The yield of methyl-*p*-trimethylsilylphenyldiphenoxysilane isolated by this procedure was 14%.

In order to minimize the self-destruction of the Grignard, methyl-*p*-bromophenyldi-*o*-cresoxysilane was substituted for the phenoxysilane. The position of the methyl group *ortho* to the silicon–oxygen bond helped to improve the yield of the ester, methyl-*p*-trimethylsilylphenyldi-*o*-cresoxysilane, to 41.5%, by hindering the attack of the Grignard upon the silicon–oxygen bond.

The preparations of methyl-*p*-dimethylaminophenyldichlorosilane (32%) and methyl-*p*-dimethylaminophenyldimethoxysilane (31%) also are described, along with that of methyl-*p*-bromophenyldichlorosilane (28%). The latter compound was used as an intermediate in the preparation of the silicon esters.

Experimental

Methyl-*p*-dimethylaminophenyldichlorosilane.—*p*-Dimethylaminophenyllithium (0.27 mole) in 225 ml. of ethereal solution was added to 80.0 g. (0.54 mole) of methyltrichlorosilane in 500 ml. of ether dropwise and with good stirring. The mix was then refluxed for 0.5 hour, cooled and filtered under nitrogen. Fractional distillation of the filtrate led to the isolation of 20.0 g. (32.0%) of methyl-*p*-dimethylaminophenyldichlorosilane distilling at 106–110° (0.7 mm.), m.p. 41.5°.

Anal. Calcd. for $C_9H_{13}Cl_2NSi$: Cl, 30.22; N, 5.99. Found: Cl, 29.20; N, 6.30.

Methyl-*p*-dimethylaminophenyldimethoxysilane.—*p*-Dimethylaminophenyllithium (0.25 mole) in 225 ml. of ethereal solution was added to 68.0 g. (0.50 mole) of methyltrimethoxysilane in 500 ml. of ether. Treatment as above led to the recovery of 20.0 g. (58.8%) of methyltrimethoxysilane, b.p. 98–100° (760 mm.), and the isolation of 15.4 g. (31.3%) of methyl-*p*-dimethylaminophenyldimethoxysilane distilling at 88–90° (0.3 mm.).

Anal. Calcd. for $C_{11}H_{19}O_2NSi$: C, 58.75; H, 8.51; N, 6.23. Found: C, 58.78; H, 8.41; N, 7.22.

Methyl-*p*-bromophenyldichlorosilane.—To a rapidly stirred solution of 112 g. (0.75 mole) of methyltrichlorosilane in 750 ml. of ether was added 0.5 mole of *p*-bromophenylmagnesium bromide in 500 ml. of ethereal solution. The mix was then refluxed for 2.0 hr., allowed to stand overnight and filtered under nitrogen. The ether and excess methyltrichlorosilane were distilled and the residual oil carefully fractionated under reduced pressure.

Cut 1 distilled at 89–91° (0.7 mm.). The distillate partially solidified on cooling. The liquid portion was decanted and redistilled. A forerun, which solidified on reaching the water condenser, distilling at 64–68° (0.3 mm.) and a liquid fraction distilling at 65–68° (0.3 mm.) were obtained. The solid was combined with that previously isolated. The liquid fraction was then subjected to vacuum sublimation; the liquid was maintained at 100° and 0.2 mm., and the solid which sublimed was caught on the walls of a cold finger condenser. Cut 2 distilled at 94–174° (0.7 mm.). This fraction was redistilled to yield a solid forerun distilling at 58–60° (0.3 mm.) and a liquid fraction distilling at 67–70° (0.3 mm.).

The combined solid was crystallized from ethanol to yield 3.0 g. of *p*-dibromobenzene melting at 83–85°. The two liquid fractions were combined to give a total of 37.1 g. (27.5%) of methyl-*p*-bromophenyldichlorosilane.

Anal. Calcd. for $C_7H_7BrCl_2Si$: C, 31.13; H, 2.58. Found: C, 31.41; H, 2.73.

Methyl-*p*-bromophenyldiphenoxysilane.—In a 1-l. flask were placed 57.9 g. (0.213 mole) of methyl-*p*-bromophenyldichlorosilane, 23 g. (0.25 mole) of triethylamine and 250 ml. of ether. To this was added 40.0 g. (0.426 mole) of phenol and 22 g. (0.25 mole) of triethylamine in 250 ml. of ether, dropwise and with good stirring. The mix was refluxed for 4 hours, cooled and filtered. The ether was distilled and the residue was fractionally distilled under reduced pressure.

