Pyridine hydrobromide perbromide[2] is a crystalline and stable salt, which is quite useful for brominations of ketones on a micro or semimicro scale, since it can be weighed very accurately in small quantities in contrast to bromine. Representative examples of monobromination and dibromination of steroid ketones are given in the experimental section. The reactions were carried out by warming equimolar quantities of the salt and ketone in glacial acetic acid or ethanol and the yields were comparable to those obtained by using bromine.

Aliphatic and alicyclic ketones, such as acetone or cyclohexanone, also readily decolorize the reagent, and details of the small scale bromination of an amino ketone are given in the experimental section. It is very likely that this reagent could be used in most brominations which are successful with bromine, with particular application to small scale experiments.

Attempts to employ pyridine perbromide,[3] a reagent which should bind any hydrogen bromide liberated, proved disappointing.

Experimental

Pyridine Hydrobromide Perbromide ($C_5H_5N \cdot HBr \cdot Br_2$).—The reagent was prepared in 85% yield by adding one mole of bromine to one mole of pyridine in 48% hydrobromic acid solution and recrystallizing the product from acetic acid; red prismatic crystals, m. p. 134° (dec.) with previous softening; lit.,[3] m. p. 132–134°. We are indebted to Dr. A. C. Shabica of our development department for a supply of this salt.

Monobromination of 3-Ketosteroids

Allo Series.—To a warm solution (40–60°) of 38 mg. of cholestanone in 1 cc. of glacial acetic acid was added 31 mg. of pyridine hydrobromide perbromide. Hydrogen bromide was evolved, the solution turned colorless and crystals of 2-bromocholestanone appeared within one minute. On cooling and filtering the crystals, 37 mg. (81%) of 2-bromocholestanone of m. p. 168–169°, $[\alpha]^{23}D$ +38.1° (chloroform) was obtained, which gave no depression in melting point on admixture with an authentic sample.[4] By the same procedure, but using methyl 3-keto*allo*etiocholanate, there was obtained 75% of the corresponding 2-bromo derivative[5] of m. p. 184–188°. Glacial acetic acid could be replaced by ethanol or a mixture of ethanol and chloroform as solvent for the bromination.

Normal Series.—A mixture of 110 mg. of methyl 3-keto-12-acetoxycholanate and 75 mg. of the hydrobromide perbromide was warmed to *ca.* 40° for one minute in 5 cc. of glacial acetic acid and diluted with a few drops of water to yield 80 mg. (61%) of the 4-bromo derivative of m. p. 165–167°, $[\alpha]^{23}D$ +91.5° (chloroform), identical (rotation and mixed m. p.) with an authentic sample prepared by the method of Burckhardt and Reichstein.[6] Similarly, coprostanone gave the 4-bromo compound[4] of m. p. 104–107°, $[\alpha]^{23}D$ +40.5° (chloroform).

Monobromination of a 12-Ketosteroid.—A mixture of 195 mg. of methyl 3(α)-acetoxy-12-ketoetiocholanate and 155 mg. of pyridine hydrobromide perbromide in 1.2 cc. of glacial acetic acid was warmed until complete solution resulted, allowed to stand at room temperature for two and one-half hours and diluted with ether. The ether solution was washed well with water, evaporated to dryness and the residue was saponified and rearranged as described by Gallagher.[7] The crude yield of 3(α),12-dihydroxy-11-ketoetiocholanic acid of m. p. 248–257° was 130 mg. (74%); one recrystallization from ethanol gave colorless prisms of the acid melting at 274–278° (uncor.), with foaming at 282°. This material gave no depression in m. p. when mixed with an authentic sample (kindly furnished by Dr. H. B. MacPhillamy of our laboratories).

Dibromination of Cholestanone.—Treatment of 380 mg. of cholestanone with 640 mg. of the reagent in the usual manner gave after ten minutes 390 mg. (73%) of 2,4-dibromocholestanone[3] of m. p. 193–194° (dec.)

Bromination of an Aminoketone.—A solution of 65 mg. of 4-piperidino-2-butanone in 1 cc. of acetic acid containing 41% of hydrogen bromide was warmed with 135 mg. of pyridine hydrobromide perbromide for *ca.* thirty seconds until all the reagent had dissolved. Excess isopropyl ether was added which precipitated a pale yellow oil, which in turn was washed several times by decantation with isopropyl ether and crystallized from isopropyl alcohol. The yield of colorless, long needles of 1-bromo-4-piperidino-2-butanone hydrobromide of m. p. 157–158[8] (dec.) was 77 mg. (55%). The product gave no depression in m. p. on admixture with a colorless sample prepared by the method of Land and co-workers[9] who reported a 44% yield of brown material of m. p. 157–158°.

