both of the dye and detergent, is homogeneous it was calculated from the experimental results that more detergent was bound than was added. The explanation is, undoubtedly, that there is heterogeneity in the binding of both anions and that the same sites are most effective in both instances. Under these circumstances the detergent is a more effective competitor than the homogeneity assumption would predict. In fact, if, as is probably the case, it is the Group 1 sites which are involved, the experimental observations are readily accounted for.

In view of the heterogeneity in the binding of anions, the interpretation of the binding of a substance by its displacing effect is subject to considerable limitation. Depending on the relative heterogeneity, the binding of the competitor may be underestimated or even overlooked entirely. When compared to data obtained by other methods, *e. g.*, electrophoretic mobility, considerable disagreement in the results may appear.

Acknowledgment.—I am indebted to Dr. C. P. Rhoads for making available to me, during the conduct of this investigation, the excellent laboratory facilities of the Sloan–Kettering Institute for Cancer Research. This work was supported by the Office of Naval Research.

Summary

The effect of bound sodium dodecyl sulfate on the binding by bovine serum albumin of an anionic azo dye has been investigated at 25° in 0.05 *M* phosphate buffer, *p*H 7.0. The amount of bound detergent was varied from 1 mole per mole of protein to 8 moles per mole protein. The data are analyzed in terms of a comparison of self-competition *versus* detergent competition. For this purpose there are introduced the quantities $\Delta(A)$ and $\Delta(B)$ which are named competition differentials and whose values can be derived from the experimental data. It is shown that the criterion for identical heterogeneity is that $\Delta(A) = \Delta(B)$ for $r_A = r_B$. A comparison of $\Delta(A)$ and $\Delta(B)$ over the whole range of r_A and r_B studied leads to the conclusion that those sites (Group 1) which bind the dye most strongly also, for the most part, bind the detergent most effectively. In terms of configurational adaptability the Group 1 sites are interpreted as being able to assume structures complementary to a wide range of configurations whereas the other sites are more restricted in this respect. The latter bind less strongly and are more selective.

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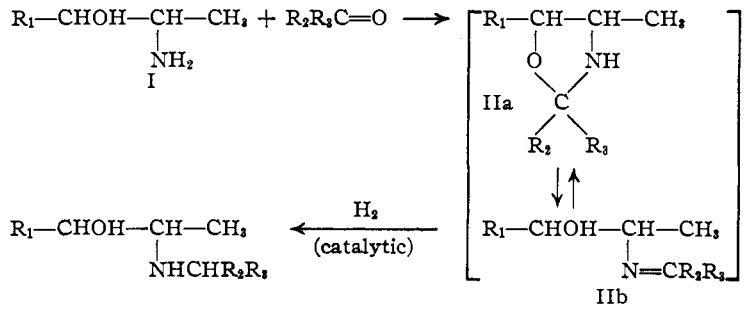
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

The Reductive Alkylation of Arylalkanolamines

BY EDWARD L. ENGELHARDT, FRANK S. CROSSLEY AND JAMES M. SPRAGUE

Cope and Hancock[1] have described a convenient method for the preparation of N-alkyl derivatives of alkanolamines by the catalytic reduction of mixtures of the alkanolamine and an aldehyde or ketone. As a part of a pharmacological study of N-alkyl derivatives of phenethanolamine we have extended the method of Cope and Hancock to the alkylation of 1-phenyl-2-amino-1-propanol and certain nuclear substituted derivatives.

With aliphatic aminoalcohols, Cope and Hancock have shown that the structure of the anhydro compounds (II) that are thought to be intermediates in the reaction, depends upon steric factors in the carbonyl compound. Aldehydes and unhindered ketones give oxazolidines (IIa) while highly branched ketones give alkylidene-aminoalcohols (IIb). The alkylaminoalkanol results either from reduction of the alkylidene intermediate (IIa) or from hydrogenolysis of the oxazolidine (IIb). Although in the present work the nature of the anhydro compounds formed from norephedrine (I, R_1 = phenyl) has not been studied, the steric effect of the phenyl group might be expected to favor the alkylidene-aminoalcohol (IIb).



