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Physiologically Active Indanamines. II. Compounds Substituted in the Aromatic Ring[1]

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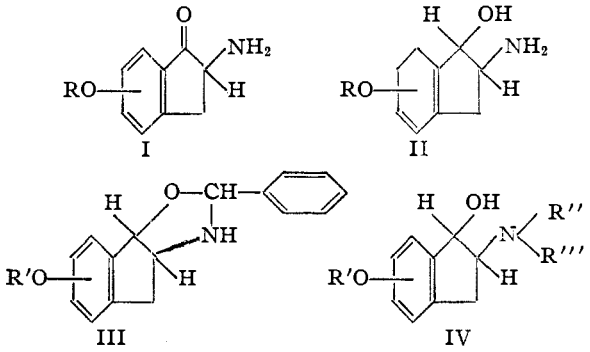
Previous work in this Laboratory[1] has shown that certain aminoindanes, aminoindanones and aminoindanols unsubstituted in the nucleus possess valuable properties as bronchodilators. For this reason it was considered desirable to prepare some derivatives of these compounds containing one or more hydroxyl or methoxyl groups in the aromatic ring. The present paper deals with indanamines substituted in this manner (I, II, III, IV).



I II

III IV

OR = 5-OH, 5-OCH_3, 6-OCH_3, 7-OCH_3, 4,5-di-OCH_3, 5-OCH_3-6-OH, 5,6-di-OCH_3, 5,6-O_2CH_2

OR′ = 5-OCH_3, 6-OCH_3, 7-OCH_3, 4,5-di-OCH_3, 5,6-di-OCH_3, 5,6-O_2CH_2

R″ = H, CH_3

R‴ = CH_3, $CH(CH_3)_2$, CH_2-C_6H_5

Much work has been done and considerable success achieved in efforts to correlate the pressor activity with the structure of phenethylamine derivatives.[2] However, when other physiological phenomena are considered, it is found that in general they do not parallel that of pressor activity. For instance, in the case of bronchodilator activity it is even found in some cases that structural changes which affect the pressor potency adversely tend to produce an increase in the bronchodilator effect.[1,3,4,5] In other cases,[5] no clear-cut relationship appears to exist between the two phenomena. In general, it may be stated that introduction of alkyl or aralkyl groups into the amino group reduces or even reverses the pressor effect, and at the same time favors bronchodilator activity[2,3,5]; large substituents of this type seem to be most effective.[5,6] This variation might thus be expected to result in the formation of an ideal bronchodilator. Extension of the side chain to three carbon atoms results in increased duration of action[7] and, as with the pressor property, confers oral activity due to increased resistance to deamination in the body.[8]

The adverse circulatory effect of alkoxyl substitution, as compared with hydroxyl substitution[2,9] in the benzene ring, has been shown recently not to apply with respect to bronchodilation.[5] Indeed, in twenty-four of thirty-one pairs studied the methoxyl derivative was equal to, or more active than, the corresponding hydroxyl derivative. These facts lend considerable interest to the compounds reported here.

The intermediate hydroxy-, methoxy- and methylenedioxyindanones were prepared from the corresponding substituted phenylpropionic acids by cyclization with anhydrous hydrogen fluoride or phosphorus pentoxide, and in one instance through their acid chlorides *via* the Friedel–Crafts reaction. Cyclization of *o*-hydroxy (methoxy) phenylpropionic acid has not been reported and difficulty in effecting ring closure in these acids having an *ortho*-directing group present was correctly anticipated.[10] Under the usual conditions,[11] attempts to cyclize with anhydrous hydrogen fluoride led to the formation of an amorphous product, insoluble in ordinary solvents,[12] together with a trace of starting material. When phosphorus pentoxide was employed under optimum conditions for this type of reaction,[13] no ring closure occurred. There was isolated a 70% yield of a compound, (m. p. 67–69.5°) whose analysis was in good agreement with the value calculated for the anhydride; on hydrolysis, the starting acid was recovered. Cyclization of *o*-nitrophenylpropionic acid,[14] as well as nitration of indanone with subsequent isolation of the 4-nitro isomer,[15] were not promising procedures because of inaccessibility of starting materials or difficulty in

(1) For the previous paper in this series, see Levin, Graham and Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

(2) For a recent discussion of the status in this field, see Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).

