The pure crystals sublime without sign of decomposition at 280°. *Anal.* Calcd.: N, 6.76. Found: N, 6.79.

DIVISION OF BIOCHEMISTRY
UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
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Diphenylacetonitrile

BY DAVID GINSBURG[1] AND MANUEL M. BAIZER

The preparation of diphenylacetonitrile, a starting material in the synthesis of Methadone (Amidone) and related analgetics, has recently been the subject of several publications.[2]

Schultz, Robb and Sprague,[2e] and Robb and Schultz[2f] report an adaptation of Hoch's synthesis,[3] in which benzyl cyanide is brominated and the resultant α-bromo-α-phenylacetonitrile is condensed with benzene in the presence of anhydrous aluminum chloride; they obtain yields of 50–60%.

The modification of Hoch's procedure which we have employed minimizes the possibility of exposure to the intermediate α-bromo-α-phenylacetonitrile, which is a potent lachrymator, and provides yields of 80% of pure diphenylacetonitrile.

Experimental

In a five-liter, three-necked flask equipped with a dropping funnel whose stem extends below the surface of the liquid, a mercury-sealed stirrer and a reflux condenser protected by a calcium chloride tube is placed 441 g. (3.76 moles, 290 ml.) of benzyl cyanide.[4] Stirring is started and the cyanide is heated to 105–110° by means of an oil-bath. Now 608 g. (3.80 moles, 195 ml.) of bromine is added in the course of sixty to ninety minutes. Throughout this period the temperature is maintained within the range indicated above. The hydrogen bromide evolved may be absorbed in a water-trap. After addition is complete, two liters of dry benzene is added and the mixture is heated under reflux for about one hour, until virtually all the hydrogen bromide has escaped. The dropping funnel is now instantly replaced by a solid rubber stopper.[5]

The reaction mixture is cooled to 20°. Stirring is continued and 507 g. (3.81 moles) of powdered anhydrous aluminum chloride is added in portions in the course of about one hour with the usual precautions.[6] The temperature in this period is maintained at 20–25°. When the addition of catalyst is complete, the temperature of the mixture is slowly raised. In about fifteen minutes, when the temperature has reached 35–40°, vigorous evolution of hydrogen bromide commences. Upon abatement of the reaction, the mixture is heated under reflux for sixty to ninety minutes and then cooled to room temperature. It is poured slowly and with stirring into a mixture of 1800 g. of ice and 760 ml. of 1:1 hydrochloric acid.

The layers are separated. The aqueous portion is extracted twice with 800-ml. portions of benzene. The combined benzene extracts are washed successively with one liter of water, one liter of 5% sodium carbonate and one liter of water. The washings are discarded; the benzene solution is dried over 250 g. of anhydrous sodium sulfate.

The benzene is distilled at atmospheric pressure and the residue is distilled under reduced pressure using a steam-heated condenser; b. p. 160–170° (5 mm.). The crude product is recrystallized from methanol (0.5 cc./g.); yield (in two crops) 585 g. (80% based on benzyl cyanide); m. p. 73–74°.

THE NEW YORK QUININE AND CHEMICAL WORKS, INC.
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(1) Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

(2) (a) Reid and Hunter, THIS JOURNAL, **70**, 3515 (1948); (b) Homeyer, U. S. Pat. 2,443,246; *C. A.*, **42**, 7338a (1948); (c) U. S. Pat. 2,447,419; (d) Freeman, *et al.*, THIS JOURNAL, **69**, 858 (1947); (e) Schultz, Robb and Sprague, *ibid.*, **69**, 2458 (1947); (f) Robb and Schultz, *Org. Syn.*, **28**, 55 (1948).

(3) Hoch, *Compt. rend.*, **197**, 770 (1933).

(4) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 107.

(5) The equipment may be originally assembled so that one of the side-necks of the flask carries a two-necked adapter. Then no detachment need be made, and all possibility of exposure to α-brom-α-phenylacetonitrile can be eliminated.

(6) It is convenient to weigh the aluminum chloride into an Erlenmeyer flask and to attach the latter by a rubber sleeve to the available neck of the flask.