The only failures encountered in the norephedrine series (Table I) occurred when acetaldehyde or acetophenone was employed as the carbonyl component. The former was polymerized, the latter apparently failed to condense with the aminoalcohol. 3,4-Dihydroxynorephedrine gave good yields of the expected products when ketones were employed as the carbonyl

(1) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942); **66**, 1453 (1944); Hancock and Cope, *ibid.*, **66**, 1738 (1944).

TABLE I

1-PHENYL-2-ALKYLAMINO-1-PROPANOLS, $C_6H_5—CHOH—\underset{\displaystyle NHR}{\underset{|}{CH}}—CH_3$

R	Alcohol volume, ml.	Moles carbonyl, cmpd.	Moles norephedrine	Catalyst, g.	Yield,[a] %	M. p., °C.[b] (base)	M. p., °C. (HCl)	Formula (base)	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
Isopropyl[d]	200	0.835	0.166	0.5	84	91.5–92	195–196	$C_{12}H_{19}NO$	...	...	...	...
n-Butyl[d]	50	0.05	.033	.3	50	.....	224–225	$C_{13}H_{21}NO$	...	...	...	...
s-Butyl[e]	450	3.0	.7	.7	63	.....	198–204	$C_{13}H_{21}NO$	5.75	5.78	14.54	14.49
Isobutyl	800	0.55	.50	.6	65	.....	210–211	$C_{13}H_{21}NO$	5.75	5.66	14.54	14.67
1,2-Dimethylpropyl[e]	800	0.80	.40	.6	65	.....	205–206	$C_{14}H_{23}NO$	5.43	5.50	13.75	13.75
1-Ethylpropyl	500	1.2	.60	.7	65	.....	148–149	$C_{14}H_{23}NO$	5.43	5.44	13.75	13.89
n-Heptyl[e]	800	0.55	.50	.6	24[f]	66–67	228–229	$C_{16}H_{27}NO$				
Cyclohexyl	150	.415	.331	.75	76	106–107	234–235	$C_{15}H_{23}NO$	5.19	5.24	13.14	13.13
1-Methyl-2-diethylaminoethyl[e]	100	.078	.078	.3	58	49.5–51	.....	$C_{16}H_{28}N_2O$	10.60[g]	10.57		
1-Phenyl-2-propyl[e]	150[h]	.20	.10	.3	...	.....	194–196	$C_{18}H_{23}NO$	4.58	4.52	11.59	11.65

[a] Yields are based on the crude crystalline product. [b] Melting points were determined with direct reading thermometers. In general the bath was preheated to 5° below the expected m. p. and the temp. raised at a rate of 2° per min. [c] These products are mixtures of diastereoisomers. [d] Hyde, Browning and Adams, THIS JOURNAL, **50**, 2287 (1928). [e] Kanao, *J. Pharm. Soc. Japan*, **49**, 157 (1929), *C. A.*, **23**, 4205 (1929). [f] Yield based on pure material. [g] *Anal.* Calcd. for $C_{16}H_{28}N_2O_2$: C, 72.68; H, 10.67. Found: C, 72.34; H, 10.53. Microanalyses by Dr. C. F. Tiedcke. [h] Solvent isopropyl alcohol.

TABLE II

1-(3,4-DIHYDROXYPHENYL)-2-ALKYLAMINO-1-PROPANOLS $HO—C_6H_3(OH)—CHOH—\underset{\displaystyle NHR}{\underset{|}{CH}}—CH_3$

R	Formula	Yield, %	M. p., °C.[b]	Analyses, % Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isopropyl	$C_{12}H_{19}NO_3 \cdot HCl$	73	208–209	5.35	5.33	55.06	54.87	7.70	7.77
s-Butyl[a]	$C_{13}H_{21}NO_3 \cdot C_7H_4N_2O_6$[c]	70	183–185 sint. 182	9.31	9.28	53.21	53.31	5.58	5.57
1-Ethylpropyl	$C_{14}H_{23}NO_3 \cdot C_7H_4N_2O_6$[c]	49	192–193	9.03	9.02	54.19	54.25	5.85	6.00
1,2-Dimethylpropyl[a]	$C_{14}H_{23}NO_3 \cdot C_7H_4N_2O_6$[c]	38	198–200	9.03	8.95	54.19	54.33	5.85	6.00
Cyclopentyl	$C_{14}H_{21}NO_3 \cdot HCl$	48	205–206[d]	4.87	4.87	58.42	58.35	7.71	7.77
Cyclohexyl	$C_{15}H_{23}NO_3 \cdot HCl$	65	238–239[e]	4.64	4.59	59.69	59.56	8.02	8.14