Cut 1 distilled at 56–90° (3.0 mm.) as a semi-solid with a pronounced phenol-like odor. Cut 2 distilled at 190–206° (1.1 mm.) as a viscous yellow oil, wt. 58.9 g. This material was redistilled to yield 43.5 g. (54.4%) of methyl-*p*-bromophenyldiphenoxysilane distilling at 183–185° (0.9 mm.), m.p. 43–44°.

Anal. Calcd. for $C_{19}H_{17}BrO_2Si$: C, 59.23; H, 4.45. Found: C, 57.63; H, 4.55.

The Methyl-*p*-bromophenyldi-*o*-cresoxysilane.—Crude methyl-*p*-bromophenyldichlorosilane was prepared by the addition of 0.70 mole of *p*-bromophenylmagnesium chloride (from 165.2 g. (0.7 mole) of *p*-dibromobenzene and 17.0 g. (0.7 g. atom) of magnesium) in 750 ml. of ether to 1.4 moles of methyltrichlorosilane in 2 l. of ether; the ethereal solution was filtered, and the ether and excess methyltrichlorosilane removed by distillation. To the crude material was added 71.0 g. (0.7 mole) of triethylamine and 1 l. of ether. A solution of 151.0 g. (1.4 moles) of *o*-cresol and 71.0 g. of triethylamine in 250 ml. of ether was added to the reaction solution in a thin stream with good stirring. The mix was then stirred overnight, filtered and the solvent distilled. The residue was then distilled under reduced pressure.

Cut 1 distilled at 60–140° (1.3 mm.). When this was redistilled at 1 atm., 44.1 g. (29.2%) *o*-cresol was recovered. Cut 2 distilled at 170–285° (1.3 mm.). This was redistilled to give a small forerun and 66.5 g. (22.3%) of methyl-*p*-bromophenyldi-*o*-cresoxysilane distilling at 196–200° (1.0 mm.).

Anal. Calcd. for $C_{21}H_{21}BrO_2Si$: C, 61.10; H, 5.12. Found: C, 61.05; H, 5.10.

Methyl-*p*-trimethylsilylphenyldiphenoxysilane.—In a 100-ml. flask were placed 14.3 g. (0.037 mole) of methyl-*p*-bromophenyldiphenoxysilane, 0.9 g. (0.37 g. atom) of magnesium turnings, 8.0 g. (0.074 mole) of trimethylchlorosilane and 50 ml. of ether. The reaction was initiated by the addition of 0.5 ml. of ethyl bromide, and was stirred and refluxed for 3.5 hr. On cooling, the mix was filtered, the ether removed by distillation and the residue distilled under reduced pressure. One fraction distilling at 156–180° (1.0 mm.) was obtained. This was redistilled to yield 2.0 g. (14.0%) of methyl-*p*-trimethylsilylphenyldiphenoxysilane distilling at 172° (1.0 mm.).

Anal. Calcd. for $C_{22}H_{26}O_2Si_2$: C, 69.80; H, 6.93. Found: C, 70.12; H, 6.12.

Methyl-*p*-trimethylsilylphenyldi-*o*-cresoxysilane.—In a 300-ml. flask were placed 31.5 g. (0.076 mole) of methyl-*p*-bromophenyldi-*o*-cresoxysilane, 16.5 g. (0.152 mole) of trimethylchlorosilane, 3.4 g. (0.15 g. atom) of magnesium turnings and 100 ml. of ether. The reaction was initiated by the addition of 4.3 g. (0.04 mole) of ethyl bromide and was then stirred and refluxed for 6 hr. The mix was cooled, filtered, the ether removed by distillation and the residue distilled under reduced pressure. After a small forerun, the fraction distilling at 175–200° (1.0 mm.) was collected. This was carefully redistilled to yield 12.8 g. (41.5%) of methyl-*p*-trimethylsilylphenyldi-*o*-cresoxysilane distilling at 182–185° (0.6 mm.).

Anal. Calcd. for $C_{24}H_{30}O_2Si_2$: C, 70.90; H, 7.44. Found: C, 72.94; H, 7.03.

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Low and High *p*H Effects in Serum Albumin[1]

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Serum albumin exhibits various anomalies in its reactivity with hydrogen ions[2] and other low molecular weight ions and molecules[3] at low and high *p*H. The cause of these anomalies would be better understood if information were available about the configuration of serum albumin over the

(1) The part of this work carried out at Cornell University was supported by the Office of Naval Research and Eli Lilly and Co.

(2) C. Tanford, *Proc. Iowa Acad. Sci.*, **59**, 206 (1952); Abstracts of September 1954 ACS meeting, p. 77C.