Reinvestigation of the Reaction of Ethylmagnesium Bromide with Pyridine

BY NYDIA GOETZ-LUTHY

Recently it has been reported[1] that 2-ethylpyridine prepared by unequivocal methods yielded a picrate which melted at 108.5–110° rather than 187–189° as reported by Bergstrom.[2] The work of Gregg and Craig was repeated and confirmed. Thus when 2-vinylpyridine (Reilly product) was reduced by hydrogenation over old Raney nickel at room temperature, there was obtained an excellent yield of a clear, colorless liquid boiling 148–150°[3] at atmospheric pressure. The picrate of 2-ethylpyridine so obtained melted at 108–109° in agreement with the results reported by Gregg and Craig.

In an effort to throw light on the discrepancy and to find out more about the nature of the reaction of pyridine with ethylmagnesium bromide at elevated temperatures, the following experiments were undertaken. An attempt was made to repeat the earlier work[4] but after three runs it became apparent that ethylmagnesium bromide and pyridine in ether solution react at 150–160° to give a mixture of products in which 2-ethylpyridine, if formed, is present in so small a quantity as to escape ready identification by the usual laboratory methods. The chief products isolated were unreacted pyridine and high boiling materials, presumably dipyridyls.

No substance boiling at 148–150° forming a picrate having a m. p. 187–189°[2,4] was obtained from the various fractions collected upon distillation of the product. Picrates were obtained which melted 165–166° and which did not lower the melting point of the picrate of a known sample of pyridine. The picrate of a higher boiling material (74–75° at about 33 mm.) which melted at 199–203° (uncor.) corresponded more

(1) Earl C. Gregg, Jr., and David Craig, THIS JOURNAL, **70**, 3138 (1948).

(2) F. W. Bergstrom and S. H. McAllister, *ibid.*, **52**, 2848 (1930).

(3) I. M. Heilbron, "Dictionary of Organic Compounds," gives the boiling point of 2-ethylpyridine at 148–150°.

(4) S. H. McAllister, Master's Thesis, Stanford University, Stanford, Calif., 1930.

closely to that of 2,4-dipyridyl, but was not further identified.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
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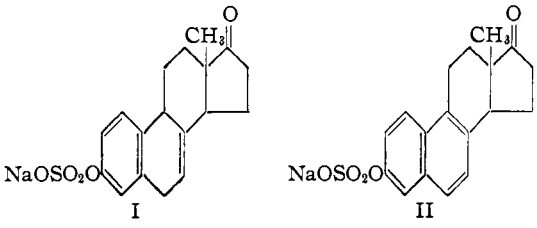
Sodium Equilin Sulfate and Sodium Equilenin Sulfate

BY GORDON A. GRANT AND WILLIAM L. GLEN

We wish to report the synthesis and biological activity of two new estrogen sulfates, namely, sodium equilin sulfate, and sodium equilenin sulfate.

The method employed was that previously reported by Butenandt and Hofstetter[1] for the preparation of sodium estrone sulfate.



I II

Sodium Equilin Sulfate (I).—Equilin (1.13 g.) dissolved in a mixture of dry pyridine (19.8 ml.) and dry chloroform (39.6 ml.) was added with cooling to 0.32 ml. chlorosulfonic acid in dry chloroform (19.8 ml.) plus dry pyridine (9.9 ml.). After twenty four hours at room temperature, the solvents were removed from the reaction mixture by concentration *in vacuo* at 27°. The residue, after washing with dry ether, was dissolved in methanol, and neutralized with *N* methanolic sodium hydroxide, to *p*H 7.8. Inorganic salt was removed by centrifugation, and the sodium equilin sulfate (1.10 g.) was obtained from the methanol solution, by fractional precipitation with ether, as a white solid soluble in water. It contained 76% equilin as determined colorimetrically by a modified Marrian-Kober test[2] (required 72.4), and had $[\alpha]^{20}D$ + 218° (H_2O). *Anal.* Calcd. for $C_{18}H_{19}O_5SNa$: C, 58.37; H, 5.13; S, 8.64. Found: C, 58.20; H, 5.10; S, 8.40.

The quinidine salt was prepared by precipitation from an aqueous solution of the sodium salt. *Anal.* Calcd. $C_{38}H_{44}O_7N_2S$: N, 4.16; equilin, 39.9. Found: N, 4.03; equilin, 45.

