[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Pyrrolidines, Piperidines and Hexahydroazepines from Glycols

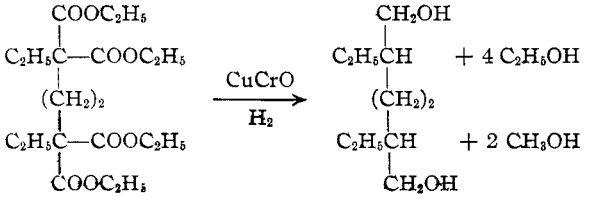
BY RALPH M. HILL AND HOMER ADKINS

Paden[1] found that various glycols reacted with amines to give substituted pyrrolidines, piperidines and hexahydroazepines. The reaction was carried out under hydrogen at 250° in dioxane under the influence of copper–chromium oxide as a catalyst. The type reaction is as follows

$$(CH_2)_n(OH)_2 + RNH_2 \longrightarrow (CH_2)_nNR + H_2O$$

Paden used diprimary glycols, having no substituent closer to the hydroxyls than the three position. The investigation reported herewith involved three primary-secondary, one disecondary, and two diprimary glycols carrying methyl or ethyl groups in the 1- or 2-position. The glycols concerned are: I, pentane-1,4-diol,[2] II, 2-methylbutane-1,4-diol, III, hexane-2,5-diol,[3] IV, hexane-1,5-diol,[4] V, heptane-1,6-diol, VI, 2,5-diethylhexane-1,6-diol.

Glycols I, IV and V were prepared by the hydrogenation of the corresponding keto esters, *i. e.*, γ-ketovalerate, δ-ketocaproate, ε-ketoenanthoate. Glycols II and III were made by the hydrogenation of α-methyl succinate and acetonylacetone, respectively. Glycol VI was made by the hydrogenation and hydrogenolysis of diethyl-2,5-diethyl-1,6-dicarbethoxyadipate.[5]



The ester was prepared by the reaction of sodium ethylmalonic ester with ethylene bromide. The data on the hydrogenations are given in Table I.

The glycols were treated with *n*-amylamine or phenethylamine under the conditions used by Paden. The yields of pyrrolidines and piperidines (Table II) were in general from 50 to 60% irrespective of which of four glycols (I, II, III, IV) or two amines were used. It made little difference in the yields whether the glycol was a diprimary, a disecondary, or a primary-secondary, whether or not there was a methyl or ethyl group on the carbon atom adjacent to the carbon holding the hydroxyl, or whether the hydroxyl groups were in the 1,4, or 1,5-position with respect to each other. The 3,6-diethyl-1-*n*-amylhexahydroazepine was obtained in a yield only slightly lower (43%) than those reported for the piperidines and pyrrolidines. However, the yields of two hexahydroazepines with a methyl group in the 2-position were distinctly lower, *i. e.*, 17%.

(1) Paden and Adkins, THIS JOURNAL, **58**, 2491 (1936).
(2) Coleman and Perkin, *J. Chem. Soc.*, **53**, 191 (1888).
(3) Duden and Lemme, *Ber.*, **35**, 1335 (1902).
(4) Perkin, *J. Chem. Soc.*, **51**, 722 (1887).
(5) Method of Connor and Adkins, THIS JOURNAL, **54**, 4686 (1932).

TABLE I

GLYCOLS BY HYDROGENATION[a]

Hydrogen acceptor, g.		%	Yield and b. p. of glycol	
100	Diethyl-2,5-diethyl-2,5-dicarbethoxyadipate	74	2,5-Di-Et-hexane-1,6-diol	133–134(1 mm.)
56	Ethyl ε-ketoenanthoate	82	Heptane-1,6-diol	94–97(1 mm.)
67	Ethyl δ-ketocaproate	85	Hexane-1,5-diol	89–91(0.5 mm.)
100	Ethyl levulinate	60	Pentane-1,4-diol	133–134(23 mm.)
100	Acetonylacetone	90	Hexane-2,5-diol	85–87(1 mm.)

[a] The hydrogenations were made in dioxane or ethanol over 5 to 10 g. of copper–chromium oxide under 200–300 atm. of hydrogen at 250° for the esters and 160–170° for the diketone. The time required varied from five minutes for the diketone to two to five hours for the esters.

TABLE II

CYCLIC AMINES FROM GLYCOLS

In 60 ml. of dioxane, with 5 g. of CuCrO for 2–5 hrs. at 250° under 100 atm. H_2

Glycol, g.	Amine, g.[a]	%	Yield of cyclic amine
20 I	16.7 a	60	1-Amyl-2-Me-pyrrolidine
15 I	17.5 b	56	1-Phenethyl-2-Me-pyrrolidine
15 II	12.8 a	60	1-Amyl-3-Me-pyrrolidine
15 II	17.5 b	54	1-Phenethyl-3-Me-pyrrolidine
20 III	14.7 a	60	1-Amyl-2,5-di-Me-pyrrolidine
20 III	21.0 b	55	1-Phenethyl-2,5-di-Me-pyrrolidine
20 IV	14.8 a	75	1-Amyl-2-Me-piperidine
20 IV	20.5 b	52	1-Phenethyl-2-Me-piperidine
15 V	9.9 a	17	1-Amyl-2-Me-hexahydroazepine
15 V	13.8 b	17	1-Phenethyl-2-Me-hexahydroazepine
20 VI	10.0 a	43	1-Amyl-3,6-di-Et-hexahydroazepine

[a] (a) *n*-amylamine and (b) phenethylamine.

