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EXTENSION OF THE BISCHLER-NAPIERALSKI REACTION—II

SYNTHESIS OF PYRROLINE DERIVATIVES

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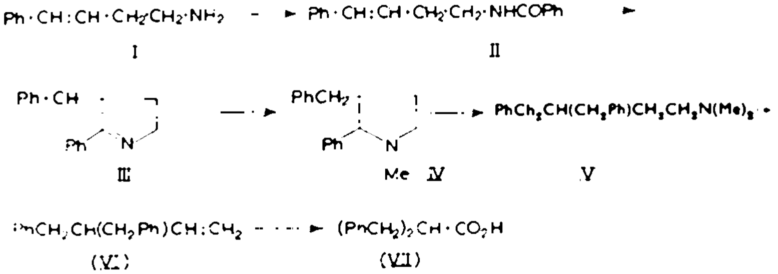
Abstract—Acyl derivatives of 4-phenyl-but-3-enylamine on treatment with phosphoryl chloride gave good yields of pyrrolines. Pyridine derivatives were not obtained.

In Part I[1] the Bischler–Napieralski reaction was applied to the cyclisation of acyl *cyclo*hexa-1:4-dienylamines yielding *iso*quinoline derivatives. The reaction has now been extended to the cyclisation of acyl derivatives of 4-phenyl-but-3-enylamine (I). Thus benz-4-phenyl-but-3-enylamide (II) cyclises to Δ^1-2-phenyl-3-benzal-pyrroline (III) the structure of which was proved by exhaustive methylation. The ultra-violet spectrum showed the presence of a fairly extended conjugated system. The infra-red spectrum showed (at a concentration of 7% in carbon tetrachloride) strong absorption at 3098 and 3048 cm^{-1} due to aromatic C—H stretching vibrations and absorption of equal intensity at 2945 and 2879 cm^{-1} due to aliphatic C—H stretching vibrations. Absorption due to C=C and C=N stretching vibrations was observed at 1636 (w) and 1563 cm^{-1} respectively. No absorption was observed in the region corresponding to the N—H stretching vibration. The methiodide of (III) was reduced catalytically to the N-methyl-tetrahydro-base (IV) which was converted through the methiodide to the hydroxide. (IV) was recovered when the latter was subjected to the Hofmann degradation but a modified Emde degradation[2] gave a dihydromethine base (V) the methiodide of which on Hofmann degradation gave 3-benzyl-4-phenyl-but-1-ene (VI), and this on oxidation gave dibenzylacetic acid (VII). Similarly, acet-4-phenyl-but-3-enylamide cyclises to give Δ^1-2-methyl-3-benzal-pyrroline. The structure was proved by a similar degradation process and the final product, β-benzylbutric acid, identified as the anilide.



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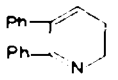
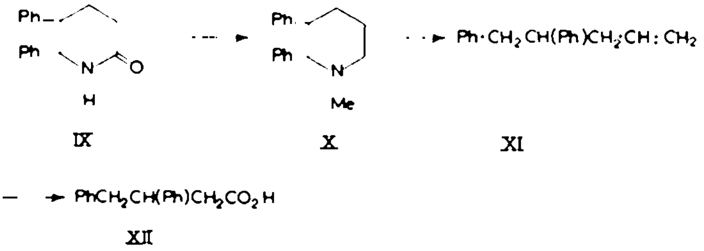
[1] S. Sugasawa and R. Tachikawa, *Tetrahedron*. In press.
[2] S. Sugasawa and H. Matsuo, *Pharm. Bull.* (*Japan*) **4**, 142 (1956).

The possibility that cyclisation of (II) might yield 5:6-diphenyl-2:3-dihydropyridine (VIII) was investigated. 5:6-diphenyl-3:4-dihydro-pyrid-2-one (IX)[3] was reduced and methylated to 1-methyl-5:6-diphenylpiperidine (X) and the quaternary iodide of the latter when subjected to Emde and Hofmann degradations gives 4:5-diphenyl-pent-1-ene (XI) which on oxidation yields β:γ-diphenylbutyric acid (XII) (m.p. 93°) identical with an authentic specimen of the acid, and a mixed m.p. with dibenzylacetic acid (m.p. 93°) showed a depression.



