mixture of benzyl chloride, pyridine and a copper catalyst.[1]

Reported yields of the mixed benzylpyridines are 40 to 50%. The isomers have usually been separated as the picrates. Yields of the pure isomers are seldom given. The article of von Braun and Pinkernelle[1b] reporting a 50% yield of the 2-isomer, is not explicit as to whether this yield is based on the starting material or on the mixture of isomers.

Need for rather large quantities of 2- and 4-benzylpyridine prompted a search for conditions giving better yields. It was found possible to obtain 75% yields of a mixture of 2- and 4-benzylpyridines, 90% of which was separated into the two isomers by fractional distillation.

Experimental

Solvent.—By using pyridine hydrochloride as a solvent, the yields of the mixed benzylpyridines were nearly double and the violence of the initial exothermal reaction between benzyl chloride and pyridine was greatly reduced. At the conclusion of the rearrangement, the pyridine hydrochloride was recovered by distillation and used for succeeding runs without purification or replenishment.

Catalyst.—Copper metal (or cuprous chloride into which the copper is assumed to be converted) has been used as the catalyst for the rearrangement of the pyridinium salt. Copper (or cuprous chloride) has been reported to cause the conversion of benzyl chloride into dibenzyl and products of unknown composition.[2] This reaction may account for most of the tarry material produced when a mixture of copper, benzyl chloride and pyridine is heated. If benzylpyridinium chloride (no catalyst) is distilled, the vapors which pass over at about 190° (liquid temperature) consist of a mixture of benzyl chloride and pyridine. Rearrangement of benzylpyridinium chloride (catalyst present) is negligible at 190°. By dissolving the catalyst in the hot pyridine–pyridine hydrochloride mixture *prior* to the addition of benzyl chloride, the amount of tar formation is negligible. Copper, equivalent quantities of copper and cupric chloride, or cupric chloride alone, may be used.

Procedure

The procedure employed was a modification of that originally used by Tschitschibabin[1a] as modified by LaForge[1a] and by Crook and McElvain.[1c] The procedure finally adopted is given in some detail since it was found to be advantageous to modify most of the steps in previously recorded procedures.

Four moles (462 g.) of pyridine hydrochloride was distilled into a one-liter flask and allowed to solidify while the flask lay on its side. This flask was fitted with a Claisen adapter carrying a dropping funnel and a water reflux condenser bearing a tube containing calcium chloride, 5 g. of anhydrous cupric chloride and 80 cc. (1 mole) of pyridine were added, and the flask heated until all the pyridine hydrochloride had melted and the cupric chloride dissolved. Heating was discontinued and 115 cc. (1 mole) of benzyl chloride (b. p. 90–91° at 40 mm.) was added during ten–fifteen minutes while the flask was shaken continuously. The mixture was then refluxed gently for twelve hours. The pyridine hydrochloride was distilled off through a 45-cm. Vigreux column at 90 mm. pressure. Distillation was stopped when the vapor temperature reached 195°. This pyridine hydrochloride was used without purification for the next run. There was a slight gain in quantity of pyridine hydrochloride with succeeding runs.

The black residue was cooled, 200 cc. of water and 15 cc. of hydrochloric acid (sp. gr. 1.2) added, and the mixture warmed until it appeared homogeneous. The brown to black liquid was made basic with ammonium hydroxide, 100 cc. of a 1-1 mixture of benzene and ligroin added and the organic layer washed with 100-cc. portions of 1-10 ammonium hydroxide until the aqueous layer ceased to acquire a blue color (2–4 times), then washed once with water.

The organic layer was dried by placing it, together with stock potassium hydroxide, in a separatory funnel and withdrawing the aqueous layer periodically until no more formed.

After removing the solvent at atmospheric pressure, the residue was distilled through a 45-cm. Vigreux column and gave 123.5–128.5 g. of a mixture of 2- and 4-benzylpyridines boiling at 175–190° (40 mm.) and a higher boiling residue of 16–20 g.

By using 0, 1 and 2 moles of pyridine hydrochloride as the solvent, the quantities of benzylpyridines and of higher boiling material were 60 and 56 g., 88 and 30 g., and 103 and 28 g., respectively. Decreasing the time of heating to six hours gave erratic results. Other modifications which did not increase yields were: heating for twenty-four hours, heating in a carbon dioxide atmosphere, stirring, continuous addition of cupric chloride during the heating period, and the use of equivalent amounts of copper and cupric chloride as the catalyst.

The isomers were separated by fractional distillation through a 1.2 × 115-cm. column packed with 0.32-cm. glass helices. In order to minimize losses of the less abundant 4-isomer, as much as possible of the 2-isomer was removed at 276.5–277° and two intermediate fractions of 277–280.5 and 280.5–289° were collected. The residue in the still was then set aside while the intermediate fractions were put through the column a second time. All material boiling at 289° and above was then returned to the still and the fraction boiling at 289–289.5° collected as 4-benzylpyridine. From 1 kg. lots, 640–680 g. of 2-benzylpyridine (b. p. 276.5–277° cor. (730 mm.)) and 245–255 g. of 4-benzylpyridine (b. p. 289–289.5° cor. (730 mm.)) were obtained.

As an indication of purity the 2- and 4-isomer gave picrates which melted without purification at 139.5–140° and 138.5–139°, respectively. Reported melting points of the picrates of the 2- and 4-isomer are 140° and 136–138°.[1a]

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(1) (a) Maier-Bode u. Altpeter, "Pyridin u. Seine Derivate in Wissenschaft u. technik," Edwards Brothers, Ann Arbor, Michigan, 1943; (b) J. von Braun and W. Pinkernelle, *Ber.*, **64**, 1871 (1931); (c) J. Overhoff and J. P. Wibaut, *Rec. chim.*, **50**, 957 (1931); K. E. Crook and S. M. McElvain, THIS JOURNAL, **52**, 4006 (1931); P. C. Teague, *ibid.*, **69**, 714 (1947).

(2) A. Onufrowies, *Ber.*, **17**, 836 (1884); T. Zincke, *ibid.*, **2**, 739 (1869).

Brominations with Pyridine Hydrobromide Perbromide

BY CARL DJERASSI AND CAESAR R. SCHOLZ

In connection with another problem, we had occasion to investigate the action of pyridine hydrobromide perbromide on some steroid ketones. Although pyridine and quinoline hydrobromide perbromides have been used occasionally as brominating agents, particularly with phenols and for the addition of bromine to double bonds,[1] no examples of the bromination of ketones with these reagents seem to have been recorded.

(1) *Cf.* Rosenmund, Kuhnhenn and Lesch, *Ber.*, **56**, 1262, 2042 (1923).

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[8] 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° (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).

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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).