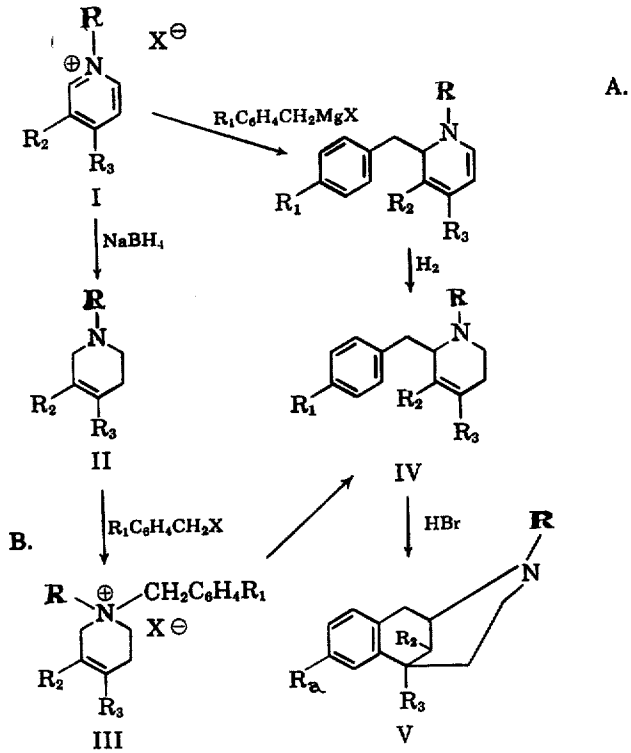
June 11, 1963 E. M. FRY ETAL 3,093,650
ALTERNATIVE SYNTHESIS OF 2'-HYDROXY-5,9-DIMETHYL-2-PHENETHYL-6,7-BENZOMORPHAN (PHENAZOCINE)
Filed July 19, 1962



EDWARD M. FRY
EVERETTE L. MAY
INVENTORS

BY Joseph G. Houghton
Attorney

United States Patent Office 3,093,650 Patented June 11, 1963

3,093,650

ALTERNATIVE SYNTHESIS OF 2' - HYDROXY-5,9 - DIMETHYL - 2 - PHENETHYL - 6,7 - BENZOMORPHAN (PHENAZOCINE)

Edward M. Fry, Darnestown, and Everette L. May, Bethesda, Md., assignors to the United States of America as represented by the Secretary of Health, Education, and Welfare

Filed July 19, 1962, Ser. No. 211,144
8 Claims. (Cl. 260—290)
(Granted under Title 35, U.S. Code (1952), sec. 266)

The present invention relates to synthesis of 2'-hydroxy-5,9 - dimethyl - 2 - phenethyl - 6,7-benzomorphan (phenazocine) and analogues thereof. Such materials are also known as 2,6-methano-3-benzazocines.

In prior application, S. N. 771,165, two methods are described for the synthesis of such compounds, one being the so-called Grewe synthesis (diagrammed as Route A in the accompanying drawing) and the other being through a β-tetralone. Of these known processes, each of which has certain disadvantages, the Grewe synthesis has been regarded as of principal interest, even through it requires the use of an unstable, hard to prepare Grignard reagent (p-methoxybenzylmagnesium chloride) as an intermediate.

The present invention has for objects: the provision of new methods of synthesis applicable for the production of benzomorphans and the 2-benzyl-1,2,5,6-tetrahydropyridine precursors thereof, and which obviate the use of said unstable Grignard reagents, and which may be employed to produce phenazocine and its analogues and their said precursors wherever, for various reasons, use of the previously known syntheses may not be desirable. These new methods of synthesis (diagrammed as Route B in the accompanying drawing) involve the application of a Stevens rearrangement to an N-benzyl-1,2,5,6-tetrahydropyridinium salt, per se, and together with associated steps contributing to the achievements of the objects of the invention.

The single FIGURE of the accompanying drawing is a diagrammatic flow-sheet comparing the syntheses and intermediates of the new method with those of the prior Grewe syntheses.

