The crude product, ethyl α,β-dicyano-β-(*o*-chlorophenyl)-butyrate, and 1 l. of 12 *N* hydrochloric acid were refluxed for 40 hours. After cooling, the water layer was decanted, 1 l. of fresh 12 *N* hydrochloric acid added and the mixture refluxed again for 40 hours. The contents of the flask were cooled and filtered. The residue was dissolved in 10% aqueous sodium hydroxide, extracted once with 200 ml. of ether, mixed with a moderate amount of charcoal and filtered. After adjusting the solution to *p*H 7, it was cooled and filtered. Acidification to congo red with 12 *N* hydrochloric acid yielded a product which was filtered and then recrystallized from hot 50% ethanol; m.p. 204–205°, yield 80 g.

Anal. Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.44; H, 4.57. Found: C, 54.14; H, 4.89.

α-(*o*-Chlorophenyl)-succinimide.—The succinimides in Table I were prepared by the general procedure described below.

Two hundred and fourteen grams (0.93 mole) of *o*-chlorophenylsuccinic acid was added portionwise to a flask containing 150 g. of concentrated ammonium hydroxide and 50 ml. of water. The solution was heated until the internal temperature increased to 200°. After cooling somewhat, the residue was dissolved in 600 ml. of hot ethanol, charcoaled and filtered. The filtrate was cooled thoroughly and the white crystalline product filtered and dried; m.p 133–135°, yield 84%.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Substituted 1-Phenyl-2-alkylaminoethanols and -propanols[1]

BY JOHN R. CORRIGAN,[2a] MARIE-JO SULLIVAN, HOWARD W. BISHOP AND A. WAYNE RUDDY[2b]

RECEIVED AUGUST 3, 1953

In order to establish better correlaton between molecular structure and bronchodilator or vasodepressor action 21 hydroxy and methoxyphenylalkylaminoethanols and -propanols were prepared and characterized. A brief summary of the correlation is presented. None of the compounds was found to be as active as 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Previous reports[3] from one of these laboratories have described the preparation of N-substituted 1-(4-hydroxyphenyl)- and 1-(3,4-dihydroxyphenyl)-2-aminoethanols as possible bronchodilators. In order to establish a better correlation between molecular structure and bronchodilator or vasodepressor action we have extended this series of compounds to include the 1-(3-hydroxyphenyl)-2-alkylaminoethanols, additional 1-(4-hydroxyphenyl)-2-alkylaminoethanols and 1-(hydroxyphenyl)-2-alkylamino-1-propanols as well as some of their methoxy analogs. Among these are a few cyclopentyl- and cyclohexylamino derivatives.

Most of the aminoalcohols were prepared by the catalytic hydrogenation of the corresponding aminoketone salts with palladium-on-charcoal catalyst. In order to avoid debenzylation the N-benzyl derivatives, 1-(4-methoxyphenyl)-2-benzylaminoethanol and 1-(4-methoxyphenyl)-2-benzylmethylaminoethanol, were prepared from their aminoketone salts by the Meerwein–Ponndorff–Verley reduction method employing aluminum isopropoxide as modified by Burger and Deinet.[4] This procedure was also used in preparing 1-(4-hydroxyphenyl)-2-diisopropylaminoethanol. Two of the tertiary amines, 1-(4-hydroxyphenyl)-2-methylisopropylaminoethanol and its 4-methoxy analog, were obtained from the available secondary aminoalcohols by reductive alkylation with formaldehyde as described by Woodruff, *et al.*[5]

The general method of Bockmühl, *et al.*,[6] was followed in the preparation of most of the aminopropanols from the corresponding benzyloxy-α-bromopropiophenones, but was modified by purifying and characterizing the intermediate α-alkylaminobenzyloxypropiophenone hydrochlorides. Hydrogenation in the presence of palladium catalyst produced a simultaneous reduction of the carbonyl group and hydrogenolysis of the benzyl ethers. After this series was completed Sprague, *et al.*,[7] reported the preparation of several of these aminopropanols by the reductive alkylation of the corresponding 2-amino-1-(hydroxyphenyl)-1-propanols.

