Summary

Measurements of sedimentation velocity, sedimentation equilibrium and diffusion have been made with solutions of the nucleohistone found in the calf thymus gland. The protein is found to be essentially monodisperse and to show the same molecular kinetic behavior between pH 5.3 and 9.0.

The following data are obtained for the nucleohistone dissolved in buffer solutions

Sedimentation constant s_{20}	31×10^{-13} cm./sec./dyne.
Sedimentation constant s_{25}	35×10^{-13} cm./sec./dyne.
Diffusion constant D_{20}	0.93×10^{-7} sq. cm./sec.
Diffusion constant D_{25}	1.06×10^{-7} sq. cm./sec.
Frictional coefficient f/f_0	2.5
Axial ratio a/b	35
Molecular weight	2,150,000

Preparation of Secondary Amines

BY JOHANNES S. BUCK AND RICHARD BALTZLY

Most of the methods for preparing secondary aliphatic amines leave much to be desired in the way of yield and homogeneity. The authors, by the use of reductive debenzylation of benzyldialkylamines, have devised a method which gives good yields of dialkylamines, and in which, moreover, purification is automatically effected at several points.

Benzaldehyde is condensed with a primary aliphatic amine to give a Schiff base II, and this is catalytically reduced to the corresponding benzylalkylamine III. Addition of alkyl halide (or, in the case of methylamines, reductive methylation[1]) gives the hydrohalide of the benzyldialkylamine IV. On catalytically reducing this, or the corresponding base V, the benzyl group is smoothly removed, giving the dialkylamine VI and toluene and, sometimes, methylcyclohexane.

$$C_6H_5CHO + NH_2R \longrightarrow C_6H_5CH{=}NR \longrightarrow$$
$$I \qquad\qquad\qquad\qquad II$$

$$C_6H_5CH_2NHR \longrightarrow C_6H_5CH_2NRR'HX \longrightarrow$$
$$III \qquad\qquad\qquad IV$$

$$C_6H_5CH_2NRR' \longrightarrow NHRR' + C_6H_5CH_3$$
$$V \qquad\qquad\qquad VI$$
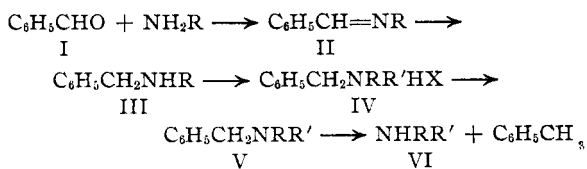
Stage I to II is virtually quantitative. The Schiff base II may be purified (e. g., by distillation) but ordinarily this is unnecessary as any unchanged primary amine is eliminated on distilling the benzylalkylamine III, while unchanged benzaldehyde is eliminated with the neutral fraction.

Stage II to III may be regarded as quantitative. In stage III to IV any unchanged benzylalkylamine not separated by distillation of the tertiary base V is eliminated on reduction, as it does not

undergo fission. Any quaternary compounds which might have been formed are separated by their non-volatility and water solubility. Alternatively, the tertiary amine hydrohalide IV may be purified by crystallization when the solubility permits.

After reduction it is only necessary to separate the secondary amine from the non-basic toluene or methylcyclohexane and any unchanged benzyldialkylamine which might have escaped reduction. This offers no difficulty as the tertiary amine is relatively non-volatile. Alternatively, the separation may be done by acetylation or other simple chemical methods.

In the experimental section the general method of preparation is given and a number of examples recorded. The process is based on the work of Baltzly and Buck.[2] The authors hope to extend the work to other than purely aliphatic amines.

Experimental

Schiff Bases.—One mol of primary amine, either in aqueous or benzene solution, was mixed with one mol of benzaldehyde. Some heat was evolved, and, after standing overnight, the Schiff base was separated from the water by extraction with ether. If benzene had been used as solvent, the water formed was separated in a separatory funnel. The ether solution was dried (anhydrous potassium carbonate); the benzene solution usually not. After evaporation of the solvent, the residual base was used, without characterization, for the next stage. In some cases the Schiff base was distilled, but this appears to be unnecessary. Some of the Schiff bases are recorded in the literature.[3]

Benzylalkylamines.—The Schiff bases obtained as above were reduced in glacial acetic acid solution, with a

(1) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(2) Baltzly and Buck, ibid., **62**, 164 (1940).

(3) Zaunschirm, Ann., **245**, 279 (1888); Einhorn and Pfeiffer, ibid., **310**, 225 (1900).