[a] These products are mixtures of diastereoisomers. [b] All compounds melt with decomposition. [c] German Patent 677,127 reports 215° (dec.). [d] German Patent 677,127 reports 242° (dec.). [e] 3,5-Dinitrobenzoic acid salts.

TABLE III

1-MONOSUBSTITUTED-PHENYL-2-ALKYLAMINO-1-PROPANOLS $X—C_6H_4CHOH\underset{\displaystyle NHR}{\underset{|}{CH}}—CH_3$

X	R	Formula	Yield, %	M. p., °C. dec.	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
m-Hydroxy	Isopropyl	$C_{12}H_{19}NO_2 \cdot HCl$	94	219–220	5.70	5.67	14.43	14.42
m-Hydroxy	Cyclohexyl	$C_{15}H_{23}NO_2 \cdot HCl$	63	228–229	4.90	4.91	12.41	12.43
p-Hydroxy	Isopropyl	$C_{12}H_{19}NO_2 \cdot HCl$	53	224–225	5.70	5.73	14.43	14.28
p-Amino[a]	Isopropyl	$C_{12}H_{20}N_2O \cdot 2HCl$	73	174–175	9.96	9.88	25.21	25.04
p-Amino[a]	Cyclohexyl	$C_{15}H_{24}N_2O \cdot 2HCl$	75	197–198	8.72	8.73	...	...
m-Isopropylamino[b]	Isopropyl	$C_{15}H_{26}N_2O \cdot 2HCl$	62	219–221	8.67	8.63	21.93	21.52

[a] Prepared by reduction of the appropriate 1-(*p*-nitrophenyl)-2-alkylamino-1-propanol hydrochloride. [b] *Anal.* Calcd.: C, 55.72; H, 8.73. Found: C, 55.55; H, 8.60.

component (Table II), but gave only tarry materials when condensed with butyraldehyde or isobutyraldehyde. *m*-Hydroxy- and *p*-hydroxy-1-phenyl-2-amino-1-propanol gave good yields of the expected products with ketones (Table III). 1-(*m*-Aminophenyl)-2-amino-1-propanol, hydrogenated in the presence of excess acetone, gave 1 - (*m* - isopropylaminophenyl) - 2 - isopropylamino-1-propanol, but *p*-aminophenethylamine and one equivalent of cyclohexanone gave predominantly 1-(*p*-aminophenyl)-2-cyclohexylaminoethane. Because of the possibility of alkylating the nuclear amino group the two 1-(*p*-aminophenyl)-2-alkylamino-1-propanols (Table III) were prepared by nitrating the corresponding 1-phenyl-2-alkylamino-1-propanols and reducing

the nitro compounds catalytically. Dalmer and Oberlin[2] have prepared several *p*-aminophenylalkanolamines by this method. The compounds containing nuclear amino groups are listed in Table III.

A solution of ephedrine and butyraldehyde in absolute alcohol absorbed no hydrogen under the usual conditions although the formation of a condensation product between the aldehyde and the aminoalcohol was suggested by the evolution of heat when the reactants were mixed. This result was not unexpected since the reductive alkylation of norephedrine has been carried out in the presence of a large excess of the carbonyl component (see Table I) and in no case has a tertiary amine been encountered. Following the method of Cope and Hancock[1] ephedrine was condensed with butyraldehyde in boiling benzene to give 2-propyl-3,4-dimethyl-5-phenyloxazolidine which underwent hydrogenolysis to N-butylephedrine over Raney nickel catalyst in hexane solution.