The preliminary data furnished by Dr. A. M. Lands and his staff of our Pharmacology Department indicate that the bronchodilator and vasodepressor activity of these compounds is decreased when a phenolic group is blocked as the methyl ether, and the activity is insignificant when the secondary amines are converted to tertiary amines. The propanols are less active than the corresponding ethanols. None of the compounds was found to be as active as 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.[3]

Acknowledgment.—The authors are indebted to Mrs. Eleanor Kovach and Mr. David Jackman for technial assistance, and to Miss Elizabeth B. Macks, Mr. M. E. Auerbach and staff for the analytical data.

Experimental[8]

Bromoketones.—The bromoketones not commercially available were obtained by bromination of the appropriate ketones in chloroform or methylene chloride. Those prepared which have been reported previously are α-bromo-4-methoxyacetophenone,[9] α-bromo-4-benzyloxypropiophenone,[10] α-bromo-3,4-dimethoxypropiophenone[11] and α-bromo-3,4-dibenzyloxypropiophenone.[10]

(1) A portion of this work was carried out in the former Research Laboratories of Frederick Stearns and Company Division of Sterling Drug, Inc.

(2) (a) Sharp & Dohme Division, Merck & Co., West Point, Pa.; (b) Warner-Chilcott Research Laboratories, Morris Plains, N. J.

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(5) E. H. Woodruff, J. P. Lambooy and W. E. Burt, *ibid.*, **62**, 922 (1940).

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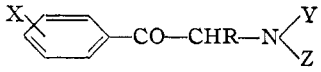
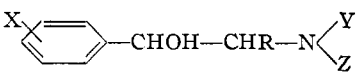
TABLE I

AMINOKETONE SALTS 

X	R	Y	Z	M.p., °C. dec.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
3-CH_3O	H	H	Isopropyl	176.6–178.4	$C_{12}H_{17}NO_2$·HCl	[a]							
3-C_6H_5COO	H	H	Isopropyl	196–198[b]	$C_{18}H_{19}NO_3$·HBr							21.12	21.08
3-HO	H	H	Isopropyl	213–216[b]	$C_{11}H_{15}NO_2$·HCl[c]					6.10	5.77	15.43	15.65
3-HO	H	Benzyl	Cyclopentyl	192.7–194	$C_{20}H_{23}NO_2$·HCl	69.45	69.31	7.00	7.29			10.25	10.22
3-C_6H_5COO	H	H	*n*-Butyl	190–191[b]	$C_{19}H_{21}NO_3$·HBr	[d]							
3-HO	H	H	*n*-Butyl	194.4–195.6	$C_{12}H_{17}NO_2$·HBr					4.86	4.94		
4-CH_3O	H	H	Isopropyl	178.4–179.8	$C_{12}H_{17}NO_2$·HBr					4.86	5.13	27.73	27.44
4-CH_3O	H	H	Benzyl	187.7–189.4	$C_{16}H_{17}NO_2$·HBr	57.15	57.87	5.40	5.30	4.17	4.11	23.77	23.60
4-HO	H	Benzyl	Cyclopentyl	122.5–124.5	$C_{20}H_{23}NO_2$·HCl	69.45	69.20	7.00	7.29			10.25	9.99
4-HO	H	H	Cyclohexyl	294–297	$C_{14}H_{19}NO_2$·HBr	53.51	53.81	6.42	6.67	4.46	4.62	25.44	25.49
4-HO	H	Ethyl	Ethyl	204.5–206	$C_{12}H_{17}NO_2$·HBr	50.01	49.99	6.30	6.39	4.86	4.98	27.73	27.73
4-CH_3O	H	Isopropyl	Isopropyl	207.2–208.5	$C_{15}H_{23}NO_2$·HBr	54.55	54.22	7.32	7.26	4.24	4.41	24.20	24.02
4-HO	H	Isopropyl	Isopropyl	228–230[b]	$C_{14}H_{21}NO_2$·HBr					4.43	4.54	25.26	25.11
4-CH_3O	H	Methyl	Benzyl	183.4–184.5	$C_{17}H_{19}NO_3$·HBr	58.29	58.50	5.76	5.78	4.00	3.87	22.81	22.52
3-$C_6H_5CH_2O$	Methyl	H	Isopropyl	211.5–212.9	$C_{19}H_{23}NO_2$·HCl	68.35	68.30	7.25	7.08			10.62	10.38
4-$C_6H_5CH_2O$	Methyl	H	Isopropyl	230.5–232	$C_{19}H_{23}NO_2$·HBr	60.32	60.48	6.39	6.22	3.70	3.88	21.14	21.23
3,4-di-$C_6H_5CH_2O$	Methyl	H	Isopropyl	212.7–214.5	$C_{26}H_{29}NO_3$·HCl	70.97	71.00	6.87	6.98			8.06	7.86
3,4-di-CH_3O	Methyl	H	Isopropyl	242.8–244.8	$C_{14}H_{21}NO_3$·HBr					4.22	4.20	24.06	23.84
3,4-di-HO	Methyl	H	Isopropyl	158–160[b]	$C_{12}H_{17}NO_3$·HBr					4.60	4.52		
3,4-di-$C_6H_5CH_2O$	Methyl	H	Cyclopentyl	208–210	$C_{28}H_{31}NO_3$·HCl	72.16	72.19	6.92	6.78			7.61	7.47