Brominations with Pyridine Perbromide ($C_5H_5N \cdot Br_2$).—Pyridine perbromide (m. p. 62–63.5°) was prepared freshly for each reaction by the method of Williams,[3] since it decomposed within a few hours. The bromination of cholestanone and coprostanone was carried out in acetic acid as described above for the hydrobromide perbromide and required three to five days for completion. Warming caused polymerization of the reagent,[10] but exposure to ultraviolet light shortened the reaction time to about twenty-four hours. No hydrogen bromide was evolved, but for substances sensitive to hydrogen bromide, N-bromosuccinimide[11] should be preferred, since the latter reagent is stable and reaction is complete after a few minutes.

(2) Englert and McElvain, THIS JOURNAL, **51**, 863 (1929).
(3) Williams, *J. Chem. Soc.*, 2783 (1931).
(4) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935).
(5) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).
(6) Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 829 (1942).
(7) Gallagher, *J. Biol. Chem.*, **165**, 211 (1946).
(8) Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946).
(9) Land, Ziegler and Sprague, *ibid.*, **69**, 125 (1947).
(10) *Cf.* McElvain and Goese, *ibid.*, **65**, 2227 (1943).
(11) Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

RESEARCH DEPARTMENT
DIVISION OF CHEMISTRY
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, N. J.
RECEIVED SEPTEMBER 4, 1947

The Stobbe Condensation with Sodium Hydride

BY GUIDO H. DAUB AND WILLIAM S. JOHNSON

In previous communications[1] it was shown that in the Stobbe condensation of a ketone with succinic ester, the use of potassium *t*-butoxide as the catalyst generally gave higher yields and purer products during shorter reaction periods than were obtained by the classical procedure with sodium ethoxide. Since sodium hydride has been employed with considerable success in place of alkoxides in certain ester condensations,[2] it seemed worth while to investigate its possible

(1) (a) Johnson, Goldman and Schneider, THIS JOURNAL, **67**, 1357 (1945); (b) W. S. Johnson, H. C. E. Johnson and Petersen, *ibid.*, **67**, 1360 (1945); (c) Johnson and Petersen, *ibid.*, **67**, 1366 (1945); (d) Johnson, Petersen and Schneider, *ibid.*, **69**, 74 (1947).
(2) See the review article of Hansley and Carlisle, *Chem. Eng. News*, **23**, 1332 (1945).

use in the Stobbe condensation. The preliminary results of our study were so promising that we are announcing them herewith. The new procedure appears to afford some advantage over the *t*-butoxide method in that it is considerably simplified, while the yields with two representative ketones, acetophenone and benzophenone, are at least as good. In a future communication we expect to report on a more extensive study of this new modification as well as on the mechanism of the condensation.

Experimental[3]

Stobbe Condensation with Acetophenone.—A mixture of 6.00 g. (0.05 mole) of the ketone, 26.13 g. (0.15 mole) of diethyl succinate and 2.4 g. (0.1 mole) of sodium hydride[4] was stirred for three and three-quarters hours at room temperature, care being taken to exclude all moisture from reagents and apparatus. The rate of evolution of hydrogen which was very slow at first graduallyincreased until after two hours it became quite rapid, slackening off toward the end of the reaction period. After three hours, 10 ml. of anhydrous benzene was added to facilitate stirring. The mixture was acidified with acetic acid, and extracted with ether. The ether solution was extracted with 5% sodium bicarbonate solution which on acidification gave 11.59 g. (93.5% yield) of pale yellow semi-solid acid undoubtedly consisting of a mixture of isomeric half-esters of Stobbe condensation product (neut. equiv., calcd., 248; found, 261). Crystallization from petroleum ether (b. p. 60–68°) rendered about one-third of the material crystalline; m. p. 111–112° after recrystallization from benzene–petrolum ether. This is probably identical with the half-ester of γ-methyl-γ-phenylisoitaconic acid, described by Stobbe[5] as melting at 110–112°. Saponification of the 112° half-ester with barium hydroxide afforded the crystalline dibasic acid, m. p. 180–182° with dec. (reported,[5] 178–179° and 183–185° with dec.).

Extraction of the ether solution, remaining after removal of the bicarbonate-soluble fraction, with 5% potassium hydroxide solution gave 1.23 g. of crude diethyl 1,4-diketocyclohexane-2,5-dicarboxylate, m. p. 117–123.5°, arising from the self-condensation of diethyl succinate. Recrystallization from alcohol raised the melting point to 126–127.5°, undepressed on admixture with an authentic specimen. This product gave a deep cherry-red color with alcoholic ferric chloride solution.

