acetic acid in the usual way and distilled. The product boiled at 175° (2 mm.); yield 27 g. (79%).

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.94; H, 8.30; N, 5.49. Found: C, 79.76; H, 8.39; N, 5.66.

These values are in agreement with the empirical formula of *o*-anilinophenyldiethylcarbinol.

The product was dehydrated by dissolving in concentrated sulfuric acid and pouring into water. Distillation of the oil obtained and crystallization from hexane separated it into a white solid, m. p. 90–91°, and an oil, b. p. 150–155° (2 mm.).

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.02; H, 8.07; N, 5.91. Found for the solid: C, 85.99; H, 8.19; N, 6.08. Found for the oil: C, 86.01; H, 8.10; N, 5.89.

The oil contained a small amount of the solid and was probably largely an *o*-pentenyldiphenylamine. The solid was shown to be 5,5-diethylacridane by its synthesis as follows: 18 g. (0.092 mole) of acridone was added rapidly to 0.3 mole of ethylmagnesium bromide in 150 cc. of *n*-butyl ether at 100°. A vigorous reaction ensued causing the temperature to rise to 120°. The mixture was refluxed and stirred for two hours. When this was poured into water a greenish precipitate separated which was filtered off after the addition of 25 cc. of acetic acid and standing overnight; yield 7 g.; m. p. 250–270°. The ether layer was separated and distilled. A fraction, b. p. 150°(2 mm.)–165° (3 mm.), weighing 11 g. and a residue of 5 g. was obtained. The fraction, b. p. 150°(2 mm.)–165° (3 mm.) gave 7 g. (34% yield) of 5,5-diethylacridane which when recrystallized from hexane melted at 90–92° alone or mixed with the solid product obtained from methyl N-phenylanthranilate.

5,5-Di-*n*-butylacridane.—This compound was prepared in refluxing ethyl ether from 13 g. (0.067 mole) of acridone and 0.4 mole of *n*-butylmagnesium bromide. The initial reaction took place rapidly. After thirty minutes the ethyl ether was distilled off and the mixture refluxed in *n*-butyl ether for thirty minutes. The mixture was hydrolyzed in the usual manner with acetic acid and the product distilled and crystallized from hexane; m. p. 87–88°, b. p. 173–183° (2 mm.). The yield of pure product was 4 g. (24%).

Anal. Calcd. for $C_{21}H_{27}N$: C, 85.94; H, 9.28; N, 4.78. Found: C, 85.96; H, 9.16; N, 4.86.

Summary

1. The preparation of 5,5-dialkylacridanes by the reaction of acridines, acridinium iodides, acridone and methyl N-phenylanthranilate with Grignard reagents is described.

2. The following new compounds were prepared: 5,5-dimethylacridane, 5,5,10-trimethylacridane, 5,5-diethylacridane, *o*-anilinophenyldiethylcarbinol, 5,5-di-*n*-butylacridane and the double compounds of acridine and 5-methylacridine with 5,5-dimethylacridane.

3. The properties of 5,5-dimethylacridane are described in considerable detail.

AKRON, OHIO RECEIVED FEBRUARY 28, 1936

[CONTRIBUTION FROM THE LABORATORIES OF THE WM. S. MERRELL COMPANY]

The Synthesis of Dibenzoyl Disulfide

BY R. S. SHELTON AND T. H. RIDER

Amberg and Brunsting[1] recently investigated the use of dibenzoyl disulfide,[2] and found it of considerable value as an antipruritic. Their favorable preliminary clinical report suggested that a detailed study of the properties and methods of preparing dibenzoyl disulfide might be of interest and value, especially as applied to the commercial production of a medicinally pure product.

A check of the previous literature[3] on this product failed to give a method of preparation which was economically feasible.

It was found early in this investigation that sodium thiobenzoate is easily formed by the reaction of benzoyl chloride with 35% aqueous sodium hydrosulfide. The thiobenzoate was not, however, oxidized to any great extent in the reaction mixture to the desired disulfide. The reaction was tried in alcoholic solution, but without much better result, due to the reaction of the alcohol with the acid chloride.

