Alkanolamines. I. Syntheses of *N*-methyl-3,4-dihydroxyephedrine hydrochloride and its derivatives. Junichi Iwao and Masayoshi Samejima. *J. Pharm. Soc. Japan* **74**, 548–50(1954).—3,4-$CH_2O_2C_6H_3COEt$ (100 g.) in 33 ml. $PhNO_2$ added dropwise to 167 g. $AlCl_3$ in 500 g. $PhNO_2$ at 20–5°, the mixt. stirred 3 hrs., poured into ice water contg. HCl, the $PhNO_2$ steam distd., and the residue extd. with Et_2O gives 78.5 g. (84.2%) 3,4-$(HO)_2C_6H_3COEt$ (**I**), columns, m. 146° (from water). **I** (10 g.) in 7.5 ml. 35% KOH shaken with 4.6 ml. Me_2SO_4 and 30% KOH alternately until 30 ml. of the KOH and 13.8 ml. of the Me_2SO_4 are used up, and the product extd. with Et_2O gives 9.8 g. (84%) 3,4-$(MeO)_2C_6H_3COEt$ (**II**), b_2 154–6°. **II** (9.2 g.) in 50 ml. $CHCl_3$ at 20–30° treated dropwise with 8 g. Br in 15 ml. $CHCl_3$, the mixt. stirred 30 min., washed with water and Na_2CO_3 soln., and the $CHCl_3$ removed gives a crude 3,4-$(MeO)_2C_6H_3COCHBrMe$ (**III**), m. 82–5°. **III** in 50 ml. C_6H_6 added to 27 g. Me_2NH in C_6H_6 at 5°, the mixt. stirred 3 hrs., allowed to stand overnight, the product filtered, and the filtrate distd. gives 7 g. (59%) 3,4-$(MeO)_2C_6H_3COCH(NMe_2)Me$ (**IV**), b_2 157–60°; **IV**.HCl.$2H_2O$, granules, m. 137–40° (decompn.). **I** (5 g.) in 35 ml. glacial AcOH refluxed 20 min. with 4.8 g. Br in 5 ml. AcOH, the product concd. *in vacuo*, extd. with Et_2O, the Et_2O removed, and the residue extd. with C_6H_6 gives 5.2 g. (73.4%) 3,4-$(HO)_2C_6H_3COCHBrMe$ (**V**), needles, m. 151–2° (from dil. alc.). **I** (5 g.) in 11 g. C_5H_5N at 15° treated with 7.2 g. Ac_2O dropwise, the mixt. allowed to stand overnight, neutralized with 10% HCl, extd. with Et_2O, and the ext. washed with $NaHCO_3$ soln. and water and distd. gives 5.2 g. (69%) 3,4-$(AcO)_2C_6H_3COEt$ (**VI**), b_4 177–8°. **VI** (6 g.) in 45 ml. $CHCl_3$ at 50° treated dropwise with 4 g. Br in 11 ml. $CHCl_3$ gives 0.6 g. (83.6%) 3,4-$(AcO)_2C_6H_3COCHBrMe$ (**VII**), granules, m. 83–5° (from petr. ether). **IV**.HCl.$2H_2O$ (7 g.) and 70 ml. concd. HCl in a sealed tube heated 3 hrs. at 160–70°, the product filtered with C, the filtrate concd. *in vacuo*, and the residue allowed to stand several days gives 5.3 g. (86.4%) 3,4-$(HO)_2C_6H_3COCH(NMe_2)Me$.HCl.$H_2O$ (**VIII**), columns, m. 108–10° (from alc.-Et_2O); or 4.7 g. **V** in 50 ml. dioxane and 3.8 g. Me_2NH in C_6H_6 stirred several hrs., allowed to stand overnight, the solvent removed, the residue taken up in 10% HCl, filtered with C, the filtrate concd., and seed crystals of **VIII** added gives 1.5 g. (31.6%) **VIII**, columns, m. 108–10°; or 4 g. **VII** in 20 ml. $CHCl_3$ and 2.5 g. Me_2NH in 30 ml. C_6H_6 allowed to stand overnight, the product filtered, the filtrate concd. *in vacuo*, the residue heated 30 min. on a water bath with 10% HCl, and the soln. concd. *in vacuo*, and allowed to stand gives 1.3 g. **VIII**; 5 g. **VIII** catalytically reduced in 60 ml. alc. with 0.2 g. PtO_2 absorbs 396 ml. H in 2 hrs., and the mixt. filtered, the filtrate concd., allowed to stand many days, and the product recrystd. from alc.