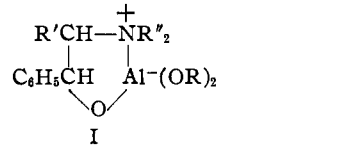
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Further Studies on the Stability of β-Hydroxyethylamines toward the Oppenauer Oxidation. *cis*- and *trans*-1-Amino-2-indanols[1]

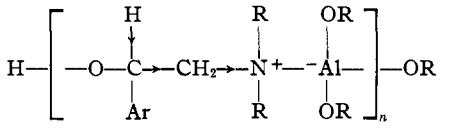
BY ROBERT E. LUTZ AND ROSSER L. WAYLAND, JR.

cis-1-Amino-2-indanol has been made from the *trans*-compound through the N-(*p*-nitrobenzoyl) derivative and the oxazoline; and both were converted into the corresponding benzylamino indanols by lithium aluminum hydride reduction of the N-benzoyl derivatives. These compounds, and also *trans*-1-piperidyl-2-indanol and *dl-trans-trans*-1-amino-bis-2-indanol, failed to undergo the Oppenauer oxidation using benzophenone and aluminum *t*-butoxide. *trans*-1-Piperidyl-2-indanol, however, was oxidized using potassium *t*-butoxide and was regenerated by aluminum isopropoxide reduction. The stabilization of β-amino alcohols under the standard Oppenauer oxidation conditions seems best interpreted in terms of electron displacements resulting from complex formation involving coördination between nitrogen and aluminum.

It has been suggested that the interference by a β-amino group with the Oppenauer oxidation of a secondary alcohol when aluminum *t*-butoxide and a ketone such as benzophenone or cyclohexanone are used, is due to the formation of a cyclic complex[2] (I).



I



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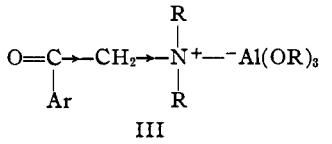
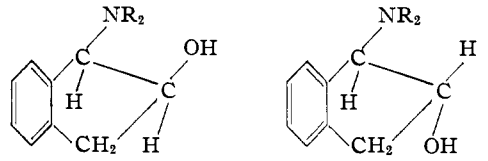


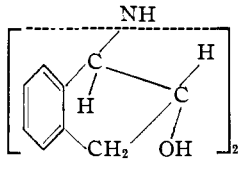
III

An alternative explanation is in terms of electron displacements in the simple (or polymeric) linear complexes [II (n = 1 or more), III][2,3]; the increased stability of the alcohol may be expressed, for example, in terms of increased hydride-hydrogen activity in the amino alcohol and acceptor activity toward hydride-hydrogen in the amino ketone. On this hypothesis such effects would fall off when the amino nitrogen is on the third carbon, and should for all practical purposes disappear when the amine group is further removed from the hydroxyl or carbonyl.

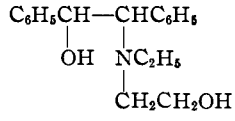
The β-amino alcohol, quinine, shows resistance to the Oppenauer oxidation.[4] Here the quinuclidine system might offer appreciable steric interference with the formation of a cyclic complex such as I. It seemed worth while to seek some *cis* and *trans* amino cyclanols where a chelated complex (I) could exist comfortably only in the *cis* arrangement and not in the *trans*, and where if the ring complex were the vital factor involved, the Oppenauer oxidation with aluminum *t*-butoxide and a ketone would be successful only in the case of the *trans* compounds. The *cis*- and *trans*-1-amino- and 1-benzylamino-2-indanols, IV and V, a and b, the *trans* piperidyl compound (Vc), and also the *dl*[5]*-trans-trans*-1-amino-bis-2-indanol (VI), were prepared for study in this connection. None of these compounds underwent the usual Oppenauer oxidation using aluminum *t*-butoxide and benzophenone. Stable ring complexes of the type I in the case of the *trans* aminoindanols, although conceivable, are open to question. In the case of the amino-bis-indanol (VI) a complex involving the nitrogen and both hydroxyls simultaneously, which would be required by the hypothesis that the oxidation of the carbinol system is prevented only in a cyclic complex, is still less likely. Incidentally attempts were made similarly to oxidize the diastereoisomeric pair, *erythro*- and *threo*-2-(ethylhydroxyethylamino)-1,2-diphenylethanols (VII)[6] in the hope that the carbinol least protected in the postulated complex might be oxidized; these compounds were recovered unchanged and no evidence of isomerization was noted.



