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EXTENSION OF BISCHLER–NAPIERALSKI REACTION—IV*

SYNTHESIS OF SOME PYRIDINE DERIVATIVES

TOMOKICHIRO FUJISAWA and SHIGEHIKO SUGASAWA†
Faculty of Pharmaceutical Sciences, University of Tokyo

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Abstract—Acyl derivatives of 5-phenylpent-4-enylamine were cyclized to give 2-substituted 3-benzal-3,4,5,6-tetrahydropyridines in good yield. This is a new synthesis of pyridine derivatives.

THE new synthesis of pyridine derivatives involves the cyclization of acyl derivatives of 5-phenyl-pent-4-enylamine (II)[1] under the usual conditions of Bischler–Napieralski reaction, giving good yields of 2-R-3-benzal-3,4,5,6-tetrahydropyridines (cf. IVa and IVb). Catalytic reduction of the metho salt of IVa gives 1-methyl-2-phenyl-3-benzylpiperidine (V), the methochloride of which was submitted to the modified Emde degradation[2] yielding N,N-dimethyl-4,4-dibenzyl-n-butylamine (VI), and the methochloride of the latter on exhaustive methylation gave 4,4-dibenzyl-but-1-ene (VII), in which the presence of an end vinyl group was revealed by I.R. spectra. On oxidation VII gave a mi) ture of acids which was converted into anilide and separated chromatographically, and only pure dibenzylacetanilide (VIII) was obtained indicating the point of cyclization of III. An impure anilide was isolated from the second eluate of the chromatographical analysis which was probably β,β-dibenzylpropionanilide (IX) which melted over a range 108–130°; an authentic specimen of IX (m.p. 126–127°) was prepared from β,β-dibenzylpropionic acid synthesized by the Arndt–Eistert method. VI was synthesized from 4,4-bibenzylbutyramide (X) which was reduced by $LiAlH_4$ to 4,4-dibenzylbutylamine (XI) which was methylated by the Eschweiler method to yield VI identical with the base obtained previously. All evidence indicates the six-membered ring nature of the cyclized base. The location of the double bond was deduced from analogy of the previous investigation,[1] and also from a strong bathochromic shift of the maxima of the U.V. spectrum of IVa by comparison with IIIa.

Dehydrogenation of IVa (Pd. C) gave 2-phenyl-3-benzyl-pyridine, and on similar treatment IVb gave a product which was not identified. 2-Methyl-3-benzylpiperidine, the reduced product from IVb, was dehydrogenated to 2-methyl-3-benzylpyridine, which on oxidation gave 3-benzoylpicolinic acid identical with the same product previously obtained.[3] The structure of IVb and its reduced product 2-methyl-3-benzylpiperidine are confirmed.

The formylderivative of II did not give 3-benzal-3,4,5,6-tetrahydropyridine (XII) but the carbethoxyformyl derivative (XIII) of II yielded XIV.

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† Present address: No. 40, 3-chome, Iogi, Suginami-ku, Tokyo.