A further investigation of the oxidation of the thiobenzoate yielded satisfactory results. Engelhardt, Latschinoff and Malyscheff[4] had previously studied the oxidation of thiobenzoic acid by the action of air, cupric sulfate, ferric chloride, potassium triiodide and potassium ferricyanide. These and other oxidation agents were investi-

(1) S. Amberg and L. A. Brunsting, *Proc. Staff Meet. Mayo Clinic*, **8**, 443 (1933).

(2) Dibenzoyl disulfide was referred to in the original clinical report[1] as "benzoyl persulphide," an inaccurate nomenclature since it does not distinguish between the di-, tri- or tetra-sulfides, all of which are known [I. Block and M. Bergmann, *Ber.*, **53**, 961 (1920)].

(3) E. Fromm, *Ann.*, **348**, 144 (1906); A. Weddige, *J. prakt. Chem.*, **2**, 459 (1871); E. Moness, W. A. Lott, F. F. Berg and W. G. Christiansen, Portland Meeting, American Pharmaceutical Association, August, 1935; Wöhler and Liebig, *Ann.*, **3**, 267 (1832); A. Engelhardt, P. Latschinoff and S. Malyscheff, *Z. chem.*, 11, 353 (1868); I. Block and M. Bergmann, *Ber.*, **53**, 961 (1920); J. v. Braun, *ibid.*, **36**, 2259 (1903); A. Binz and Th. Marx, *ibid.*, **40**, 3855 (1907); S. Mosling, *Ann.*, **118**, 305 (1861); L. Szperl, *Roczniki Chemji*, **10**, 510 (1930); *C. A.*, **25**, 503 (1931).

(4) A. Engelhardt, P. Latschinoff and S. Malyscheff, *Z. chem.*, 11, 353 (1868).

gated and concentrated hydrogen peroxide was found to give the best results. It was found also that thiobenzoic acid is oxidized more smoothly than the sodium salt, and that oxygen was very useful in aiding the oxidation of the thiobenzoate as it was formed in the reaction mixture. From these preliminary findings, a method was developed,[5] easily applicable to large-scale production, in which thiobenzoic acid is oxidized as completely as possible by air and oxygen at the time of its formation in the reaction mixture, and after acidification the oxidation of the filtrate is completed with concentrated hydrogen peroxide.

$$C_6H_5COCl + 2NaHS \longrightarrow C_6H_5SOSNa + NaCl + H_2S$$

$$2C_6H_5COSNa \text{ (also } C_6H_5COSH) + H_2O_2 \xrightarrow{[O]} C_6H_5COSSCOC_6H_5 + H_2O$$

Experimental

A 22-liter flask is fitted with a motor stirrer, inlet tubes for oxygen, a tube connected to the water pump to aid in the removal of hydrogen sulfide and a dropping funnel. The flask is placed in an ice-bath, and to it is added 10.6 liters of commercial 35% sodium hydrosulfide solution. The stirrer and suction pump are adjusted, the flow of oxygen started, and through the dropping funnel 7.4 liters of benzoyl chloride are added slowly over a period of five or six hours. The first 500 cc. of benzoyl chloride must be added slowly, allowing sufficient intervals of time for the materials to react completely. Failure to observe these precautions results in a violent reaction which is difficult to control. After the addition of the benzoyl chloride has been completed, an excess of sodium hydrosulfide solution is added to make sure that the reaction has gone to completion. A completed reaction is evidenced by the cessation of hydrogen sulfide evolution. The reaction mixture is then allowed to stand overnight.

The following day the precipitate (about 4700 g.) is filtered, washed thoroughly with water to remove adhering chlorides and dried in a stream of air. Any thiobenzoic acid which has escaped oxidation and which may have adhered to the precipitate is oxidized completely by this process. The filtrate and washings are cooled in an ice-bath, then acidified with concentrated sulfuric acid. Air or oxygen is bubbled through the cool solution, and 1200 cc. of 30% hydrogen peroxide added in 25-cc. portions over a period of three or four days.

It is important that during this time the solution be kept acid, and that the oxidation by means of air and oxygen be continued until no more precipitate is formed. The precipitate is then filtered, washed with about 5 liters of water and added to the original crop of dibenzoyl disulfide. The crude material is then broken up in small portions and air dried for several days.