TABLE I
BENZYLDIALKYLAMINES

Alkyl groups	Base, b. p., °C.	Mm.	Salt, m. p., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H
Methyl, ethyl	80	16	HCl 151–152	$C_{10}H_{16}NCl$[a]	64.66	8.69	64.62	8.64
Methyl, n-propyl	96–98	15		$C_{11}H_{17}N$[a]	80.94	10.57	81.27	10.99
Methyl, n-butyl	113	16		$C_{12}H_{19}N$	81.29	10.81	81.47	10.73
Methyl, n-amyl	126	15		$C_{13}H_{21}N$	81.59	11.08	81.60	10.88
Methyl, lauryl			HCl 133–134	$C_{20}H_{36}NCl$	73.66	11.14	73.96	11.13
Ethyl, n-propyl			HBr 162	$C_{12}H_{20}NBr$[a]	55.80	7.81	55.93	7.87
Ethyl, n-butyl	115–116	12		$C_{13}H_{21}N$[a]	81.59	11.08	81.86	11.55
Ethyl, n-amyl	117–121	8		$C_{14}H_{23}N$[b]				
n-Propyl, n-butyl	117	8	HI 172	$C_{14}H_{24}NI$	50.45	7.26	50.59	7.54
n-Butyl, n-amyl	145–146	9		$C_{16}H_{27}N$[b]				

[a] Wedekind and Ney, *Ber.*, **45**, 1312 (1911). [b] Not obtained in a homogeneous state.

TABLE II
N-α-NAPHTHYL-N′,N′-DIALKYLTHIOUREAS

Alkyl groups	Appearance	Cryst. solvent	M. p., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H
Methyl, ethyl	Flat prisms	Dil. methanol	129–130	$C_{14}H_{16}N_2S$	68.78	6.61	68.80	6.78
Methyl, n-propyl	Prisms	Dil. methanol	108	$C_{15}H_{18}N_2S$	69.74	7.03	69.95	7.19
Methyl, n-butyl	Irregular leaflets	Dil. methanol	88.5–89.5	$C_{16}H_{20}N_2S$	70.54	7.41	70.62	7.67
Methyl, n-amyl	Irregular platelets	Ether–hexane	73.5–75	$C_{17}H_{22}N_2S$	71.24	7.75	71.43	7.74
Methyl, lauryl	Needle prisms	Hexane	74	$C_{24}H_{36}N_2S$	74.93	9.44	75.09	9.65
Ethyl, n-propyl	Needles	Ethyl acetate	123–124	$C_{16}H_{20}N_2S$	70.54	7.41	70.54	7.45
Ethyl, n-butyl	Needles	Ethyl acetate–hexane	125–126	$C_{17}H_{22}N_2S$	71.24	7.78	71.18	8.06
Ethyl, n-amyl	Felted needles	Ether–hexane	97	$C_{18}H_{24}N_2S$	71.95	8.06	72.09	7.96
n-Propyl, n-butyl	Felted needles	Ethyl acetate	140	$C_{18}H_{24}N_2S$	71.95	8.06	72.14	8.15
n-Butyl, n-amyl	Fine needles	Ethyl acetate–hexane	117	$C_{20}H_{28}N_2S$	73.10	8.60	73.00	8.49

platinum oxide catalyst, at room temperature. After reduction, which was rapid and complete, the solution was diluted with water, the catalyst filtered off, and a slight excess of hydrochloric acid added. The solution was then evaporated to dryness under reduced pressure and the residue dissolved in water and extracted with ether to remove any neutral material. The secondary amine was liberated by sodium hydroxide solution, extracted with ether, the ether dried over anhydrous potassium carbonate, and the solvent removed by distillation. The residual oil was distilled under reduced pressure. Some of the secondary amines have been recorded previously.[3]

Benzyldialkylamines.—For convenience, the benzylmethylalkylamines were prepared from the benzylalkylamines by a modified Eschweiler method,[1] the yields approaching the theoretical.

Tertiary amines not containing a methyl group were made by direct alkylation of the benzylalkylamine with the appropriate alkyl bromide or iodide. The secondary amine, dissolved in two volumes of an alcohol (preferably the one corresponding to the halide, although methanol may be used) was treated with one mol of alkyl halide and the whole then heated under a reflux condenser on the steam-bath to approximate neutrality, up to seventy-two hours being required in some cases. Where the solid hydrohalide of the tertiary amine separated out, it was filtered off. Otherwise the solvent was distilled off and the amine liberated by basification, and extracted with ether. After drying over anhydrous potassium carbonate, the ether was driven off and the residue distilled *in vacuo*. Bases and salts are listed in Table I in the form in which they were used for the reductive debenzylation.

Dialkylamines.—The benzyldialkylamine, as base or salt, dissolved in twice its weight of glacial acetic acid was reduced with platinum oxide catalyst, at 65–75° and 3 atmospheres pressure. With sufficient catalyst (usually 1% of the weight of amine used) one-tenth mole could ordinarily be reduced in less than eight hours. After diluting with a little methanol and filtering off the catalyst, excess of hydrochloric acid was added and the whole evaporated to dryness *in vacuo*. To break up any acetylated secondary amine which might be present, the residue was digested on the steam-bath with concentrated hydrochloric acid (50 cc. per 0.1 mole of amine) for two to three hours. After evaporation to dryness *in vacuo* there remained a solid or sirupy residue, which was crystallized or converted into another salt, or from which the base was liberated and subsequently distilled.

