300 cc. of water. The dibromides were washed with sodium carbonate and sodium thiosulfate solutions, dried and weighed.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF DELAWARE
NEWARK, DELAWARE RECEIVED OCTOBER 16, 1951

X-Ray Measurements of Terramycin Salts

BY J. ROBERTSON, I. ROBERTSON, P. F. EILAND AND R. PEPINSKY

The hydrochloride of terramycin crystallizes from aqueous solution in the form of yellow elongated plates. These are biaxial negative with parallel extinction, and have the refractive indices $\mu_g = 1.639$, $\mu_m = 1.686$, $\mu_p = 1.721 \pm 0.003$. The highest refractive index is shown when the electric vector vibrates parallel to the direction of elongation (the *a* axis). The crystals are orthorhombic, with space group $P2_12_12_1$, unit cell dimensions $a = 11.19$ Å., $b = 12.49$ Å., $c = 15.68$ Å., and four molecules per cell. The density, found from experiment to be 1.51, gives the value 499 ± 5 for the molecular weight of the asymmetric unit. As it is probable that this unit consists of one molecule of the antibiotic, without water of crystallization, the molecular weight of the free antibiotic, as given by the X-ray data, is 462.5 ± 5. This is in agreement with the molecular weight found approximately by titration methods,[1] and with the formula $C_{22}H_{24}N_2O_9 \cdot HCl$, which corresponds to the analysis reported by P. P. Regna and I. A. Solomons.[1]

Terramycin hydrobromide crystallizes as a dihydrate, in space-group $P2_1$. The unit cell dimensions are $a = 12.2$ Å., $b = 11.4$ Å., $c = 18.0$ Å., with β very nearly 90°. There are four molecules per cell, and thus two molecules of $T \cdot HBr \cdot 2H_2O$ in each asymmetric unit.

Since the molecular structure of terramycin is not known, efforts have been exerted toward a complete X-ray analysis. The hydrobromide dihydrate was not suitable for this analysis because of the existence of two molecules in the asymmetric unit, doubling the number of atomic parameters to be determined. The hydrochloride was selected for further study, and a full three-dimensional Patterson synthesis was carried out on X-RAC, the electronic computer for crystal analysis,[2] using data obtained with CuKα radiation. The chloride ion parameters were found to be (0.075, 0.08, 0.00). These ions form nets at $z = 0$ and $z = 1/2$, with the ions 7.0 and 9.9 Å. distant from one another, in sheets which are 15.7 Å. apart.

Attempts at interpretation of the three-dimensional Patterson were made by means of the Vector Convergence Density method, utilizing photographic super-position of displaced Patterson sections.[3] This technique strongly indicated positions of eleven carbon, oxygen or nitrogen atoms in the molecule, and suggested six additional positions of atoms of similar weight. These peaks were all concomitant with acceptable interatomic distances, but their number and distribution were insufficient to suggest a molecular configuration. Atomic coördinates found by the Vector Convergence Density method are now being used to compute structure factor phases for a three-dimensional density map.

This investigation is supported by fellowship grants from Charles Pfizer and Company and the Research Corporation, and under Contract No. N6-onr-26916, T. O. 16 with the Office of Naval Research.

(1) P. P. Regna and I. A. Solomons, *Ann. N. Y. Acad. Sci.*, **53**, 229 (1950).
(2) R. Pepinsky, *J. Appl. Phys.*, **18**, 604 (1947).
(3) C. A. Beevers and J. H. Robertson, *Acta Cryst.*, **3**, 164 (1950).

DEPARTMENT OF PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNA. RECEIVED NOVEMBER 7, 1951

o-Nitrobenzoates

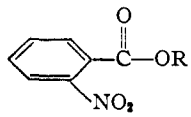
BY J. U. LOWE

During an investigation of aryl nitro compounds, it became necessary to prepare several *o*-nitrobenzoates; these were prepared in satisfactory yields by the interaction of pure *o*-nitrobenzoyl chloride and the monohydric alcohols.

o-Nitrobenzoates.—*o*-Nitrobenzoyl chloride[1] (0.2 mole) and the monohydric alcohol (0.4 mole) were refluxed for 3–7

(1) K. Auwers and M. Duesberg, *Ber.*, **53**, 1207 (1920).

TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR BENZOATES OF TYPE: 

R	Yield, %	B.p., °C.	Mm.	$n^{25}D$	d^{25}_4	Sapn. equiv. Calcd.	Sapn. equiv. Found	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found
n-C_4H_9	69	110–113	0.13	1.5132	1.1423	223.2	221.2	6.28	6.02
i-C_4H_9	65	97–99.3	.09	1.5117	1.1507	223.2	221.2	6.28	6.00
s-C_4H_9	45	97.3–99.8	.05	1.5107	1.1572	223.2	227.4	6.28	6.15
n-C_5H_{11}	47	122.5–123.2	.08	1.5100	1.1222	237.3	240.0	5.94	5.75
i-C_5H_{11}	76	110.2–113.5	.08	1.5070	1.1211	237.3	237.7	5.94	4.99
$(CH_3)_2CH(CH_2)_2$	56	113.5–113.8	.07	1.5100	1.1324	237.3	235.7	5.94	5.72
n-C_6H_{13}	64	120.8–122	.04	1.5070	1.1191	251.3	249.9	5.58	5.75
Cyclohexyl	52	133.8–136.5[b]	.08	....	....	249.2	246.1	5.62	5.40
$CH_3O(CH_2)_2$	63	118–119.5	.07	1.5214	1.2510	225.2	216.2	6.22	6.11
$CH_2OC_4H_9CH_2$	55	132.5–135.3	.08	1.5059	1.1233	267.3	261.5	5.24	4.73
s-C_5H_{11}		113.3–114.6	.07	1.5075	1.1274	237.3	237.5	5.94	6.08

[a] Nitrogen content determined by a macro adaptation of the semi-micro Kjeldahl procedure of R. A. Harte, *Ind. Eng. Chem., Anal. Ed.*, 7, 432 (1935). [b] M.p. 50–51° (corrected).

hours on a steam-bath. The resulting crude ester was extracted successively with water, 10% calcium chloride solution, water, 5% sodium bicarbonate solution, and finally with water. After standing over Drierite for 24 hours, the esters were distilled *in vacuo*. The benzoates were pale yellow oils.

A summary of the physical constants and analytical data is described in Table I.

Materials.—The alcohols were distilled from freshly crushed lumps of calcium oxide. A constant boiling fraction was taken for conversion to the *o*-nitrobenzoate. The *o*-nitrobenzoyl chloride used in these preparations had a f.p. of 19°.

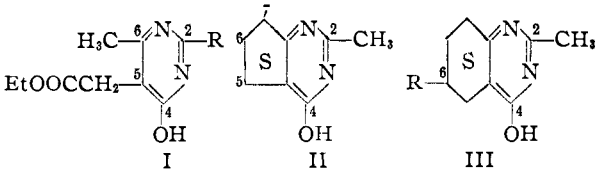
Acknowledgment.—The author expresses appreciation to Mr. Solomon C. Westbrook, Jr., and Dr. Carl M. Hill for assistance in this investigation.

DEPARTMENT OF CHEMISTRY
TENNESSEE AGRIC. AND INDUST. STATE COLLEGE
NASHVILLE 8, TENNESSEE RECEIVED NOVEMBER 2, 1951

Derivatives of Pyrimidol-4 and Quinazolinol-4

BY G. E. MCCASLAND AND JOHN R. G. BRYCE

In continuation of studies on pyrimidine derivatives[1,2] we wish to report the synthesis of two pyrimidines (I), one trimethylenepyrimidine (II), and two tetramethylenepyrimidines (tetrahydroquinazolines) III.



I R = $-CH_3$, $-CH_2OH$ II III R = $-H$, $-OCH_3$

The reaction of diethyl acetosuccinate with acetamidine gave 5-carbethoxymethyl-2,6-dimethylpyrimidol-4 (I, R = $-CH_3$), and with hydroxyacetamidine gave 5-carbethoxymethyl-2-hydroxymethyl-6-methylpyrimidol-4 (I, R = $-CH_2OH$).

The reaction of acetamidine with 2-carbethoxycyclohexanone gave 2-methyl-5,6,7,8-tetrahydroquinazolinol-4 (III, R = $-H$); and with the corresponding cyclopentane ketoester gave 2-methyl-5,6-trimethylenepyrimidol-4 (II). The corresponding reaction with 2-carbethoxy-4-methoxycyclohexanone gave 6-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolinol-4 (III, R = $-OCH_3$). Certain intermediates and products were isolated or characterized as dinitrophenylhydrazones, hydrochlorides or picrates.

Experimental

Melting points are corrected. Microanalyses by Mr. R. Pyke.

Condensation of the Amidine and Keto-Ester (General Procedure).—To a solution containing 2 to 5% excess of sodium ethoxide in warm absolute ethanol (21–83 ml. per gram of sodium) was added the solid acetamidine (or hydroxyacetamidine) hydrochloride. After ten minutes with shaking, sodium chloride was removed by filtration, and the keto-ester (one mole per mole of amidine) was added. Under anhydrous conditions, the mixture was allowed to stand and/or refluxed until reaction was nearly complete. If the product did not separate spontaneously after cooling, sufficient water was added to dissolve any precipitate, and the reaction mixture was adjusted to *p*H 4–6 by adding dilute hydrochloric acid and sodium bicarbonate solutions. The neutralized solution was vacuum-distilled to dryness, and the product separated from inorganic materials by extracting it with a suitable boiling solvent.

2-Methyl-5,6,7,8-tetrahydroquinazolinol-4 (2-Methyl-5,6-tetramethylenepyrimidol-4).—The general procedure was used with 12.5 ml. of ethanol, 2.38 g. of acetamidine hydrochloride (British Drug Houses, Toronto), and 4.25 g. of 2-carbethoxycyclohexanone[3] (b.p. 99–101° (9 mm.)). The reaction time was 24 hours at 25° plus four hours at reflux temperature. On cooling, long colorless needles separated. These were collected, washed with a limited amount of ethanol and dried, weight 1.9 g., m.p. 206–209.5°.

By extracting the evaporated filtrate with boiling benzene a second crop of 0.5 g., m.p. 205–209°, was obtained, making the total yield 2.4 g. (59%).

On recrystallization of a sample from benzene, for analysis, the m.p. was raised to 208–209°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.37; N, 17.06. Found: C, 65.97; H, 7.87; N, 17.74.

4-Hydroxy-2-methyl-5,6,7,8-tetrahydroquinazolinium Picrate.—Addition of saturated benzene solution of picric acid to a boiling saturated benzene solution of the quinazoline gave an immediate yellow crystalline precipitate. The crystals after washing with benzene and drying, melted at 202–205.5°. After two recrystallizations from *n*-butanol a 61% yield of picrate, bright yellow crystals, m.p.

(1) G. E. McCasland, D. Stanley Tarbell, R. B. Carlin and Nancy Shakespeare, THIS JOURNAL, **68**, 2390 (1946).

(2) G. E. McCasland and D. Stanley Tarbell, *ibid.*, **68**, 2393 (1946).

(3) H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

207–208°, was obtained. A mixed m.p. of the picrate with the free base was depressed to 150–170°.

Anal. Calcd. for $C_{15}H_{18}N_6O_8$: N, 17.81. Found: N, 17.97.