(3) Curtius, *J. Pharmacol.*, **35**, 321 (1929).

(4) Konzett, *Arch. Exptl. Path. Pharmakol.*, **197**, 27 (1940).

(5) Graham, Cartland and Woodruff, *Ind. Eng. Chem.*, **37**, 149 (1945).

(6) See, for instance, the German product "Aludrine" containing an *iso*propylamino group on the side chain; *C. A.*, **40**, 5154[2] (1946).

(7) Alles and Prinzmetal, *J. Pharmacol.*, **48**, 161 (1933).

(8) Beyer and Lee, *J. Pharmacol.*, **74**, 155 (1942); Beyer and Morrison, *Ind. Eng. Chem.*, **37**, 143 (1945).

(9) Tainter, Pedden and James, *J. Pharmacol.*, **51**, 371 (1934); Pedden, Tainter and Cameron, *ibid.*, **55**, 242 (1935); Cameron and Tainter, *ibid.*, **57**, 152 (1936).

(10) See, for example, Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945).

(11) Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).

(12) The substance was partially soluble in pyridine, and dissolved in concentrated sulfuric acid to give a cherry-red solution.

(13) W. S. Johnson, "Organic Reactions," Vol. II, 1944, p. 170.

(14) Hoyer, *J. prakt. Chem.*, **139**, 94 (1934).

(15) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923).

isolating the desired isomer. When the excellent cyclization procedure for *p*-methoxyphenylpropionic acid, using the Friedel–Crafts reaction,[10] was reported by Johnson, these conditions were applied to the *ortho*-isomer. There was obtained 46% of starting material, 45% of amorphous material (m. p. about 220–30°), soluble in pyridine, but not in the usual organic solvents, 6% of an alkali insoluble product (m. p. 103–110°), and a trace of alkali-insoluble material (m. p. about 140°) whose analysis was inconclusive but approached that of the desired indanone.

Of the other three monosubstituted indanones, the 5-hydroxy-(methoxy-) and 7-hydroxy-(methoxy-)indanones were prepared by cyclization of *m*-hydroxyphenylpropionic acid with anhydrous hydrogen fluoride,[16] followed by methylation; the 7-isomer can be prepared in only insignificant yields by this method. 6-Methoxyindanone was made by Johnson's Friedel–Crafts procedure[10]; however, using Ohio-Apex grade aluminum chloride the best yield obtained in a 10-g. batch was 39%.

Cyclodehydration of 2,4-dimethoxyphenylpropionic acid could not be achieved by the methods used; anhydrous hydrogen fluoride yielded a tar, and from an attempted cyclization using phosphorus pentoxide there was recovered 43% of starting material and 35% of an oil which appeared to be the acid anhydride. It is interesting that while 2,3-dimethoxy- and 3-methoxy-4-hydroxy-phenylpropionic acid could be cyclized in excellent yield using liquid hydrogen fluoride, this method was not applicable to 3,4-methylenedioxyphenylpropionic acid.

The substituted indanones were converted, through the 2-isonitroso derivatives, to the amino ketones and amino alcohols essentially as described[1] for the unsubstituted analogs. The tendency for solutions of the aminoketone hydrochlorides to become slightly red was prevented to a considerable extent by the addition of a trace of alcoholic hydrogen chloride during any recrystallization.

Reaction of the aminoindanols with benzaldehyde produced, instead of the Schiff bases, a mixture of bases which could be separated by fractional crystallization and converted to their respective hydrochlorides. In the monosubstituted series one of these proved to be the starting material, and the other, the oxazolidine (III), which is isomeric with the Schiff base.[17] Hydrogenation with active palladium charcoal gave the desired benzylaminoindanol hydrochlorides. In the disubstituted series, reaction of the aminoindanols with benzaldehyde produced, instead of the Schiff bases, racemic mixtures of diastereoisomeric oxazolidines which were separated and purified by fractional crystallization. The isomers on hydrogenation with palladium charcoal gave different benzylaminoalcohols. These benzylaminoalcohols could also be obtained as isomeric mixtures by reductive alkylation with benzaldehyde.