With Benzophenone.—When 9.11 g. (0.05 mole) of benzophenone and 26.13 g. (0.15 mole) of diethyl succinate were treated with 2.4 g. (0.1 mole) of sodium hydride as described above, no appreciable reaction took place even at steam-bath temperature. The addition of 10 drops of ethanol, however, initiated the reaction which proceeded readily at room temperature. The rate of hydrogen evolution increased as the reaction progressed until the sodium hydride was consumed (about eight hours). After about five hours 25 ml. of dry ether was added to facilitate the stirring of the mixture, which had become quite thick. The bicarbonate-soluble material, isolated as described above, amounted to 15.05 g. (a 97% yield) of almost colorless crystals, m. p. 124.5–125.5°, undepressed on admixture with an authentic specimen of β-carbethoxy-γ,γ-diphenylvinylacetic acid (m. p. 125–126°).[1c]

The 1,4-diketocyclohexane-2,5-dicarboxylate isolated by extraction with potassium hydroxide amounted to 1.58 g., m. p. 119–123.5°.

LABORATORY OF ORGANIC CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN RECEIVED SEPTEMBER 4, 1947

(3) All melting points are corrected.

(4) Procured from Electrochemicals Department, E. I. du Pont de Nemours and Company.

(5) Stobbe, *Ann.*, **308**, 114 (1899).

Kinetics of the Oxidation of Acetone by Selenious Acid

BY FREDERICK R. DUKE

The discovery of intermediates in appreciable concentration during the glycol-splitting type of specific oxidation[1] prompted this investigation of the selenious acid–acetone reaction. The stoichiometry is represented by the equation[2]

$$CH_3C(=O)-CH_3 + H_2SeO_3 \longrightarrow CH_3C(=O)C(=O)H + 2H_2O + Se \quad (1)$$

The reaction was studied extensively by Mel'nikov and Rokitskaya.[3] They found that the common alkyl esters of selenious acid decomposed at high temperatures to yield the corresponding aldehyde or ketone and selenium, and from this concluded that the oxidation of aldehydes and ketones proceeded through the enol ester intermediate. Data on the ease of oxidation of a series of aldehydes and ketones was used by these investigators to arrange the compounds in order of ease of enolization.

In the present investigation, the effects of high hydrogen ion and acetone concentrations on the rate of the reaction were studied in an attempt to demonstrate kinetically the presence of an intermediate. The data obtained clearly show that no appreciable amount of intermediate accumulates; however, certain conclusions may be drawn from the results and these are presented below.

Experimental

C. P. reagents were used. The specific gravity of the acetone was 0.7890 (25°/4°), fixing the water content at less than 1.5%.[4] Fifty-ml. volumetric flasks were used as reaction vessels; in Experiments I the appropriate amount of 5 *M* perchloric acid, 5 *M* sodium perchlorate, pure water and acetone and 2.0 ml. of 0.1 *M* selenious acid were pipetted into the flasks; then the latter were filled to the mark with *t*-butanol. After fifteen minutes in the constant temperature bath, sampling was begun with a 5-ml. pipet. The samples were quenched in acidified 5% KI solution, and the iodine titrated with 0.01 *N* thiosulfate. *t*-Butanol was used to maintain the reaction mixture at approximately constant dielectric as the acetone concentration was varied; the alcohol possesses the additional desirable property of low reactivity in esterification and aldol formation.

Experiments II were run in the same manner as Experiments I, except that the reacting mixture was prepared from 2 *M* acetone and 2 *M* perchloric acid. The acetone concentration was kept sufficiently low that the solutions in all cases may be considered truly aqueous. Sodium perchlorate was added where necessary to maintain constant ionic strength.

Experiments III were identical with the low-temperature runs of Experiment I except that the water concentration was varied and the acetone kept constant.

The constant temperature-bath was water maintained to ±0.1°.

Results.—In each of the experiments, the concentrations of reactants were chosen such that

(1) Duke, THIS JOURNAL, **69**, 2885 (1947); **69**, 3054 (1947).

(2) Riley, Morley and Friend, *J. Chem. Soc.*, 1875–1883 (1932).

(3) Mel'nikov and Rokitskaya, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1532–1538, 2738–2746 (1937); **8**, 1369–1380 (1938); **9**, 1158–1161, 1808–1812 (1939); **10**, 1439–1441, 1713–1716 (1940).

(4) Hughes and Hartley, *Phil. Mag.*, [7] **15**, 61 (1933).