Many solvents were investigated in a study of the purification of the crude dibenzoyl disulfide, but none was found to give a pure white material from one recrystallization. Purification is best accomplished as follows. The crude dibenzoyl disulfide is dissolved in ethylene dichloride at 60° in the ratio of 3 kg. to 6 liters of solvent. The resulting solution is faintly pink. It is important that the temperature of the solvent at the time of solution be 60° or less since the disulfide assumes a decided permanent pink color above that temperature. One liter of saturated sodium bicarbonate solution is added, and the mixture stirred vigorously for an hour. This is done in the absence of heat, as the prolonged heating of benzoyl disulfide in the presence of alkalies results in its decomposition, *i. e.*

$$C_6H_5COSSCOC_6H_5 + 2NaOH \longrightarrow C_6H_5COSNa + C_6H_5COONa + S + H_2O$$

The alkali purification removes the benzoic acid which is present as an impurity. It was found that sodium bicarbonate gave less decomposition than dilute sodium hydroxide.[6] The layers are allowed to separate, and the ethylene dichloride layer is filtered. Two liters of alcohol (special denatured formula 3A is satisfactory) are added to the filtrate which is then cooled overnight at a temperature of from 0 to 5°. The precipitate is filtered and washed with about 300 cc. of ether. The filtrate is then cooled to −15° and a second crop is obtained, generally of sufficient purity to be added to the first crop. The total yield of purified dibenzoyl disulfide, after air drying, is about 5.5 kg. (yields of 5.9 kg. were obtained on some runs). Yields of about 80% of crude material were obtained; yields of purified material were about 65 to 70% of the theoretical.

Dibenzoyl disulfide is reported in the literature as a white to faintly pink crystalline solid, but there is lack of agreement as to its melting point. Dibenzoyl disulfide, purified by the method described, is a faintly pink (Norite did not remove this coloration) crystalline solid, melting with decomposition to a pink liquid between 128 and 129°, in a capillary tube preheated to 100°. Further recrystallization from ethylene dichloride or carbon disulfide gave beautiful colorless plates melting at 129–130° in the preheated capillary tube or at 132° on the bar.[7]

Anal. Calcd. for $C_{14}H_{10}O_2S_2$: C, 61.27; H, 3.67; S, 23.38. Found: C, 60.68; H, 4.21; S, 23.55.

Analytical Degradations of Dibenzoyl Disulfide[8]

In an effort to establish beyond doubt the structure of the product prepared by the above method, we have found that in addition to the routine sulfur analysis, it was advisable to work out a method of analytical degradation by which the benzoic acid could be recovered. While it was found possible to prepare benzanilide quantitatively by simple refluxing with aniline, it was impossible to free the benzanilide completely from sulfur without loss of the benzanilide. Dibenzoyl disulfide was found to be quite resistant to hydrolysis under most conditions, but the following method gave yields of from 98 to 99.2% of benzoic acid.

(5) T. H. Rider and R. S. Shelton, U. S. Patent 2,028,246, January 21, 1936.

(6) Grateful acknowledgment is made to Dr. E. S. Cook for suggesting the use of sodium bicarbonate and for checking the method of preparation and purification.

(7) L. M. Dennis and R. S. Shelton, THIS JOURNAL, **52**, 3128 (1930).

(8) The method described was worked out by E. S. Cook and Karl Bambach.

Procedure for Analytical Degradation of Dibenzoyl Disulfide to Benzoic Acid.—Reflux 1 g. of dibenzoyl disulfide with 30 cc. of 40% w/v potassium hydroxide solution in a 100-cc. round-bottomed flask for three hours. Cool, transfer to a separatory funnel (rinsing out flask with water), acidify with concentrated hydrochloric acid, and allow to cool. Shake the benzoic acid into ether, using five portions (total of 120 cc.) and collect the ether extracts in another separatory funnel. Wash the ether with 25 cc. of approximately 0.1 *N* hydrochloric acid, and then wash this aqueous portion with 15 cc. of ether. Combine the ether extracts and filter through cotton into a beaker, washing the cotton with fresh ether. Evaporate the ether with the aid of a stream of air. (Evaporation may be hastened by placing the beaker in a water-bath at not over 40° until 30 cc. remains; then remove from water-bath and complete removal with air.) Treat the residue with a solution of 1.5 g. of sodium bicarbonate in 50 cc. of water. Warm the mixture and allow it to stand until all the benzoic acid has dissolved; the sulfur will be practically insoluble. Filter the liquid through a coarse filter paper into a separatory funnel and wash the paper thoroughly with water. Acidify the sodium benzoate solution with 10% hydrochloric acid, allow it to cool, and shake out the benzoic acid with chloroform, using five portions (total of 100 cc.). Collect the chloroform extracts in another separatory funnel. Wash the chloroform with 20 cc. of approximately 0.1 *N* hydrochloric acid, and then wash this aqueous portion with 10 cc. of chloroform. Filter the combined chloroform extracts through cotton into a tared beaker and evaporate the chloroform with the aid of a stream of air, placing the beaker in a water-bath at a temperature of not over 40° as before. Dry the benzoic acid overnight in a vacuum desiccator over sulfuric acid and weigh.

