N-Alkylation of 2- and 4-Carbamoylpyridine

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A number of new N-alkylated carbamoylpyridines required for a series of pharmacological investigations [1] have been prepared. Since adaptation of the usual alkylation methods to the carbamoylpyridines presented some difficulties, inasmuch as, *e.g.*, all attempts to use alkyl chlorides as alkylating agents were unsuccessful, the synthetic procedures finally adopted are reported in the following.

1,1'-Trimethylene-bis-(4-carbamoylpyridinium bromide). A solution of 30.5 g (0.25 mole) of isonicotinamide (prepared according to Prijs, Lutz and Erlenmeyer [2]) and 20 g (0.09 mole) of 1,3-dibromopropane in 200 ml of ethanol was heated in a stainless steel autoclave at 120° for one hour. After cooling the crystals were filtered by suction, washed with ether and dried at room temperature. Yield 26 g. After recrystallisation from 50 % ethanol, 18.7 g (43 %) of a dihydrate was obtained as small, colourless crystals, m.p. 256–257° (decomp.). (Found after drying at 50°/2 mm: N 11.81; Br 33.79; H_2O (Karl Fischer titration) 7.96. Calc. for $C_{15}H_{18}N_4O_2Br_2$, $2H_2O$: N 11.62; Br 33.19; H_2O 7.47).

1,1'-Trimethylene-bis-(4-carbamoylpyridinium chloride). To a solution of 48.2 g (0.10 mole) of 1,1'-trimethylene-bis-(4-carbamoylpyridinium bromide) dihydrate in 200 ml of water was added freshly precipitated silver chloride, prepared from 68 g (0.40 mole) of silver nitrate. The suspension was stirred for 10 min at 100°, the precipitate removed by filtration, and the filtrate evaporated. The crude product was recrystallised from 90 % methanol to give a dihydrate in very small, colourless crystals. Yield 25 g (64 %) m.p. 263–264° (decomp). (Found after drying in the air: H_2O (Karl Fischer titration) 8.83. Calc. for $C_{15}H_{18}N_4O_2Cl_2$, $2H_2O$: 9.16. Found after drying at 50°/2 mm: C 50.24; H 5.19; N 16.22; Cl 19.62. Calc. for $C_{15}H_{18}N_4O_2Cl_2$: C 50.43; H 5.08; N 15.68; Cl 19.85).

2-Carbamoyl-1-methylpyridinium iodide. 13.1 g (0.10 mole) of α-picolinamide (prepared according to Engler [3]) and 28.4 g (0.20 mole) of methyl iodide were heated at 85° for 3 h in a 250 ml Duran glass autoclave. The excessive methyl iodide was distilled off and the residue washed with ether and dried at room temperature. Yield 22.5 g. After recrystallisation from methanol, 15.8 g (60 %) of small, yellow crystals were obtained, m.p. 171–172° (decomp.). (Found after drying at 50°/2 mm: N 10.51; I 48.20. Calc. for $C_7H_9N_2OI$: N 10.61; I 48.06).

2-Carbamoyl-1-methylpyridinium chloride. To a solution of 13.2 g (0.05 mole) of 2-carbamoyl-1-methylpyridinium iodide in 100 ml of water was added freshly precipitated silver chloride, prepared from 17 g (0.10 mole) of silver nitrate, and the suspension was treated as described above. After recrystallisation from 90 % ethanol, 6 g (63 %) of a monohydrate was obtained as small, colourless crystals, m.p. 223–224° (decomp.). (Found after drying in the air: H_2O (Karl Fischer titration) 9.43. Calc. for $C_7H_9N_2OCl$, H_2O: 9.45. Found after drying at 50°/2 mm: C 48.63; H 5.43; N 15.98; Cl 20.38. Calc. for $C_7H_9N_2OCl$: C 48.71; H 5.26; N 16.23; Cl 20.54).

The elementary analyses were performed by Dr. A. Bernhardt, Max-Planck-Institut, Mühlheim.

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α-Longipinene, A Sesquiterpene with A New Carbon Skeleton *, **

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Longicyclene [1] and β-bergamotene [2] have recently been isolated from Indian turpentine oil (from *Pinus longifolia*) and

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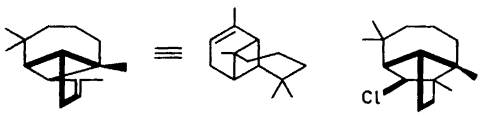
from the oil of *Valeriana wallichi*, respectively. A closely related sesquiterpene obviously possessing structure (1) ("*a*-longipinene") has now been isolated in this Laboratory.



1 *2*

The compound has been isolated from Swedish sulphate turpentine, but has also been shown by chromatographic methods to be present in extracts from the wood of Scots pine, *Pinus silvestris*. We intend to report our results of an investigation of other neutral pine constituents in a forthcoming publication.[3]

The hydrocarbon was isolated in an almost pure state by repeated vacuum distillation and chromatography on alumina of a fraction (b.p. 115–130° at 20 mm) of the crude turpentine. Final purification was achieved by means of chromatography on silver nitrate-impregnated silica gel.[4]

The compound ($C_{15}H_{24}$, b.p. 102–106° at 10 mm, n_D^{22} 1.4924, d_4^{22} 0.9122, M_D 65.01, $[\alpha]_D^{22}$ + 36.9° ($CHCl_3$, *c* 2.2)) consumed one mole of hydrogen (platinum catalyst, acetic acid) to give a saturated product. This indicates that the compound is tricyclic.

The molecular refraction indicates that one of the rings is three- or four-membered. (Required for one double bond and one three- or four-membered ring 65.10 and 64.96, resp.).

On ozonolysis, a ketoacid (2,4-dinitrophenylhydrazone, m.p. 138°, semicarbazone, m.p. 117°) was formed in good yield. The double bond is thus trisubstituted.

On treatment with anhydrous hydrogen chloride in ether at −20°, the compound yielded (+)-longibornyl chloride (2) (m.p. and mixed m.p. 59–60°, identical optical rotations, superimposable IR spectra).[5]

These results require that the formation of the hydrochloride involves a rearrangement (*cf.* the conversion of *a*-pinene to bornyl chloride).

The nuclear magnetic resonance spectrum (in carbon tetrachloride) exhibits characteristic signals at τ 9.18 (two methyl groups) and τ 9.10 (one methyl group) as well as at τ 4.86 (one vinyl proton) and τ 8.36 (one methyl group attached to an unsaturated carbon atom). The two latter signals are almost identical with respect to both chemical shifts and signal patterns with those originating from the corresponding protons in *a*-pinene.

In the ultraviolet region the log ε curves of *a*-pinene and *a*-longipinene are almost superimposable, and in the infrared region the characteristic double bond absorptions appear at the same frequencies within less than 5 cm^{-1}. It is interesting to note the strong UV end absorptions of these compounds (ε_{210} 5000, ε_{215} 4070, ε_{220} 2570, ε_{225} 1170, ε_{230} 389 for *a*-longipinene).

The results are consistent with structure (1) for the new sesquiterpene. It is true that two additional structures, related to the fenchenes, could account for the results but it is very unlikely that compounds possessing these structures would be capable of producing homogeneous longibornyl chloride on addition of hydrogen chloride. No isomers could be detected in the crude product by gas-liquid chromatography. (Addition of hydrogen chloride to fenchene, *cf.* Ref.[6])

For obvious reasons it would be interesting to know whether in *Pinus silvestris* *a*-longipinene, longifolene,[3] and longicyclene [3] co-occur with *β*-longipinene, and attempts to isolate the latter are under way.

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