[a] Hydrogenated without further purification. [b] Uncorrected m.p. [c] Hydrobromide m.p. 235–237° dec. (uncor.). [d] Hydrolyzed directly and analyzed as the 3-HO compound.

TABLE II

AMINOALCOHOL SALTS 

X	R	Y	Z	M.p., °C.[g]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
3-CH_3O	H	H	Isopropyl	143.5–144.6	$C_{12}H_{19}NO_2$·HCl[a]	58.65	58.75	8.20	8.11	5.70	5.66	14.43	14.23
3-HO	H	H	Isopropyl	152.3–154	$C_{11}H_{17}NO_2$·$C_2H_4O_2$[b]	61.15	61.26	8.29	8.13	5.49	5.37		
3-HO	H	H	Isopropyl	210.4–213.6	$(C_{11}H_{17}NO_2)_2$·H_2SO_4[c]					5.73	5.76	[d]	
3-HO	H	H	*n*-Butyl	119–120[e]	$C_{12}H_{19}NO_2$·HCl					5.70	5.60	14.43	14.48
3-HO	H	H	Cyclopentyl	143.3–145.1	$C_{13}H_{19}NO_2$·HCl	60.57	60.82	7.82	8.06			13.76	13.57
4-CH_3O	H	H	Isopropyl	123.6–124.8	$C_{12}H_{19}NO_2$·HCl[f]					5.70	5.52	14.43	14.38
4-CH_3O	H	H	Benzyl	185–187[g,l]	$C_{16}H_{19}NO_2$·HCl					4.77	4.61	12.07	12.09
4-HO	H	H	Cyclopentyl	159.2–161.4	$C_{13}H_{19}NO_2$·HCl	60.57	60.77	7.82	7.88			13.76	13.58
4-HO	H	H	Cyclohexyl	179.2–180.6	$C_{14}H_{21}NO_2$·HCl[h]					5.15	5.15	13.04	13.05
4-HO	H	Ethyl	Ethyl	170–172[g]	$C_{12}H_{19}NO_2$·$C_2H_4O_2$[b]					5.20	5.32		
4-HO	H	Methyl	Isopropyl	171.5–172.3	$C_{12}H_{19}NO_2$·HCl	58.65	58.75	8.20	7.91	5.70	5.78	14.43	14.41
4-CH_3O	H	Methyl	Isopropyl	134–135[g]	$C_{13}H_{21}NO_2$·HCl					5.39	5.35	13.65	13.56
4-CH_3O	H	Isopropyl	Isopropyl	172.2–173.4	$C_{15}H_{23}NO_2$·HCl					4.86	4.75	12.32	12.55
4-HO	H	Isopropyl	Isopropyl	178.6–179.8[g]	$C_{14}H_{23}NO_2$·HBr					4.40	4.63	24.91	24.80
4-CH_3O	H	Methyl	Benzyl	150–152[g]	$C_{17}H_{21}NO_2$·HCl					4.55	4.49	11.52	11.51
3-HO	Methyl	H	Isopropyl	226.9–228[g,i]	$C_{12}H_{19}NO_2$·HCl	58.65	58.37	8.20	7.92			14.43	14.20
4-HO	Methyl	H	Isopropyl	228.2–228.8[g]	$C_{12}H_{19}NO_2$·HBr	49.66	49.21	6.95	6.73	4.83	4.99	27.54	27.60
3,4-di-HO	Methyl	H	Isopropyl	216–218[g,g]	$C_{12}H_{19}NO_3$·HBr					4.57	4.26	26.10	25.96
3,4-di-HO	Methyl	H	Isopropyl	217.8–218[g,j]	$C_{12}H_{19}NO_3$·HCl	55.06	55.00	7.70	7.57			13.55	13.36
3,4-di-CH_3O	Methyl	H	Isopropyl	169.6–170.8	$C_{14}H_{23}NO_3$·HBr					4.19	4.23	23.91	24.23
3,4-di-HO	Methyl	H	Cyclopentyl	208–208.5[g,k]	$C_{14}H_{21}NO_3$·HCl	58.46	58.56	7.71	7.98			12.32	12.15