2-Methyl-5,6-trimethylenepyrimidol-4 (2-Methyl-6,7-dihydrocyclopentapyrimidol-4).—The general procedure was used with 10 ml. of ethanol, 0.47 g. of acetamidine hydrochloride and 0.78 g. of 2-carbethoxycyclopentanone[4] (b.p. 99–100.5° (10 mm.)). The reaction time was 12 hours at 25° plus 3.5 hours at reflux temperature. The extraction solvent was ethyl acetate. On cooling, the extract deposited long colorless needles. These when collected, washed with a little ethyl acetate, and dried, weighed 180 mg., m.p. 208–212°. From the filtrate by partial evaporation 54 mg. more material, of m.p. 207–212°, was obtained, making the total yield 234 mg. (31%).

The material sublimed easily at 2 mm. (125° bath), but this did not improve the purity. Repeated recrystallization of the material from ethyl acetate raised the m.p. to 214.5–215.5°. Analysis indicated that the compound was still not entirely pure, but it gave a picrate of satisfactory purity.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 64.91; H, 7.10; N, 19.36.

4-Hydroxy-2-methyl-5,6-trimethylenepyrimidinium Picrate.—The crude picrate, prepared as described for the above quinazoline, was obtained in 51% yield, m.p. 178.5–182.5°. After recrystallization from *n*-butanol it melted at 184.5–185°.

Anal. Calcd. for $C_{14}H_{13}N_5O_8$: C, 44.33; H, 3.45; N, 18.47. Found: C, 44.11; H, 3.84; N, 18.29.

2-Carbethoxy-4-methoxycyclohexanone.—Hydrogenation[5] of commercial 4-methoxyphenol gave a *cis–trans* diastereomeric mixture of **4-methoxycyclohexanol**, b.p. 98–107° (15 mm.), in 89% yield.

The product was oxidized according to the procedure of Helfer[6] but to obtain the reported yield it was necessary to reduce the proportion of dichromate to a slight excess. **4-Methoxycyclohexanone** was obtained in 50–55% yield as a colorless liquid, b.p. 82–83° (13 mm.). A sample was converted to the 2,4-dinitrophenylhydrazone, m.p. 147–148° (reported[7] 150°).

The method of Cook and Lawrence[8] for the preparation of **2-carbethoxyformyl-4-methoxycyclohexanone** was modified as follows: The mixture of 4-methoxycyclohexanone (11.4 g.) and diethyl oxalate (14.7 g.) was added *to* the solution of sodium ethoxide in absolute ethanol (distilled from sodium). The reaction was conducted at 0–5° under dry nitrogen. After 2–3 hours stirring at 0°, the mixture was left overnight (with stirring), and after chilling to 0° was acidified and extracted.

The decarbonylation procedure[8] was modified by adding 100 mg. of powdered glass and 10 mg. of powdered iron to the entire batch of crude diketo-ester (a viscous oil), heated in a Claisen flask at 190°. The vigorous evolution of carbon monoxide was complete in 20 minutes, and 4.42 g. (25%, based on methoxycyclohexanone) of **2-carbethoxy-4-methoxycyclohexanone**, b.p. 128–135° (14 mm.), was obtained. On redistillation the product was obtained as a colorless liquid (3.69 g.), b.p. 139–141° (18 mm.) (reported[8] 131–133° (10 mm.)), $n^{20}D$ 1.4783, D_{20} 1.102, $M^{20}D$ 51.40 (theor. 49.50). The product gave a 2,4-dinitrophenylhydrazone of m.p. 125–128° dec., reported[8] 129–131° dec.

6-Methoxy-2-methyl-5,6,7,8-tetrahydroquinazolinol-4 Hydrochloride.—The general procedure was used with 0.47 g. of 2-carbethoxy-4-methoxycyclohexanone. The reaction time was three days at 25°. The extraction solvent was absolute ethanol. The hot filtered extract was cooled to 0°. Dry hydrogen chloride was passed into the solution for ten minutes. The colorless crystalline precipitate was collected, washed with ethanol and dried, giving 0.62 g. (54%) of product, m.p. 217–220° dec. After recrystallization of the product from absolute ethanol the m.p. was 221–222° dec.

Anal. Calcd. for $C_{10}H_{15}ClN_2O_3$: C, 52.06; H, 6.55; N, 12.15. Found: C, 52.24; H, 6.94; N, 12.15.

In earlier experiments the free base was isolated from the reaction mixture as colorless crystals, m.p. 129–137°. The yield was only 12% and purification was difficult.

5-Carbethoxymethyl-2,6-dimethylpyrimidol-4.—The general procedure was used with acetamidine hydrochloride (0.47 g.), 10 ml. of ethanol and 1.08 g. of diethyl acetosuccinate[9] (b.p. 103.5–106.5° (1 mm.), $n^{20}D$ 1.4348, $M^{20}D$ 52.22 (theor. 52.81). The reaction time was three days at 25°. The extraction solvent was ethyl acetate. The colorless crystals which separated from the extract were collected, washed (ethyl acetate) and dried, weight 159 mg. The filtrate on vacuum distillation to half-volume and dilution 1:1 with benzene gave 24 mg. more, making the total yield 182 mg. (18%), m.p. 177–179.5°. After recrystallization of the product from ethyl acetate–benzene (1:1) the m.p. was 181.5–182°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.80; H, 6.59; N, 13.39.

5-Carbethoxymethyl-2-hydroxymethyl-6-methylpyrimidol-4.—The general procedure was used with 1.10 g. of hydroxyacetamidine hydrochloride[2] (m.p. 147–148.5°), 22 ml. of ethanol and 2.16 g. of diethyl acetosuccinate.[9] (The amidine HCl was predissolved in half of the ethanol at the b.p.) The reaction time was 24 hours at 25° followed by 3 hours refluxing. The extraction solvent was 40 ml. of benzene (refluxed 20 minutes). The hot filtered extract on cooling deposited colorless needles which were collected, washed (benzene), and dried, giving 330 mg. (15%) of product, m.p. 137–142°. Repeated recrystallization of the product from benzene raised the m.p. to 143–144.5°.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.39. Found: C, 52.48; H, 6.03; N, 11.61.

On heating with hydrazine hydrate the ester yields a colorless crystalline hydrazide, which can be recrystallized from ethanol and melts at about 225° (rapid heating), but which has not yet been purified sufficiently for analysis.

(4) R. P. Linstead and E. M. Meade, *ibid.*, p. 119.

(5) E. M. Van Duzee and H. Adkins, THIS JOURNAL, **57**, 147 (1935).

(6) L. Helfer, *Helv. Chim. Acta*, **7**, 950 (1924).

(7) C. S. Marvel and W. L. Walton, *J. Org. Chem.*, **7**, 88 (1942).

(8) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938).

(9) H. Adkins, N. Isbell and B. Wojcik, ref. 3, p. 262.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TORONTO
TORONTO, CANADA

RECEIVED SEPTEMBER 21, 1951

Anion Exchange Studies. IV.[1,2] Cobalt and Nickel in Hydrochloric Acid Solutions

BY GEORGE E. MOORE AND KURT A. KRAUS

The anion exchange behavior of nickel(II) and cobalt(II) in 0.5 to 12 *M* hydrochloric acid was studied by measuring their elution constants $E = dA/V$, where d is the distance (cm.) an absorption band moves when V (cc.) of eluent have been passed through a column of A (cm.^{2}) cross-sectional area.

Glass columns of the practically colorless resin Dowex-1 (a "strong base" quaternary amine polystyrene–divinylbenzene resin) were used, whose cross-sectional areas were 0.023 cm.^{2}. Since both nickel and cobalt are colored (the latter has a characteristic blue color on the resin) the band positions (and hence E) were determined visually. Approximately 1 mg. of Co and Ni were used per experiment. In addition a few experiments were carried out with tracer cobalt (Co^{60}) and d determined with the automatic scanner previously described.[3]

The results for cobalt are summarized in Fig. 1. E_{Co} rapidly decreases from approximately 2.5 in less than 3 *M* HCl to *ca.* 0.02 in 9 *M* HCl and

(1) This document is based on work performed for the Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) Previous paper: K. A. Kraus and G. E. Moore, THIS JOURNAL, **73**, 2900 (1951).

(3) K. A. Kraus and G. E. Moore, *ibid.*, **73**, 9 (1951).

then increases again to *ca.* 0.055 in 12 *M* HCl. E_{Ni} on the other hand was found to be *ca.* 2.5 throughout the whole acid range. The difference in the adsorption behavior of the two elements is sufficient to permit excellent separation. Since as discussed earlier[3] $E = 1/(i + D)$ where i is the fractional interstitial space and D the distribution coefficient (amount per ml. of resin/amount per ml. of solutions), small values of E indicate good adsorption. Furthermore, E will reach a maximum value ($E_{max} = 1/i$) when D becomes zero. Using sodium and potassium tracers and assuming that their ions are not adsorbed E_{max} = *ca.* 2.5 was found for these columns. Hence there is negligible adsorption of nickel in the range 0.5 to 12 *M* HCl and of cobalt in the range 0.5 to 3 *M*.

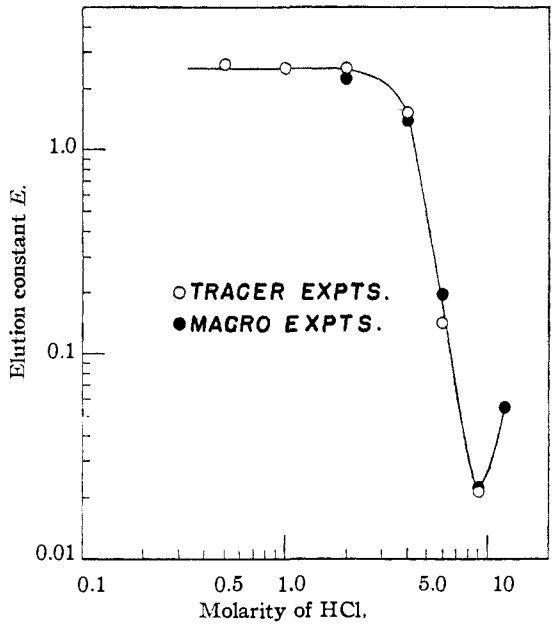


Fig. 1.—Adsorption of cobalt on Dowex-1.

Cobalt is adsorbed as a blue band which is sufficiently intense to permit detection of traces of cobalt (0.5 microgram in 9 *M* HCl was detectable on a 0.023 cm.^{2} column). Such tests have also been carried out as batch experiments. For example, 1 mg. of Dowex-1 was stirred into 0.5 cc. of 9 *M* HCl containing 4 mg. of reagent grade $NiCl_2 \cdot 6H_2O$ (with 0.13% cobalt). The suspension was slowly dropped onto filter paper. A blue ring of resin (indicating cobalt) formed as the green solution dispersed through the paper.

A comparison of the adsorption data of cobalt with those of iron(III)[4] is of interest. The latter shows very much greater adsorption in concentrated HCl and no maximum as does cobalt near 9 *M* HCl. It had been shown earlier[3] that very strong adsorption in concentrated HCl is probably characteristic of singly negatively charged complex ions and that doubly (or higher) negatively charged complexes in this medium are relatively poorly adsorbed. The adsorbed ion in the case of iron has been identified with $FeCl_4^-$ through resin-capacity measurements,[5] further supporting the earlier conclusions. Additional evidence for the reasonably general applicability of this rule comes from the observation that gallium (probably as $GaCl_4^-$) is adsorbed quantitatively similarly to iron ($FeCl_4^-$).[6] One might thus tentatively assume that $FeCl_4^-$ and $CoCl_3^-$ are also approximately equally strongly adsorbed. On this basis the fraction of cobalt as $CoCl_3^-$ can be estimated to be considerably less than 1% even in 9 *M* HCl, the adsorption maximum.