When a solution of epinephrine in a mixture of absolute alcohol and glacial acetic acid was reduced in the presence of excess acetone, only resinous material resulted. No oxazolidine could be isolated from a similar reaction mixture before hydrogenation.

The aminoalcohols that were used as starting materials in the reductive alkylations are all thought to have the norephedrine configuration. Therefore, the N-alkyl derivatives are assumed to have the same configuration since no stereochemical change would be expected during the course of the reductive alkylation. This view is supported by the results with ephedrine since the N-butylephedrine obtained by reductive alkylation was identical with a sample prepared from ephedrine and butyl bromide by the method of Feng and Wilson.[3] The products prepared from aldehydes and symmetrical ketones consist of a single racemic modification. The products from the unsymmetrical ketones are mixtures of diastereoisomers. In this work an effort was made to purify these products with as little separation of stereoisomers as possible.

The pharmacological properties of these compounds have been studied in the Department of Pharmacology of this Laboratory. All possess depressor, antispasmodic and bronchodilator activity in varying degree. The catechol derivatives (Table II) are the most active series. The most active compound is 1-(3,4-dihydroxyphenyl)-2-isopropylamino-1-propanol which has about half of the bronchodilator activity of 3,4-dihydroxy-N-isopropylphenethanolamine ("Aludrine").

Experimental

Starting Materials.—The norephedrine and ephedrine used in this work were the commercial products.

The hydroxyphenylpropanolamines were prepared by catalytic reduction of the corresponding hydroxy-substituted α-aminopropiophenones.[4] 1-(3,4-Dihydroxyphenyl)-2-amino-1-propanol was prepared from the hydrochloride as described in the patent literature.[5]

1-*m*-Aminophenyl-2-amino-1-propanol was prepared from *m*-nitro-α-oximinopropiophenone[6] and from *m*-acetamidopropiophenone by the methods developed by Hartung and Foster[7] for the preparation of the *p*-amino isomer.

Reduction of *m*-nitro-α-oximinopropiophenone gave 1-(*m*-aminophenyl)-2-amino-1-propanol, isolated as the dihydrochloride. The purification was difficult, six recrystallizations from a mixture of benzene and alcohol being required. The yield of pure material m. p. 252–253° (dec.) was 15–18%.

Anal. Calcd. for $C_9H_{14}N_2O \cdot 2HCl$: N, 11.72; Cl, 29.65. Found: N, 11.72; Cl, 29.55.

Nitrosation of *m*-acetamidopropiophenone[8] gave *m*-acetamido-α-oximinopropiophenone[9] in 65% yield. The product crystallized from aqueous alcohol as the monohydrate which was stable on drying at room temperature. A reproducible melting point could not be obtained on this hydrate.

Anal. Calcd. for $C_{11}H_{12}O_3N_2 \cdot H_2O$: N, 11.76; H_2O, 7.56. Found: N, 11.70; H_2O, 7.40.

On drying the monohydrate at 100° the anhydrous product m. p. 158–159° was obtained.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: N, 12.72. Found: N, 12.70.

Hydrogenation of *m*-acetamido-α-oximinopropiophenone in absolute alcohol containing dry hydrogen chloride under the specified conditions[7] gave 1-(*m*-aminophenyl)-2-amino-1-propanol dihydrochloride. The yield of product, m. p. 251–252° (dec.) was 72%.

1-Phenyl-2-alkylamino-1-propanols (Table I).—A solution of norephedrine (1 mole) and the carbonyl compound (1–5 moles) in absolute alcohol or anhydrous alcohol containing 5% methanol, was subjected to hydrogenation over Adams platinum catalyst at room temperature and pressures of 1–3 atmospheres. In general, the reduction proceeded smoothly and rapidly till one mole of hydrogen per mole of carbonyl compound added was absorbed. The catalyst then was separated and the solvent evaporated on the steam-bath under reduced pressure. In some cases the product was purified by recrystallization from benzene, hexane, or a mixture of the two. In most cases the crude product was converted to the hydrochloride which was purified by recrystallization from anhydrous alcohol or a mixture of anhydrous alcohol and ether.