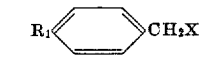
As shown in Route B of the accompanying drawing, in accordance with the more comprehensive aspects of the present method, a benzomorphan compound (V) is produced by (*a*) reducing a pyridinium halide (I) with sodium borohydride or equivalent to produce a 1,2,5,6-tetrahydropyridine base (II), (*b*) quaternizing said tetrahydropyridine base with a benzyl halide to form a quaternary tetrahydropyridinium salt (III), (*c*) reacting said tetrahydropyridinium salt with ethereal phenyllithium or equivalent to produce a 2-benzyl-tetrahydropyridine base (IV), and (*d*) contacting said 2-benzyltetrahydropyridine base with a cyclizing agent to produce the benzomorphan compound.

More specifically, in this general method the pyridinium halide employed in step (*a*) above is preferably one substituted in the 4-position with an alkyl group R_3 containing not more than 4 carbon atoms, and more preferably one substituted in the 3- and 4-positions with alkyl groups R_2 and R_3 wherein the sum of the numbers of carbon atoms in the said alkyl groups is not over 6.

The N-attached member R of the pyridinium halide employed in step (*a*) above may be varied without interfering with the operation of the method and as set forth in copending application S. N. 771,165 may be hydrogen, or may be an organic radical containing from 1 to 9 carbon atoms, and preferably is an alkyl or a phenethyl radical having not more than 9 carbon atoms although a p-methoxyphenethyl substituent may be used. The halo-

gen atom X of this pyridinium halide is preferably iodine or bromine.

The benzyl halide employed in step (*b*) above has the general formula



The member R_1 may be varied without interfering with the operation of the method, and as set forth in copending application S. N. 771,165 may be a lower alkyl or lower acyloxy radical, but preferably is hydrogen or a methoxy radical. The member X of the benzyl halide is preferably chlorine.

Any suitable cyclizing agent may be employed. When aqueous 48% hydrobromic acid (preferred) or aqueous 85% phosphoric acid are employed, and R_1 is a methoxy group, O-demethylation occurrs concurrently with the cyclizing to produce a hydroxyl group at R_a. When cyclization is effected with $AlCl_3$ or $AlBr_3$ in carbon disulfied, then such O-dealkylation does not occur, but if required, may be effected by a post treatment with aqueous hydrobromic acid or phosphoric acid.

As shown in the accompanying drawing the immediate precursors IV of the benzomorphans V are the same in the present method as in the previously known Grewe synthesis. Hence while the present invention has for one object the provision of a new route for attaining the desired benzomorphans V, it also, and more specifically, has for further objects the provision of new methods of obtaining the useful intermediate or precursor compounds IV by application of Stevens rearrangements to the new compounds III, as well as new methods for obtaining the compounds III from pyridinium halides I.

The foregoing and other objects and advantages of the invention will be apparent to those skilled in the art from the foregoing discussion and from the specific examples herewith set forth. The invention resides in the new methods of synthesis and the new materials herein disclosed and is more particularly pointed out in the appended claims. The application of the invention to typical materials to produce typical products in the following examples is to be considered illustrative, and not restrictive, of the invention, the scope of which is pointed out more particularly in the claims.

EXAMPLES

To avoid repetition in the ensuing examples the conversions of the pyridine salts (I) to the N-benzyl-1,2,5,6-tetrahydropyridinium salts (III) will be set forth in Section A, the rearrangement of the N-benzyl materials III to form the 2-benzyl materials IV will be set forth in Section B, and the conversions of the materials IV to the benzomorphans V will be set forth in Section C. As set forth herein, temperatures are in ° C., melting points are uncorrected, and the NMR spectra, 60 mc., are with tetramethylsilane as internal reference standard and deuterochloroform as solvent.

Section A

The N-methyltetrahydropyridines (II) were prepared in N-sodium hydroxide solution using a molar equivalent of sodium borohydride. The ratio of solution to the weight of hydride was approximately 50 to 1. If the reduction did not start spontaneously the solution was warmed to ca. 50°. The exothermic reaction was gentle and the end point was marked by disappearance of yellow color and cessation of effervescence. The bases were recovered with ether and converted to the quaternary salts (III) by addition of the benzyl halide to either an acetone or ether solution of the base.