Since in concentrated HCl a negatively charged complex of cobalt almost certainly exists in considerable concentration[7,8,9] one can conclude that it is not strongly adsorbed. Since this ion probably has a charge of minus two ($CoCl_4^=$)[7,8] this relatively poor adsorption in concentrated HCl is in general agreement with the earlier conclusion that in this medium only singly negatively charged complexes are extremely strongly adsorbed.

The non-adsorbability of Ni(II) by the resin suggests very strongly that negatively charged complexes of this element are not formed in appreciable concentration even in concentrated hydrochloric acid.

(4) G. E. Moore and K. A. Kraus, THIS JOURNAL, **72**, 5792 (1950).
(5) K. A. Kraus and G. E. Moore, unpublished results.
(6) K. A. Kraus, F. Nelson and G. W. Smith, unpublished results.
(7) M. Bobtelsky and K. S. Spiegler, *J. Chem. Soc.*, 143 (1949).
(8) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. II, Clarendon Press, Oxford, 1950.
(9) According to recent paper electromigration work cobalt begins to migrate toward the anode in *ca.* 8 *M* HCl; K. A. Kraus and G. W. Smith, unpublished results; for technique see THIS JOURNAL, **72**, 4329 (1950).

OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENN.
RECEIVED JULY 18, 1951

Ethyl α,α-Dibromo-γ,γ,γ-trifluoroacetoacetate

BY WILLIAM L. MOSBY

Although the preparation of ethyl γ,γ,γ-trifluoroacetoacetate was described some time ago,[1] little seems to be known of its α-halogenated derivatives. The preparation and properties of ethyl α-chloro-γ,γ,γ-trifluoroacetoacetate are described by Hill, Towne and Dickey.[2] The bromination of ethyl γ,γ,γ-trifluoroacetoacetate is mentioned by Henne and Mencher,[3] but no details are given.

Ethyl α,α-dibromo-γ,γ,γ-trifluoroacetoacetate has been prepared by the bromination of ethyl γ,γ,γ-trifluoroacetoacetate in the presence of pyridine, using (a) bromine itself, and (b) pyridine perbromide hydrobromide.[4] Both methods gave essentially the same rather low yield of product. In view of the facile chlorination of ethyl γ,γ,γ-trifluoroacetoacetate,[2] perhaps the simpler direct treatment of the ester with bromine would be effective, but as no further work on this compound is contemplated, our data are presented now. The considerable fore-run obtained in the distillations probably represents products formed by cleavage of the ester. Ethyl α,α-dibromo-γ,γ,γ-trifluoroacetoacetate is a colorless, mobile liquid, with a slight, but not unpleasant, odor (in contrast to

(1) F. Swarts, *Bull. Sci. Acad. Roy. Belg.*, [5] **12**, 679 (1950).
(2) H. M. Hill, E. B. Towne and J. B. Dickey, THIS JOURNAL, **72**, 3289 (1950).
(3) A. L. Henne and L. Mencher, Abstracts of Papers, 118th Meeting A. C. S., Chicago, Ill., Sept. 3-8, 1950, p. 10L.
(4) C. Djerassi and C. R. Scholz, THIS JOURNAL, **70**, 417 (1948).

ethyl α-chloro-γ,γ,γ-trifluoroacetoacetate).[2] As would be expected, it fails to form a chelate compound with copper salts.

In an all-glass apparatus, protected from moisture by a calcium chloride tube, a solution of 45 g. (0.245 *M*) of ethyl γ,γ,γ-trifluoroacetoacetate in 100 ml. of dry chloroform was stirred and cooled to about −78° in a Dry Ice–acetone-bath. A solution of 45 g. (0.570 *M*) of dry pyridine and 78.5 g. (0.490 *M*) of dry bromine in 200 ml. of dry chloroform was added dropwise. When all of the bromine solution had been added, the reaction was allowed gradually to warm to room temperature, with gentle stirring for 12 hours, then stirred four hours at 55–60°. The bulk of the chloroform was removed *in vacuo*, and the orange residue warmed and stirred with 400 ml. of dry petroleum ether (b.p. 20–40°). The mixture was filtered, the crystals washed well with more petroleum ether, and the filtrate stripped of solvent *in vacuo*. Vacuum distillation of the residue gave 49.7 g. of orange liquid, b.p. 37–81° (9 mm.). This was redistilled through a small Widmer column from a trace of zinc dust, giving 28.3 g. (34%) of ethyl α,α-dibromo-γ,γ,γ-trifluoroacetoacetate, b.p. 74–5° (9 mm.), $n^{26}D$ 1.4420.

Anal. Calcd. for $C_6H_5O_3F_3Br_2$: C, 21.03; H, 1.45; F, 16.67; Br, 46.8. Found: C, 21.04; H, 1.46; F, 14.44; Br, 47.4.

CENTRAL RESEARCH LABORATORIES
GENERAL ANILINE AND FILM CORPORATION
EASTON, PENNSYLVANIA RECEIVED SEPTEMBER 27, 1951

The Dipole Moment of Ethylgermanium Trichloride

BY ROBERT C. OSTHOFF[1] AND EUGENE G. ROCHOW

Ten years ago Smyth[2] determined the dipole moments of some trialkylgermanium halides, but the dipole moment of ethylgermanium trichloride was not included. Since ethyl- and diethylgermanium chlorides may now be prepared quite readily and conveniently by the direct synthesis,[3] the authors have determined the electric moment of ethyl germanium trichloride and have further characterized this material.

Experimental

Ethylgermanium Trichloride.—Ethylgermanium trichloride was prepared by the direct reaction of ethyl chloride with mixed copper and germanium powders at 317° in the manner that has previously been described.[4] The desired compound was isolated from the reaction mixture by fractional distillation. The fraction boiling at 140.0° and 763 mm. was collected as ethylgermanium trichloride.

The purity of the ethylgermanium trichloride was established by cryoscopic measurement of its molecular weight in anhydrous benzene and by the determination of the molar refraction of the compound. In a typical experiment, a 0.57% solution in benzene showed a depression of the freezing point corresponding to a molecular weight of 202 (calcd., 207.9). At 25.0° the refractive index of the pure ethylgermanium trichloride was found to be 1.4719. By employment of a dilatometric pycnometer the density of this liquid was found to be 1.5953 g./cm.³ at 25.0°. These physical constants lead to a value of the molar refraction, $R^{25}D$, of 36.50 cm.³. If the bond refraction of the Ge–C bond is assumed to be 4.13 cm.³ and the bond refraction of the Ge–Cl bond is taken as 7.89 cm.³, these values in combination with the bond refractivities of Denbigh[5] lead to a calculated molar refraction of 36.1 cm.³.

Benzene.—Merck and Co., Inc., Reagent Grade benzene was further purified by drying over phosphorus pentoxide for several weeks. The anhydrous benzene then was fractionated, and the portion boiling at 80.1° at 765 mm. was collected; $n^{25}D$ 1.49825 (previously published value, $n^{25}D$ 1.49821[6]).

Dipole Moment.—Dielectric constants of dilute solutions in benzene were measured with a modified heterodyne–beat apparatus which was similar to that which has been described by Stranathan.[7] By employment of the method of calculation which has been described by Smyth[8], the dipole moment of ethylgermanium trichloride was evaluated. In the calculation of the electric moment the dielectric constant of benzene was taken as 2.273[9] at 25.0°.

In Table I are presented the observed data which were used in the calculation of the dipole moment.

TABLE I

Mole fraction of solute c_2	Density d, g./cm.³	Dielectric constant E	Total molar orientation polarization P_2, cm.³
0.011649	0.88386	2.422	217.83
.007887	.87959	2.373	217.44
.004905	.87615	2.328	196.98
.002150	.87332	2.294	169.11
		$P_{2\infty}$ = 145.0	

In this table $P_{2\infty}$ represents the total molar orientation at infinite dilution (obtained by graphical extrapolation). If the sum of the electronic and atomic polarizations is taken as 1.05 $R^{25}D$, *i.e.*, 38.35 cm.³, the dipole moment of ethylgermanium trichloride is calculated to be 2.28 ± 0.09 *D*. This value is about 10% higher than those of most alkyl chlorides, and compares with 2.06 *D* for 1,1-dichloropropane and 2.028 for *n*-propyl chloride.[10] No value for 1,1,1-trichloropropane is available.[10]

(1) Procter and Gamble Fellow in Chemistry, Harvard University, 1951. Research Laboratory, General Electric Company, Schenectady, New York.

(2) C. P. Smyth, *J. Org. Chem.*, **6**, 421 (1941).

(3) E. G. Rochow, THIS JOURNAL, **69**, 1729 (1947).

(4) E. G. Rochow, *ibid.*, **72**, 198 (1950).

(5) K. G. Denbigh, *Trans. Faraday Soc.*, **36**, 936 (1940).

(6) K. Matsuno and K. Han, *Bull. Chem. Soc. Japan*, **11**, 321 (1936).

(7) J. Stranathan, *Rev. Sci. Instruments*, **5**, 334 (1934).

(8) C. P. Smyth, "Dielectric Constant and Molecular Structure," (Chemical Catalog Co.), Reinhold Publ. Corp., New York, N. Y., 1931.

(9) J. Hanard, *Compt. rend.*, **204**, 1234 (1937).

(10) L. G. Wesson, "Tables of Electric Dipole Moments," Technology Press, Cambridge, Mass., 1948.

DEPARTMENT OF CHEMISTRY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASS. RECEIVED OCTOBER 12, 1951

Preparation and Polymerization of Aryl Methacrylates and N-Arylmethacrylamides

BY S. PATAI, M. BENTOV AND M. E. REICHMANN

In contradistinction with aliphatic esters and amides of methacrylic acid and with aralkyl methacrylates,[1] only very few aryl methacrylates and N-arylmethacrylamides have been described.[2]

In the framework of a larger investigation, the preparation of the polymers of aryl methacrylates and of N-arylmethacrylamides was desired. The normal method of transesterification of methyl methacrylate failed, when applied to the preparation of the aryl methacrylates; good results were achieved, when methacrylyl chloride was treated with the appropriate sodium phenoxides. In the

(1) C. E. Barnes, U. S. Patent 2,404,267 (1946); *C. A.*, **40**, 6296 (1946); C. W. Mac Mullen, U. S. Patent 2,401,261 (1946); *C. A.*, **40**, 5071 (1946), E. O. Ramler, U. S. Patent 2,456,318 (1948); *C. A.*, **43**, 4512 (1949); H. A. Bruson and G. E. Butler, U. S. Patent 2,407,131 (1946); *C. A.*, **41**, 288 (1947).

(2) Anon., *Ind. Eng. Chem.*, **28**, 1161 (1936); Ch. Weizmann, M. Sulzbacher and E. Bergmann, THIS JOURNAL, **70**, 1157 (1948); E. M. Filachione, *et al.*, *ibid.*, **72**, 839 (1950); Norton Co., British Patent 528,438 (1940), (*C. A.*, **35**, 7418 (1941)); R. A. Jacobson, THIS JOURNAL, **67**, 1998 (1945); J. Heyboer and A. J. Staverman, *Rec. trav. chim.*, **69**, 787 (1950); W. M. D. Bryant and J. Mitchell, THIS JOURNAL, **60**, 2748 (1938); P. Bieber, *Compt. rend.*, **231**, 291 (1950).