1-(3,4-Dihydroxyphenyl)-2-alkylamino-1-propanols.—Several of these compounds did not form crystalline salts with hydrochloric, hydrobromic, sulfuric or phosphoric acids. These were isolated as the 3,5-dinitrobenzoic acid salts which were converted to the hydrochlorides for the pharmacological work as follows. The 3,5-dinitrobenzoate was dissolved in water and the solution treated with one equivalent of hydrochloric acid. The 3,5-dinitrobenzoic acid which was precipitated was separated by filtration, and the remainder removed by extracting with ether. The compounds are listed in Table II. A typical procedure is given.

1-(3,4-Dihydroxyphenyl)-2-*s*-butylamino-1-propanol.—1-(3,4-Dihydroxyphenyl)-2-amino-1-propanol, 5.00 g. (0.0273 mole) and methyl ethyl ketone, 5.9 g. (0.082 mole) were dissolved in a mixture of 90 ml. of absolute alcohol and 10 ml. of glacial acetic acid. The solution was hydrogenated over 0.3 g. of Adams platinum catalyst

(2) Dalmer and Oberlin, U. S. Patents 1,898,258, 1,865,880.

(3) Feng and Wilson, *Chinese J. Physiol.*, **4**, 231 (1930).

(4) Hartung, Munch, Miller and Crossley, THIS JOURNAL, **53**, 4149 (1931).

(5) German Patent 254,438, Friedlaender, *Fortschritte der Teerfarbenfabrikation*, **11**, 1017 (1912-1914).

(6) Hartung and Crossley, U. S. Patent 2,248,035 (1941).

(7) Hartung and Foster, *J. Am. Pharm. Assoc.*, **35**, 15 (1946).

(8) Keneford and Simpson, *J. Chem. Soc.*, 354 (1948).

(9) This compound was prepared originally in this laboratory by W. H. Hartung and D. L. Gibson.

at an average pressure of 40 lb. per sq. in. The reduction was complete in three hours. The catalyst was separated and the solvent evaporated at 50–55° under reduced pressure. The crystalline residue, the acetic acid salt of the product, was suspended in 30 ml. of absolute alcohol and a hot solution of 5.8 g. (0.0273 mole) of 3,5-dinitrobenzoic acid in 25 ml. of absolute alcohol added. The mixture was warmed until homogeneous then cooled in the refrigerator. The 3,5-dinitrobenzoic acid salt of 1-phenyl-2-*s*-butylamino-1-propanol crystallized in bright yellow needles. The yield of product, m. p. 181–183° (dec.) (sintered 179°) was 8.6 g. (70%). Two recrystallizations from absolute alcohol containing a few drops of water gave product, m. p. 183–185° (sintered 182°).

1-(*m*-Hydroxyphenyl)-2-cyclohexylamino-1-propanol.—This procedure is typical of the preparation of the 1-hydroxyphenyl-2-alkylamino-1-propanols listed in Table III. 1-(*m*-Hydroxyphenyl)-2-amino-1-propanol hydrochloride, 5.00 g. (0.0246 mole) was dissolved in 50 ml. of absolute alcohol. A solution of 2.1 g. (0.025 mole) of anhydrous sodium acetate in 50 ml. of glacial acetic acid was added, and the precipitate of sodium chloride separated by filtration. Cyclohexanone, 2.54 g. (0.026 mole) and 0.1 g. of Adams platinum catalyst were added and the mixture saturated with hydrogen at atmospheric pressure. The catalyst was separated and the solvent distilled below 50° under reduced pressure in an atmosphere of nitrogen. The residue was triturated with 50 ml. of 20% potassium carbonate solution and the solution extracted with three 100-ml. portions of ethyl acetate. The ethyl acetate was evaporated, the residue dissolved in alcohol and the solution treated with a 10% excess of dry hydrogen chloride in absolute alcohol. The solution was evaporated to dryness and the white crystalline residue recrystallized from alcohol to give 4.15 g. (63%) of 1-*m*-hydroxyphenyl-2-cyclohexylamino-1-propanol hydrochloride, m. p. 225–226° (dec.). Two recrystallizations from alcohol gave product, m. p. 228–229° (dec.).