IV (a) $NR_2 = NH_2$ V
(b) $NR_2 = NHCH_2C_6H_5$
(c) NR_2 = piperidyl



VI



VII

From the results of the above experiments it would seem that the evidence points away from the idea that cyclic complexes are necessary in the stabilization of the β-amino alcohols under the usual Oppenauer oxidation conditions, and toward an explanation in terms of simple electron displacements in complexes involving coördination between the nitrogen and aluminum, whether the complexes be linear, polymeric or cyclic.

(1) The work of this paper was supported in large part by a grant-in-aid from the National Institutes of Health, and is in coöperation with the National Cancer Institute. Many of the compounds were prepared for testing for possible tumor-necrotizing activity.

(2) Lutz, Jordan and Truett, THIS JOURNAL, **72**, 4085 (1950).

(3) *Cf.* Adkins, Elofson, Rossow and Robinson, *ibid.*, **71**, 3622 (1949).

(4) Woodward, Wendler and Brutschy, *ibid.*, **67**, 1425 (1945).

(5) The designation "*dl*" is given here to distinguish this compound from the *meso-trans-trans* isomer, but elsewhere, for those compounds involving two dissimilar asymmetric carbons, it has been omitted.

(6) The experiments on these compounds and the preparation of the *threo* isomer which is new, were carried out in this Laboratory by Preston H. Leake.

The Preparation of the *cis* and *trans* Amino-indanols.[7]—Attempts to make *cis*-1-piperidyl-2-indanol were unsuccessful. *trans*-1-Piperidyl-2-indanol (Vc) (known[7d]) was readily obtained by the action of piperidine on 2-bromoindanol-1. It was oxidized by potassium *t*-butoxide and benzophenone to the corresponding 1-piperidyl-2-indanone which on reduction by aluminum isopropoxide regenerated the *trans* amino alcohol (Vc).

The known *trans*-1-amino-2-indanol (Va)[7b,c] was converted into the *cis* compound by the method of McCasland and Smith[8] by conversion into the N-(*p*-nitrobenzoyl) derivative and the oxazoline, and hydrolysis. The *cis* configuration is assumed from this mode of synthesis[8] and from the fact that a new isomer is actually obtained.

The *cis*- and *trans*-1-benzylamino-2-indanols (IVb and Vb) were made through the N-benzoyl derivatives of the *cis* and *trans*-1-amino-2-indanols (IVa and Va) by lithium aluminum hydride reduction.[9] The *trans* compound (Vb) obtained in this way was shown to be identical with a sample prepared[6] by the action of benzylamine on 2-bromoindanol-1, and this relationship served as a check on the configurations assigned.

It should be noted that the configurations assigned ultimately depend on: (a) the validity of the assumption of *trans* aminolysis of the oxide ring[10] in the syntheses directly from an oxide which in the five-membered cyclics is necessarily *cis*, or indirectly through an oxide starting from a halohydrin such as 2-bromoindanol-1[7]; and (b) analogy between the conversion of the supposedly *trans*-aminoindanol and other[8] *trans* cyclic amino alcohols through oxazolines to the *cis* isomers, and the known conversion of a monoacetate of a *trans* cyclic glycol through a detosylation step to the *cis* isomer.[11]

Experimental[12]

***trans*-1-Aminoindanol-2 (Va)** was prepared[7] in 68% yield from 2-bromoindanol-1[13] using, however, a larger excess of ammonia. The amino-bis-indanol[7c] (VI) was best obtained using only a small amount of ammonia.

***trans*-1-(*p*-Nitrobenzoylamino)-indanol-2.**[8]—A solution of 9.3 g. (0.05 mole) of *p*-nitrobenzoyl chloride in 75 ml. of warm benzene was added to 7.5 g. (0.05 mole) of 1-amino-indanol-2 (Va) in 150 ml. of water, and 40 ml. of 5% sodium hydroxide was then added slowly and the mixture stirred until a heavy precipitate formed in the benzene layer. The precipitate was filtered (15.5 g.) and recrystallized from ethanol, m.p. 232–233°, yield practically quantitative.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$, C, 64.42; H, 4.73. Found: C, 64.67; H, 4.79.

2-*p*-Nitrophenyl-4,5-*cis*-indanoöxazoline-2 was prepared according to the directions followed by McCasland and Smith[8] in the corresponding cyclopentane system. A mixture of 25 ml. of thionyl chloride and 3.0 g. (0.01 mole) of *trans*-1-(*p*-nitrobenzoylamino)-indanol-2 was allowed to stand overnight. Ether was added to precipitate the oxazoline hydrochloride and the mixture was filtered. The hydrochloride, which melted at 223–225° after two recrystallizations from ethanol (yield 2.8 g., 88%), was converted to the free base and crystallized from ethanol, m.p. 208–210°.