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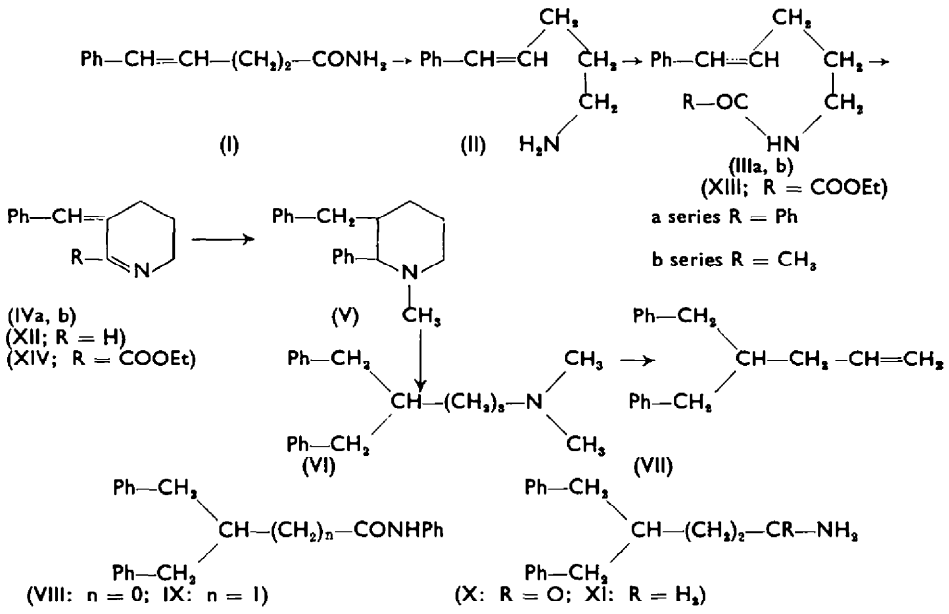

EXPERIMENTAL

5-Phenylpent-4-enoylamide (I). Crude 5-penylpent-4-enoyl chloride was added dropwise to excess conc ammonia at 0° with stirring. A quantitative yield of the *amide* (I) was obtained as colourless needles from benzene m.p. 133–134°, (Found: C, 75·3; H, 7·6; N, 8·0. $C_{11}H_{13}ON$ requires: C, 75·4; H, 7·5; N, 8·0%).

5-Phenylpent-4-enylamine (II). Lithium aluminium hydride (17·5 g) was suspended in a mixture of anhydrous ether (100 ml) and dioxan (130 ml) and to this mixture a solution of I (40 g) dissolved in dioxan (350 ml) was added with stirring at 10°. After additional stirring for 12 hr at room temp the mixture was heated at 50° for 1 hr, and the product worked up as usual. A colourless oil b.p. 111° (3 mm) was obtained (29·4 g, 80%) from which the following crystalline derivatives were prepared.

Hydrochloride. Colourless rhombs m.p. 180° (decomp) from ether–ethanol, (Found C, 66·9; H, 8·2; N, 7·0. $C_{11}H_{16}NCl$ requires: C, 66·8; H, 8·15; N, 7·1%).

Picrate. Yellow needles m.p. 157–158° from ethanol–diisopropylether, (Found C, 52·1; H, 4·8; N, 14·6. $C_{17}H_{18}O_7N_4$ requires: C, 52·3; H, 4·65; N, 14·35%).

N-(5-Phenylpent-4-enyl)-benzamide (IIIa). This was obtained in almost quantitative yield from II by benzoylation. The product separated in colourless feathers m.p. 63–64° when crystallized from a mixture of benzene and ligroin (b.p. 80–120°), (Found C, 81·6; H, 7·1:, N, 5·0. $C_{18}H_{19}ON$ requires: C, 81·5; H, 7·2; N, 5·3%) U.V. λ_{max}^{EtOH} 252, 283, 293 mμ, (log ε 4·42, 2·37, 2·20).

N-(5-Phenylpent-4-enyl)-acetamide (IIIb). II was acetylated with acetic anhydride yielding IIIb almost quantitatively as colourless feathers m.p. 65–66° crystallizing from a mixture of benzene and petroleum ether. (b.p. 45–80°) (Found C, 76·5; H, 8·45; N, 7·0. $C_{13}H_{17}ON$ requires: C, 76·8; H, 8·4; N, 6·9%).

N-(5-Phenylpent-4-enyl)-formamide. II (0·8 g) was heated with ethyl formate (0·5 g). The product (0·92 g, 98%) was crystallized from petroleum ether (b.p. 45–80°) in colourless scales m.p. 59·5–60·5°. (Found: C, 76·3; H, 7·9; N, 7·65. $C_{12}H_{15}ON$ requires: C, 76·15; H, 8·0; N, 7·4%).