1-(*m*-Isopropylaminophenyl)-2-isopropylamino-1-propanol.—1-(*m*-Aminophenyl)-2-amino-1-propanol dihydrochloride, 4.56 g. (0.019 mole) was dissolved in absolute alcohol, 100 ml., containing 3.13 g. (0.038 mole) of anhydrous sodium acetate. The precipitated sodium chloride was separated by filtration and acetone, 3.33 g. (0.0573 mole), was added to the solution, which then was hydrogenated over 0.3 g. of Adams platinum catalyst at an average pressure of 38 lb. per sq. in. Two hours were required to complete the reduction. After separation of the catalyst the solution was treated with dry hydrogen chloride and evaporated at 55–60° under reduced pressure. The white crystalline residue was recrystallized from a mixture of alcohol and ether to give 3.85 g. (62%) of the dihydrochloride of the product, m. p. 216–217° (dec.). A second recrystallization gave pure material, m. p. 219–221° (dec.).

1-(*p*-Aminophenyl)-2-cyclohexylaminoethane.—*p*-Aminophenethylamine, 2.25 g. (0.0165 mole) and cyclohexanone, 1.62 g (0.0165 mole) were dissolved in 50 ml. of absolute alcohol. The mixture was hydrogenated over 0.3 g. of Adams platinum catalyst at atmospheric pressure and room temperature. The reduction was complete in 75 minutes. After separating the catalyst the solvent was evaporated on the steam-bath and the residue distilled. The product b. p. 160–165° (1 mm.) weighed 1.1 g. In addition 0.9 g. of material boiling below 160° was obtained. There was very little residue. The product gave a positive test for a diazotizable amino group[10] and was identified by conversion to known derivatives.[11] The diacetyl derivative melted at 128.5–130.5° after recrystallization from a mixture of benzene and hexane, and the picrate melted at 145–147° after recrystallization from a mixture of alcohol and water.

1-(*p*-Nitrophenyl)-2-isopropylamino-1-propanol.—1-Phenyl-2-isopropylamino-1-propanol, 16.8 g. (0.087 mole) dissolved in 35 ml. of glacial acetic acid was added dropwise with stirring to a mixture of 26.1 ml. of concentrated nitric acid (sp. gr. 1.4) and 26.1 ml. of concentrated sulfuric acid, keeping the temperature at 24–26°. The addition required twenty minutes. The reaction mixture then was poured over 200 g. of ice and the mixture neutralized with 180 ml. of 20% ammonium hydroxide. After saturating the solution with sodium chloride a yellow oil separated. The mixture was extracted with a solution of 50 ml. of alcohol in 200 ml. of isopropyl ether. After drying over sodium sulfate the extract was saturated with dry hydrogen chloride. A viscous yellow oil separated which became crystalline on standing in the refrigerator. Recrystallization from a mixture of alcohol and ethyl acetate gave 4.8 g. (20%) of the hydrochloride of 1-(*p*-nitrophenyl)-2-isopropylamino-1-propanol, m. p. 209–211° (dec.).

Anal. Calcd. for $C_{12}H_{18}N_2O_3 \cdot HCl$: N, 10.20; Cl, 12.91. Found: N, 9.99; Cl, 12.93.

1-(*p*-Nitrophenyl)-2-cyclohexylamino-1-propanol was prepared by the procedure used for the isopropyl analog. The yield of the hydrochloride, m. p. 210–211° (dec.), was 24–28%.

Anal. Calcd. for $C_{15}H_{22}N_2O_3 \cdot HCl$: N, 8.90; Cl, 11.26. Found: N, 8.66; Cl, 11.36.

1-(*p*-Aminophenyl)-2-isopropylamino-1-propanol.—1-(*p*-Nitrophenyl)-2-isopropylamino-1-propanol hydrochloride, 4.14 g. (0.0151 mole) was dissolved in 50 ml. of 90% (by volume) alcohol. The solution was saturated with hydrogen over 0.5 g. of 10% palladium on charcoal catalyst at atmospheric pressure. Approximately three hours was required to complete the reduction. The catalyst was separated, the solution acidified with a solution of hydrogen chloride in alcohol and the solvent evaporated under reduced pressure below 50°. The crude product was reprecipitated from absolute alcohol by the cautious addition of absolute ether to give 3.1 g. (73%) of the dihydrochloride of the product, m. p. 173–174° (dec.). Recrystallization from a mixture of absolute alcohol and ether gave pure material, m. p. 174–175° (dec.).