The products of reaction were separated by fractionation through electrically heated Widmer

TABLE III

PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compound	B. p. °C.	Mm.	$n^{25}D$	d^{25}	M_D Calcd.	M_D Found	Analysis[a] Calcd.	Found
1-*n*-Amyl-3-Me-pyrrolidine	82–85	24	1.4361	0.8074	50.13	50.35	155M	156
							9.03N	9.14
1-*n*-Amyl-3-Me-pyrrolidine picrate				M. p. 134–135°			14.60N	14.74
1-*n*-Amyl-2-Me-pyrrolidine	96–97	41	1.4385	0.8104	50.13	50.26	155M	156
							9.03N	9.18
1-*n*-Amyl-2-Me-pyrrolidine picrate				M. p. 114–115°			14.60N	14.67
1-*n*-Amyl-2,5-di-Me-pyrrolidine	105–107	43	1.4383	0.8152	54.75	54.45	169M	169
							8.28N	8.35
1-*n*-Amyl-2,5-di-Me-pyrrolidine picrate				M. p. 95–96°			14.07N	14.27
1-Phenethyl-3-Me-pyrrolidine	136–137	17	1.5082	0.9305	60.38	60.42	189M	188
							7.41N	7.52
1-Phenethyl-3-Me-pyrrolidine picrate				M. p. 163–164°			13.39N	13.32
1-Phenethyl-2-Me-pyrrolidine	132–133	16	1.5116	0.9326	60.38	60.75	189M	190
							7.41N	7.54
1-Phenethyl-2-Me-pyrrolidine picrate				M. p. 141–142°			13.39N	13.48
1-Phenethyl-2,5-di-Me-pyrrolidine	106–108	2	1.5055	0.9218	65.00	65.37	203M	2.03
							6.90N	6.96
1-Phenethyl-2,5-di-Me-pyrrolidine picrate				M. p. 131–132°			12.96N	12.98
1-*n*-Amyl-2-Me-piperidine	104–105	23					169M	170
1-*n*-Amyl-2-Me-piperidine picrate				M. p. 94–95°			14.07N	14.18
1-Phenethyl-2-Me-piperidine	148–149	27	1.5152	0.9401	65.00	65.14	203M	202
							6.90N	6.93
1-Phenethyl-2-Me-piperidine picrate				M. p. 118–119°			12.96N	13.18
1-*n*-Amyl-2-Me-hexahydroazepine	117–118	22	1.4530	0.8381	59.29	59.02	183M	184
							7.65N	7.77
1-*n*-Amyl-2-Me-hexahydroazepine picrate				M. p. 79–80°			13.60	13.57
1-Phenethyl-2-Me-hexahydroazepine	106–109	1	1.5097				217M	219
							6.45N	6.49
1-Phenethyl-2-Me-hexahydroazepine picrate				M. p. 105–106°			12.55N	12.47
1-*n*-Amyl-3,6-di-Et-hexahydroazepine	98–100	2	1.4570	0.8437	73.22	72.64	225M	230
							6.22N	6.27
2,5-Diethyl-hexane-1,6-diol	133–134	1	1.4621	0.9307	51.17	51.28	68.98C	69.28
							12.73H	12.72
2,5-Di-Et-hexane-1,6-diol, phenylurethan of				M. p. 135–136°			6.79N	6.84
Heptane-1,6-diol, phenylurethan of				M. p. 97–98°			7.57N	7.79

[a] N and M refer to nitrogen and molecular weight (neut. equiv.), respectively.

or modified Widmer columns.[6] They were characterized by analysis, by neutral equivalents, by formation and analysis of picrates, and by a comparison of the calculated and found molecular refractions. These data are shown in Table III. The samples of amines obtained were shown to be free of secondary amines by their failure to react with benzenesulfonyl chloride. For the sake of comparison of the derivatives, 1-*n*-amyl-2-methylpiperidine and the 1-phenethyl-2-methylpiperidine were also made by the reaction of 2-methylpiperidine with amyl and phenethyl alcohols at 250° over copper–chromium oxide.