Example A1. — Preparation of 1-p-methoxybenzyl-1,4-dimethyl-1,2,5,6-tetrahydropyridinium chloride.—A mix-

ture of 12 g. (0.05 mole) of gamma-picoline methiodide (compound I, R_2=H, R=R_3=CH_3, X=I), 100 ml. of N sodium hydroxide, and 2 g. of sodium borohydride was stirred (temperature rose to 54° during 15 min.) for 3 hrs. Sodium chloride was added and the mixture was extracted thrice with ether. Drying (sodium sulfate) and distillation of the ether at atmospheric pressure gave a quantitative yield of apparently stable 1,4-dimethyl-1,2,5,6-tetrahydropyridine (II) which, in 25–30 ml. of acetone, was treated with 9 g. (slight excess) of p-methoxybenzyl chloride (R_1=OCH_3). After one hour at room temperature and 2–3 hrs. at −5° the crystalline 1-p-methoxybenzyl-1,4-dimethyl-1,2,5,6-tetrahydropyridinium chloride was obtained in a yield of 11 g. (82% from the compound I) and was purified from absolute ethanol-ether. Hygroscopic, it was dried at 60°/50 mm. prior to analysis; M.P. 181–182°. *Analysis.*—Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28. Found: C, 67.36; H, 8.37.

Example A2.—Preparation of 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium bromide was effected by applying the same procedures to 3,4-dimethylpyridine methiodide (compound I, R=R_2=R_3=CH_3) and using benzyl bromide (R_1=H, X=Br) in lieu of the p-methoxybenzyl chloride (R_1=OCH_3, X=Cl). The 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium bromide, obtained in 73% yield, was purified from acetone-alcohol, M.P. 206–208° C. *Analysis.*—Calcd. for $C_{15}H_{22}BrN$: C, 60.81; H, 7.49. Found: 60.61; H, 7.43.

Examples A3 and A3a.—Preparation of 1-p-methoxybenzyl - 1,3,4 - trimethyl - 1,2,5,6 - tetrahydropyridinium chloride was effected in the same manner

($R=R_2=R_3=CH_3$; $R_1=OCH_3$; X=Cl)

and obtained in 61% yield. It crystallized from acetone containing a little absolute alcohol in rods of M.P. 169–171°. The somewhat hygroscopic material was dried at 60°/40 mm. for analysis. *Analysis.* — Calcd. for $C_{16}H_{24}ClNO$: C, 68.20; H, 8.58. Found: C, 68.09; H, 8.86.

The iodide was obtained by adding KI to an aqueous solution of the chloride. Purified from alcohol it melted at 175–178°. *Analysis.*—Calcd. for $C_{16}H_{24}INO$: C, 51.48; H, 6.48. Found: C, 51.28; H, 6.47.

Example A4.—Preparation of 1-p-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (compound III, R=CH_3; R_1=OCH_3; R_2=R_3=C_2H_5) was effected in the same manner. The product was obtained in 39% yield, was purified from acetone and melted at 157–160°. The hygroscopic crystals were dried at 78°, high vacuum, prior to analysis. *Analysis.*—Calcd. for $C_{18}H_{28}ClNO \cdot \frac{1}{2}H_2O$: C, 67.77; H, 9.16. Found: C, 68.06; H, 9.40.

After drying at 135° in high vacuum the weight loss was 2.94% (calcd. for $\frac{1}{2}H_2O$, 2.82%). *Analysis.*—Calcd. for $C_{18}H_{28}ClNO$: C, 69.76; H, 9.11. Found: C, 70.04; H, 9.38.

Examples A5–A8.—In similar fashion corresponding compounds III were formed with additional variations, viz.:

Example	R	R_1	R_2	R_3
A5	CH_3	OCH_3	H	C_2H_5
A6	$PhCH_2CH_2$	OCH_3	H	C_2H_5
A7	CH_3	OCH_3	CH_3	C_2H_5
A8	CH_3	OCH_3	C_2H_5	CH_3

and these compounds were similarly characterized.