VIII



EXPERIMENTAL

2-Phenyl-3-benzalpyrroline (III). 4-Phenyl-3-butenylamine (I) obtained by catalytic reduction of cinnamyl cyanide[4] was benzoylated giving benz-4-phenyl-but-3-enylamide (II). The latter (5 g) was cyclised by refluxing (3 hr) with benzene (30 cc) and phosphoryl chloride (25 cc). The yellow reaction mixture was distilled *in vacuo* to remove benzene and excess phosphoryl chloride, then treated with ice and the acid solution neutralised with potassium carbonate. The oil which separated was extracted with benzene and the basic product extracted from the benzene solution with 3% HCl. The crude base (4·35 g, 93·5%) obtained from the acid solution in the usual way crystallised from hexane as colourless needles, m.p. 110–111°. (Found: C, 87·0; H, 6·5; N, 6·1; $C_{17}H_{15}N$ requires: C, 87·5; H, 6·4; 6·0%). The *picrate* formed yellow needles m.p. 192·5–193·5° from ethanol (Found: C, 59·5; H, 3·7; N, 11·8; $C_{23}H_{18}O_7N_4$ requires: C, 59·7; H, 3·9; N, 12·1%). Infra-red: 1636 cm^{-1} (w. C C), 1563 cm^{-1} (s. C=N). No absorption in the region of the NH stretching vibration. Ultra-violet: 248 mμ (log ε = 4·05), 254 mμ (log ε = 4·05), 293 mμ (log ε = 4·37). An attempt to dehydrogenate (III) by heating (5 hr) with palladium carbon in *p*-cymene and ethyl cinnamate at 190° gave a scarlet compound m.p. 205° the analysis of which indicated a trimer of dehydrogenated (III). (Found: C, 88·7; H, 5·85; N, 5·4; mol. wt. 694; $(C_{17}H_{13}N)_3$ requires: C, 88·3; H, 5·7; N, 6·1%).

1-Metyl-2-phenyl-3-benzylpyrrolidine (IV). The base (III) when treated with methanolic methyliodide gave a methiodide m.p. 169·5–170·5° (decomp). The latter (4·4 g) converted to the chloride was reduced in ethanol over Adam's platinum until 2 molar equivalents of hydrogen were absorbed yielding (IV, 3·01 g, 85%) m.p. 71°.

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[3] A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.* 959, (1956).

[4] D. Barnard and L. Bakeman, *J. Chem. Soc.* 926 (1950).

(Found: C, 86·05; H, 8·1; N, 5·5; $C_{17}H_{19}N$ requires: C, 86·0; H, 8·4; 5·6%). The *picrate* formed yellow needles m.p. 200·5–201·5° from ethanol. (Found: C, 60·0; H, 4·6; N, 11·3; $C_{24}H_{24}O_7N_4$ requires: C, 60·0; H, 5·0; N, 11·7%). The *methiodide* separated in colourless needles m.p. 192° from methanol-ether. (Found: C, 58·1; H, 6·0; N, 3·45; $C_{19}H_{24}NI$ requires: C, 58·0; H, 6·15; N, 3·6%). 1-*Methyl-2-phenyl-3-benzalpyrrolidine*. When the hydrogenation of the chloride was stopped after uptake of 1 molar equivalent of hydrogen the dihydro-compound was obtained. This is a low-melting base characterised as its *methiodide* m.p. 226° (decomp) from methanol. (Found: C, 58·2; H, 5·7; N, 3·3; $C_{19}H_{22}NI$ requires C, 58·3; H, 5·7; N, 3·6%).

N:N-*Dimethyl-3-benzyl-4-phenylbutylamine* (V). The methiodide of (IV) (1·1 g) converted to the corresponding chloride was dissolved in aqueous sodium hydroxide (20 cc, 20%), and Raney nickel alloy (0·5 g) added in portions at 20–25° with stirring (2 hr). The metal was filtered off, the base extracted with benzene, washed with saturated sodium chloride solution, dried and the solvent removed. The residue distilled at 171–175°/3·5 mm to give the pure amine in nearly quantitative yield. The amine reacted exothermically with methyl iodide to form the methiodide which crystallised from methanol-ether in white scales m.p. 165–167°. (Found: C, 58·9; H, 7·0; N, 3·3; $C_{20}H_{28}NI$ requires: C, 58·8; H, 6·9; N, 3·4%). The *picrate* separated in yellow rhombic crystals m.p. 125–125·5° from methanol-ether. (Found: C, 60·6; H, 5·7; N, 11·4; $C_{25}H_{28}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3%).

