Experimental[7]

Methyl diacetyl-L-threuronate (I) was prepared according to the directions of Lucas and Baumgarten,[8] and the constants agreed closely with those reported: m. p. 82–83°; $[\alpha]^{20}D$ −55.8° → −39.0° after 5 days (33.9 mg. per ml. in MeOH).

The decarboxylation of I in 12% hydrochloric acid was carried out in a manner similar to that described by Yackel and Kenyon,[9] the evolved carbon dioxide being absorbed in tubes filled with Ascarite and weighed.

Treatment of Methyl Diacetyl-L-threuronate with Sulfuric Acid.—The procedure described by Neuberg, *et al.*,[5] for the conversion of dihydroxyacetone to methylglyoxal was used. To a 100-ml. distilling flask equipped with a dropping funnel were added 1 g. of I and a mixture of 10 ml. of water and 2 g. of concentrated sulfuric acid. The mixture was distilled, water being added through the dropping funnel at such a rate as to maintain a constant liquid volume in the flask. Two hundred and forty ml. of distillate was collected, which yielded 0.567 g. of crude methylglyoxal phenylosazone (52%). Recrystallization from ethanol yielded 0.452 g. of product melting at 143.5–145°.

For the preparation of the semicarbazide derivative[6] 200 ml. of distillate was collected from 0.85 g. of I. One g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate (anhyd.) were added, whereupon the solution quickly became cloudy and a crystalline precipitate formed. The mixture was heated on a steam-bath for half an hour. After standing in a refrigerator for twelve hours, the crystals were filtered off and washed with water. Pure methylglyoxal bis-semicarbazone (0.283 g.) of m. p. 270° (with decomposition) was thus directly obtained. The m. p. remained unchanged on recrystallization from a methanol–water mixture. On concentrating the mother liquor to 20 ml., 0.012 g. of solid melting at 260–262° (with decomposition) was obtained. The total yield was 39%.

Treatment of I with Hydrochloric Acid.—One gram of I in 25 ml. of 12% hydrochloric acid was heated on a steam-bath for one-half hour. A hot solution of 0.5 g. of 2,4-dinitrophenylhydrazine in 25 ml. of 12% hydrochloric acid was then added, whereupon an immediate reddish-orange precipitate was obtained. The solution was filtered while hot and the precipitate washed copiously with hot water, then with a small amount of ethanol and dried (wt., 0.45 g.). Upon recrystallization from dioxane, 0.23 g. of fine reddish-orange needles of methylglyoxal 2,4-dinitrophenylosazone of m. p. 305–306° (with decomposition) were obtained.

(7) All melting points are corrected.

(8) Lucas and Baumgarten, THIS JOURNAL, **63**, 1653 (1941).

(9) Yackel and Kenyon, *ibid.*, **64**, 121 (1942).

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF AGRICULTURE
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

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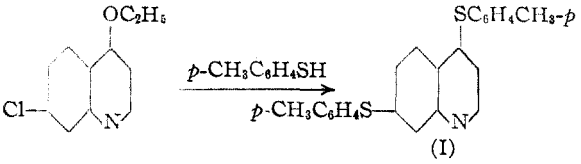
Displacement of Nuclear Hydroxyl in Quinoline Series by Aryl-S Group

BY G. ILLUMINATI AND HENRY GILMAN

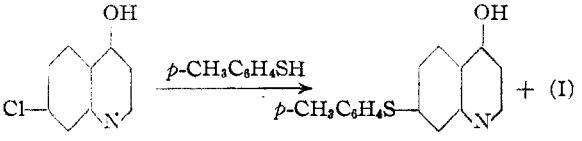
In connection with studies[1] concerned with the cleavage of alkoxy-substituted heterocycles by thiols, one of the reactions examined was that of 4-ethoxy-7-chloroquinoline with *p*-thiocresol. It was observed that the chief product of this reaction was 4,7-di-(*p*-thiocresoxy)-quinoline.

We are now reporting the interesting replacement of a nuclear hydroxyl group, under corresponding conditions, by the *p*-$CH_3C_6H_4S$– group.

(1) Illuminati and Gilman, THIS JOURNAL, **71**, 3349 (1949); see, also, Hughes and Thompson, *Nature*, **164**, 365 (1949).



When 4-hydroxy-7-chloroquinoline is heated with *p*-thiocresol, there is obtained a mixture of 4-hydroxy-7-*p*-thiocresoxyquinoline, and 4,7-di-(*p*-thiocresoxy)-quinoline.