Reductive alkylation of 6-methoxy-2-aminoindanol and 5,6-dimethoxy-2-aminoindanol using acetone yielded the corresponding isopropylaminoindanols; when one mole of formaldehyde was used instead of acetone only the dimethylaminoindanols were formed.

The pharmacology of the aminoketones, aminoalcohols, oxazolidines and substituted aminoalcohols will be reported elsewhere.

The authors wish to acknowledge the technical assistance of Mr. Brooke D. Aspergren in a portion of this work.

Experimental[18]

Substituted Phenylpropionic Acids

The requisite cinnamic acids were prepared from the appropriately substituted benzaldehydes and malonic acid by the Doebner reaction.[19,20]

The cinnamic acids were converted to the corresponding phenylpropionic acids by electrolytic reduction or catalytic hydrogenation using Adams platinum catalyst.[21] The former procedure frequently resulted in products difficult to purify and almost invariably in lower yields.

In view of the difficulty in preparing *m*-hydroxybenzaldehyde,[23] the Schwenk–Papa Raney nickel reduction procedure[24] for preparing *m*-hydroxyphenylpropionic acid from the readily available piperonylacrylic acid was investigated. After numerous attempts and variations of this procedure had been made the maximum yield obtained was only 35%.

(16) Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 218 (1944).

(17) Indeed it appears that the compounds referred to by Levin, Graham and Kolloff[1] as Schiff bases are also oxazolidines. For instance, a sample (m. p. 163–165°) identical with their compound XX and prepared by their procedure was ether-soluble and formed a hydrochloride, m. p. 178–180° (dec.); the oxazolidine free base (m. p. 163–164°) could be regenerated from the hydrochloride. Our oxazolidine hydrochlorides showed a tendency to hydrolyze, even during recrystallization from alcohol and ether.

(18) Melting points are uncorrected. Microanalyses by Mr. C. H. Emerson and the staff of the microanalytical laboratory.

(19) "Organic Reactions," Vol. I, 1942, pp. 226–227.

(20) When condensation was carried out with crude *m*-hydroxybenzaldehyde (m. p. 98.5–100.5°) for four hours on the steam-bath, or for twelve days at room temperature, the yield of *m*-hydroxycinnamic acid after two crystallizations was 68 and 69.5%, respectively; however, when once-crystallized aldehyde (m. p. 102°) was employed under the latter conditions the yield was 93% and the product without purification melted higher than the twice purified acid above and could be hydrogenated directly. In the case of 3-methoxy-4-hydroxybenzaldehyde, the prolonged low-temperature modification (ref. 19, pp. 235 and 250) increased the yield from 50% to 94%.

(21) It was necessary to stop the hydrogenation of *p*-methoxycinnamic acid when one mole of hydrogen had been absorbed since hydrogen uptake continued rapidly until four moles had been consumed; even slight over-reduction caused purification difficulties. Catalytic hydrogenation (PtO_2) of piperonylacrylic acid in ethanol was too slow to be practicable due to its insolubility; hydrogenation was also too slow in glacial acetic acid even at an elevated temperature. The sodium salt of the acid could not be hydrogenated in aqueous alcohol or in distilled water. Toward the end of this work hydrogenation of the acid in warm dioxane was reported.[22] This method proved satisfactory; after having been filtered from the catalyst and concentrated to half the volume, the dioxane solution was mixed with chipped ice and shaken, whereupon the product was deposited as fine, glistening crystals.

(22) Barltrop, *J. Chem. Soc.*, 958 (1946).

(23) "Organic Syntheses," Vol. 25, p. 55.

(24) Schwenk and Papa, *J. Org. Chem.*, **10**, 232 (1945).

Indanones, Aminoindanones and Aminoindanols

Cyclization of the substituted phenylpropionic acids was carried out as indicated in Table I.

5-Methoxy-6-hydroxyindanone.—Fifty grams of crude hydroferulic acid (m. p. 85–88°), prepared by catalytic hydrogenation of ferulic acid and evaporation of the alcoholic solution to dryness, was placed in a pint copper retort. Four hundred grams of chilled anhydrous hydrogen fluoride was added, the top quickly clamped in place, the retort swirled gently once and left overnight with the side arm projecting into the vent of a good hood. The amber liquid was then evaporated gently on the steam-bath in a copper beaker to a purple paste and then to a gray-purple powder. This was suspended in 8 to 10 liters of boiling water, treated with charcoal, filtered quickly while hot, and allowed to cool; yield, 38.2 g. (85%) of beautiful, long, golden needles, m. p. 192–192.5°. Concentration of the filtrate to 3 liters gave 2.0 g. more, and re-extraction of the residue from the first extraction with 750 cc. of boiling water gave an additional 0.8 g.; total yield, 41 g. or 91%.