(3) I. M. Klotz and J. Ayers, *Disc. Faraday Soc.*, **13**, 189 (1953).

whole *p*H range. Recently,[2] the suggestion has been made that serum albumin has a greatly expanded or unfolded configuration at low and high *p*H, a suggestion which is supposedly reconciled with various hydrodynamic and thermodynamic data. It is the purpose of this note to point out that heterogeneity may play a role not heretofore considered, thereby raising a question about previous interpretations based on the assumption that the albumin is monodispersed. This heterogeneity at low and high *p*H is observed in both human and bovine serum albumin.

Experimental

Materials.—The bovine albumin was Armour crystallized product (lot No. ACB 30 and 370295B) while the human albumin was prepared at Harvard Medical School. All non-protein components were reagent grade materials.

Ultracentrifuge.—Sedimentation velocity experiments were carried out with the Spinco ultracentrifuge at 59,780 r.p.m. at room temperature. Sedimentation constants were computed in the usual manner.[4]

Results and Discussion

In the intermediate *p*H range (4–11) both human and bovine albumin have a sedimentation pattern showing a single peak. It may be noted, however, that even the best of the preparations had about 5% of a heavier component detectable as a small shoulder on the main peak. Figure 1 shows the sedimentation patterns of bovine and human albumin in the *p*H region of interest. The protein concentration is 1 g./100 ml. in most cases. The sedimentation constant depends on *p*H and is approximately 4 Svedberg units at this concentration under the temperature and buffer conditions of the ultracentrifuge runs.

At low *p*H, both sodium acetate and sodium chloride in high concentrations (about 0.3 *M*) produce sedimentation patterns suggestive of heterogeneity. For example, at *p*H 3.5 bovine serum albumin in an acetate buffer (NaAc = 0.1 *M*) appears homogeneous, even after aging for two days at 1°. However, if the ionic strength is increased with sodium acetate or sodium chloride, or if the solution is allowed to stand at 1° for a long period of time, heavy components appear with sedimentation values of approximately 6 and 19 Svedberg units in a 1% solution. The behavior of human and bovine albumin differs in the distribution of the heavier components, and in the rates at which they appear. These effects are reversible, *i.e.*, if the acid solution is dialyzed against alternate changes of distilled water and a *p*H 6.6 phosphate buffer (ionic strength = 0.1), the heterogeneity disappears and the turbidity returns to its original appearance.

Similarly, at and above *p*H 11.5 the sedimentation patterns of bovine serum albumin in the presence of high salt concentration indicate heterogeneity (Fig. 1).

The sedimentation behavior of modified albumins differs somewhat from that of the native human and bovine albumin. Thus, methylated bovine serum albumin[5] with approximately all of the carboxyl groups esterified showed a single peak in acid solutions with low concentrations of salt, and more than one peak with both increasing salt concentration and increasing *p*H. Crystalline guanidinated human serum albumin with approximately all of the lysine amino groups converted to