For identification of the amines, as the α-naphthylthioureas, the crude hydrochloride was taken up in a little methanol, absolute ether added and the solution then allowed to stand overnight over barium oxide. After filtration, an approximately equivalent amount of α-naphthylisothiocyanate, dissolved in ether, was added. The thiourea separated on standing and was filtered off and recrystallized. No evidence of the presence of benzylalkylamines was found. The thioureas are recorded in Table II.

Palladized charcoal may be used as catalyst. It retains its activity longer but is less convenient. Fresh platinum oxide should be used for each run. Raney nickel may be used with the base in alcohol, but the platinum catalyst is superior.

In some instances, where very pure materials were reduced, the calculated end-point was exceeded. This was

due to reduction of the toluene produced to methyl-cyclohexane. In such cases the reduction was continued well beyond the calculated end-point. No reductive fission of a benzylalkylamine has been observed, although, in one case where such an amine was known to be present, the corresponding hexahydrobenzylalkylamine was formed.

The authors are indebted to Mr. W. S. Ide for the microanalyses recorded. Melting points are corrected.

Summary

By reductive debenzylation of benzyldialkyl-amines, dialkylamines may be obtained readily in a state of purity.

Condensation of Methoxyacetaldehyde to 2,4-Dimethylaldotetrose: Methoxyacetaldehyde and Ethoxyacetaldehyde

By Charles D. Hurd and John Leo Abernethy

In 1938 Drake[1] and collaborators published directions for the synthesis of methoxyacetaldehyde and ethoxyacetaldehyde by dehydrogenation of the corresponding alcohols over a hot copper catalyst. Yields were 8–10%, based on the starting materials. In catalytic efficiency, copper chromite was stated to be less effective than copper. In independent work performed prior to the appearance of this article, we obtained about 5% conversion of β-methoxyethyl alcohol over copper chromite at 360° to methoxyacetaldehyde and had abandoned it in favor of a method wherein the alcohol was oxidized in the wet way. Based on the starting materials, the yields by this process were 17% for methoxyacetaldehyde and 10% for ethoxyacetaldehyde. This method, therefore, gives actual yields as good as or better than those obtained by dehydrogenation, it uses equipment which is considerably simpler, and it does not involve the preparation of the catalyst.

Dichromic oxidizing mixture was used, the essential feature of the process being the rapid removal of the aldehyde from the reaction mixture once it was formed. This was done by an adaptation of the method[2] used for the oxidation of propyl alcohol to propionaldehyde; but the method was less satisfactory with methoxyacetaldehyde than with propionaldehyde because the greater volatility of the latter makes it easier to remove it promptly from the solution. Propionaldehyde boils at 48° whereas methoxyacetaldehyde[1] boils at 90–92° (azeotrope with 12.8% water, b. p. 83–86°, or 88.8°). The somewhat higher boiling

point of ethoxyacetaldehyde[1] (b. p. 105–106°; azeotrope with 21.8% water, b. p. 90–91°) makes for greater difficulty of prompt removal of it from water, thereby explaining the somewhat smaller yield.

A study of the molecular weight of these alkoxyaldehydes was undertaken in view of the anomalous results reported in the article by Drake and collaborators. Their observed value (99.5) for ethoxyacetaldehyde is reasonably near theory (88), but the value given (117) for methoxyacetaldehyde obviously is much too high (theory, 74). It was found in the present study that the values for the molecular weights of these compounds increase with time, suggesting the onset of a polymerization process. The rate of this process fell off after the first few hours. Black taped vessels were ineffective in preventing this polymerization. The effect of hydroquinone was negligible also. Polymerization also occurred in a tinned container which contained hydroquinone, but at a little slower rate.

Condensation to 2,4-Dimethylaldotetrose.—The original purpose of this investigation was to study the condensation of methoxyacetaldehyde to see if it would give rise to a methylated tetrose. This condensation occurred fairly readily in the presence of solutions of either potassium carbonate or potassium cyanide, somewhat better yields being obtained with the carbonate.

It seemed reasonable to infer that the 2,4-dimethylaldotetrose formed would possess open chain structure I rather than cyclic structure II. If so, this opens a new route to methylated derivatives of aldehyde forms of sugars.

(1) Drake, Duvall, Jacobs, Thompson and Sonnichsen, This Journal, 60, 73 (1938).

(2) Hurd and Meinert, "Organic Syntheses," Vol. XII, John Wiley and Sons, New York, N. Y., 1932, p. 64.