Experimental

4-Hydroxy-7-chloroquinoline.—A solution of 30 g. (0.1515 mole) of 4,7-dichloroquinoline (m. p. 84–85°) in 375 ml. of 10% hydrochloric acid was refluxed for ten hours. On allowing the solution to stand for a few hours in a refrigerator, most of the product separated. The filtrate from these white crystals yielded more of the product after making the solution strongly alkaline, filtering, and acidifying with acetic acid. The combined yield of 4-hydroxy-7-chloroquinoline, melting 270–275°, was 26.5 g. (97%). Recrystallization from hot pyridine gave 18 g. (66.1%) of compound melting at 276–280°. The melting point of 4-hydroxy-7-chloroquinoline obtained[2] by decarboxylation of 3-carboxy-4-hydroxy-7-chloroquinoline was 270–272°.

Anal. Calcd. for C_9H_6ONCl: Cl, 19.73. Found: Cl, 19.79.

It should be noted, in connection with the subsequent reactions of this compound, that the 4-hydroxy-7-chloroquinoline could not have been contaminated by any 4-ethoxy-7-chloroquinoline.

Reaction of 4-Hydroxy-7-chloroquinoline with *p*-Thiocresol.—A mixture of 13.3 g. (0.075 mole) of 4-hydroxy-7-chloroquinoline and 27.9 g. (0.225 mole) of *p*-thiocresol was heated at reflux temperature (the initial internal temperature being 190°). The quinoline compound dissolved after heating for a few hours, and the mixture became homogeneous when the temperature was about 210°. The total time of heating was eight hours. The reaction mixture, on cooling, had a glassy appearance. This mixture was resolved into its components by treatment with an ether (100 cc.)–5% sodium hydroxide solution (100 cc.). The shaking was repeated with fresh solvents until complete solution was attained. To the alkaline layer was added petroleum ether (b. p. 63–67°), and this mixture was acidified with acetic acid. The solid which separated on acidification was 4-hydroxy-7-*p*-thiocresoxyquinoline. The crude yield of this compound (m. p. 215–235°) was 6.7 g. Recrystallization from 95% ethanol gave 5.2 g. (26%) of crystals melting at 237–242°. The sample used for analysis melted at 242–245°.

Anal. Calcd. for $C_{16}H_{13}ONS$: S, 12.02. Found: S, 12.15.

The other product, 4,7-di-(*p*-thiocresoxy)-quinoline, was isolated from the ether layer in the usual manner. The crude yield was 18.2 g. (m. p. 90–96°). Recrystallization from 95% ethanol gave 11.5 g. (43.2%) melting at 97–99°. Another crystallization gave the pure compound melting at 100.5–101.5°. This compound was shown to be identical, by the method of mixed melting points, with the compound described previously,[1] which was obtained by reaction of 4,7-dichloroquinoline with *p*-thiocresol.

(2) Price, *et al.*, THIS JOURNAL, **68**, 1204–1208 (1946). See Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944), for the preparation of 4-hydroxy-6-chloroquinoline by the hydrochloric acid hydrolysis of 4,6-dichloroquinoline.

Essentially similar results were obtained in another experiment.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

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Effect of Wetting on the Nitrogen Adsorption–Desorption Isotherm of a Silica Aerogel

BY MARVIN F. L. JOHNSON AND HERMAN E. RIES, JR.

A large pore, high area silica aerogel has been transformed without sintering into a small pore xerogel structure with negligible change in BET area.[1] The silica aerogel was prepared under the supervision of Dr. J. L. Gring of these Laboratories, using the methanol exchange method of Kistler.[2] The small pore xerogel type sample was obtained by immersing the aerogel in water (room temperature, 1.5 hours) followed by drying (110°, 12 hours; 593°, 2 hours).

The two nitrogen adsorption–desorption isotherms (Fig. 1) nearly coincide in the lower relative pressure region indicating similar BET areas: aerogel, 796 sq. m./g.; wetted aerogel (xerogel), 813 sq. m./g. BET plots are good straight lines in the 0.05 to 0.25 relative pressure range for both materials. The aerogel adsorption at p_0 is six times that of the small pore system whose structure is a xerogel type. Pore volumes are thus, respectively, 3.90 cc./g. and 0.66 cc./g. Average pore radius (or platelet separation) calculations[3] from pore volume and BET area show a reduction from 98 to 16 Å. by the treatment. These average radii are in qualitative agreement with Kelvin radii calculated from the steepest portions of the desorption curves; that of the aerogel is also in agreement with electron microscope observations. The desorption isotherms, furthermore, demonstrate narrow pore size distributions for both materials.