N-(5-Phenylpent-4-enyl)-ethoxycarbonylformamide (XIII). To a mixture of II (2·85 g), ether (50 ml), $KHCO_3$ (8 g) and water (20 ml) was added ethoxycarbonylformyl chloride (3 g) dropwise at 0° with stirring. After stirring for 1 hr the product (4·27 g, 92%) crystallized in colourless needles m.p. 62–64° from n-hexane, (Found: C, 68·9; H, 7·4; N, 5·4. $C_{15}H_{19}O_3N$ requires: C, 68·9; H, 7·3; N, 5·4%).

2-Phenyl-3-benzal-3,4,5,6-tetrahydropyridine (IVa). A mixture of IIIa (9·0 g), phosphoryl chloride (37 ml) and benzene (54 ml) was refluxed for about 4 hr. On working up the reaction product IVa

was obtained (6·52 g, 77·5%) and crystallized from petroleum ether (b.p. 45–80°), colourless rhombs, m.p. 70–71°. (Found: C, 87·5; H, 6·7; N, 5·9. $C_{18}H_{17}N$ requires: C, 87·4; H, 6·9; N, 5·7%). U.V. λ_{max}^{EtOH} 286 mμ (log ε 4·33).

The *picrate* formed yellow rhombs from ethanol m.p. 183–184°, (Found: C, 60·6; H, 4·25; N, 11·7. $C_{24}H_{20}O_7N_4$ requires: C, 60·5; H, 4·2; N, 11·8%).

The *methiodide* separated in yellow needles m.p. 193–194° from a mixture of ether and methanol. (Found: C, 58·7; H, 5·3; N, 3·5. $C_{19}H_{20}NI$ requires: C, 58·6, H, 5·2; N, 3·6%).

2-*Methyl*-3-*benzal*-3,4,5,6-*tetrahydropyridine* (IVb). A mixture of IIIb (2 g), phosphoryl chloride (9 ml) and benzene (12 ml) gave after being refluxed for 1·5 hr a yellowish red oily base (1·81 g). The crude base was dissolved in benzene and purified through an alumina column. The pale yellow oil (IVb, 1·3 g, 71·2%) was characterized as the *picrate*, which formed yellow plates m.p. 187–188° from methanol, (Found: C, 55·1; H, 4·4; N, 13·5. $C_{19}H_{18}O_7N_4$ requires: C, 55·45; H, 4·4; N, 13·9%).

2-*Ethoxycarbonyl*-3-*benzal*-3,4,5,6-*tetrahydropyridine* (XIV). A mixture of XIII (0·62 g), phosphoryl chloride (2·7 cc) and benzene (2·7 cc) was refluxed for 30 min to give XIV (0·21 g, 36%). The *picrate* formed yellow needles m.p. 152–153° from ethanol, (Found: C, 53·2; H, 4·3; N, 12·0. $C_{21}H_{20}O_9N_4$ requires: C, 53·4; H, 4·3; N, 11·9). The *methiodide* crystallized in yellow needles m.p. 126° (decomp) from methanol–ether, (Found: C, 49·6; H, 5·0; N, 3·5. $C_{16}H_{20}O_2NI$ requires: C, 49·9; H, 5·2; N, 3·6).

2-*Phenyl*-3-*benzyl*-1-*methylpiperidine* (V). The methiodide (4 g) of IV was converted into the corresponding chloride and was reduced over Adams Pt-catalyst in ethanol. (ca. 2 molar equivalents of H_2 being absorbed). The product (V) was a colourless oily base b.p. 145–146° (2 mm) (2·32 g, 85·2%). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·73). The *picrate* formed yellow needles m.p. 190–191° from ethanol, (Found: C, 61·0; H, 5·5; N, 11·45. $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3).

N,N-*Dimethyl*-4,4-*dibenzyl*-*n*-*butylamine* (VI).

