

620. Ready Formation of Ketals by 4-Piperidones.

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Ready formation of ketals by 1-benzyl- and 1-*n*-butyl-4-piperidones is recorded and correlated with previous observations.

BOLYARD and McELVAIN¹ crystallised the hydrochlorides of a series of 1-alkyl-4-piperidones (alkyl = Me, Et, Prⁿ, Buⁿ, CH₂Buⁱ, and CH₂Ph·CH₂) from alcohol-ether. The only analyses recorded were for chlorine, and the values for the *n*-butyl and phenethyl derivatives were considerably lower than the theoretical. "Unusual care was exercised in their preparation and purification but no change in the analytical data could be obtained," and the cause of the discrepancy was not found. Bolyard² later reported the preparation of the hydrochlorides of 1-phenyl- and 1-benzyl-4-piperidone and observed that "Both of these piperidone hydrochlorides when crystallised from an alcohol-ether mixture gave chlorine analyses considerably lower than the calculated value, but when crystallised from an acetone-ether mixture the analyses checked with the calculated values." The anomaly was attributed to solvation but drying had no effect on the analyses. Shortly afterwards Kuettel and McElvain³ reported an anomalous chlorine content for 4-piperidone hydrochloride crystallised from alcohol-ether, and, eighteen years later, McElvain and McMahon,⁴ repeating this preparation, concluded from the behaviour of the substance on attempted catalytic hydrogenation that it was in fact the diethyl ketal hydrochloride; they also pointed out that the chlorine figure obtained previously¹ for the hydrochloride of 1-phenethyl-4-piperidone corresponded to that of the hydrochloride of the diethyl ketal.

As 1-benzyl-4-piperidone was required as an intermediate in the work described in the preceding communication, it was prepared by Bolyard's method.² The crude hydrochloride did not immediately crystallise satisfactorily from acetone-ether, and was therefore crystallised first from ethanol-ether and then twice from acetone-ether. The product had m. p. 172—173°, compared with the m. p. 159—161° quoted by Bolyard² for the 1-benzylpiperidone hydrochloride for which he had obtained a correct chlorine analysis. It gave no oxime and had no infrared absorption band in the carbonyl-stretching region. It was, in fact, the diethyl ketal hydrochloride, as shown by a complete elementary analysis and an ethoxyl determination. Hydrolysis with 3*N*-hydrochloric acid and evaporation to dryness gave a product of m. p. 156—158°, showing a strong infrared band at 1725 cm.⁻¹, and giving 1-benzyl-4-piperidone oxime on treatment with hydroxylamine hydrochloride in pyridine. Unfortunately Bolyard² gave no details of the compounds which he thought were 1-phenyl- and 1-benzyl-piperidone hydrochlorides containing alcohol of crystallisation but there can be little doubt that they too were ketals formed on recrystallisation of the crude products, still containing traces of hydrogen chloride, from alcohol-ether.

McElvain and McMahon⁴ have already noted that the chlorine figure (11.49%) recorded previously¹ for 1-phenethyl-4-piperidone hydrochloride corresponded with that (11.32%) required for the diethyl ketal hydrochloride, but the chlorine figure (14.62%) reported¹ for the reputed 1-*n*-butyl-4-piperidone hydrochloride, m. p. 178—180°, is closer to that (14.9%) required for the dimethyl ketal hydrochloride than to that (13.4%) required for the diethyl ketal hydrochloride. The following experiments seem to show that the substance of m. p. 178—180° reported by Bolyard and McElvain¹ may have, in fact, been the dimethyl ketal hydrochloride. When 1-*n*-butyl-3-ethoxycarbonyl-4-piperidone was hydrolysed with 20%

¹ Bolyard and McElvain, *J. Amer. Chem. Soc.*, 1929, **51**, 922.

² Bolyard, *ibid.*, 1930, **52**, 1030.

³ Kuettel and McElvain, *ibid.*, 1931, **53**, 2692.