2-Propyl-3,4-dimethyl-5-phenyloxazolidine.—Ephedrine, 66.1 g. (0.4 mole) and butyraldehyde, 31.7 g. (0.44 mole) were mixed. An exothermic reaction took place. Benzene, 100 ml., was added and the mixture heated to refluxing for ninety minutes under a continuous water separator. The volume of water collected was 7.0 ml. After distillation of the benzene the product was distilled under reduced pressure. The yield of clear colorless liquid, b. p. 110° (1 mm.)–112° (2 mm.), $n^{25}D$ 1.5050, was 78 g. (89%).

Anal. Calcd. for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.33.

Refluxing a 5.0-g. sample of this oxazolidine with 50 ml. of 6 *N* hydrochloric acid afforded 1.2 g. of ephedrine hydrochloride, m. p. 212–213°. When mixed with an authentic sample, the m. p. was 213–214°.

N-Butylephedrine.—2-Propyl-3,4-dimethyl-5-phenyloxazolidine, 30.0 g (0.137 mole), dissolved in 30 ml. of hexane was hydrogenated over 0.5 g. of Raney nickel catalyst at a temperature of 100° and an initial hydrogen pressure of 1400 lb. per sq. in. The product was a colorless liquid, b. p. 106–108° (1 mm.), $n^{25}D$ 1.5088, $[\alpha]^{25}D$ −15 ± 1° (*c*, 5.0 in 0.25 *N* hydrochloric acid).

A portion of the product was treated with excess methyl iodide at room temperature. After recrystallization from alcohol the methiodide had the following properties: m. p. 151–152°, $[\alpha]^{25}D$ −18 ± 1° (*c*, 5.0 in 95% alcohol).

Anal. Calcd. for $C_{15}H_{26}INO$: I, 34.94; N, 3.86. Found: I, 35.02; N, 3.86.

After refluxing a sample of N-butylephedrine with 6 *N* hydrochloric acid for three hours, 93% was recovered and identified as the methiodide.

A sample of N-butylephedrine, prepared from ephedrine and butyl bromide by the method of Feng and Wilson,[3] had physical constants in agreement with those observed for the product obtained by reductive alkylation and gave a methiodide identical with that described above.

(10) Sprague, Land and Ziegler, THIS JOURNAL, **68**, 2156 (1946).

(11) v. Braun and Blessing, *Ber.*, **56B**, 2159 (1923), report 129° and 147° for the diacetyl derivative and the picrate, respectively.

Acknowledgment.—The authors wish to thank Mrs. Thelma P. Buchanan and Mr. K. B. Streeter for the microanalyses.

Summary

A number of 1-phenyl-2-alkylamino-1-propanols have been prepared by the catalytic hydrogenation of mixtures of norephedrine or certain nuclear substituted derivatives with aldehydes or ketones, following the general method of Cope and Hancock. When the aminoalcohol contains a catechol nucleus, only ketones can be employed as the carbonyl component. A nuclear amino group may be alkylated simultaneously if an excess of carbonyl compound is employed.