TABLE I

ARYL METHACRYLATES $CH_2=C(CH_3)COOR$

No.	R	Yield, %	M.p. or b.p., °C.	Physical properties; solvent	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	4-Chlorophenyl	82	142–146 (23 mm.)	Colorless oil	61.1	61.1	4.6	4.7
II	2,4-Dichlorophenyl	50	56	Colorless needles; dil. EtOH	52.0	52.4	3.5	3.7
III	2-Nitrophenyl[a]	12	169–171 (15 mm.)	Yellow oil	58.0	57.3	4.4	3.8
IV	4-Nitrophenyl	25	93–94	Flat needles or plates; dil. EtOH	58.0	58.6	4.4 N, 6.8	4.4 N, 6.7
V	2-Naphthyl	64	66	Colorless; dil. EtOH	79.2	79.3	5.7	5.8
VI	4-Biphenylyl	66	110	Colorless; EtOH	80.6	80.9	5.9	5.7
VII	4-Phenylazophenyl	50	113	Yellow; EtOH	72.2	72.2	5.3 N, 10.5	5.2 N, 10.5

[a] Even after repeated redistillation, the product was slightly contaminated by 2-nitrophenol.

TABLE II

N-ARYLMETHACRYLAMIDES $CH_2=C(CH_3)CONHR$ AND BIS-METHACRYLARYLENEDIAMINES $(CH_2=C(CH_3)CONH)_2R$

No.	R	Yield, %	M.p., °C.	Physical properties; solvent	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
VIII	Phenyl (see ref. 2)	76	85	Col. needles; dil. EtOH						
IX	2-Tolyl	40	94–95	Col. needles; dil. EtOH	75.4	75.5	7.5	7.3	8.0	7.5
X	3-Tolyl	55	76	Col. needles; dil. EtOH	75.4	75.1	7.5	7.4	8.0	8.0
XI	4-Tolyl	45	87	Col. plates; dil. EtOH	75.4	74.6	7.5	7.2	8.0	7.7
XII	4-Anisyl	87	89–90	Col. needles and plates; dil. EtOH	69.1	69.4	6.9	6.8	7.3	7.0
XIII	3-Nitrophenyl	45	111–112	Col. plates; EtOH	58.2	58.0	4.9	4.9	13.6	13.7
XIV	4-Nitrophenyl	78	148	Yellow needles; dil. EtOH	58.2	58.1	4.9	5.0	13.6	13.7
XV	2-Methyl,5-nitrophenyl	30	127	Needles and plates; dil. EtOH	60.0	59.9	5.5	5.3	12.7	12.6
XVI	1-Naphthyl	90	111–112	Col. needles; dil. EtOH	79.6	79.2	6.2	6.3	6.6	6.8
XVII	2-Naphthyl	80	138–139	Col. needles; dil. EtOH	79.6	79.7	6.2	6.0	6.6	6.6
XVIII	4-Phenylazophenyl	93	139–143	Orange plates; benzene	72.4	72.7	5.7	6.0	15.8	16.4
XIX	*o*-Phenylene	52	120–122	Plates; dil. EtOH	68.8	68.7	6.6	6.3	11.5	11.7
XX	*p*-Phenylene	50	249–251	Brown needles and plates; dil. MeOH	68.8	68.8	6.6	6.6	11.5	11.5
XXI	4,4'-Biphenylene	50	270–271	Grayish plates; pyridine	75.0	75.1	6.3	6.1	8.7	9.0

TABLE III

POLYMERIZATION OF ARYL METHACRYLATES AND N-ARYL METHACRYLAMIDES

No.[f]	Solvent	In solution[a] Monomer, %	Bz_2O_2, %	Yield, %	Intrinsic viscosity	Temp., °C.	In bulk Bz_2O_2, %	Time, hours[b]
I	Benzene	10	1	64	0.27	120	0.7	74
II	[c]					60	.5	12
III	Toluene	35	3	42	.07	60	.5	12
IV	Cyclohexanone	20	2	90	.33	110	1	20
V	Toluene	10	0.3	92	.35	70	1	24
VI	Toluene	10	.3	85	.14	114	1	27
VII	Toluene	10	.3	65	.10	150	0.5	48
VIII	Benzene	25	1	84	.24	95	1	18
IX	[c]					95	1	50
X	[c]					80	1	48
XI	Cyclohexanone	10	5	50	.06	90	1	32
XII	Cyclohexanone	10	5	50	.42	[d]		
XIII	Cyclohexanone	10	1	40	.32	120	5	48
XIV	Methyl ethyl ketone	10	2	27	.16	150	1	30
XV	Cyclohexanone	10	2	30	.17	130	1	62
XVI	[c]					[d]		
XVII	Cyclohexanone	20	0.6	50	.09	[d]		
XVIII	Benzene	10	1	62	.25	140	1	50
XIX	Benzene	7	1	86	.14	130	1	54
XX	[e]					290	2	64
XXI	[e]					290	2	64

[a] Heating time: 12–15 hours at 60°. [b] Termination by additional heating at a temperature 10–15° higher than stated, for 15–20% of the stated time. [c] No polymerization in solution with up to 3% Bz_2O_2. [d] No polymerization in bulk with up to 5% Bz_2O_2. [e] No suitable solvent found. [f] The numbers correspond to the Roman numerals in Tables I and II.

case of 2,6-disubstituted phenols, such as 2,4,6-trichlorophenol or picric acid, even this method gave no results, possibly for steric reasons; nor could the desired esters be prepared by interaction

of sodium methacrylate with 2,4-dinitro-, or 2,4,6-trinitrochlorobenzene[3] (see Table I).

Aromatic amines with free ortho-position reacted smoothly with methacrylyl chloride; ortho-substituted arylamines, *e.g.*, 2-nitroaniline and 2,6-disubstituted anilines, failed to react. Diamines yielded only the corresponding diamides with methacrylyl chloride, even when a large excess of the diamine was employed. Equally, *p*-aminophenol gave only the amide–ester. The products are described in Table II.

Polymerization of the new esters and amides was studied both in solution and in bulk, and the intrinsic viscosity of the polymers was determined. Turbidimetric determination of the molecular weight of poly-4-nitrophenyl methacrylate (31,000) led to the conclusion, that multiplication of the intrinsic viscosity data (Table III) by 10^5 gives a good approximation for the molecular weights of the polymers.

Acknowledgment.—This investigation was carried out under the auspices of the Scientific Department, Ministry of Defence, Israel, and is published with its permission. The authors wish to thank Dr. E. D. Bergmann for suggesting this investigation, and for constant help and advice.

Experimental

Methacrylyl chloride was prepared from methacrylic acid and benzoyl chloride in accordance with the directions given for the preparation of acrylyl chloride[4]; b.p. 93–94° (700 mm.), yield 85–90%.

Procedure for the Preparation of Aryl Methacrylates (Table I).—The phenol (0.04 mole) was dissolved in an excess of aqueous sodium hydroxide (5%); the solution cooled in an ice-bath, and 4.2 g. (0.04 mole) of methacrylyl chloride added with stirring in the course of 5–10 minutes. Stirring was continued with cooling for ten minutes, and then at room temperature for 30 minutes. The resulting ester was purified either by crystallization or by distillation.

4-Methacrylylamidophenyl methacrylate was obtained by the above procedure from 0.04 mole of 4-aminophenol and 0.04 mole of methacrylyl chloride, in 24.5% yield; m.p. (from dilute ethanol), 126–127°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.6; H, 6.2; N, 5.7. Found: C, 67.8; H, 6.0; N, 5.9.

Procedure for the Preparation of N-Arylmethacrylamides (Table II).—To a saturated solution of the amine (0.04 mole) in ether or benzene, there was added at room temperature and with stirring 0.04 mole of methacrylyl chloride in the course of 5–10 minutes. Stirring was continued for 20–30 minutes, the mixture filtered, and both precipitate and filtrate washed with dilute hydrochloric acid and water. The solvent was then evaporated, and the residue recrystallized together with the precipitate. Some of the methacrylonitroanilides gave stable molecular compounds with the parent amines; only by prolonged shaking with hydrochloric acid could they be separated into the components. Two molecules of XIII gave a compound, m.p. 95°, with one molecule of 3-nitroaniline. *Anal.* Calcd. for $C_{26}H_{26}O_8N_6$: C, 56.7; H, 4.8; N, 15.3. Found: C, 57.6; H, 4.9; N, 14.9. One molecule of XV gave a compound, m.p. 84°, with one molecule of 2-methyl-5-nitroaniline. *Anal.* Calcd. for $C_{18}H_{20}O_5N_4$: C, 58.1; H, 5.4; N, 15.0. Found: C, 57.9; H, 5.4; N, 15.4.

DEPARTMENT OF ORGANIC CHEMISTRY
THE HEBREW UNIVERSITY, AND
THE LABORATORIES OF THE SCIENTIFIC DEPARTMENT
ISRAELI MINISTRY OF DEFENCE
JERUSALEM, ISRAEL

RECEIVED JULY 11, 1951

(3) The claim of R. F. Cellini (*Anales real. soc. espan. fis. y quim.*, **45B**, 1131 (1949), *C. A.*, **44**, 8859 (1950)), that picryl methacrylate can be prepared by refluxing methacrylyl chloride with picric acid, could not be substantiated.

(4) G. H. Stempel, *et al.*, THIS JOURNAL, **72**, 2299 (1950).

Phenylalanylphenylalanine Ethyl Ester Synthesis by Chymotrypsin

BY HENRY TAUBER

It previously has been reported that insoluble high molecular weight (250,000–500,000) protein-like substances are synthesized by chymotrypsin from protein-free peptic digests.[1-3] Recently Brenner and associates[4] found by filter paper chromatography that soluble peptides form when chymotrypsin is added to certain α-amino acid esters at an alkaline *p*H. It has now been observed that L-phenylalanine ethyl ester is rapidly converted to the water-insoluble and readily crystallizable phenylalanylphenylalanine ethyl ester by chymotrypsin. The compound has been isolated in pure crystalline form. The reaction probably occurs in the following manner

L-phenylalanine ethyl ester + phenylalanine ⟶ phenylalanylphenylalanine ethyl ester

Enzymic Synthesis.—In a 50-ml. beaker were placed 3 g. of L-phenylalanine ethyl ester hydrochloride and 12 ml. of distilled water. Sodium hydroxide (2 *N*) was added to yield a solution of *p*H 8.8. Salt-free chymotrypsin (Worthington), (12 mg.) in 1 ml. of distilled water was added, and the volume was made up to 24 ml. The beaker was kept at 37° and the mixture was stirred occasionally. Precipitation began in 10 minutes. Sodium hydroxide was added during the remaining 30 minutes of the reaction period to maintain the *p*H above 8.6. The yield of dipeptide ester decreases in a less or more alkaline medium.

Isolation of the Dipeptide Ester.—The insoluble product was collected by centrifuging for 10 minutes at 3000 r.p.m. It was washed twice with 20 ml. of distilled water and extracted three times, each time with 25 ml. of acetone in which most dissolved. The acetone extract was concentrated *in vacuo* to 20 ml. The slight amorphous precipitate which formed was removed and discarded. When the acetone was removed 280 mg. of white powder was obtained. It was extracted with 20 ml. of ether. The ether-soluble fraction was discarded. The ether insoluble portion was extracted with 20 ml. of acetone in which almost all dissolved. To the acetone solution distilled water was added to obtain a 45% acetone concentration. The solution was kept for 3 days at room temperature; the dipeptide ester separated in the form of microscopic needles which were collected by centrifuging and dried *in vacuo*, m.p. 188–190° with decomposition.