⁴ McElvain and McMahon, *ibid.*, 1949, **71**, 901; cf. Dickerman and Lindwall, *J. Org. Chem.*, 1949, **14**, 532.

hydrochloric acid and the solution was taken to dryness, crystallisation of the crude product from ethanol-ether gave a solid of m. p. 160—165°; two further recrystallisations from the same solvent mixture gave a product of m. p. 194°, which showed a strong infrared band at 1735 cm.⁻¹ and gave correct analyses for 1-*n*-butyl-4-piperidone hydrochloride. If, however, the once crystallised material of m. p. 160—165° was recrystallised from ethanol-ether containing a trace of hydrogen chloride the product had m. p. 169—171°, showed no infrared absorption in the carbonyl-stretching region, and gave analyses for the diethyl ketal hydrochloride. The m. p. of this authentic diethyl ketal hydrochloride was 18° lower than that recorded by Bolyard and McElvain for their compound, but, when 1-*n*-butyl-4-piperidone hydrochloride was boiled with methanol containing hydrogen chloride, the resulting dimethyl ketal hydrochloride had m. p. 176—179°, bearing favourable comparison with the m. p. recorded by Bolyard and McElvain¹ for their compound.

A number of stereochemical and polar factors are obviously concerned in the ease of formation and stability of 4-piperidone ketals. 1-*n*-butyl-4-piperidone diethyl ketal hydrochloride was converted into 1-*n*-butyl-4-piperidone hydrochloride under conditions of recrystallisation to which 1-benzyl-4-piperidone diethyl ketal hydrochloride appeared to be stable and 1-*n*-butyl-4-piperidone dimethyl ketal hydrochloride was stable to normal recrystallisation from methanol-ether as well as from ethanol-ether. It may be noted that Noller and Baliah⁵ prepared a series of twenty substituted 4-piperidones and crystallised the hydrochlorides of the majority from alcohol-containing solvents without finding a low chlorine content on analysis, yet Nazarov, Sokolov, and Rakcheeva⁶ observed that on formation of the picrate of 2:5-dimethyl-4-piperidone in hot methanol a substantial proportion of the picrate of the corresponding dimethyl ketal was also obtained, while Cardwell⁷ noted that quaternisation of 1-ethyl-4-piperidone with methyl iodide in methanol affords the dimethyl ketal of the quaternised product in quantitative yield, although quaternisation proceeded without ketal formation in *isopropyl* alcohol.⁸

EXPERIMENTAL

Infrared light absorption measurements were made on pressed potassium chloride discs; data are recorded for the region 2000—650 cm.⁻¹.

1-Benzyl-4-piperidone Diethyl Ketal Hydrochloride.—1-Benzyl-3-ethoxycarbonyl-4-piperidone hydrochloride (24 g.) was dissolved in 20% hydrochloric acid and boiled under reflux for 2 hr. The solution was taken to dryness under reduced pressure and the crude product (23.4 g.) was crystallised from ethanol-ether. Further recrystallisation from acetone-ether afforded 1-benzyl-4-piperidone diethyl ketal hydrochloride as colourless plates, m. p. 172—173° (Found: C, 64.2; H, 8.6; N, 4.8; Cl, 11.8; EtO, 29.3. C₁₈H₂₅O₂N.HCl requires C, 64.1; H, 8.7; N, 4.7; Cl, 11.9; 2EtO, 30.0%), ν_{\max} . 1505, 1483(m), 1455(m), 1440(s), 1425(m), 1390(m), 1375(m), 1365(m), 1345, 1320(m), 1300, 1285(m), 1265, 1245(m), 1220(m), 1160(s), 1150(s), 1125(s), 1110(s), 1100(s), 1080—1075(s), 1060(s), 1050(s), 1035(s), 1010(s), 985(s), 970(s), 945(m), 930(m), 920(m), 885, 880(m), 785, 740(s), 690(s) cm.⁻¹.

1-Benzyl-4-piperidone Hydrochloride.—1-Benzyl-3-ethoxycarbonyl-4-piperidone hydrochloride (33 g.) was heated as above with 20% hydrochloric acid (150 c.c.) for 2 hr. The solution was taken to dryness under reduced pressure and the crude solid was taken up in water (50 c.c.). The solution was rendered strongly alkaline with excess of 50% aqueous sodium hydroxide and extracted with ether (3 × 100 c.c.). The ethereal solution was dried (Na₂SO₄) and saturated with dry hydrogen chloride. The precipitated 1-benzyl-4-piperidone hydrochloride (22 g.) separated from acetone-ether in plates, m. p. 158—160°, ν_{\max} . 1725(s), 1500, 1460(s), 1420—1410(m), 1375, 1345(m), 1330(m), 1240, 1215(m), 1200(m), 1150(m), 1110(m), 1085(m), 1045(m), 1010(m), 985(m), 970(m), 940, 920, 755(m), 745(m), 700(s) cm.⁻¹.