(i) A mixture of V (2·32 g), methyl iodide (5 ml) and methanol (6 ml) was refluxed to form the methiodide of V which was directly converted into methochloride. The latter was dissolved in aq. NaOH (70 ml, 20%) to which powdered Raney nickel alloy (2 g) was added gradually with stirring. After addition of the alloy the mixture was stirred at 30° for 4 hr and then extracted with benzene, dried and the solvent removed. The residue distilled at 152–154° (1·5 mm) as a colourless oil (2·3 g, 93%), (Found: C, 85·5; H, 9·9; N, 5·3. $C_{20}H_{27}N$ requires: C, 85·35; H, 9·7; N, 5·0%). The *picrate*, yellow plates m.p. 101–102° from ethanol, (Found: C, 61·2; H, 6·0; N, 11·1. $C_{20}H_{30}O_7N_4$ requires: C, 61·2; H, 5·9; N, 11·0%). The *methiodide* separated as colourless scales from methanol–ether m.p. 144–145°, (Found: C, 59·75; H, 7·4; N, 3·9; I, 30·3. $C_{21}H_{30}NI$ requires: C, 59·6; H, 7·1; N, 3·3; I, 30·0%).

(ii) Dibenzylacetyl chloride was converted by the Arndt–Eistert method into the diazoketone, pale yellow needles from n-hexane m.p. 77–77·5° (84%), (Found: C, 77·3; H, 6·3. $C_{17}H_{16}ON_2$ requires: C, 77·25; H, 6·1%). The diazoketone (1·4 g) in ethanol (15 ml) and a small amount of silver oxide was warmed at 55° until evolution of gas had ceased (15 min). Active charcoal powder was added and the mixture was filtered and the solvent removed leaving a residue of ethyl 3,3-dibenzylpropionate, which was hydrolysed yielding 3,3-dibenzylpropionic acid, colourless prisms m.p. 84–85·5° from petroleum ether, (Found C, 80·5; H, 6·95. $C_{17}H_{18}O_2$ requires: C, 80·3; H, 7·1%).

4,4-*Dibenzylbutyramide* (X). 3,3-Dibenzylpropionyl chloride (b.p. 162°, 0·12 mm) (0·91 g) was treated with diazomethane (from nitrosomethylurea 1·8 g) and the crude diazoketone was added to a mixture of dioxan (5 ml) and conc ammonia (7·5 ml) and to the solution silver nitrate (2 ml, 10%) was added dropwise. The evolution of nitrogen ceased after ½ hr at 70° and the amide was dissolved in benzene, washed and dried and the solvent evaporated. The amide was dissolved in benzene and purified through an alumina column, and crystallized from a mixture of n-hexane and benzene in colourless needles m.p. 88–89° (0·69 g, 65%), (Found: C, 81·1; H, 8·0: N, 5·3. $C_{18}H_{21}ON$ requires: C, 80·9; H, 7·9: N, 5·2%).

4,4-*Dibenzylbutylamine* (XI). The amide (0·5 g) in ether (20 ml) and dioxan (20 ml) was added dropwise to $LiAlH_4$ (0·15 g) in ether (10 ml), and the mixture refluxed for 6 hr. On working up, the product distilled at 178–180° (3 mm) as a colourless oil (0·32 g, 67·5%). The *picrate*, yellow plates m.p. 135–136° crystallized from ethanol and diisopropylether, (Found C, 59·8; H, 5·7; N, 11·9. $C_{24}H_{26}O_7N_4$ requires: C, 59·7; H, 5·4; N, 11·6%). The *amine* XI (0·25 g) dissolved in formic acid

(0·3 g, 85%) and aqueous formaldehyde solution (0·3 ml, 35%) was heated at 100° for 2·5 hr. The *base* (VI) was obtained as an oil (0·215 g, 77·3%), b.p. 180° (2 mm). The *picrate* crystallized in yellow needles m.p. 101–103° from ethanol, and the *methiodide*, colourless scales m.p. 144–145° from methanol–ether were found to be identical with those from V described previously.