Example A9.—Preparation of 1-p-methoxybenzyl-1-phenethyl-3,4-dimethyl-1,2,5,6-tetrahydropyridinium chloride.—To a stirred mixture of 15 g. (0.05 mole) of 3,4-dimethyl-1-phenethylpyridinium bromide (compound I, R=$PhCH_2CH_2$; R_2=R_3=CH_3) 2.5 g. of sodium hydroxide, 30 ml. of water and 50 ml. of methanol was added in one lot 2.1 g. of sodium borohydride. The reaction was exothermic and during 5–7 minutes the temperature rose to a maximum of 59°. The temperature was maintained at 50–60° for 60–90 minutes. The mixture was diluted with cold water and extracted thrice with ether. The combined extracts (40–45 ml.) were washed once with 25 ml. of cold water, dried over sodium sulfate and evaporated to dryness leaving 10.7 g. of tetrahydropyridine derivative (II, R=$PhCH_2CH_2$, R_2=R_3=CH_3). This was treated with 8.5 g. of p-methoxybenzyl chloride (R_1=OCH_3, X=Cl) and 15 ml. of acetone and the solution warmed briefly on the steam bath, then left at 25–30° for 18–24 hours. Addition of 15 ml. of dry ether, thorough stirring by hand and decantation, left a white dough which was similarly treated with another portion of ether. The residual chloride (compound III, R_1=OCH_3, R=$PhCH_2CH_2$, R_2=R_3=CH_3) was dried to constant weight at the water pump at a bath temperature of 45–50° (30–60 minutes); a nearly white, fluffy, amorphous powder weighing 17.7 g. (95%) resulted. This powder (M.P. 70–90° to a glass) gave a correct analysis for chlorine, lost 3.8% on drying in vacuo at 78°, and gave characteristic bands in the infrared at 2.97 and 4.06μ (in $CHCl_3$).

Section B

The 2-benzyl-1,2,5,6-tetrahydropyridines (IV) were prepared by the addition of excess 0.9 N phenyllithium in ether to the quaternary salts (III). The reaction was exothermic and at its completion (2–4 hr., stirring) the mixture was decomposed with ice and the product recovered by drying and evaporation of the ethereal layer.

Example B1.—2-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine was obtained from the product of Example A2, and is an oil. Its picrate was isolated in 13% yield and was purified from alcohol. It proved identical with the corresponding compound isolated in the Grewe synthesis, M.P. 127–129°. *Analysis.* — Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.88; H, 5.45.

Example B2.—2-p-methoxybenzyl - 1,3,4 - trimethyl-1,2,5,6-tetrahydropyridine, obtained from the product of Example A3, is an oil. Its picrate was obtained in 38% yield. Purified from alcohol it melted at 168–174°. *Analysis.*—Clcd. for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52. Found: C, 55.92; H, 5.40.

Example B3.—2-p-methoxybenxyl-1,4-dimethyl-1,2,4,5-tetrahydropyridine was a constituent of an oil obtained from 9 g. of the chloride product of Example A1. The base was distilled at 95–105°/0.1 mm., and weighed 7.4 g. preliminary to ring closure.

Example B4.—2-p-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridine was part of a mixture. Six grams of the chloride product of Example A4, yielded after rearrangement 5.4 g. of evaporatively distilled oil (0.07 mm., bath at 150–175°) for use in the ring closure.

Examples B5–B9.—In similar fashion corresponding compounds IV were prepared from the compounds produced by Examples A5–A9, viz.:

Example	R	R_1	R_2	R_3
B5	CH_3	OCH_3	H	C_2H_5
B6	$PhCH_2CH_2$	OCH_3	H	C_2H_5
B7	CH_3	OCH_3	CH_3	C_2H_5
B8	CH_3	OCH_3	C_2H_5	CH_3
B9	$PhCH_2CH_2$	OCH_3	CH_3	CH_3

and these compounds were similarly characterized.

Section C

The benzomorphans V were prepared by ring closure of the precursor compounds IV with 48% hydrobromic acid using the published procedure (see J. Org. Chem. 22, 1366; J. Org. Chem. 24, 1432; and copending application S.N. 771.165) and were identified by melting points, mixed melting points, and infrared spectrograms.

Example C1.—2,5,9-trimethyl-6,7-benzomorphan was

obtained by cyclizing the product of Example B1, as aforesaid.

Example C2.—2'-hydroxy-2,5,9-trimethyl - 6,7 - benzomorphan was obtained by cyclizing the product of Example B2, as aforesaid.

Example C3.—2'-hydroxy-2,5-dimethyl-6,7-benzomorphan was obtained by cyclizing the product of Example B3, as aforesaid.

Example C4.—2'-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan was obtained by cyclizing the product of Example B4, as aforesaid.

Examples C5–C8.—In like fashion compounds V were prepared by cyclizing (and O-demethylating) the products of Examples B5 to B8, viz.:

Example	R	R_1	R_2	R_3
C5	CH_3	OH_3	H	C_2H_5
C6	$PhCH_2CH_2$	OH_3	H	C_2H_5
C7	CH_3	OH_3	CH_3	C_2H_5
C8	CH_3	OH_3	C_2H_5	CH_3

and these benzomorphans were similarly characterized.