-Et_2O gives 4.2 g. (82.3%) 3,4-$(HO)_2C_6H_3CH(OH)CH(NMe_2)Me$.HCl (**IX**), granules, m. 157–8°. On catalytic reduction in 15 ml. abs. alc. with 0.1 g. PtO_2, 1 g. **IV**.HCl.$2H_2O$ absorbed the required amt. of H in 2.5 hrs. and gave 0.8 g. (80%) 3,4-$(MeO)_2C_6H_3CH(OH)CH(NMe_2)Me$.HCl (**X**), granules, m. 211–13° (from alc.). 3,4-$CH_2O_2C_6H_3COCHBrMe$ (10.2 g.) and 42.5 g. 33% Me_2NH-MeOH allowed to stand, the MeOH removed, and the residue made alk., extd. with Et_2O, and distd. gave an oil, b_{10} 164–8°, which, treated in Et_2O with HCl gas, yielded 6.2 g. (71.8%) 3,4-$CH_2O_2C_6H_3COCH(NMe_2)Me$.HCl (**XI**), m. 253–4° (decompn.) (from MeOH); on catalytic reduction with 0.1 g. PtO_2 1.2 g. **XI** absorbed the required amt. of H in 3 hrs. and gave 1 g. (84%) 3,4-$CH_2O_2C_6H_3CH(OH)CH(NMe_2)Me$.HCl, granules, m. 217–18.5° (from alc.).

II. Syntheses of *N*-methylephedrone and its derivatives. Application of the Voigt reaction. J. Iwao, Chikara Kowaki, and Hideo Kakemi. *Ibid.* 551–4.—PhCHBrAc (16.6 g.), 15 g. AcONa, and 50 ml. glacial AcOH refluxed 3 hrs., the AcOH removed *in vacuo*, and the residue taken up with water, extd. with Et_2O, and distd. gives 8.4 g. (55%) PhCH(OAc)Ac (**XII**), b_{10} 132–4°; 10 g. **XII** in 35 ml. 70% MeOH and 10 g K_2CO_3 allowed to stand overnight, the MeOH removed, and the residue extd. with Et_2O and distd. gives 4.7 g. (60%) PhCH(OH)Ac (**XIII**), b_5 98–102°; oxime, m. 115–17°; semicarbazone, m. 195°. BzCHBrMe (50 g.), 40 g. AcONa, and 200 ml. AcOH refluxed 6 hrs., the product concd. *in vacuo*, water added, the mixt. extd. with Et_2O, and the extd. distd. gives 29 g. (65%) BzCH(OAc)Me (**XIV**), b_9 128–30°; 57.5 g. **XIV** in 200 ml. 70% MeOH and 57.5 g. K_2CO_3 allowed to stand overnight, the MeOH removed, and the residue extd. with Et_2O gives 35 g. (78%) BzCH(OH)Me (**XV**), b_{14} 125–6°. **XIII** (5 g.) and 20 g. 30% Me_2NH-MeOH in a sealed tube heated 3 hrs. at 170–80°, the excess Me_2NH and MeOH removed, HCl added, the mixt. extd. with Et_2O, the HCl layer made alk. with K_2CO_3, extd. with Et_2O, the Et_2O removed and the base purified as the HCl salt gives 1.3 g. (18.3%) BzCH(NMe_2)Me.HCl (**XVI**), columns, m. 202–4°; similarly, Me_2NH and **XV** and **XIV** yielded 10.6 and 31.2%, resp. of **XVI**; Et_2NH and **XIII** and **XIV** yielded 21.3% and a trace, resp., of BzCH(NEt_2)Me.HCl, m. 175–8°; piperidine and **XIII**, **XII**, and **XV** yielded 45.6, 27.2, and 29.5%, resp., of BzCHRMe.HCl (R = piperidino), m. 213–16°; 4-methylpiperazine (**XVIIa**) and **XIII**, **XV**, and **XIV** yielded 23.0, 33.3, and 44.0%, resp., of BzCHRMe.2HCl (**XVII**) (R = 4-methyl-1-piperazinyl), m. 235–9°; **XII** (2 g.), 5 g. $PhCH_2NHMe$, and 5 g. MeOH in a sealed tube heated 3 hrs. at 170–80° and the product treated as for **XVI** gives 2.3 g. oily BzCH($NMeCH_2Ph$)Me.HCl; catalytic reduction with Pd-C yields 0.9 g. (43%) *dl*-ephedrine-HCl, m. 185–6°. **XV** (1 g.) and 2 g. **XVIIa** refluxed 1 hr. at 170–80° and the product treated as for **XVI** gives 0.6 g. (29.5%) **XVII**, m. 235–7°. BzCHBrMe (5 g.), 2.8 g. **XVIIa**, 25 ml. C_6H_6, and 1.6 g. K_2CO_3 allowed to stand overnight, extd. with 10% HCl, taken up in Et_2O, and distd. gives the free base of **XVII**, b_{10} 130–40° (**XVII**, m. 235–9°). 3,4-$CH_2O_2C_6H_3COCHBrMe$ (27 g.), 120 ml. AcOH, and 18 g. AcONa refluxed 5–6 hrs., the soln. filtered, the filtrate concd. *in vacuo*, and the residue taken up with water, extd. with Et_2O, and distd. gives 15.8 g. (64%) 3,4-$CH_2O_2C_6H_3COCH(OAc)Me$ (**XVIII**), b_5 165–70°; 2 g. **XVIII**, 1.6 g. Me_2NH, and 10 ml. MeOH in a sealed tube heated 3 hrs. at 170°, the Me_2NH and MeOH removed, the mixt. extd. with Et_2O, treated with HCl gas, and the product recrystd. from MeOH gives 0.9 g. **XI**, m. 253–4° (decompn.); 2 g. **XVIII** and 4.1 g. $PhCH_2NHMe$ in a sealed tube heated 3 hrs. at 170°, the excess amine removed *in vacuo*, the product taken up in Et_2O, and HCl gas passed in gives 3,4-$CH_2O_2C_6H_3COCH[NMe(CH_2Ph)]Me$, oil; catalytic reduction with Pd-C yields 0.55 g. (26.5%) 3,4-$CH_2O_2C_6H_3CH(OH)CH(NHMe)Me$.HCl (**XIX**), needles, m. 207–9° (from MeOH and Et_2O) (picrate, m. 172–3°). 3,4-$CH_2O_2C_6H_3COCHBrMe$ (5 g.) in 30 ml. C_6H_6 at 5° added dropwise to 3 g. $MeNH_2$ in 5 ml. C_6H_6, the mixt. allowed to stand overnight, the C_6H_6 layer washed with water, the C_6H_6 removed, the residue treated in Et_2O with HCl gas, and the product recrystd. from MeOH-EtOH gives 2.2 g. (46.5%) 3,4-$CH_2O_2C_6H_3COCH(NHMe)Me$.HCl (**XX**), m. 225–7° (decompn.); catalytic reduction of 1 g. **XX** in alc. with 0.05 g. PtO_2 gives 0.7 g. (70%) **XIX**, m. 207–9°. 3,4-$(AcO)_2C_6H_3COCHBrMe$ (23 g.), 100 ml. AcOH, and 12 g. AcONa refluxed 8 hrs., the AcOH removed, and the residue taken up with water, extd. with Et_2O, and distd. gives 7.5 g. (30%) 3,4-$(AcO)_2C_6H_3COCH(OAc)Me$ (**XXI**), b_5 200–10°; 2 g. **XXI**, 1.2 g. Me_2NH, and 10 ml. MeOH in a sealed tube heated 3 hrs. at 150–60°, and the product concd. *in vacuo*, extd. with 10% HCl, and evapd. to dryness gives 0.5 g. sirup, which has the same R_f value as that of **VIII**. BzCH_2OAc (2 g.), 2 g. Me_2NH, and 5 ml. MeOH in a sealed tube heated 3 hrs. at 150–70°, the MeOH removed, the residue treated in Et_2O with HBr gas, and the product recrystd. from MeOH-EtOH gives 1.5 g. (55%) BzCH_2-NMe_2.HBr, m. 185–8°.

K. Kitsuta