All cyclizations of this type attempted in open or partially covered copper beakers gave poor to negative results, probably due to condensation of moisture from the air on the cold walls of the beaker.

As indicated in Table I, the isonitrosoindanones were prepared by three methods: using methyl nitrite and anhydrous ethereal hydrogen chloride, butyl nitrite and concentrated hydrochloric acid in methanol, or butyl nitrite and dry hydrogen chloride gas in ether. In general they had to be recrystallized at least twice to attain sufficient purity to undergo subsequent hydrogenation. Conversion (two atmospheres pressure of hydrogen and active palladium Norite) to the aminoketone hydrochlorides was carried out in absolute alcoholic hydrogen chloride, and these were then hydrogenated to the amino-alcohol hydrochlorides in distilled water (Table II); yields were practically quantitative. Occasionally an elevated temperature and two or three additions of catalyst were necessary to effect complete reduction. The aminoindanone hydrochlorides are considerably less soluble in alcohol than the aminoindanol hydrochlorides. With both classes of compounds water was occasionally added in small amounts to dissolve the product away from the catalyst, and during recrystallization to keep the volume down. Raney nickel and also PtO_2 (elevated temperature) were used in the reduction of one of the aminoketone hydrochlorides and were found to be satisfactory catalysts. The hydroxymethoxyamine hydrochlorides seemed to be somewhat more unstable than the corresponding dimethoxy compounds.

Oxazolidines and Benzylaminoindanols (Table III)

Preparation of the monosubstituted oxazolidines may be illustrated by the formation of III from 5-methoxy-aminoindanol hydrochloride.

Two and sixteen-hundredths grams (0.01 mole) of the amino alcohol hydrochloride was heated under reflux for six hours in 50 cc. of 95% alcohol with 1.20 cc. (0.012 mole) of benzaldehyde and 0.84 g. (0.01 mole) of sodium bicarbonate. The solution was filtered from the sodium chloride, concentrated to about one-third, excess water added and the oily suspension chilled, giving 2.52 g. (94%) of buff-colored solid. After recrystallization (Norite) from about 15 cc. of 3A alcohol a product was obtained which proved to be the free base of the starting material.

The filtrate from the alcohol recrystallization of the free base was treated with water and chilled, giving about one gram of white solid, m. p. 85°. Without purification it was converted into the oxazolidine hydrochloride which, after recrystallization from alcohol–ether, melted at 154.5° (dec.).

Anal. Calcd. for $C_{11}H_{13}O_2NCl$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.16; H, 5.69; N, 4.60.

Similarly in the disubstituted series attempts to prepare the Schiff bases by treating the amino alcohol hydrochlorides with an equivalent amount of benzaldehyde and sodium bicarbonate in 3A alcohol resulted in the formation of oxazolidines in all cases; here, however, conditions were such that two racemic mixtures of the latter could often be isolated. For example, with 5,6-dimethoxy-indanol hydrochloride two racemic mixtures of the oxazolidine were formed by this procedure, and also when a dry fusion of the amine hydrochloride, benzaldehyde and sodium acetate was made *in vacuo* at 100 to 150°; a dry fusion at room temperature for several days gave smaller yields of the desired products as well as some starting material as the free base and some which analyzed as the acetate of the starting base. The formation of isomeric mixtures made estimation of yields as well as melting points difficult.

In the case of 5,6-dimethoxyaminoindanol hydrochloride the solid product, obtained by precipitation from the reaction mixture with water, was recrystallized from acetone–ether; fractionation resulted in separation of the isomers. In the remainder of the disubstituted series the oxazolidines were ether-soluble; the precipitate was either recrystallized from dilute alcohol to separate the isomers or converted to the hydrochloride prior to fractionation from alcohol–ether.