Example C9.—Preparation of 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide (Phenazocine, NIH 7519).—Fifteen grams of the light-colored crude oil obtained as product in Example B9 were treated with 50 ml. of 48% HBr and 20 ml. of 30% HBr–AcOH. The solution was kept at a bath temperature of 140–145° (air condenser) for 20–30 hours, cooled and made basic with concentrated NH_4OH while keeping the temperature below 40°. The mixture was extracted with 50–75 ml. of chloroform in three portions. The combined extracts were dried and evaporated at the water pump. The residue was dissolved in 15 ml. of hot acetone. On standing the solution gradually deposited crystals of 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan. Cooling finally to −15°, filtering and washing with cold acetone gave 2.6–2.9 g. (15–18% overall from 3,4-dimethyl-1-phenethylpyridinium bromide) of base, M.P. 179–182°. It was suspended in 8–10 ml. of absolute alcohol and neutralized to a pH of 3 to 4 with 48% hydrobromic acid (ca. 0.83–0.90 ml.) with stirring and warming to solution. The solution was decolorized with activated carbon and the filtrate was evaporated to dryness in vacuo. The residue was crystallized from 10 ml. of acetone by addition of 5–10 ml. of ethyl acetate. Cooling to −15° gave 3.0–3.5 g. of hydrobromide salt (phenazocine·HBr), M.P. 165–170°. Characteristic infrared bands (Nujol (white mineral oil)) to 6.5μ are 3.5 (broad, strong), 3.71, 3.80 (medium), 6.19 (medium), 6.28 (weaker) μ.

Publication has been made of subject matter of the present invention, within the year next preceding the execution of the present specification, as follows:

J. Org. Chem., 26, 2592–3 (published July 25, 1961)
J. Org. Chem., 27, 245 (published 1962)
J. Org. Chem., 27, 948 (published 1962)

and the disclosures in these publications are made a part hereof by reference, and may be consulted for further characterizing data with respect to the products prepared by the present invention and the racemic, isomeric, and other variations thereof.

The invention described herein, if patented, may be practiced and used by and for the Government of the United States for governmental purposes without the payment to us of any royalty thereon in accordance with the provisions of the Patent Act of 1952 (35 USC, Sec. 266).

We claim as our invention:

1. A method of producing a 2-benzyl-1,2,5,6-tetrahydropyridine base which essentially comprises contacting an N-benzyl-quaternary - 1,2,5,6 - tetrahydropyridine salt with ethereal phenyllithium for a sufficient time to induce shift of the benzyl substituent to the 2-position of the tetrahydropyridine.

2. A method of preparing a 2-benzyl-1,2,5,6-tetrahydropyridine base which essentially comprises

(*a*) reacting a 1,2,5,6-tetrahydropyridine base with a benzyl halide to form an N-benzyl quaternary 1,2,5,6-tetrahydropyridine salt, and

(*b*) reacting said tetrahydropyridine salt with ethereal phenyllithium for a sufficient time to induce shift of the benzyl substituent to the 2-position of the 1,2,5,6-tetrahydropyridine.

3. A method of producing a 2-benzyl-1,2,5,6-tetrahydropyridine base which essentially comprises

(*a*) reducing a pyridinium halide with sodium borohydride to produce a 1,2,5,6-tetrahydropyridine base,

(*b*) reacting said tetrahydropyridine base with a benzyl halide to form an N-benzyl quaternary 1,2,5,6-tetrahydropyridine salt, and

(*c*) reacting said tetrahydropyridine salt with ethereal phenyllithium for a sufficient time to induce shift of the benzyl substituent to the 2-position of the 1,2,5,6-tetrahydropyridine.

4. A method as claimed in claim 3, in which said pyridinium halide is substituted in the 4-position with an alkyl group containing not more than 4 carbon atoms.

5. A method as claimed in claim 3, wherein said pyridinium halide is substituted in the 3- and 4-positions with alkyl groups, and wherein the sum of the numbers of carbon atoms in said alkyl groups is not over 6.

6. A method as claimed in claim 3, wherein the pyridinium halide is a methiodide.

7. A method as claimed in claim 3, wherein the benzyl halide is p-methoxybenzyl chloride.

8. A method as claimed in claim 7, wherein the cyclizing agent is aqueous hydrobromic acid.

References Cited in the file of this patent

May et al.: J. Org. Chem., volume 22, pages 1366–69 (1957).

Fery et al.: Bull. Soc. Chim., Belg., volume 68, pages 65–84 (1959).