Summary

A new practical method for preparing medicinally pure dibenzoyl disulfide is described.

CINCINNATI, OHIO RECEIVED APRIL 6, 1936

[CONTRIBUTION FROM THE BURROUGHS WELLCOME AND CO., U. S. A., EXPERIMENTAL RESEARCH LABORATORIES]

Some N-Aryl Barbituric Acids

BY JOHANNES S. BUCK

In connection with a study of the hypnotic action of certain unsymmetrical alkylaryl ureas,[1] it was desirable to obtain a series of 1-aryl barbituric acids, having the aryl group the same both for the ureas and for the barbituric acids. Two series were therefore prepared, one having 5,5-diethyl groups and the other 5,5-ethyl-*n*-butyl groups, the N-aryl groups in both series being phenyl, *o*-, *m*- and *p*-tolyl, *o*-, *m*- and *p*-anisyl, *o*-, *m*- and *p*-phenetyl, and α- and β-naphthyl.

Hjort and Dox[2] have previously described briefly four of the diethyl compounds, but they failed to crystallize the 1-phenyl-5,5-ethyl-*n*-butyl compound, and to obtain the 1-*p*-ethoxyphenyl-5,5-ethyl-*n*-butyl derivative. The complete series (24) is here described. The pharmacological examination will be published in another place.

Experimental

The ethyl diethylmalonate used was purchased. Ethyl *n*-butylethylmalonate was prepared in good yield by butylating ethyl ethylmalonate, in the usual way by means of sodium ethylate and *n*-butyl iodide. The ester boiled sharply at 109° (1.4 mm.) or 125–126° (11 mm.). When prepared by ethylating ethyl *n*-butylmalonate, no sharp boiling point could be obtained.

The barbituric acids were all prepared by the usual reaction. 0.05 mole (10.8 g. and 12.2 g.) of the dialkylmalonate was added to 0.2 atom (4.6 g.) of sodium dissolved in the minimum amount of absolute alcohol; 0.05 mole of the requisite urea was added and the mixture refluxed for four to five hours. The solution was then cooled, diluted with water, made just acid to Congo red, and most of the alcohol removed, by a current of air, on the steam-bath. The residue was extracted with ether and the ether washed three times with saturated sodium bicarbonate solution, to remove hydrolysis products (very little of the barbituric acid was lost). The washed ether was then extracted with 80 cc. of 10% sodium hydroxide solution, water being added if necessary. On acidification of the alkaline solution the barbituric acid separated, usually as an oil, and was extracted with ether or filtered off and recrystallized until pure, alcohol or slightly aqueous alcohol being the solvent, unless otherwise noted. A few of the ethyl-*n*-butyl compounds were very difficult to purify and required elaborate treatment.

The bicarbonate washings contain uncyclized compounds, which are usually small in amount. They can be isolated by acidifying the solution. Some were examined but are not recorded here. The residual ether contains unchanged urea, ester and decomposition products.

The barbituric acids are tabulated below. Variations in the foregoing procedure are indicated in footnotes. The compounds are all white, crystalline and tasteless. They are soluble in cold 5% sodium hydroxide solution, practically insoluble in water, slightly soluble to insoluble in petroleum ether (the low-melting ones are more soluble), moderately to readily soluble in ether, readily soluble to very soluble in alcohol, and from moderately soluble to

(1) Hjort, deBeer, Buck and Ide, *J. Pharmacol.*, **55**, 152 (1935).
(2) Hjort and Dox, *ibid.*, **35**, 155 (1929).