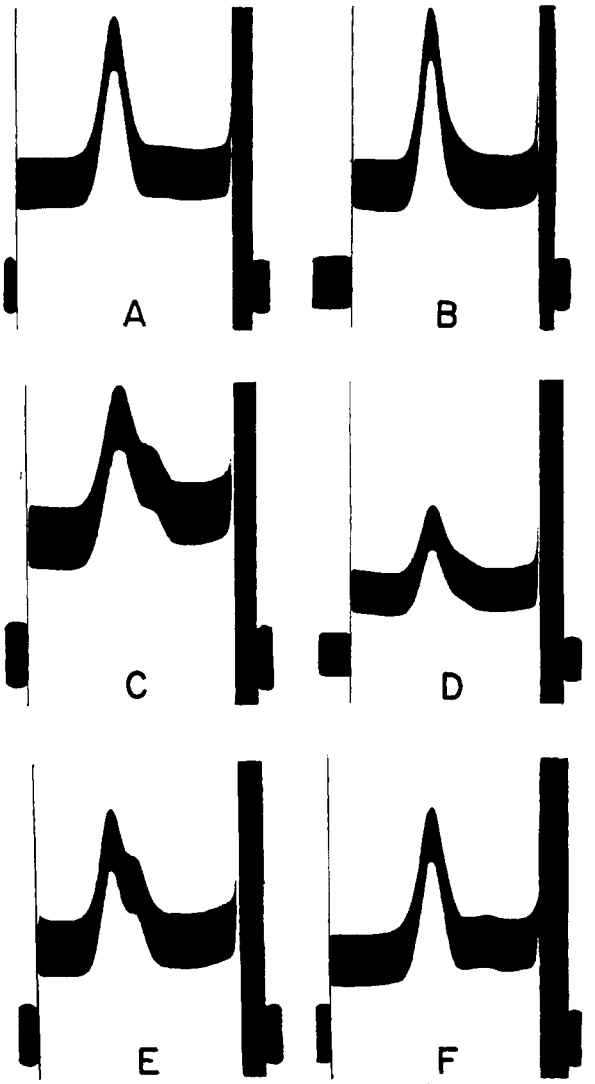

Fig. 1.—Sedimentation patterns of human and bovine serum albumin at 59,780 r.p.m.; concn. 1 g./100 ml. unless otherwise specified: A, bovine albumin, 96 min. in 0.1 *M* potassium chloride, *p*H 4.9, $S_{20,w}$ = 4.0; B, bovine albumin, 88 min. in 0.1 *M* sodium acetate, *p*H 3.5, age of solution one day, $S_{20,w}$ = 3.4; C, human albumin, 1.25 g./100 ml., 98 min. in 0.046 *M* sodium acetate and 0.3 *M* sodium chloride, *p*H 3.5, age of solution two days, at 23°, $S_{20,w}$ = 3.9 and 6. Bovine albumin under these conditions has a similar sedimentation pattern; D, bovine albumin, 86 min. in 0.5 *M* potassium chloride, *p*H 11.5. The heterogeneity becomes more pronounced at *p*H 12 (not shown); E, bovine albumin, 96 min. in 0.1 *M* sodium acetate, *p*H 3.5, age of solution 5 months below 3°, $S_{20,w}$ = 3.4 and 6; F, bovine albumin jelled in 0.3 *M* sodium chloride, *p*H 3.5, at room temperature for two weeks. Redissolved by dialyzing against water and *p*H 6.6 phosphate buffer. Sedimentation run, 96 min. in sodium phosphate, ionic strength = 0.1, *p*H 6.6, $S_{20,w}$ = 3.9.

(4) The authors are indebted to E. R. Adamik for some of the sedimentation determinations.

(5) H. A. Saroff, N. R. Rosenthal, E. R. Adamik, N. Hages and H. A. Scheraga, *J. Biol. Chem.*, **205**, 255 (1953).

the guanidino group[6] exhibited heterogeneity at about *p*H 5 and remained monodispersed at *p*H 6.5. The appearance of heterogeneity in both of these albumin derivatives was found to be reversible.[7]

Further work is being done on this problem in the intermediate *p*H range of 4 to 11.

In view of these heterogeneity effects, some of which also have been observed by Reichmann and Charlwood,[8] it would seem questionable as to whether one could make an unambiguous statement about the configuration of albumin at low and high *p*H. It is, therefore, not yet possible to decide whether the anomalous reactivity of serum albumin at low and high *p*H can be attributed either to expansion of the molecule[2] or to reversible formation and breakage of internal hydrogen bonds.[9] It may be that both effects are present.

(6) W. L. Hughes, Jr., H. A. Saroff and A. L. Carney, THIS JOURNAL, **71**, 2476 (1949).

(7) The sedimentation studies on the guanidinated albumin were made several years ago by H. A. Saroff while at the Department of Physical Chemistry, Harvard Medical School.

(8) M. E. Reichmann and P. A. Charlwood, *Can. J. Chem.*, **32**, 1092 (1954).

(9) M. Laskowski, Jr., and H. A. Scheraga, THIS JOURNAL, **76**, 6305 (1954).

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A Mechanical Resolution of *dl*-Methadone Base

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The potent analgesic *l*-methadone has been separated from its much less active optical antipode by a number of workers. Crystallization of the diastereoisomeric acid *d*-tartrates from acetone[1] and *n*-propyl alcohol[2] leads to the preferential deposition of *l*-methadone *d*-tartrate. A cleaner separation is obtained with *d*-α-bromocamphor-π-sulfonic acid which forms a water-insoluble salt with *d*-methadone and a water-soluble one with the *l*-form.[3]

This note reports a successful resolution of *dl*-methadone by slow crystallization of the base from a concentrated petroleum ether solution seeded with two crystals of the pure *d*-base and two crystals of the pure *l*-base, both obtained in the conventional manner by preliminary resolution through the acid *d*-tartrates. Nearly 50% of the original *dl*-mixture was recovered in the form of four crystals (one weighed 11 g.), far from physically perfect, but of optical purity equal to that of the seeds from which they were grown.