GLENOLDEN, PA. RECEIVED DECEMBER 2, 1949

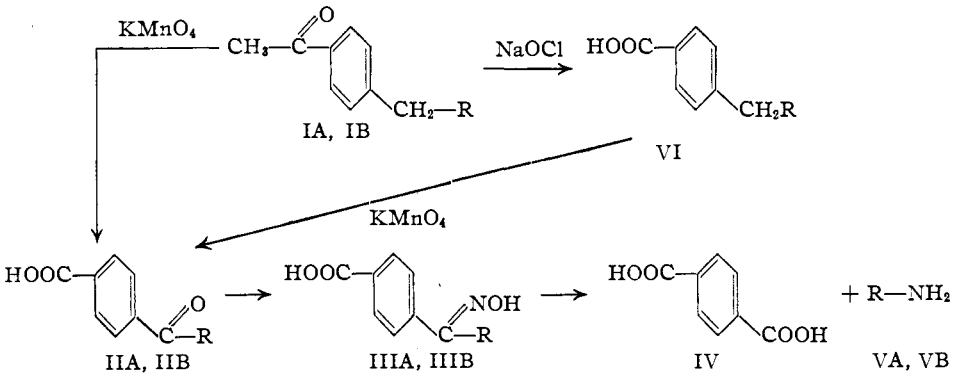
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

The Chemistry of the Benzylpyridines. I. 2-(4-Acetylbenzyl)- and 4-(4-Acetylbenzyl)-pyridines[1]

BY FRANK J. VILLANI AND DOMENICK PAPA

For the synthesis of new derivatives of benzylpyridines, 2-(4-acetylbenzyl)-pyridine (IA) and 4-(4-acetylbenzyl)-pyridine (IB) were required as intermediates. This paper describes the synthesis and proof of structure of these two compounds and several derivatives.

2-(4-Acetylbenzyl)- and 4-(4-acetylbenzyl)-pyridines were synthesized by the Friedel–Crafts reaction of the appropriate benzylpyridine and acetyl chloride. When the reaction was carried out by the conventional Friedel–Crafts procedure, using either nitrobenzene, carbon disulfide or acetylene tetrachloride as solvents, little or none of the expected acetyl products were obtained. However, in the absence of solvent and employing the same ratio of reactants as that described for the synthesis of 2,5-dichloroacetophenone,[2] namely, one part by weight of acetyl chloride and the benzylpyridine and two parts by weight of aluminum chloride, 60–70% yield of IA and IB were consistently obtained.



For A series, R = 2-pyridyl; for B series, R = 4-pyridyl.

The structure of the acetylbenzylpyridines was established by the following series of transformations. Oxidation of IA with alkaline permanganate yielded the keto acid IIA. The oxime of IIA was subjected to the Beckmann rearrangement[3] and the resulting amide, on hydrolysis yielded terephthalic acid (IV) and 2-aminopyridine (VA). These products were identified by known derivatives. Similarly, IB yielded IV and 4-aminopyridine (VB). The acidic product of the Beckmann rearrangement of IIIA and IIIB did not yield any phthalic acid indicating that no *o*-acetylbenzylpyridines were formed during the Friedel–Crafts reaction.

The oxidation of IA with sodium hypochlorite yielded the carboxylic acid VI, which could not be obtained analytically pure. Further oxidation of 2-(4-carboxybenzyl)-pyridine (VI) with alkaline permanganate resulted in the formation of the keto acid (IIA).

Experimental

All melting points are corrected.

2-(4-Acetylbenzyl)-pyridine (IA).—In a 2-l. flask equipped with a Hershberg type tantalum stirrer and a reflux condenser, was placed 200 g. of 2-benzylpyridine and 200 g. of acetyl chloride. The mixture was cooled in an ice–salt-bath and 400 g. of aluminum chloride was added slowly in small portions under anhydrous conditions. After all of the aluminum chloride had been added, the ice-bath was removed and the mixture was allowed to warm to room temperature and finally heated on the steam-bath for six hours. The brown viscous material was poured onto ice and a large excess of 50% sodium hydroxide solution was added.[4] The organic layer was extracted several times with chloroform, washed with water, dried over anhydrous sodium sulfate and distilled. The product dis-

(1) Presented in abstract before the Division of Organic Chemistry of the American Chemical Society, Atlantic City Meeting, September 19, 1949.

(2) Sen and Bhargava, *J. Ind. Chem. Soc.*, **24**, 371 (1947).

(3) After this investigation had been completed, Huntress and Walter [THIS JOURNAL, **70**, 3702 (1948)] described the Beckmann rearrangement of 2-benzoylpyridine oxime.

(4) A large excess of sodium hydroxide is necessary in order to dissolve the aluminum hydroxide which precipitates.