TABLE I

INDANONES AND ISONITROSOINDANONES

Indanone	Condensing agent	Yield, %	Yield of isonitroso-indanone, %
4-OCH_3	HF, P_2O_5, $AlCl_3$	0, 0, 0	
5-OH	HF[a]	89.5	78[b]
5-OCH_3	[c]	89	96[d]
6-OCH_3	$AlCl_3$	80[e]	77[d]
7-OH	HF[a]	7	
7-OCH_3	[f]	85	88[g]
4,5-di-OCH_3	HF[h]	80–85	90[i]
4,6-di-OCH_3	HF[j]	0	
5-OCH_3-6-OH	P_2O_5, HF[k]	0, 80–91	81[l]
5,6-di-OCH_3	[m]	92	95[n]
5,6-O_2CH_2	HF, P_2O_5	0, 72[p]	77[q]

[a] For prep., see ref. 16. [b] M. p., 212–214° (dec.). [c] From the -OH compound. [d] See ref. (25). [e] From a 3 g. batch; yield for larger batches much less; using HF yield was 1%, recovery of starting material, 88%, see ref. 10. [f] From the -OH compd., m. p., 99.5–100°; *anal*: calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.21; found: C, 74.09; H, 6.27. [g] M. p. about 250° (dec.); *anal.* calcd. for $C_{10}H_9O_3N$: C, 62.82; H, 4.74; N, 7.33; found: C, 62.82; H, 4.74; N, 7.32. [h] Previously prepared using P_2O_5, no yield given, see ref. (26); and $AlCl_3$ (yield good), see ref. (27). [i] See ref. 28. [j] This indanone unknown. [k] Previously prepared using H_2SO_4 (yield about 30%), ref. 29. [l] Prepared with butyl nitrite in absolute CH_3OH; recrystallized from 50% alcohol; m. p. 240° (dec.); N: calcd., 6.76; found, 6.89. [m] Prepared from 5-methoxy-6-hydroxyindanone; m. p. 118.5°. [n] Using method of ref. 1; 61% by method of ref. 30; 92% using methyl nitrite, see ref. 31. [p] Based on acid added; 22% of starting material recovered; previously prepared using $AlCl_3$ (yield 15%), ref. 32; P_2O_5 (87%), ref. 32; and since this work was completed, using $SnCl_4$ by the Friedel–Craft reaction (92%), ref. 22. [q] For preparation, see ref. 30.

(25) Chakravarti and Swaminathan, *J. Ind. Chem. Soc.*, **11**, 101 (1934).
(26) Perkin and Robinson, *J. Chem. Soc.*, 2388 (1914).
(27) Ruhemann, *Ber.*, **53**, 280 (1920).
(28) Perkin and Robinson, *J. Chem. Soc.*, 2389 (1914).
(29) Konek and Szamak, *Ber.*, **55**, 106 (1922).
(30) Perkin and Robinson, *J. Chem. Soc.*, 1073 (1907).
(31) "Org. Synth.," Coll. Vol. II, 1944, p. 363.
(32) Perkin and Robinson, *J. Chem. Soc.*, 1084 (1907).

TABLE II

AMINOINDANONES AND AMINOINDANOLS

Ring substituent	Aminoindanone hydrochlorides: M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Aminoindanol hydrochlorides: M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-OH	[a]	54.17	54.18	5.05	5.10	7.02	7.12	[b]	53.60	53.64	5.96	5.95	6.95	7.13
5-OCH_3	225–227 (dec.)	56.21	56.22	5.66	5.56	6.56	6.44	[c]	55.68	55.78	6.54	6.62	6.50	6.54
6-OCH_3	[d]	56.21	56.32	5.66	5.68	6.56	6.65	[e]	55.68	55.65	6.54	6.53	6.50	6.56
7-OCH_3	[f]	56.21	56.39	5.66	5.62	6.56	6.47	170 (dec.)	55.68	55.69	6.54	6.68	6.50	6.44
4,5-di-OCH_3	185 (dec.)	54.21	54.16	5.79	6.02	5.75	5.48	183 (dec.)	53.77	53.94	6.56	6.64	5.70	6.02
5-OCH_3-6-OH	[g]	48.49	48.49[h]	5.70	5.73[h]	5.66	5.73[h]	[i]	51.83	51.72	6.09	6.20	6.05	6.19[j]
5,6-di-OCH_3	245 (dec.)	54.21	54.11	5.79	5.82	5.75	5.82[k]	[l]	53.77	53.94	6.56	6.59	5.70	5.69[m]
5,6-O_2CH_2	[n]	52.80	53.05	4.41	4.47	6.16	5.98	[p]	52.30	52.60	5.25	5.22	6.10	6.08