Experimental

The apparatus consisted of a cylindrical glass jar 90 mm. in diameter with straight sides 80 mm. high fitted with a metal screw cap (neither lined nor gasketed) in the center of which a round hole was cut to accommodate a no. 4 rubber stopper. A glass tube (8 mm. inside diameter), extending through the stopper, was equipped with a silicone lubricated rubber seal which served as a bearing for the stirrer. The stirrer was made of a 5-mm. glass rod bent at a point just below the end of the bearing tube so that the resulting radius of eccentricity of the rotating stirrer was approximately half the radius of the cylindrical container.

Fifty-six grams of *dl*-methadone base was dissolved in 225 cc. of boiling petroleum ether (b.p. 63–68°, Skellysolve B) and filtered by gravity into the open cylindrical jar. The solution was concentrated on the steam-bath to a volume of 145 cc. The metal cap with the stirrer inserted was then screwed to the top of the jar which was placed in an oven held at 40°. During the cooling process stirring at 240–250 r.p.m. was accomplished by means of a constant speed stirring motor placed above the oven and attached to the stirrer shaft extending through the oven vent. (A temperature-controlled water-bath probably could be substituted for the oven, with the result that observational conditions of the experiment would be greatly improved.)

When temperature equilibrium was attained, the cap was removed and two seeds each of pure *d*- and *l*-methadone base were placed in alternating order around the perimeter of the container bottom, so that seeds of like sign were directly opposite each other. The seeds used were approximately 2–3 mm. across and were taken, still wet with solvent, directly out of the petroleum ether (Skellysolve B) solution from which they had been freshly crystallized. The screw cap was replaced and stirring was resumed at the same rate as before and was continued at 40° for 125 hours. During this time approximately one-fourth of the solvent evaporated through the threads of the screw cap and two large and two smaller crystals grew from the original seeds. The two crystals of *l*-methadone weighed 8.8 g. ($[\alpha]^{25}D$ −35.7°, *c* 4, Skellysolve B) and 4.2 g. ($[\alpha]^{25}D$ −36.2°, *c* 4, Skellysolve B). The two crystals of *d*-methadone weighed 11.2 g. and 1.9 g. (combined $[\alpha]^{25}D$ + 36.0°, *c* 4, Skellysolve B). The total of 26.1 g. of resolved material represents a 46% yield, but 29.0 g. of *dl*-methadone was obtained from the residual solution to give a nearly quantitative recovery of product.

The optical purity of the resolved material was further tested by grinding together the two crystals of like sign and measuring the rotation of a solution in absolute ethanol: *l*-form, $[\alpha]^{27}D$ −26.8° (*c* 4.10, *l* 2 dcm.); *d*-form, $[\alpha]^{27}D$ +26.5° (*c* 4.00, *l* 2 dcm.).

Brode and Hill[1] reported the values $[\alpha]^{22}D$ −29.91° (*c* 2.66, *l* 2 dcm., absolute ethanol) for *l*-methadone base and $[\alpha]^{26}D$ +29.51° (ethanol) for the *d*-form. Larsen and coworkers[2] reported the values $[\alpha]^{25}D$ −26° and +26° (*c* 1.5, U.S.P. ethanol) for *l*- and *d*-methadone, respectively. Walton, Ofner and Thorp[4] reported the values $[\alpha]^{22}D$ −32° (alcohol) and $[\alpha]^{20}D$ +28° (alcohol) for the two optical isomers of methadone.

(1) W. R. Brode and M. W. Hill, *J. Org. Chem.*, **13**, 191 (1948).

(2) A. A. Larsen, B. F. Tullar, B. Elpern and J. S. Buck, THIS JOURNAL, **70**, 4194 (1948).

(3) E. E. Howe and M. Sletzinger, *ibid.*, **71**, 2935 (1949).

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Substituted Malononitriles of the Type Aryl $CH_2CX(CN)_2$

BY J. C. WESTFAHL AND T. L. GRESHAM

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Recent work in this Laboratory has made available a series of monosubstituted malononitriles of the type Aryl $CH_2CH(CN)_2$.[1] This paper reports some of the results of a study of these compounds.

In agreement with the observations of Hessler,[2] benzylmalononitrile (I) and in general Aryl $CH_2CH(CN)_2$ were soluble in aqueous sodium hydroxide, and when precipitated promptly by the addition of a mineral acid were recovered unchanged.

(1) J. C. Westfahl and T. L. Gresham, THIS JOURNAL, **76**, 1076 (1954).

(2) J. C. Hessler, *Am. Chem. J.*, **22**, 181 (1899)