1-Benzyl-4-piperidone hydrochloride was also obtained by warming 1-benzyl-4-piperidone

⁵ Noller and Baliah, *J. Amer. Chem. Soc.*, 1948, **70**, 3853.

⁶ Nazarov, Sokolov, and Rakcheeva, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1954, 80; *Chem. Abs.*, 1955, **49**, 6250.

⁷ Cardwell, *J.*, 1950, 1059.

⁸ Cardwell and McQuillin, *J.*, 1949, 708.

diethyl ketal hydrochloride with 3*N*-hydrochloric acid, evaporation of the solution to dryness, and crystallisation of the residue from acetone-ether.

1-n-Butyl-4-piperidone Diethyl Ketal Hydrochloride.—This substance was prepared by a procedure analogous to that described above for 1-benzyl-4-piperidone diethyl ketal hydrochloride, but the final product was crystallised from ethanol-ether containing a drop of saturated ethanolic hydrogen chloride. *1-n-Butyl-4-piperidone diethyl ketal hydrochloride* separated in plates, m. p. 169—171° (Found: C, 58·6; H, 10·6; Cl, 13·1; EtO, 32·3. $C_{13}H_{27}O_2N, HCl$ requires C, 58·9; H, 10·5; Cl, 13·4; 2EtO, 33·9%), ν_{max} . 1485(m), 1465(s), 1455(s), 1430(m), 1410, 1395—1380(m), 1370(m), 1350, 1330, 1310, 1285, 1270, 1235(m), 1220(s), 1175(s), 1165(s), 1125(s), 1100(s), 1065(s), 995, 975(s), 960(s), 895, 880(m), 795 cm^{-1}).

1-n-Butyl-4-piperidone Hydrochloride.—The method described by Bolyard and McElvain was followed but the ethereal solution of the crude 1-*n*-butyl-4-piperidone was dried and fractionated, affording an oil, b. p. 111—114°/15 mm. An ethereal solution of the pure base was saturated with dry hydrogen chloride, and the precipitated hydrochloride was thoroughly washed with ether to remove excess. Recrystallisation from ethanol-ether then gave *1-n-butyl-4-piperidone hydrochloride* as colourless prisms, m. p. 194—196° (Found: C, 56·2; H, 9·8; N, 7·5; Cl, 18·6. $C_9H_{17}ON, HCl$ requires C, 56·4; H, 9·4; N, 7·3; Cl, 18·6%), ν_{max} . 1735(s), 1480(m), 1465(s), 1410(s), 1385(m), 1330(m), 1220(m), 1205(s), 1165, 1145, 1120, 1100(m), 1060(m), 1050(m), 970, 940 cm^{-1}).

1-n-Butyl-4-piperidone Dimethyl Ketal Hydrochloride.—1-*n*-Butyl-4-piperidone hydrochloride (0·2 g.) was dissolved in the minimum volume of methanol, and a drop of saturated methanolic hydrogen chloride was added. The solution was boiled under reflux for 2—3 min., and addition of ether precipitated *1-n-butyl-4-piperidone dimethyl ketal hydrochloride* (0·21 g.), which separated from methanol-ether or from ethanol-ether in needles, m. p. 176—179° (Found: C, 55·2; H, 9·9; N, 6·0; MeO, 25·0. $C_{11}H_{23}O_2N, HCl$ requires C, 55·7; H, 10·1; N, 5·7; 2MeO, 26·1%), ν_{max} . 1455(m), 1435(m), 1380(m), 1350, 1340, 1310, 1285, 1275, 1240, 1230, 1185(m), 1170(m), 1125(s), 1065(s), 1045(s), 985(m), 935(m), 920(s) cm^{-1}).

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