[a] Discolors about 227°; melts (dec.) only if immersed at 275°, otherwise gradual softening and decomposition. [b] Darkens at about 120°; no real melting even when immersed at 135°. [c] Softens rapidly (dec.) when immersed at 165°, but only slowly at 160°. [d] Decomposes from 210 to 232° depending on rate of heating and temperature of immersion. [e] M. p. (dec.) from 217 to 222° depending on rate of heating, etc. [f] Decomposes about 250° when immersed at about 245°. [g] Melts (dec.) when immersed at 300° or above. [h] Analysis calcd. for monohydrate. [i] Melts (dec.) when immersed at 258° or above. [j] Cl: calcd., 15.31; found, 15.42. [k] Cl: calcd., 14.56; found, 14.54. [l] Darkens about 200°. [m] Cl: calcd., 14.43; found, 14.50; free base, from benzene–petroleum ether, m. p. 113–116°; *anal.*: calcd. for $C_{11}H_{15}O_3N$: C, 63.16; H, 7.23; N, 6.70; found: C, 63.51; H, 7.21; N, 6.74. [n] Darkens about 230°; m. p. 243° (dec.). [p] Melts (dec.) when immersed at 240° or above.

TABLE III

OXAZOLIDINES AND BENZYLAMINOINDANOL HYDROCHLORIDES

Ring substituents	Oxazolidines (A) Isomers	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Benzylamines (B) Isomers	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-OCH_3	A-HCl	154.5 (dec.)	67.21	67.16	5.97	5.69	4.61	4.60	B-HCl	189.5	66.77	66.56	6.59	6.60	4.58	4.62
6-OCH_3	A-HCl	137[a]	67.21	[b]	5.97	[b]	4.61	[b]	B-HCl	211–213	66.77	66.56	6.59	6.79	4.58	4.60
7-OCH_3	A-HCl	187.5[c]	67.21	67.01	5.97	5.97	4.61	4.64	B-HCl	181	66.77	66.75	6.59	6.75	4.58	4.52
4,5-di-OCH_3	A	90.5–93	72.71	72.79	6.44	6.19	4.71	4.89								
	A-HCl	148–150 (dec.)	64.75	65.10	6.00	6.43	4.19	4.33	B-HCl	168.5–169[d]	64.37	64.26	6.60	6.72	4.17	4.44
5,6-di-OCH_3	A_1	165.5–166.5	72.71	72.95	6.44	6.65	4.71	4.99	B_1	143–144	72.20	72.23	7.07	7.02	4.68	4.52
	A_1-HCl	192 (dec.)[e]	64.75	65.04	6.00	5.99	4.19	4.35	B_1-HCl	200 (dec.)	64.37	64.39	6.60	6.71	4.17	4.37
	A_2	123–124	72.71	72.54	6.44	6.44	4.71	4.70	B_2	156–156.5[f]	72.20	72.24	7.07	7.11	4.68	[f]
									B_2-HCl	184 (dec.)	64.37	63.90	6.60	6.69	4.17	4.44
5,6-O_2CH_2	A_1	184.5–185.5[g]	72.58	72.80	5.38	5.58	4.98	4.92	B_1	169.5–173	72.07	72.40	6.04	6.07	4.95	4.72
	A_2	95–96	72.58	72.83	5.38	5.67			B_2	148–149.5[h]	72.07	72.03	6.04	6.40		

[a] Approximate; free base melts about 80–82°. [b] Compound hydrolyses progressively on recrystallization, even from absolute alcohol–ether, giving a progressively higher decomposition point; *anal.* after 2 recrystallizations: C, 63.15; H, 6.33; N, 5.12. [c] Free base, m. p. 150.5–152°. [d] Obtained also a second crop, m. p. 180° (dec.) (isomeric?). [e] Without recrystallization; recrystallization, even from absolute alcohol, causes conversion into a product, darkening, but not melting, below 200°, and giving a m. p. depression with the unrecrystallized material; may result from hydrolysis to the original aminoalcohol–HCl. [f] Mixed m. p. with B_1, 130°; compound too highly charged to permit good combustions, or any nitrogen analysis. [g] Hydrochloride darkens about 191°. [h] Mixed m. p. with B_1, 136°.