Dibenzylacetic acid. The methiodide (2·87 g) of the amine (V) was converted to the hydroxide which was subjected to crack-distillation *in vacuo* yielding a fraction (b.p. 160°/3 mm) consisting of unchanged amine and a non-basic product. The letter (0·95 g, 64·8%) was freed from the amine by treatment with HCl. The ultra-violet spectrum, 259 mμ (log ϵ = 2·53), indicated the absence of a double bond conjugating with the phenyl nucleus. The infra-red, observed in a cell (0·15 mm thickness) 1641 cm^{-1} (s. C=C), 994, 910 cm^{-1} (s. C—H out of plane deformation vibration of vinyl group). It is presumed that the non-basic product is 3-benzyl-4-phenyl-but-1-ene (VI). The latter (70 mg) was oxidised in acetone by addition of $KMnO_4$ (140 mg) in acetone (14 cc) at room temp. with stirring. MnO_2 was removed by filtration, washed with water and the washings added to the acetone filtrate. The acetone was removed *in vacuo* and the aqueous solution shaken with benzene, separated and acidified with HCl, when dibenzylacetic acid was deposited as an oil, which solidified and crystallised from *n*-hexane as colourless crystals m.p. 92–93° (Found: C, 80·2 H, 6·4. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). The acid was identified with an authentic specimen of debenzylacetic acid.

5:6-*Diphenyl*-3:4-*dihydropyrid-2-one*[3] (IX). A solution of δ-oxo-γ:δ-diphenylvaleronitrile (20 g) in *tert.*-butanol was refluxed with methanolic potassium hydroxide solution (30%), mixed with *tert.*-butanol (400 cc) for 10 hr during which the pyridone (IX) separated as a solid (13·7 g, 68·4%) and crystallised from ethanol as colourless prisms m.p. 215° (Found: C, 81·85; H, 6·1. Calc. for $C_{17}H_{15}ON$: C, 81·9; H, 6·1%). Infra-red (Nujol) 3220, 3110 cm^{-1}. (N—H), 1665 cm^{-1} (lactam C=O), 1638 cm^{-1} (C C).

5:6-*Diphenyl-piperid*-2-*one*. The pyridone (IX, 1·6 g) methanol-dioxane (7 : 5) on hydrogenation at 50° over Adams platinum cataylst, absorbed a molar equivalent of hydrogen in 2 hr. The crude product was purified from ethanol (1·15 g, 73%) as colourless fine needles m.p. 183·5–184·5° (Found: C, 81·0; H, 7·0; N, 5·5. $C_{17}H_{17}ON$ requires: C, 81·2; H, 6·8; N, 5·6%). The band at 1638 cm^{-1} had disappeared.