[a] Base, m.p. 91–92° (uncor.). *Anal.* Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.81. [b] Acetate salt. [c] Hydrochloride hygroscopic; converted to sulfate with silver sulfate. Base, m.p. 123–124.5° (uncor.). [d] *Anal.* Calcd.: S, 6.56. Found: S, 6.61. [e] Uncorrected m.p. [f] Base, m.p. 89–90° (uncor.). *Anal.* Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.66. [g] With decomposition. [h] Base, m.p. 172–174° (uncor.). *Anal.* Calcd. for $C_{14}H_{21}NO_2$: N, 5.93. Found: N, 6.12. [i] Ref. 7 reported m.p. 219–220° dec. [j] Ref. 7 reported m.p. 208–209° dec. [k] Ref. 7 reported m.p. 205–206° dec. Ref. 6 reported m.p. 215° dec. [l] W. Gruber and H. Renner, *Monatsh.*, **81**, 751 (1950), reported m.p. 150–151°.

α-Bromo-3-methoxyacetophenone, m.p. 63.0–64.3°, was obtained in 65% yield.

Anal. Calcd. for $C_9H_9BrO_2$: Br, 34.89. Found: Br, 34.92.

Benzylcyclopentylamine.—The cyclopentylamine was prepared in 84% yield by a catalytic amination of cyclopentanone with excess ammonia using Raney nickel at 50 lb. of hydrogen and 50°; b.p. 106–108°, $n^{25}D$ 1.4478.

To one mole of cyclopentylamine in 100 ml. of methanol was added one mole of benzaldehyde with cooling. After allowing to stand for about an hour the solution was diluted to a total volume of 350 ml. with methanol and hydrogenated with platinum oxide catalyst at 40 lb. pressure. The reduction was complete in two hours. After removing the catalyst the solution was acidified with hydrochloric acid and the alcohol and neutral materials removed under reduced pressure. The amine was liberated with 35% sodium hydroxide, taken up in ether and dried over sodium hydroxide pellets. Benzylcyclopentylamine was obtained in 92% yield, b.p. 114–116° (5 mm.), $n^{25}D$ 1.5264. A sample of amine when converted to the hydrochloride melted at 221.5–223.5°.

Anal. Calcd. for $C_{12}H_{17}N$·HCl: N, 7.99; Cl, 20.23. Found: N, 8.02; Cl, 20.18.

Aminoketones.—The alkylaminoacetophenones described in Table I were prepared by procedures outlined in previous communications[3] employing either isopropyl alcohol or chloroform as the reaction solvent. Two of the compounds, α-diisopropylamino-4-hydroxyacetophenone and α-isopropylamino-3,4-dihydroxypropiophenone, were prepared by hydrobromic acid demethylation of the corresponding methoxy compounds in the usual manner. The yields of aminoketone salts varied between 40 and 90%.

The alkylaminopropiophenones were prepared by the

general method of Bockmühl, *et al.*[6] The reaction time was shortened by refluxing the bromoketone with two equivalents of amine in absolute alcohol. The alcohol was removed completely under reduced pressure, ether was added and the amine hydrobromide removed. The ether filtrate was acidified with hydrochloric acid and the oily product induced to crystallize. It was then recrystallized from alcohol and ether. The yields ranged from 67 to 80%.

Aminoalcohols.—The aminoethanols were synthesized from the corresponding aminoketone salts by catalytic hydrogenation with palladium-on-charcoal in water. Methanol was used as the solvent for reduction of the benzyloxyaminopropiophenones. By careful removal of the solvent many of the final products were obtained directly. However, in a few cases it was necessary to precipitate the aminoalcohol bases with ammonia and reconvert to stable salts in anhydrous media.

In order to avoid catalytic debenzylation the N-benzyl derivatives, 1-(4-methoxyphenyl)-2-benzylaminoethanol and 1-(4-methoxyphenyl)-2-benzylmethylaminoethanol, were prepared from appropriate aminoketone salts by reduction with aluminum isopropoxide.[4]

1-(4-Hydroxyphenyl)-2-isopropylaminoethanol[3] and its 4-methoxy analog were N-methylated by reductive alkylation with formaldehyde.[5]

The aminoethanols, obtained in yields of 50 to 95%, and the aminopropanols, obtained in yields of 75 to 85%, are described in Table II.