During the work-up of several of the oxazolidines there were indications that these compounds were gradually hydrolyzing to yield benzaldehyde and the amino alcohol. This was most apparent in the case of the 6-methoxy compound. Here the odor of benzaldehyde persisted throughout the fractionation from dilute alcohol, even though the alcohol solutions were diluted with water at room temperature. During the purification of the oxazolidine hydrochloride considerable amounts of the starting amino alcohol hydrochloride (identified by analysis and mixed melting point) were isolated. The oxazolidine hydrochloride (m. p. about 137° (dec.)) analyzed poorly, and further recrystallization from absolute alcohol–ether caused the melting point to broaden and rise toward that of the amino alcohol; the filtrate from this yielded considerable benzaldehyde, identified as the dinitrophenylhydrazone. Conversion of the oxazolidine to the benzylamino alcohol was considered as sufficient evidence of structure.

Hydrogenation of the bases (platinum oxide or active palladium charcoal) gave the desired benzylamines which were converted into the hydrochlorides. In some cases, however, it was found advantageous to hydrogenate the oxazolidine hydrochlorides to the benzylamine hydrochlorides, using active palladium charcoal; reaction was usually complete in about three quarters of an hour.

Reductive Alkylations

6-Methoxy-2-isopropylaminoindanol-1 Hydrochloride.—Four and thirty-one hundredths grams (0.02 mole) of 6-methoxy-2-aminoindanol-1 hydrochloride, 1.6 cc. (0.022 mole) of acetone and 2.12 g. (0.02 mole) of sodium carbonate were shaken in a Parr hydrogenation apparatus in the presence of 0.5 g. of pre-reduced Adams platinum catalyst in absolute ethanol under a hydrogen pressure of two atmospheres. Hydrogenation was complete in an hour and the filtrate from the catalyst was poured into cold ethereal hydrogen chloride and chilled. After recrystallization from absolute alcohol the white crystals melted at 214° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.57; H, 7.82; N, 5.44. Found: C, 60.54; H, 7.66; N, 5.29.

6-Methoxy-2-dimethylaminoindanol-1 Hydrochloride.—This compound was prepared similarly to that above except that slightly more than two molecular equivalents of formaldehyde (as a 37% solution) were used. The filtrate from the catalyst was concentrated to about a third before conversion to the hydrochloride. After recrystallization the product melted at 215–215.5° (dec.).

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: C, 59.13; H, 7.44; N, 5.75. Found: C, 59.07; H, 7.23; N, 5.84.

5,6-Dimethoxy-2-benzylaminoindanol-1 Hydrochloride.—Four and ninety-one hundredths grams (0.02 mole) of the primary aminoalcohol hydrochloride, 2.12 g. (0.02 mole) of freshly distilled benzaldehyde and 2.12 g. (0.02 mole) of sodium carbonate were added to a suspension of freshly reduced Adams platinum catalyst in absolute ethanol and the mixture subjected to hydrogenation at three atmospheres pressure. The calculated uptake of hydrogen occurred in thirty minutes after which the suspension was warmed, filtered from the catalyst and the filtrate poured into chilled ethereal hydrogen chloride. After chilling, the white precipitate was collected and recrystallized several times from absolute alcohol. The pure white, crystalline product melted at 181.5° (dec.).

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.36; H, 6.58; N, 4.41.

In some cases starting material was isolated by the addition of ether to the alcohol filtrate from the main product.

5,6-Dimethoxy-2-isopropylaminoindanol-1 Hydrochloride.—By a procedure similar to that described above but using acetone, there was obtained a product which, after several recrystallizations from absolute alcohol, amounted to 2.3 g. and melted at 190° (dec.).

Anal. Calcd. for $C_{14}H_{22}O_3NCl$: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.54; H, 7.66; N, 5.05.