Ethyl levulinate, b. p. 103–105° (24 mm.),[7] ethyl α-ketocaproate, b. p. 64–66° (1 mm.),[8] and ethyl ε-ketoenanthoate, b. p. 98–99° (6 mm.),[9] were made by the reaction of ethyl alcohol with the corresponding acids in the presence of hydrogen chloride. They were freed of halogen containing impurities by being refluxed over Raney nickel. Acetonylacetone, b. p. 87–88° (23 mm.), was a commercial product. The sample of 2-methylbutane-1,4-diol, b. p. 126–127° (14 mm.),[10] had been prepared by Wojcik. The hitherto undescribed 2,5-diethylhexane-1,6-diol was characterized by the fact that it gave two moles of methane per mole of glycol when treated with methylmagnesium iodide, and reacted with phenyl isocyanate to give a urethan. *n*-Amylamine and phenethylamine were prepared by the hydrogenation of the corresponding cyanides over Raney nickel.

(6) Martha E. Smith and Adkins, THIS JOURNAL, **60**, 662 (1938).

(7) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York City, 1932, p. 328.

(8) Lease and McElvain, THIS JOURNAL, **55**, 807 (1933).

(9) Derich and Hess, *ibid.*, **40**, 551 (1918).

(10) Wojcik and Adkins, *ibid.*, **55**, 4939 (1933).

Diethyl α,α′-diethyl-α,α′-dicarbethoxyadipate.[11]—One hundred and twenty-two g. (5.2 moles) of powdered sodium under 2.5 liters of xylene was placed in a five-liter three-necked flask provided with a mechanical stirrer, reflux condenser and dropping funnel. One kilogram of diethyl ethylmalonate was added gradually over a period of two hours, the mixture being cooled in an ice-bath. The mixture was then heated to the boiling point of xylene, whereupon it became a red colored homogeneous solution. Ethylene bromide (500 g., 2.65 moles) was then added during the course of one and one-half hours to the boiling solution. Refluxing was continued for ten hours. The mixture was cooled to room temperature and 1.5 liters of water added. After standing crystals of the desired ester separated at the xylene–water interface. The crystals were filtered out and the xylene layer fractionated through a Widmer column, first at 740 mm. pressure for the removal of xylene. Unreacted ester (250–300 g.) was obtained at 90–102°(7 mm.). After all material boiling below 165°(1 mm.) was removed the residue was allowed to cool and another crop of crystals obtained. After recrystallization from 95% alcohol, 230–250 g. of the desired ester, m. p. 95–96°, was obtained which corresponds to a yield of about 30%. The ester was characterized by conversion to the corresponding acid, m. p. 210–211° (with decomposition), and to the α,α′-diethyladipic acid, m. p. 129–131°.[11]

(11) Lean, *J. Chem. Soc.*, **65**, 1004 (1894).

Summary

Five variously substituted glycols have been found to react with *n*-amylamine or phenethylamine to give 40–70% yields of the corresponding pyrrolidines, piperidines or hexahydroazepines. Heptane-1,6-diol gave only 17% yields of the 1-*n*-amyl or 1-phenethyl-2-methylhexahydroazepine.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

d-Alpha, Alpha-Galaoctose and Some of its Derivatives[1]

BY W. DAYTON MACLAY, RAYMOND M. HANN AND C. S. HUDSON

Study of the aldoheptoses[2,3] derived from *d*-galactose has supplied many data supporting the hypothesis that the physical and chemical properties of an aldose sugar and its ring derivatives are conditioned in first measure by the space configurations of carbon atoms one to five of the sugar molecule. In the present communication the properties of an eight carbon aldose, *d*-α,α-galaoctose, and some of its derivatives, will be described. This octose was obtained as a crystalline monohydrate by Fischer,[4] who, however, did not establish its configuration. This has now been accomplished by the preparation of the amide and the phenylhydrazide of the corresponding *d*-α,α-galaoctonic acid; their levorotations indicate by the amide and phenylhydrazide rules that the hydroxyl group on carbon atom two is to the left, when the carbon chain is written vertically with the carboxyl group at the top.

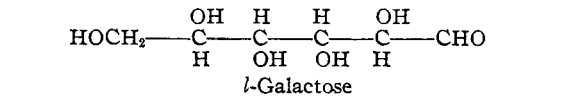
(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Hann, Merrill and Hudson, THIS JOURNAL, **57**, 2100 (1935).

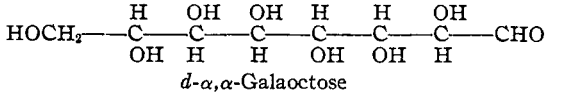
(3) Hann and Hudson, *ibid.*, **59**, 548 (1937).

(4) Fischer, *Ann.*, **288**, 150 (1895).

The configuration of carbon atoms one to five in the octose, which is derived from *d*-α-galaheptose, is therefore the same as in *l*-galactose (see formulas) and it is to be expected that the mag-



l-Galactose



d-α,α-Galaoctose

nitudes of the rotations of the octose and its ring derivatives will be near those of like substances in the *d*-galactose series but opposite in sign. This inference is well substantiated by the measurements (see Table I). The signs of rotation in all cases are as expected; the magnitudes of the molecular rotations of corresponding substances are near each other except in the case of the sugar acetates where they differ considerably.

In addition to this parallelism of rotations there also exists in these series a parallelism of other physical properties and also of chemical