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.10; N, 8.23. Found: C, 70.07; H, 6.99; N, 8.14.

Identification of Phenylalanine.—About 10% of the L-phenylalanine ethyl ester employed in the synthesis was converted to L-phenylalanine and was isolated as such from the supernatant of the enzyme reaction mixture. It was identified by filter paper chromatography.

General Properties of the Dipeptide Ester.—The phenylalanylphenylalanine ethyl ester is soluble in glacial acetic acid and in acetone, but insoluble in water, 2.5 *N* sodium hydroxide and 2.5 *N* sulfuric acid. The dipeptide (phenylalanylphenylalanine) itself, however, is readily soluble in dilute acids and alkalies.[5] The dipeptide ester gives a much lighter ninhydrin spot test than L-phenylalanine, it is hydrolyzed by mold peptidase and is slightly hygroscopic.

Enzymic Hydrolysis.—Enzymic hydrolysis, 0.75 mg. of the compound in 0.3 ml. of acetone was mixed with 0.7 ml. of distilled water and 1.0 ml. of phosphate buffer (*p*H 7.5). A flocculent precipitate was produced. To this mixture was added 1.0 ml. (10 mg.) of mold peptidase. The final *p*H was 7.7. Toluene (0.1 ml.) was added to prevent bacterial growth. The mixture was kept at 37°. The precipi-

(1) H. Tauber, THIS JOURNAL, **71**, 2952 (1949).

(2) H. Tauber, *ibid.*, **73**, 1288 (1951).

(3) H. Tauber, *ibid.*, **73**, 4965 (1951).

(4) M. Brenner, H. R. Müller and R. W. Pfister, *Helv. Chim. Acta*, **33**, 568 (1950).

(5) E. Fischer, *Ber.*, **37**, 3068 (1904).

tate disappeared completely after 18 hours. A control without added enzyme remained turbid. Crystalline trypsin and chymotrypsin produced no visible effect on the mixture.

Cysteine ethyl ester, glycine ethyl ester and arginine methyl ester were not converted to insoluble compounds by chymotrypsin. Crystalline trypsin and crystalline carboxypeptidase did not produce insoluble compounds from L-phenylalanine ethyl ester.

Acknowledgment.—The author is grateful to Miss Sadie Herndon for the elementary analyses and to Mr. E. L. Petit for technical assistance.

THE VENEREAL DISEASE EXPERIMENTAL LABORATORY
U. S. PUBLIC HEALTH SERVICE
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C. RECEIVED OCTOBER 15, 1951

The Fluorination of Thiophene with Cobalt Trifluoride

BY JULIUS SCHULTZ AND MURRAY HAUPTSCHEIN

The fluorination of thiophene over cobalt trifluoride in a Fowler-type[1] apparatus resulted in extensive cleavage of the molecule with the formation of various low boiling sulfur fluorides and fluorocarbon cleavage products. Two compounds of interest were isolated, one a sulfur-free fluorinated butane derivative, and the other a fluorine-free sulfur-containing polymer.

A series of ten fluorinations was carried out in the usual manner. In each case a 21-g. sample of thiophene was introduced at the rate of 30.0 g. per hour in a stream of dry nitrogen at a rate of 30–35 cc. per minute. The reactor temperature was varied from 150–250°, and 350 g. of cobalt trifluoride was used in each case. Nearly complete reduction to cobalt difluoride was noted. The yield of products was not very much dependent on the temperature of the reaction, which on the introduction of the charge would increase suddenly from 30 to 50° due to the very exothermic reaction.

The two products of interest were isolated from the two traps closest to the system, cooled in water–ice and Dry Ice–acetone, respectively. The average weight of products collected in these traps was 59 g. resulting from the fluorination of 21 g. of thiophene. Approximately 16 g. of product boiling at 30–40° was recovered. On further rectification of this fraction, most of the product boiled at 36.5–37°, f.p. app. −55°, d^0_4 1.5653, $d^{10.5}_4$ 1.5404, $\Delta d/\Delta t$ −0.0024, and corresponded to the dihydride $C_4H_2F_8$.

Anal.[2] Calcd. for $C_4H_2F_8$: C, 23.76; H, 1.00; F, 75.24; mol. wt., 202. Found: C, 23.67; H, 1.08; F, 75.76; mol. wt., 203.

The dihydrofluorocarbon is alkali resistant, reduces permanganate, and is chlorinated slowly in the vapor phase under ultraviolet illumination, to form the corresponding dichloride, b.p. 62–63°, mol. wt., found, 270; mol. wt., calcd. for $C_4Cl_2F_8$: 271.

The other product isolated in the first copper trap cooled in water–ice was a brown solid (5 to 6 g.), which was formed only when the system did not include a sodium fluoride tube for removing the hydrogen fluoride formed. No evidence was found for the formation of this solid in either the fluorinator or the copper tubing connecting lines. After washing this solid with dilute bicarbonate solution to remove any hydrogen fluoride, it was extracted with hot glacial acetic acid to remove any copper contamination. The insoluble powder was then freed of acid and exhaustively extracted with ether. The ether extracts were negligible. The dried powder, which was essentially insoluble in the common organic solvents (except carbon disulfide in which it was slightly soluble) as well as in 10% acid and alkali, could be dissolved in hot fuming nitric acid. Analysis[2] of the purified product gave on an ash-free basis C, 55.8; H, 3.92; S, 40.3. This corresponds closely to the formula $(C_4H_{4.4}S_{1.1})_x$. This formula does not differ greatly from that for a polymer of thiophene, *i.e.*, $(C_4H_4S)_x$, but the deficiency in hydrogen may be significant.

Acknowledgment.—The authors wish to express their sincere appreciation to the U. S. Air Force, Air Materiel Command, for their financial support of part of this work.

RESEARCH INSTITUTE OF TEMPLE UNIVERSITY
PHILADELPHIA, PENNSYLVANIA RECEIVED AUGUST 13, 1951

(1) R. D. Fowler, *et al.*, *Ind. Eng. Chem.*, **39**, 292 (1947).

(2) Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

Perfluoroalkyl Halides Prepared from Silver Perfluoro–Fatty Acid Salts. III. 1,3-Dibromohexafluoropropane and 1,3-Dichlorohexafluoropropane

BY MURRAY HAUPTSCHEIN, CHARLES S. STOKES AND ARISTID V. GROSSE

In our first paper of this series[1] we reported the preparation of an 18% yield of 1,3-diiodohexafluoropropane by the thermal degradation of silver hexafluoroglutarate by an excess of iodine. That reaction was shown to proceed mainly with formation of perfluorobutyrolactone probably through cyclization of the intermediate gamma iodo salt, $ICF_2CF_2CF_2CO_2Ag$. We have now treated silver hexafluoroglutarate with bromine and chlorine by the method previously described[2] and have isolated the new compound 1,3-dibromohexafluoropropane and 1,3-dichlorohexafluoropropane in 80.3 and 64.5% yield, respectively. No evidence was found for the formation of any perfluorobutyrolactone. The larger size of the iodine atom, *i.e.*, the closer spacial proximity to the silver atom, may be the principal factor in favoring cyclization and lactone formation in the previous case only.

Since the yield of AgBr was 100% and that of AgCl was 90% of theory (*vide infra*), it is likely that similar proportions of dihalides were formed in the reaction, and the lower yields actually isolated resulted from losses in the recovery processes.

The infrared spectra[3] are shown in Figs. 1 and 2. It is of interest to note the absence of any prominent bands below 7.85 microns in the spectra of these 1,3-dihaloperfluoropropanes. This picture is consistent with that for 1,3-diiodohexafluoropropane given previously,[1] and in marked contrast with that for perfluoroalkyl halides containing $-CF_3$ groups where intense absorption bands appear at 7.3 to 7.52 microns.[1,2]

Experimental

Preparation of $CF_2BrCF_2CF_2Br$.—A 45.38-g. (0.10 mole) sample of finely powdered silver hexafluoroglutarate reacted with 42 g. (0.26 mole) of bromine. The reaction was carried out at 80–90° and was completed in four hours. The yield of AgBr was 37.5 g. (100%). There was obtained 24.84 g. (80.3% yield) of washed and dried dibromide. 1,3-Dibromohexafluoropropane is a water-white liquid, b.p. 74.2°, $n^{0.5}D$ 1.3684, $n^{30.2}D$ 1.3536, $d^{0.0}_4$ 2.1966, $d^{27.8}_4$ 2.1162, MR (found) 31.81, AR_F 1.14.

(1) M. Hauptschein and A. V. Grosse, THIS JOURNAL, **73**, 2461 (1951).

(2) M. Hauptschein and A. V. Grosse, XIIth International Congress of Pure and Applied Chemistry, New York City, September 10–13, 1951.

(3) Determined with a Baird Associates Infrared Recording Spectrophotometer of Samuel P. Sadtler & Sons, Inc., Philadelphia.

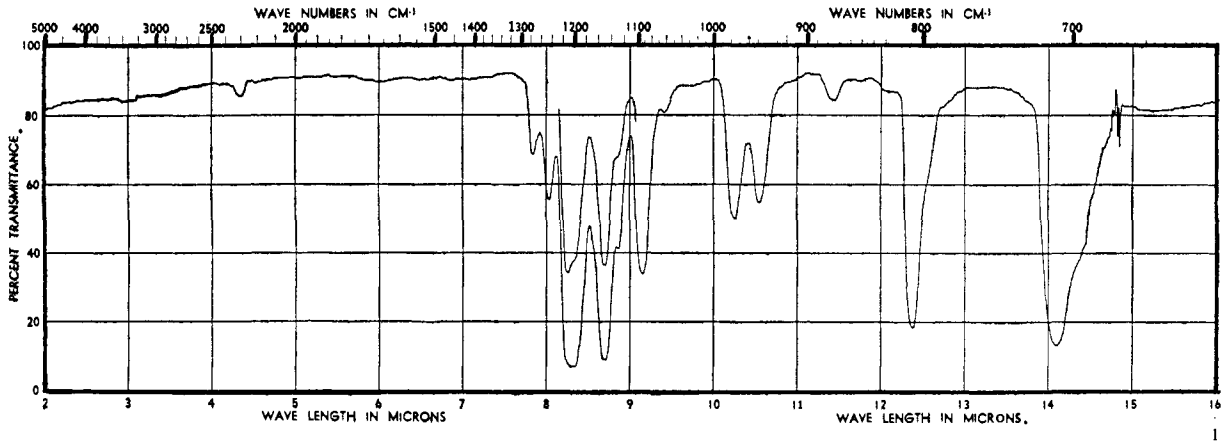


Fig. 1.—Infrared spectrum of 1,3-dibromohexafluoropropane. The spectra of Figs. 1 and 2 were taken in a 5-cm. gas cell. In these figures the lowest curve is for the vapor at 760 mm., and the other curve for vapor diluted with dry nitrogen gas.