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

Reactions of Aminoalcohol–Aldehyde Anhydro Compounds

BY EUGENE P. GOLDBERG[1] AND HAROLD R. NACE

RECEIVED AUGUST 20, 1953

Reactions of three aminoalcohol–aldehyde anhydro products, 2-propyl-4-ethyloxazolidine (10% Schiff base), 2-benzylideneamino-1-butanol (100% Schiff base) and 2-(2-ethylhexylideneamino)-1-butanol (80% Schiff base), have been investigated. Despite their different structural compositions, all three compounds yield oxazolidine derivatives with nitrosyl chloride, α-naphthyl isocyanate and phenyl isothiocyanate. A shift of the Schiff base–oxazolidine equilibrium to the cyclic structure is thus indicated. Nitrosation of anhydro compounds with nitrosyl chloride in anhydrous ether–pyridine provides the most satisfactory synthesis of N-nitrosoöxazolidines.

Aldehydes and ketones react with 1,2-aminoalcohols to yield anhydro compounds which are frequently referred to as oxazolidines or Schiff bases although they are most often equilibrium mixtures of the two forms. Bergmann[2] demonstrated that a general relationship exists between the structures of the reactants and that of the anhydro product. Bergmann[2] and McCasland[3] suggested that chemical evidence was inconclusive for the determination of the anhydro product structure and additional evidence is presented here in support of this conclusion.

In reactions such as reduction or hydrolysis, either of the two structural forms (oxazolidine or Schiff base) gives the same product.[2] However, with reagents that react with secondary amines and not with Schiff bases, the anhydro product structure might be expected to influence the reaction course. Both Bergmann[2] and McCasland[3] obtained N-benzoyl oxazolidines from anhydro products which were predominantly in the Schiff base form. Heusser[4] reported the N-acetylation of a steroid oxazolidine and Henry and Dehn[5] obtained substituted ureas from the reaction of Schiff base types with isocyanates, but did not establish the structure of the products. These works suggest that Schiff bases may isomerize to oxazolidines in reacting. However, Bergmann[2] has recently attempted the anisoylation of a Schiff base type and obtained only the N,O-dianisoylated aminoalcohol.

In the work reported here, reactions of three anhydro products having different oxazolidine–Schiff base compositions were studied and additional evidence for an equilibrium is presented.

The first anhydro product studied was 2-propyl-4-ethyloxazolidine, previously prepared[6] and estimated to be 90% in the cyclic form. The second compound studied was 2-benzylideneamino-1-butanol. This viscous liquid was prepared by azeotroping water from a boiling benzene solution of 2-amino-1-butanol and benzaldehyde. The infrared spectrum showed a very strong C=N band at 6.11μ and a molar refraction exaltation of 1.5 units (above the calculated Schiff base value) was found. These data indicated that this material was almost entirely in the Schiff base form.

The third anhydro compound investigated was 2-(2-ethylhexylideneamino)-1-butanol. This material was prepared, as above, from 2-amino-1-butanol and 2-ethylhexanal, and was identical with the previously reported 2-(2-ethyl-2-hexenylideneamino)-1-butanol reduction product.[6] From the molar refraction it was estimated that about 80% of this material was in the Schiff base form. The infrared spectrum showed a moderately strong C=N absorption at 6.02μ.

Since the nitrosation of 2-propyl-4-ethyloxazolidine using aqueous sodium nitrite and acetic acid had already been reported,[6] this reaction was applied to the latter two anhydro products. 2-Benzylideneamino-1-butanol afforded an 80% yield of benzaldehyde as well as 38% of 2-propyl-3-nitroso-4-ethyloxazolidine. Similarly, nitrosation of 2-(2-ethylhexylideneamino)-1-butanol yielded 2-ethylhexanal (64%) and 2-propyl-3-nitroso-4-ethyloxazolidine. It was evident that the Schiff bases had hydrolyzed in the aqueous media and that the resulting 2-amino-1-butanol underwent deamination, rearrangement and nitrosation to the previously reported N-nitrosoöxazolidine.[7] It was

(1) Brown University Fellow 1952–1953.

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