Kistler, Fischer and Freeman have suggested a three-dimensional network of needles or filaments as the probable structure of silica aerogels and presumably of xerogels.[4] According to this picture and the adsorption data, drying a wetted aerogel causes shrinkage or the closer packing of the needle-like fibers whose combined surfaces comprise the total catalyst area. Additional observations qualitatively supporting this picture of the structure are: the very low bulk density of the aerogel, 0.14 g./cc.; the increase in density to 0.49 g./cc. on treatment; the extreme fragility of the aerogel compared to the xerogel. Furthermore, the optical microscope shows uniformity in the xerogel structure in agreement with the narrow distribution of pore size.

The above observations indicate that reexposure of an aerogel to water effects a contraction with no significant change in the surface area. Presumably, the same surface tension forces are operative as those which cause any hydrogel to contract during drying to the xerogel stage. The data appear to support the proposed picture of gel structure.[4] The results also support the applicability of the BET area method to small pore structures since it is generally accepted for large pore systems.

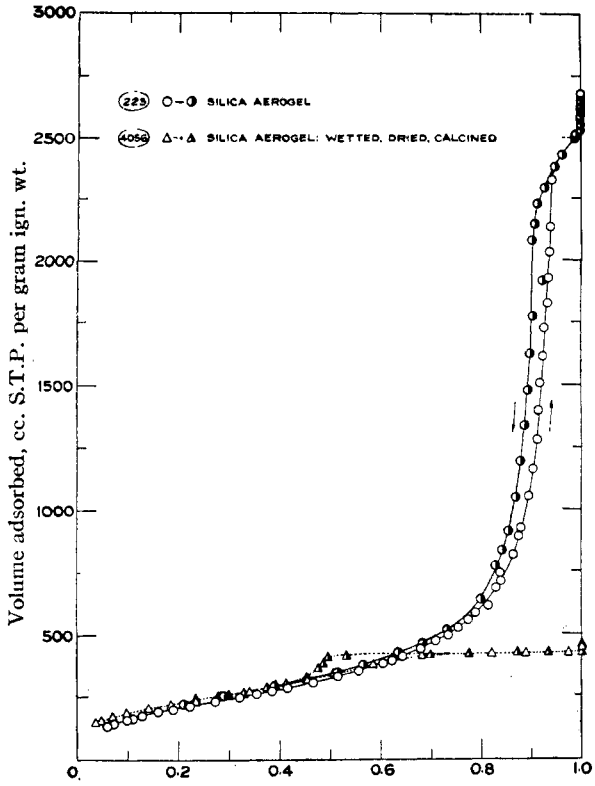

Fig. 1.—Effect of wetting on the nitrogen adsorption–desorption isotherm of a silica aerogel.

RESEARCH AND DEVELOPMENT DEPARTMENT
SINCLAIR REFINING COMPANY
HARVEY, ILLINOIS

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Inhibition of Trypsin by Cholesteryl Malonic Acids and by *i*-Cholesteryl Acetic Acid

BY EMIL KAISER AND ROBERT HUBATA

The trypsin inhibiting effects of crystalline proteins prepared from pancreas,[1] from soybean meal,[2] and from egg white[3] have been reported. Salts of fatty acids,[4] salts of citric acid,[5] carbonyl

(1) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).
(2) Kistler, *J. Phys. Chem.*, **36**, 52 (1932).
(3) Ries, Johnson and Melik, *J. Phys. Colloid Chem.*, **53**, 638 (1949).
(4) Kistler, Fischer and Freeman, THIS JOURNAL, **65**, 1909 (1943).

(1) (a) Northrop, Kunitz and Herriott, "Crystalline Enzymes," Columbia University Press, New York, N. Y., 1948; (b) Kazal, Spicer and Brahinsky, THIS JOURNAL, **70**, 3034 (1948).
(2) (a) Ham and Sanstedt, *J. Biol. Chem.*, **154**, 505 (1944); (b) Bowman, *Proc. Soc. Exp. Biol.*, **57**, 139 (1944); (c) Kunitz, *J. Gen. Physiol.*, **30**, 219 (1947).
(3) Balls and Swensen, *J. Biol. Chem.*, **106**, 409 (1934).
(4) Peck, THIS JOURNAL, **64**, 487 (1942).
(5) Pamfil and Maxim, *Klin. Woch.*, **17**, 1651 (1938).