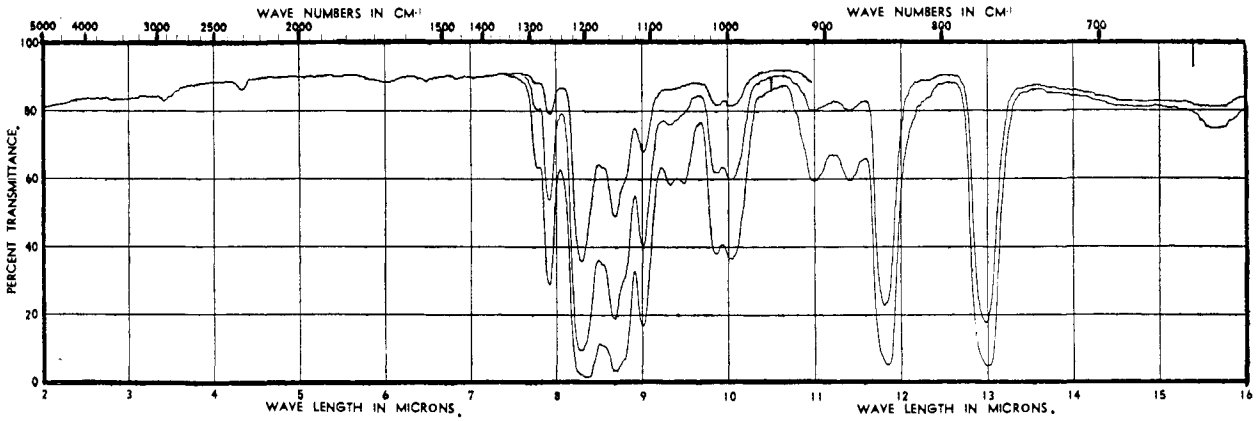


Fig. 2.—Infrared spectrum of 1,3-dichlorohexafluoropropane in vapor phase. The spectrum of this compound over the range of 9 to 15 microns has been given previously.[8] The main discrepancy in this range is the presence of a small band at 14.4 microns which is absent in our case. We have also taken infrared spectra in a 0.01-mm. liquid cell, and while they are very similar to that of Young and Murray,[8] the weak band at 14.4 microns is again absent in our case.

Anal.[4] Calcd. for $C_3F_6Br_2$: C, 11.63; Br, 51.58; mol. wt., 309.9. Found: C, 11.86; Br, 50.73; mol. wt. (gas density balance), 309.

Preparation of $CF_2ClCF_2CF_2Cl$.—An excess of chlorine was slowly passed through a long Pyrex tube, equipped with a Dry Ice refluxer and refrigerated collecting traps. This tube contained 45.38 g. (0.10 mole) of powdered silver hexafluoroglutarate. The reaction tube was heated intermittently with a bunsen flame at approximately 100° for eight hours. The yield of AgCl was 25.8 g. (90%). After washing and drying there was isolated 12.9 g. (64.5% yield) of 1,3-dichlorohexafluoropropane,[5] b.p. 35.7°, mol. wt. (found) 221, $n^{0.5}D$ 1.3134, $n^{22.2}D$ 1.3022, $d^{0.0}_4$ 1.6225, $d^{27.2}_4$ 1.5518, MR (found) 26.52, AR_F 1.22; known for $CF_2ClCF_2CF_2Cl$[5]: b.p. 35.8°, mol. wt. (calcd.) 221, $n^{20}D$ 1.3030, d^{20}_4 1.5730.

It should be noted that the boiling points of both 1,3-isomers are 1.2° higher than that of the 1,2-isomers: known b.p. $CF_3CFBrCF_2Br$, 73.0[6]; known b.p. $CF_3CFClCF_2Cl$, 34.5°,[8] 34.7°,[7] 34.5°.[8]

THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY
PHILADELPHIA, PENNSYLVANIA RECEIVED AUGUST 24, 1951

(4) Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

(5) B. L. Baker and A. M. Whaley, THIS JOURNAL, **73**, 4010 (1951), prepared this compound by a three-step procedure from 1,2-dichloro-2-propene. Other references are cited therein.

(6) M. Hauptschein and L. A. Bigelow, *ibid.*, **73**, 1428 (1951).

(7) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496 (1946).

(8) E. G. Young and W. S. Murray, *ibid.*, **70**, 2814 (1948).

Perfluoroalkyl Halides Prepared from Silver Perfluoro-fatty Acid Salts. IV. 1-Haloundecafluoropentanes

BY MURRAY HAUPTSCHEIN, RICHARD L. KINSMAN AND ARISTID V. GROSSE

The silver salt of *n*-perfluorocaproic acid has been prepared and converted to the new 1-iodo-, 1-bromo- and 1-chloroperfluoropentanes by the previously reported procedures.[1,2]

The reaction of silver *n*-undecafluorocaproate and an excess of halogen resulted in the formation of 1-iodoundecafluoropentane, 1-bromoundecafluoropentane and 1-chloroundecafluoropentane in yields of 73.9, 82.5 and 71.2%, respectively.

The physical constants of the perfluoroamyl halides are presented in Table I, and the infrared spectra[3] are shown in Figs. 1–4. The spectrum of

(1) M. Hauptschein and A. V. Grosse, THIS JOURNAL, **73**, 2461 (1951).

(2) M. Hauptschein and A. V. Grosse, XIIth International Congress of Pure and Applied Chemistry, New York City, September 10–13, 1951.

(3) Determined with a Baird Associates Infrared Recording Spectrophotometer of Samuel P. Sadtler & Sons, Inc., Philadelphia.

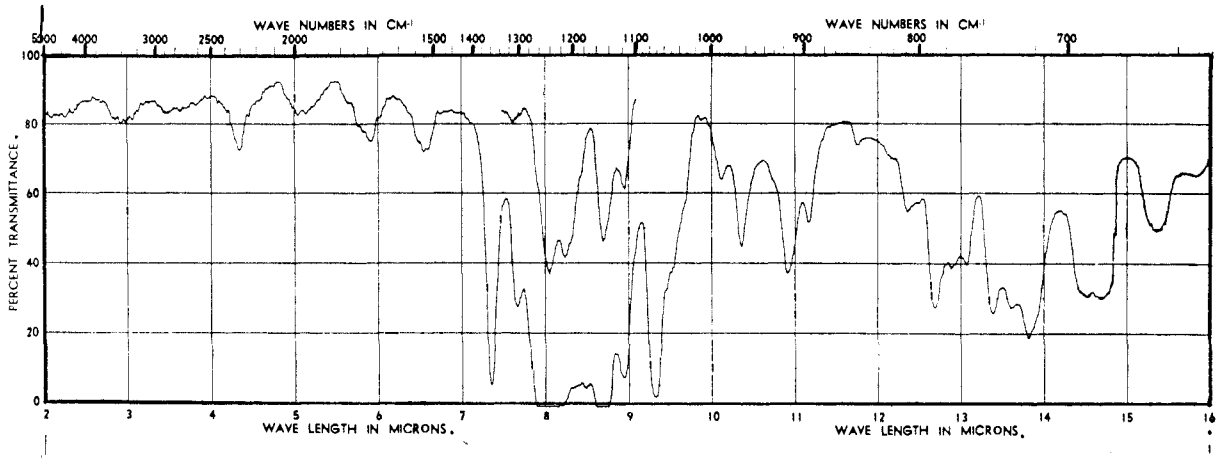


Fig. 1.—Infrared spectrum of 1-iodoundecafluoropentane: lower curve was taken in a 0.01-mm. liquid cell; upper curve was taken in a 0.005-mm. liquid cell.

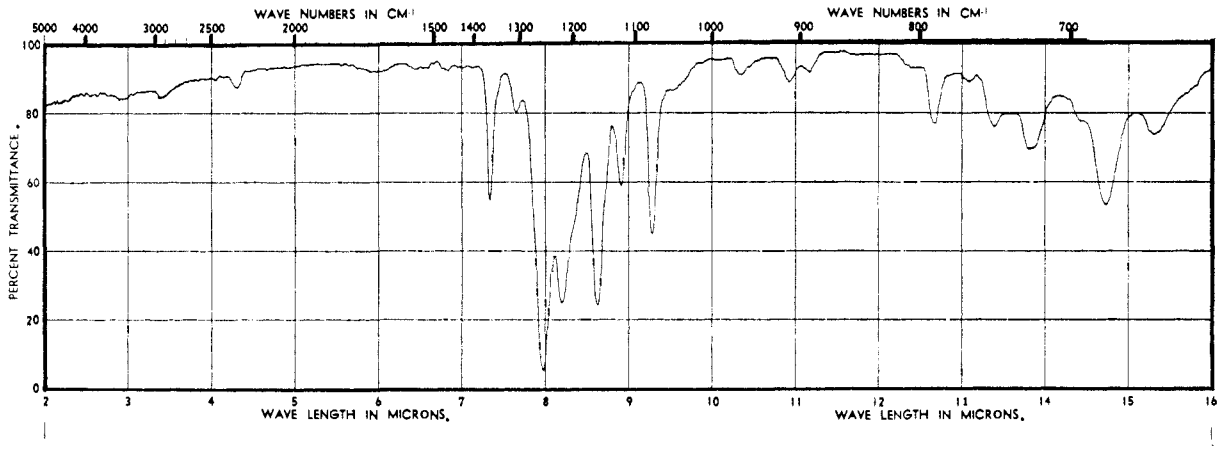


Fig. 2.—Infrared spectrum of 1-iodoundecafluoropentane in vapor phase taken in 5-cm. gas cell.

1-iodoundecafluoropentane is given for both the vapor and liquid phase, and exhibits a slight shift in most of the absorption bands due presumably to differences in physical state.

TABLE I

PHYSICAL PROPERTIES

Compound	B.p., °C.	n^tD	t	d^t_4	t	MR Found[b]	AR_F[c]
$CF_3(CF_2)_3CF_2I$[a]	94.4	1.3243	31.5	2.0349	27.8	39.18	1.20
		1.3389	0.5	2.1141	0.0		
$CF_3(CF_2)_3CF_2Br$	73.9	1.2920	27.8	1.8522	28.4	34.19	1.20
		1.3042	0.0	1.9324	0.0		
$CF_3(CF_2)_3CF_2Cl$	59.5	1.2736	25.4	1.6450	25.8	31.77	1.25
		1.2845	0.0	1.7150	0.0		

[a] Melting point (*ca.*) −50°. [b] MR (Found) denotes the molecular refraction calculated by Lorentz–Lorenz formula. [c] AR_F is the atomic refraction for fluorine, obtained from MR (Found) by subtracting the customary increments for C, I, Br and Cl.

Experimental

Preparation of Silver *n*-Undecafluorocaproate.—$CF_3CF_2CF_2CF_2CF_2CO_2Ag$ was prepared by adding 10% excess of silver oxide (52.0 g.) to a homogeneous solution of 127.0 g. (0.404 mole) of *n*-perfluorocaproic acid in 340 ml. of water. This quantity of acid was not completely miscible in 200 ml. of water. The reaction mixture was heated on a hot-plate at 50–60°, but the silver *n*-undecafluorocaproate was only partially soluble in the amount of water used. Therefore the product was extracted with an equal amount of ether and the excess silver oxide was filtered off. On evaporation of both the ethereal and aqueous layer 116.7 g. of silver salt was collected from the ether extract and 34.9 g. of silver salt from the water extract or a total yield of 89.2%. The silver salt melted at 286–288°. It was analyzed for silver by the Volhard method.

Anal. Calcd. for $C_5F_{11}CO_2Ag$: Ag, 25.63. Found: Ag, 25.70.