Sodium Equilenin Sulfate (II).—Sodium equilenin sulfate (260 mg.), from 570 mg. of equilenin, was isolated as described above, except that the final methanol solution required decolorizing with a little norite.

It was a white solid soluble in water, and contained 70% equilenin (required 68.9%), and had an $[\alpha]^{20}D$ + 70° (H_2O). *Anal.* Calcd. $C_{18}H_{17}O_5SNa \cdot H_2O$: C, 55.95; H, 4.92; S, 8.29. Found: C, 55.59; H, 4.86; S, 8.31.

The quinidine salt prepared as above contained 42% equilenin ($C_{38}H_{42}O_7N_2S$ requires 39.7).

Biological Activity.—The compounds were assayed for their estrogenic activity by oral administration to adult ovariectomised rats. The amount (total dose) of each compound which brought about a 50% estrogenic response (RD 50) is given below. Results obtained with sodium estrone sulfate[3] are included for comparison. The values in parentheses are those obtained for the unesterified estrogens in each case, *i. e.*, estrone, equilin and equilenin.

Compound	RD 50 (Total dose) γ
Sodium estrone sulfate	148 (249)
Sodium equilin sulfate	108 (210) 120
Sodium equilenin sulfate	1200 (1000)

Sodium estrone sulfate and sodium equilin sulfate were each considerably more active than the respective unconjugated estrogen, when assayed in the above manner. The sodium equilenin sulfate was a much less active estrogen.

RESEARCH AND BIOLOGICAL LABS.
AYERST, MCKENNA AND HARRISON, LTD.
MONTREAL, CANADA RECEIVED MARCH 21, 1949

(1) Butenandt and Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).

(2) Venning, Evelyn, Harkness and Browne, *J. Biol. Chem.*, **120**, 225 (1937).

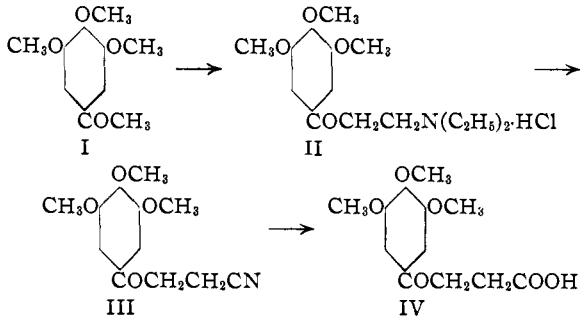
(3) Grant and Souch, Biological Division, Pittsburgh meeting of the American Chemical Society, September, 1943.

The Preparation of β-(3,4,5-Trimethoxybenzoyl)-propionic Acid

BY ELEANOR HAGGETT AND S. ARCHER

In connection with some other work the need arose for substantial quantities of β-(3,4,5-trimethoxybenzoyl)-propionic acid. This substance had been prepared previously by Haworth and co-workers[1] who alkylated ethyl 3,4,5-trimethoxybenzoylacetate with ethyl bromoacetate and then hydrolyzed and decarboxylated the resulting diester.

Since, in our hands, the method did not seem to be entirely satisfactory we resorted to the preparation outlined in the following equations.



The required ketone, I, was prepared from 3,4,5-trimethoxybenzoyl chloride according to Hauser's method.[2] The ketone was converted to II under the usual Mannich conditions. In addition, the corresponding piperidyl and dimethylamino ketones were prepared. The salt, II, gave better yields of the nitrile, III, than either the piperidyl or dimethylamino derivatives, when treated with potassium cyanide in dilute hydrochloric acid solution.[3] Preliminary experiments indicated that the conversion of the nitrile to the acid, IV, proceeded in better yield when carried out stepwise through the intermediate ethyl ester rather than by direct acid hydrolysis. In this way the desired acid, IV, was obtained in 21% over-all yield from 3,4,5-trimethoxybenzoyl chloride.

(1) Haworth, Richardson and Sheldrick, *J. Chem. Soc.*, **135**, 1580 (1935).

(2) Walker and Hauser, THIS JOURNAL, **68**, 1386 (1946).

(3) Knott, *J. Chem. Soc.*, 1190 (1947).