5,6-Dimethoxy-2-dimethylaminoindanol-1 Hydrochloride.—By a procedure analogous to that described above but using one mole of formaldehyde there was obtained no monomethylamine, but only the dimethylaminoindanol hydrochloride, melting at 172° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.03; H, 7.36; N, 5.12. Found: C, 56.87; H, 7.46; N, 5.58.

Summary

A series of thirty-six aminoindanones, aminoindanols and N-substituted aminoindanols containing one or more hydroxyl, methoxyl or methylenedioxy groups in the aromatic ring, have been synthesized. The nitrogen substituents were hydrogen, dimethyl, isopropyl and benzyl; the benzylaminoindanols were prepared through the intermediate oxazolidines and were in some cases isolated in two racemic forms.

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The Structures of Some Isopropylidene-*aldehydo*-L-arabinose Derivatives

BY JAMES ENGLISH, JR., AND PAUL H. GRISWOLD, JR.[1]

In a previous paper[2] the positions of the isopropylidene groups in di-isopropylidene-*aldehydo*-L-arabinose and the products of its reaction with Grignard reagents were left indeterminate. An extension of our work on C-substituted pentitols has disclosed evidence leading to the establishment of the structures of these arabinose derivatives in both the D- and L- series.

The triacetone mannitol of Fischer[3] has been shown by Wiggins[4] to be 1,2:3,4:5,6-triacetone mannitol. A graded hydrolysis of this substance[4,5] has been found to yield a diacetone mannitol which Wiggins has converted to an *aldehydo*-diacetone-D-arabinose by lead tetraacetate oxidation. In view of the earlier work of Brigl and Grüner[6] and of Baer and H. O. L. Fischer[7] the structure of this arabinose derivative may be considered established beyond reasonable doubt as 2,3:4,5-diacetone-*aldehydo*-D-arabinose.

2,3:4,5-Di-isopropylidene-*aldehydo*-D-arabinose prepared by the method of Wiggins, or better by periodate oxidation of the same starting material, was treated with cyclohexylmagnesium chloride to form a crystalline di-isopropylidene-1-C-cyclohexylpentitol. This substance was found to be the enantiomorph of the di-isopropylidene-1-C-cyclohexylpentitol previously prepared in this Laboratory[2] from di-isopropylidene-*aldehydo*-L-arabinose. On recrystallizing an equimolar mixture of the two enantiomorphs there resulted a di-isopropylidene-D,L-1-C-cyclohexylpentitol which gave a depression in mixed melting points with both isomers.

In the preparation of di-isopropylidene-L-arabinose diethyl mercaptal the intermediate monoisopropylidene derivative was obtained in a manner analogous to that reported by Gätzi and Reichstein[8] for the D-isomer. Since this substance can be converted into the di-isopropylidene derivative[8] by excess acetone it is evident that the isopropylidene group in this case must be on either the 2,3 or the 4,5 carbon atoms. A lead tetraacetate oxidation of monoisopropylidene-L-arabinose diethyl mercaptal followed by removal of the mercaptal and isopropylidene groups, led to a mixture from which glyoxal was identified as its nitrophenylhydrazone and dinitrophenylhydrazone. This established the structure of this substance as 4,5-isopropylidene-L-arabinose diethyl mercaptal, since no other monoisopropylidene derivative would be expected to yield glyoxal.

Hence it may be concluded that the positions of the isopropylidene groups in this series are as shown in the reaction scheme below.

It is worthy of note that in both the D- and L-series the ratio of the two stereoisomeric pentitols obtained in the reaction of *aldehydo*-di-isopropylidene arabinose with cyclohexylmagnesium chloride is far from unity. In one case as much as

(1) Taken from the thesis presented by Paul H. Griswold, Jr., to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) J. English, Jr., and P. H. Griswold, Jr., THIS JOURNAL, **67**, 2039 (1945).

(3) E. Fischer, *Ber.*, **28**, 1167 (1895).

(4) Wiggins, *J. Chem. Soc.*, 13 (1946).

(5) Irvine and Patterson, *ibid.*, 898 (1914).

(6) Brigl and Grüner, *Ber.*, **66**, 931 (1933).

(7) H. O. L. Fischer and Baer, *Helv. Chim. Acta*, **17**, 622 (1943).

(8) Gätzi and Reichstein, *ibid.*, **21**, 914 (1938).