Preparation of 1-Iodoundecafluoropentane.—A 50.0-g. (0.119 mole) sample of powdered silver *n*-undecafluorocaproate was treated with 33.2 g. (10% excess) of powdered iodine at 100° for six hours. The yield of AgI was 28.0 g. (100% of theory). There was obtained 34.7 g. (73.9% yield) of washed and dried *n*-$C_5F_{11}I$, b.p. 93.4–94.4° (almost entirely 94.4° at 760 mm.). This compound distils as a water-white liquid, but on exposure to air and light turns slowly pink.[4]

Anal.[5] Calcd. for $C_5F_{11}I$: C, 15.16; H, none; mol. wt., 396. Found: C, 15.06; H, none; mol. wt. (gas density balance), 398, 396.

Preparation of 1-Bromoundecafluoropentane.—A 40.0-g. (0.095 mole) sample of powdered silver *n*-undecafluorocaproate reacted with 24 g. (0.15 mole) of bromine at 80–90° for 5 hours. The yield of AgBr was 17.8 g. (100%). There was isolated 27.36 g. (82.5% yield) of washed and dried, water-white, *n*-$C_5F_{11}Br$, b.p. 73.1–73.9° (almost entirely 73.9° at 760 mm.).

Anal.[5] Calcd. for $C_5F_{11}Br$: C, 17.21; H, none; mol. wt., 349. Found: C, 17.16; H, none; mol. wt. (gas density balance), 350.

(4) J. H. Simons and T. J. Brice, U. S. Patent 2,554,219, May 22, 1951, indicated the preparation of $C_5F_{11}I$ by a method differing from the above by the addition of inert silica-containing diluents and *fluorocarbon* solvents.

(5) Microanalysis by Clark Microanalytical Laboratory, Urbana, Illinois.

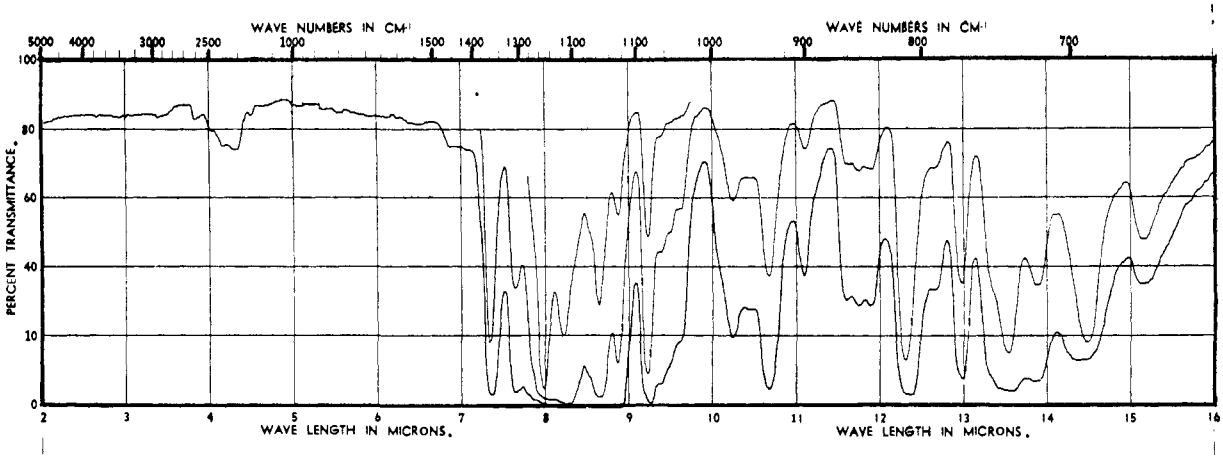


Fig. 3.—Infrared spectrum of 1-bromoundecafluoropentane: lower curve was taken in a 5-cm. gas cell; upper curves are for vapor diluted with dry nitrogen gas taken in same cell.

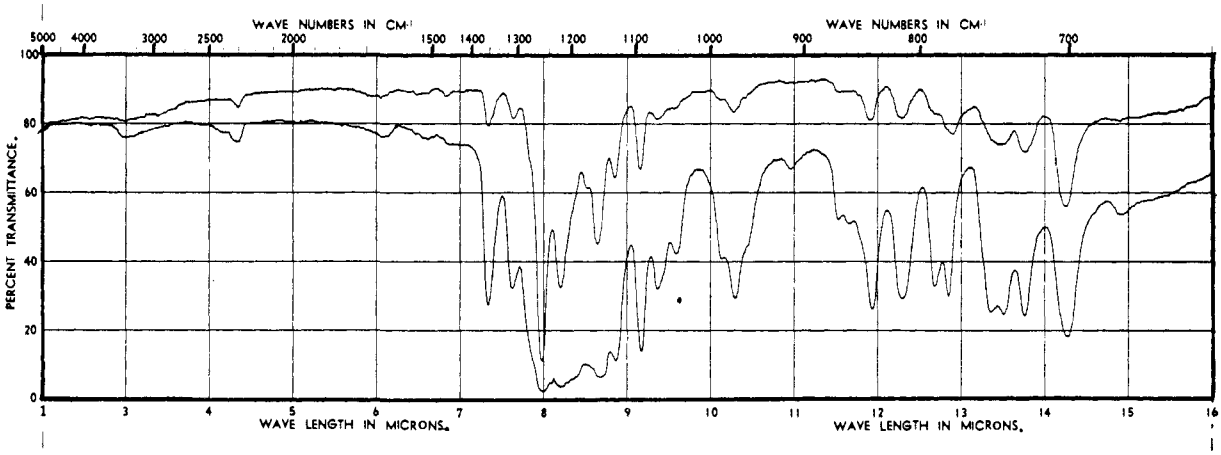


Fig. 4.—Infrared spectrum of 1-chloroundecafluoropentane: lower curve was taken in a 5-cm. gas cell; upper curve is for vapor diluted with dry nitrogen gas taken in same cell.

Preparation of 1-Chloroundecafluoropentane.—An excess of chlorine was passed through a long Pyrex tube, equipped with a Dry Ice refluxer and refrigerated collecting traps. The tube was partially filled with 23 g. (0.0546 mole) of powdered silver *n*-undecafluorocaproate, which was heated intermittently with a bunsen flame at approximately 100° for eight hours. The yield of AgCl was 93% of theory. After washing and drying there was isolated 11.84 g. (71.2% yield) of the water-white liquid, *n*-$C_6F_{11}Cl$, b.p. 59.0–59.5° (almost entirely 59.5° at 760 mm.).

Anal.[5] Calcd. for $C_5F_{11}Cl$: mol. wt., 304.5; C, 19.72. Found: mol. wt. (gas density balance), 304; C, 19.70.

Acknowledgment—The authors wish to express their sincere appreciation to the Minnesota Mining & Manufacturing Co., Saint Paul, Minnesota, for supplying the perfluorocaproic acid used in these experiments.

THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY
PHILADELPHIA, PENNSYLVANIA RECEIVED AUGUST 27, 1951

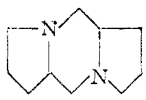
Reductive Cyclization of Butyl Pyroglutamate. Synthesis of a New Nitrogen Heterocycle, Decahydrodipyrrolo[a,d]pyrazine

BY EDWARD SEGEL

The only reported product from the hydrogenation of the α-amido ester, ethyl pyroglutamate, is 5-hydroxymethyl-2-pyrrolidone[1,2]; the amide group does not enter into the observed reaction. However, by using a somewhat higher reaction temperature (250°) than that used by Sauer and Adkins (210–220°),[1] the amide group can be completely hydrogenated. The amino alcohol, 2-hydroxymethylpyrrolidine, logically expected as the product, is not actually isolated; while it may have a transitory existence during the reaction, it cannot remain under the experimental conditions employed. The alkylating action of alcohols on amines at elevated temperatures in the presence of copper–chromium oxide catalyst and hydrogen is well established[3]; ring closure accompanying such alkylation has also been noted.[4,5] Since hydrogenation of the ester group of butyl pyroglutamate results in the formation of two alcohols, butanol, and 5-hydroxymethyl-2-pyrrolidone, either of which can then react with amino nitrogen when it arises by hydrogenation of the amide group. If the two

(1) J. C. Sauer and H. Adkins, THIS JOURNAL, **60**, 402 (1938).
(2) H. Adkins and H. R. Billica, *ibid.*, **70**, 3121 (1948).
(3) H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 26.
(4) J. P. Bain and C. B. Pollard, THIS JOURNAL, **61**, 532, 2704 (1939).
(5) B. G. Wilkes, U. S. Patent 2,479,657.

alcohols react with the amine at comparable rates, two products are possible, N-butyl-2-hydroxymethylpyrrolidine and decahydrodipyrrolo[a,d]pyrazine (I).



I

Compound I may be thought of as arising from ring closure between two molecules of 2-hydroxymethylpyrrolidine, the amino group of each being alkylated by the hydroxyl group of the other. The over-all reaction is another example of reductive cyclization, a concept employed in syntheses of the octahydropyrrocoline nucleus[6] and 1-azabicyclo compounds.[7]

Two products were actually isolated from the reaction mixture resulting when butyl pyroglutamate was hydrogenated over copper–chromium oxide at 250°. One, a white crystalline solid, exhibited a titration curve corresponding to a diamine of molecular weight 167 (theory for Compound I, 166); its elementary analysis was in good agreement with that calculated for decahydrodipyrrolo[a,d]pyrazine. The other product was a liquid exhibiting the titration curve of a monoamine of molecular weight 152 (theory for N-butyl-2-hydroxymethylpyrrolidine, 157).

If the line of reasoning outlined above is correct, hydrogenation in the absence of butanol should eliminate the formation of N-butyl-2-hydroxymethylpyrrolidine and correspondingly increase the yield of decahydrodipyrrolo[a,d]pyrazine. This conclusion was confirmed by experiment. Since the hydrogenation of butyl pyroglutamate occurs stepwise, it was possible to prevent butylation. Butyl pyroglutamate was hydrogenated in dioxane at 150°, the solvent was completely removed by distillation and hydrogenation was completed at 250° in fresh dioxane. By this procedure the yield of decahydrodipyrrolo[a,d]pyrazine was almost tripled. Furthermore, when a sample of pure 5-hydroxymethyl-2-pyrrolidone was hydrogenated, the yield of decahydrodipyrrolo[a,d]pyrazine was practically quantitative.

Experimental

Dioxane used as reaction medium was purified according to the method of Fieser.[8] Catalyst was prepared as described by Riener.[9] Hydrogenations were effected in a 480-ml. stainless steel bomb at a hydrogen pressure of 2000–3000 p.s.i.

Butyl Pyroglutamate.—Two moles of commercial glutamic acid, 16 moles of butanol and 2.5 moles of sulfuric acid were refluxed for 9 hours. The refluxing liquid was fractionated through an 18″ silvered vacuum-jacketed column, and the water phase was continuously collected and removed. The reaction mixture was brought to *p*H 4.5 with 1 *M* Na_2CO_3, stripped of butanol *in vacuo*, and then brought to *p*H 9.5 with 5 *N* NaOH while being stirred with 1000 ml. of benzene. The aqueous phase was extracted with three 500-ml. portions of benzene. The combined benzene solution was washed with saturated NaCl solution and distilled through a 6″ Vigreux column. Crude product was collected between 158–163° (1.0 mm.). Redistillation gave 242 g. (65% yield), b.p. 157–160° (1.3 mm.).

Anal. Calcd. for $C_9H_{15}NO_3$: N, 7.56. Found: N, 7.39.