For exhaustive methylation, the methiodide (2·05 g) was triturated with methanol and freshly prepared silver oxide, filtered and the residue submitted to distillation *in vacuo* which yielded an oil (b.p. 160°, 2 mm) consisting of a basic fraction soluble in HCl and a neutral fraction (0·19 g, 16·6%) which was 4,4-dibenzylbut-1-ene (VII) b.p. 140° (2 mm). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·76). I.R. (C=C) 1642 cm^{-1} 996, 912 cm^{-1} (—CH=CH_2). The basic fraction was VI identified as the *methiodide*.

A solution of potassium permanganate (0·34 g) in acetone (35 ml) was added dropwise to a solution of VII (0·175 g) in acetone (7 ml) at room temp. The product (0·11 g) could not be crystallized and was converted to the anilide (0·08 g) m.p. 110–112° which was purified through an alumina column using a mixture of benzene and n-hexane. The first fraction yielded colourless needles of dibenzylacetanilide m.p. 156–157°, (Found: C, 83·8; H, 6·8; N, 4·5. $C_{28}H_{31}ON$ requires: C, 83·8; H, 6·7; N, 4·4). A second fraction yielded a solid m.p. 108–130° from which nothing definite could be isolated; it probably contained the anilide of β,β-dibenzylpropionic acid, an authentic specimen of which was prepared, m.p. 126–127°, (Found: C, 84·2; H, 7·15; N, 3·9. $C_{23}H_{23}ON$ requires: C, 83·85; H, 7·0; N, 4·25%).

2-Phenyl-3-benzylpyridine. A mixture of IVa (0·2 g), 30% Pd—C (50 mg) and ethyl cinnamate (4 ml) was refluxed in an atmosphere of nitrogen for 1 hr. On cooling, the product was extracted with dilute HCl and the acid solution was basified to separate an oily base, which was collected in benzene, washed, dried, and the solvent removed. The yellowish oil (0·14 g, 70·5%) was characterized as the *picrate*, yellow plates from methanol m.p. 157–158°, (Found: C, 60·6; H, 3·9; N, 11·9. $C_{24}H_{18}O_7N_4$ requires: C, 60·8; H, 3·8; N, 11·8%). The *base* recovered from the picrate formed a colourless syrup, b.p. 215–220° (2 mm). U.V. λ_{max}^{EtOH} 272 mμ (log ε 3·65).

2-Methyl-3-benzylpyridine. IVb (1·36 g) in ethanol (40 ml), acidified by adding conc HCl (2 ml), was reduced catalytically over Adams Pt-catalyst, 2 molar equivalents of H_2 being absorbed. *2-Methyl-3-benzylpiperidine* distilled at 109–110° (2 mm) yielding colourless oil (0·68 g). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·38). This (0·2 g) was dehydrogenated and a yellowish oil was obtained which was characterized as the *picrate*, yellow needles from methanol, m.p. 148–150°, (Found: C, 55·55; H, 4·0; N, 13·6. $C_{19}H_{16}O_7N_4$ requires: C, 55·3; H, 3·9; N, 13·6%). The *base* recovered from the picrate was a colourless oil, b.p. 130° (2 mm). UV λ_{max}^{EtOH} 265 mμ (log ε 3·62).

3-Benzoylpicolinic acid. The foregoing base (0·11 g) was warmed (steam-bath) and oxidized by adding aq. solution of potassium permanganate until no more decolourization was observed. The filtrate from MnO_2 was concentrated to a small volume, acidified by HCl and mixed with aq. cupric acetate to precipitate blue copper salt of the acid, which was collected and decomposed with H_2S. From the filtrate 0·1 g of the acid was obtained, which formed colourless prisms from water, m.p. 147° (decomp). An authentic specimen also melted and decomposed at the same temp. and their identity was also established beyond doubt by comparing their I.R. spectra.

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