2:3-*Diphenylpiperidine*. To an ether solution of lithium aluminium hydride (0·1 g) the above piperidone (0·58 g) in dioxane was added and refluxed for 3 hr. Wet ether was added to decompose the adduct and the solvents removed *in vacuo*. The residue a mixture of unchanged piperidone and 2:3-*diphenylpiperidone* was distilled, yielding the pure piperidine which on recrystallisation from ethanol gives colourless prisms m.p. 86·5–87·5° (Found: C, 85·9; H, 8·2; N, 6·0. $C_{17}H_{19}N$ requires C, 86·0; H, 8·1; N, 5·9%). On treatment with formic acid and aqueous form aldehyde the piperidine gave 1-*methyl*-5:6-*diphenylpiperidine* (X) which was purified by distillation b.p. 159–160°/1·5 mm. The *picrate* m.p. 149–150·5° and the *methiodide* colourless cubes m.p. 254° decomp. from ethanol (Found: C, 57·7; H, 6·3; N, 3·5. $C_{19}H_{24}NI$ requires: C, 58·0; H, 6·15; N, 3·6%) were not identical with those of (IV). The methiodide, subjected to the Emde degradation with sodium amalgam (5%) under the usual conditions, gave N:N:4:5 diphenylpentylamine, b.p. 165°/2-2·5 mm (64%). The *picrate* formed yellow scales, m.p. 121 122°, from ether-methanol (Found: C, 60·7; H, 5·7; N, 11·5. $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3%). The methiodide was obtained in quantitative yield as plates m.p. 164–165° from methanol-ether (Found: C, 58·6; H, 6·9; N, 3·7. $C_{20}H_{28}NI$ requires C, 58·7; H, 6·9, N, 3·4%). The methiodide converted to the methohydroxide (0·5 g) submitted to crack-distillation *in vacuo*, gave Δ^{1}4:5-*diphenylpentene* (XI) b.p. 144–146° (0·16 g, 59) and the latter on oxidation gave β:γ-diphenylbutyric acid (XII), as colourless cubes from hexane m.p. 93° (Found: C, 79·6; H, 6·7. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). Mixed with dibenzylacetic acid (VII) m.p. 93°, the mixture melted over a range 70–77°. (XII) was found to be identical with a specimen synthesised by condensation of desoxybenzoin with ethyl cyanacetate according to Cope.[5] The synthetic acid crystallised as colourless prisms m.p. 94–95·5° (Found: C, 79·7; H, 6·8. Calc. for $C_{16}H_{16}O_2$; C, 80·0; H, 6·7%). Mixed with (XII) there was no depression. Infra-red spectra of the two acids were also identical over the whole range.

Acet-4-phenyl-but-3-enylamide. Acetylation of 4-penyl-but-3-enylamine (2·42 g) with acetic anhydride (5 cc) on a steam-bath gave the acetyl compound in good yield which crystallised from *n*-hexane in colourless plates m.p. 73–74° (Found: C, 76·1; H, 8·1; N, 7·5; Calc. for $C_{12}H_{15}ON$: C, 76·15; H, 8·0; N, 7·4%). Treatment of the acetyl compound with phosphoryl chloride in boiling benzene gave Δ^{1}-2-*methyl*-3-*benzalpyrroline* (90%) which crystallised from *n*-hexane in prisms m.p. 61–63°. The *picrate* formed yellow needles m.p. 224° (decomp.) from ethanol. (Found: C, 54·1; H, 4·4; N, 14·3; $C_{18}H_{16}O_4N_4$ requires: C, 54·0; H, 4·0; N, 14·0%). The *methiodide* formed colourless needles m.p. 266·5° (decomp.) from methanol-ether (Found: C, 49·7; H, 5·3; N, 4·8; $C_{13}H_{16}NI$ requires: C, 49·9; H, 5·15; N, 4·5%). Reduction of the methiodide with Adams platinum catalyst absorbed 2 molar equivalents of hydrogen and gave 1:2-*dimethyl*-3-*benzylpyrrolidine* b.p. 109–112°/2·5–3 mm the *methiodide* of which crystallised from methanol-ether in needles m.p. 212–213° (decomp.) (Found: C, 50·6; H, 6·9; N, 4·0; $C_{14}H_{22}NI$ requires: C, 50·8; H, 6·7; N, 4·2%). The methiodide (1·07 g) on treatment with Raney nickel (in the presence of alkali) gave N:N dimethyl 3-benzylpentylamine, (the methiodide of which formed) colourless plates from methanol-ether m.p. 115·5 116·5° (Found: C, 51·8; H, 7·4;

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[5] L. Phalnikar and S. K. Nargund, *J. Univ. Bombay*, 3, 1849 (1939); *Chem. Abstr.* 34, 2819 (1940).

N, 4·0. $C_{15}H_{26}NI$ requires: C, 51·9; H, 7·55; N, 4·0%). On exhaustive methylation (Hofmann) the methiodide (0·42 g) gave a nitrogen free compound (0·08 g. 41%). The latter (60 mg) oxidised by $KMnO_4$ in acetone gave α-benzylbutyric acid (40 mg) which was converted to the anilide, colourless needles from hexane m.p. 90° (Found: C, 80·3; H, 7·7; N, 5·5; Calc. for $C_{17}H_{19}ON$: C, 80·6; H, 7·6; N, 5·5%). It was identical with an authentic specimen prepared from α-benzylbutyric acid, obtained from benzylethylmalonic acid.

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