5-Hydroxymethyl-2-pyrrolidone.—Thirty-seven grams (0.2 mole) of butyl pyroglutamate in 125 ml. of dioxane was hydrogenated over 18.5 g. of copper–chromium oxide at 150° for 4 hours. The pressure dropped 820 lb. in the first 3 hours and 10 lb. in the last hour. Catalyst was removed by filtration. Titration of an aliquot of the filtrate demonstrated the absence of amino nitrogen. Solvent was distilled *in vacuo*, leaving a residue which readily crystallized; yield 21.5 g. (96%), m.p. 76–78°; recrystallized from benzene, 16 g., m.p. 84–85°.

One-step Hydrogenation of Butyl Pyroglutamate.—Butyl pyroglutamate (37.0 g., 0.2 mole) in 150 ml. of dioxane was hydrogenated over 18.5 g. of copper–chromium oxide at 250° for 5.5 hours. Catalyst and solvent were removed. The residue (20.0 g.) was set in a refrigerator overnight.

Crystals which formed were collected on a buchner funnel; wt. 4.5 g. (27%), m.p. 69–77°. Recrystallization from hexane brought the m.p. to 84.0–84.5°; this solid did not depress the m.p. of an analyzed sample of decahydrodipyrrolo[a,d]pyrazine.

The filtrate remaining after the solid was filtered from the reaction mixture was distilled through a 3″ Vigreux column; yield 6.0 g. (19%), b.p. 70–73° (1.2 mm.). Its titration curve corresponded closely to that expected for N-butyl-2-hydroxymethylpyrrolidine.

Anal. Calcd. for $C_9H_{19}NO$: N, 8.8. Found: N, 8.0.

Two-step Hydrogenation of Butyl Pyroglutamate.—Hydrogenation was effected as in the one-step process, but for 4.5 hours at 150°. Catalyst was filtered off and solvent was completely removed from the filtrate by vacuum distillation. The residue (21.1 g.) was hydrogenated for 5.5 hours at 250° in 150 ml. of dioxane over 21.1 g. of copper–chromium oxide. Catalyst and solvent were again removed. The residue was a white crystalline solid; yield 12.8 g. (77%), m.p. 77–80°. Two recrystallizations from hexane raised the m.p. to 84.0–84.5°; the m.p. was unchanged by an additional crystallization.

Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.26; H, 10.90; N, 16.85. Found: C, 72.43; H, 10.45; N, 17.22.

Hydrogenation of 5-Hydroxymethyl-2-pyrrolidone.—A mixture of 1.4 g. of 5-hydroxymethyl-2-pyrrolidone, 0.7 g. of copper–chromium oxide and 25 ml. of dioxane was hydrogenated for 5.5 hours at 250°. The product was isolated in the usual way; yield 1.0 g. (100%), m.p. 81–82°, mixed m.p. with an analyzed sample, 82.0–82.5°.

GEORGE M. MOFFETT RESEARCH LABORATORIES
CORN PRODUCTS REFINING COMPANY
ARGO, ILLINOIS
RECEIVED JULY 27, 1951

(6) N. J. Leonard and J. H. Boyer, THIS JOURNAL, **72**, 2980 (1950).
(7) N. J. Leonard and W. E. Goode, *ibid.*, **72**, 5404 (1950).
(8) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 369.
(9) T. W. Riener, THIS JOURNAL, **71**, 1130 (1949).

The Preparation of High Purity Silver Chloride

BY WILLIAM ZIMMERMAN, III

Silver chloride containing <0.001% metallic impurities was prepared in large quantities for the growth of single crystals used in plastic flow, solarization and recrystallization studies. Reagent grade AgCl was not sufficiently pure and although a method[1] was available which gave a product containing <0.02% metallic impurities, this method was laborious and time consuming and the product dried to a cake which was difficult to manipulate. The procedure described here gave a granular, easily washed product which dried with the minimum formation of lumps. No single metallic impurity exceeded 0.001%. Reagent grade chemicals were used throughout and were checked spectrographically to determine impurities which might be introduced during preparation. Ammonium hydroxide showed about 0.25% SiO_2,

(1) R. N. Maxson, "Inorganic Syntheses," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, pp. 2–4.

80% of which was removed by filtration. The balance did not interfere since <0.001% SiO_2 was found in the product. All filtrations were carried out in fritted-glass funnels, since any filter paper shreds in the final product caused reduction of AgCl during single crystal growth. Scrap silver salts, washed free of oil and grease with petroleum ether, reagent grade silver salts and silver metal were used as starting materials.

Experimental

The silver salts[2] were reduced with granular zinc (20 mesh, low in As, Fe and Pb) in (1:10) HCl, and the resulting metal was washed thoroughly, first by decantation, and then by filtration. The metallic silver was dissolved in a minimum amount of dilute (1:1) HNO_3. The resulting solution was diluted and tin, antimony, and the insoluble chlorides allowed to settle out. After filtration, the solution was heated, made ammoniacal, and filtered, removing Fe, Al, most of the Tl and some of the SiO_2. The filtrate was made just acid with HNO_3 and evaporated to a small volume, cooled, filtered and the resulting $AgNO_3$ was dissolved in water and filtered. AgCl was precipitated from the filtrate with concentrated HCl in slight excess.[3] After filtration, AgCl was dissolved in a minimum amount of NH_4OH and any residue filtered off. The solution was gently heated with continuous stirring until crystallization began. Removed from the heat, the solution was placed in the dark. Vigorous stirring was continued to prevent formation of a crust and to allow NH_3 to escape. After a sufficient crop of crystals had formed, they were washed, first with water, then with HCl and finally with water. The solution was reheated and a second and third crop of crystals gathered in the same manner. Proper care was taken throughout to recover silver from filtrates and residues.

(2) Silver metal was dissolved in a minimum amount of HNO_3; AgCl was precipitated and washed free of nitrates, then treated as above.

(3) When thallium was present in excess of 0.50%, repetition of the preceding steps was necessary; and when copper was present in large quantities, repetition was deemed advisable.

CRYSTAL BRANCH, METALLURGY DIVISION
NAVAL RESEARCH LABORATORY
WASHINGTON, D. C.

RECEIVED OCTOBER 1, 1951

NEW COMPOUNDS

Preparation of N-Acetylphenyl-2-thienylamine[1,2]

Ten grams (0.075 mole) of acetanilide, 20 g. (0.123 mole) of 2-bromothiophene, 5 g. (0.037 mole) of anhydrous potassium carbonate, about 0.1 g. of a mixture of powdered potassium iodide and powdered copper, a crystal of iodine and 50 ml. of nitrobenzene[3] were stirred in a three-necked 250-ml. flask in a nitrogen atmosphere for 25 hours at 160–170°. The dark mixture was neutralized, steam distilled and the residue cooled. The oil layer was extracted with ether, the ether solution dried with calcium chloride, and the ether removed by vacuum distillation at 100°. The solid, which weighed 14 g., was washed with 50 ml. of Skellysolve A, then dissolved in 25 ml. of hot absolute ethanol, treated with Norite A and filtered. The crystals which separated on cooling were collected on a filter and dissolved in 400 ml. of boiling water by addition of the minimum amount of ethyl alcohol. The precipitate which separated on cooling was collected on a filter and dried in vacuum over sulfuric acid, yielding 2.2 g. (14%) of white crystals melting at 100–101°.

Anal. Calcd. for $C_{12}H_{11}ONS$: N, 6.44; S, 14.74. Found: N, 6.33; S, 14.76.

Experimental conditions sufficiently vigorous to cause hydrolysis of N-acetylphenyl-2-thienylamine invariably resulted in formation of tars.

When 2-iodothiophene was substituted for 2-bromothiophene in the above procedure, a yield of 2.5 g. (31%) of crude N-acetyl phenyl 2-thienylamine was obtained. When 2-chlorothiophene was used, no product was obtained. Use of the method with N-acetyl-2-aminothiophene and iodobenzene gave less than a gram of crude N-acetyl phenyl 2-thienylamine. From N-acetyl-2-aminothiophene and 2-bromothiophene no acetyl-di-2-thienylamine could be obtained.

(1) From the M.S. thesis of Peter Panzera, June, 1949.

(2) This work was supported in part by a Research Corporation Grant-in-aid.

(3) I. Goldberg, *Ber.*, **40**, 4541 (1907).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF KENTUCKY
LEXINGTON, KENTUCKY
REEDUS RAY ESTES
PETER PANZERA

RECEIVED OCTOBER 15, 1951

Preparation of Ethyl Pyrazinoylacetate

A mixture of 13.8 g. of methyl pyrazinoate and 14.8 g. of ethyl acetate was added slowly with stirring to 10.7 g. of alcohol-free sodium ethoxide. After standing at room temperature for one hour, the mixture was refluxed for five hours. The reaction mixture was then cooled, dissolved in 125 ml. of water and extracted with ether to remove the unreacted esters. The solution was neutralized to a *p*H of 7 with hydrochloric acid and exhaustively extracted with ether. The ether extract was dried over sodium sulfate and evaporated to a small volume to give 13 g. (67%) of ethyl pyrazinoylacetate (yellow crystals), which melted at 66–67° when recrystallized from petroleum ether.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 55.6; H, 5.15; N, 14.4. Found: C, 55.7; H, 5.28; N, 14.4.

The following derivatives of ethyl pyrazinoylacetate were prepared: 2,4-dinitrophenylhydrazone, yellow crystals which melted at 187–189° when recrystallized from ethanol.

Anal. Calcd. for $C_{15}H_{16}O_6N_6$: N, 22.5. Found: N (Dumas), 22.8.

Phenylhydrazone, yellow crystals which melted at 131–132° when recrystallized from ethanol.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$: N, 19.7. Found: N (Dumas), 19.5.

3-(2-Pyrazyl)-pyrazolone-5 light tan crystals which melted with decomposition at 245–246° when recrystallized from methanol.

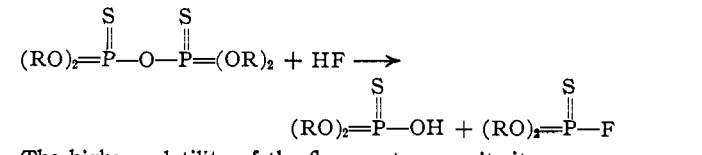
Anal. Calcd. for $C_7H_6N_4O$: N, 34.6. Found: N (Dumas), 34.6.

NEPERA CHEMICAL CO., INC.
NEPERA PARK
YONKERS, NEW YORK
T. I. FAND
DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, N. Y.
P. E. SPOERRI

RECEIVED OCTOBER 5, 1951

Diethylthionomonofluorophosphate

The preparation of dialkylmonofluorophosphoric esters, $(RO)_2POF$, by the interaction of anhydrous hydrogen fluoride with symmetrical pyrophosphoric acid diesters has been previously described.[1] A similar procedure has now been found satisfactory for obtaining analogous thioesters. The general reaction is



The higher volatility of the fluoro-ester permits its separation by fractional distillation from the acid ester.

To 7.8 g. of anhydrous hydrogen fluoride in a platinum bottle cooled in ice 101.2 g. of tetraethyldithionopyrophosphate[2] was slowly added. In spite of some vaporization

(1) A. Hood and W. Lange, THIS JOURNAL, **72**, 4956 (1950).

(2) The tetraethyldithionopyrophosphate was kindly supplied by the Victor Chemical Works. For description of this and related compounds, see A. D. F. Toy, *ibid.*, **73**, 4670 (1951).