Anal. (free base). Calcd. for $C_{16}H_{12}N_2O_3$: N, 10.00. Found: N, 9.74. *Anal.* (hydrochloride). Calcd. for $C_{16}H_{12}N_2O_3$.HCl: N, 8.64. Found: N, 8.53.

***cis*-1-Aminoindanol-2 (IVa).**—A solution of 4.8 g. of 2-*p*-nitrophenyl-4,5-*cis*-indanoöxazoline-2 in 150 ml. of water and 30 ml. of concd. sulfuric acid was refluxed for 3 hours. It was filtered to remove the *p*-nitrobenzoic acid formed, made basic with concd. sodium hydroxide, chilled in an ice-bath, and filtered. The product (1.7 g., 76%) was recrystallized from ethanol, benzene and ethyl acetate, m.p. 133° (a mixture melting point with (Va) showed a 20° depression).

Anal. Calcd. for $C_9H_9H_{11}NO$: C, 72.45; H, 7.43. Found: C, 72.18; H, 7.52.

***cis*-1-(Benzoylamino)-indanol-2.**—A solution of 4.2 g. (0.03 mole) of benzoyl chloride in 30 ml. of benzene was added to a mixture of 4.5 g. of IVa (0.03 mole) and 100 ml. of water. A solution of sodium hydroxide was then added and the mixture stirred until a precipitate formed in the benzene layer. The precipitate was filtered and recrystallized from ethanol and an ethyl acetate–ligroin mixture; yield 4.6 g. (61%), m.p. 155–156°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.30.

***cis*-1-Benzylaminoindanol-2 (IVb).**—Five grams (0.02 mole) of *cis*-1-benzoylaminoindanol-2 was placed in a thimble in a Soxhlet extractor and extracted by ether into an ether solution of 0.8 g. of lithium aluminum hydride. After all of the amide had been carried down, water and then 10% sodium hydroxide were added to the reaction mixture, and the ether layer was separated, washed, dried over sodium sulfate, and evaporated. The white crystalline residue melted at 92–93° after several recrystallizations from ethanol and isoöctane; yield 3 g. (68%).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.27; H, 6.99.

Hydrochloride: crystallized from absolute ethanol and ether; m.p. 236–237°.

Anal. Calcd. for $C_{16}H_{17}NO{\cdot}HCl$: N, 5.08. Found: N, 5.22.

***trans*-1-Benzylaminoindanol-2 (Vb)**, prepared according to standard method,[7] melted at 118–120° (L. G. and K.[7d] reported 101–103°). It was obtained also from Va by the directions given above for the *cis* isomer (IVb). A mixture melting point of the two samples showed no depression.

Anal. Calcd. for (base) $C_{16}H_{17}NO$: N, 5.85. Found: N, 5.85.

Anal. (hydrochloride m.p. 215–216°) Calcd. for $C_{16}H_{17}NO{\cdot}HCl$: N, 5.08. Found: N, 5.26.

***trans*-1-Piperidylindanol-2 (Vc)** was prepared according to standard directions[7d]; m.p. 168–170°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.36; H, 8.76.

The conditions of the attempted Oppenauer oxidations involved one molar equivalent of the amino-alcohol, four of aluminum *t*-butoxide and ten of benzophenone in toluene solution under reflux for 24 hours. The reaction mixtures were extracted with 10% sodium hydroxide and then with 10% hydrochloric acid. The acid extracts were made basic with 10% sodium hydroxide and extracted with ether. The ether extracts were dried over sodium sulfate overnight and evaporated. The residues were recrystallized from a suitable solvent. The free bases were used in the following cases, IVa, IVb, Va, Vb, Vc, VI and VIII (*erythro*); VIII (*threo*) was used as the hydrochloride. These amino alcohols were recovered in good yields and identified by mixture melting points with authentic starting material.

One compound, 1-phenyl-4-piperidylbutanol-1, used as the base in a parallel control Oppenauer oxidation, gave the corresponding amino ketone.[2]

1-Piperidylindanone-2.—A mixture of 5 g. of potassium *t*-butoxide, 9.1 g. of benzophenone, 2.17 g. of *trans*-1-piperidylindanol-2 and 100 ml. of toluene was refluxed

(7) (a) Pope and Reid, *J. Chem. Soc.*, **99**, 2071 (1911); (b) **101**, 758 (1912); (c) Braun and Weissbach, *Ber.*, **63**, 3052 (1930); (d) Levin, Graham and Koloff, *J. Org. Chem.*, **9**, 380 (1944).

(8) McCasland and Smith, THIS JOURNAL, **72**, 2190 (1950).

(9) For the successful prior use of this method of alkylating amino alcohols, *cf.* dissertation by William L. Truett, University of Virginia, August, 1950.

(10) *Cf.* discussion, Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2019 (1948).

(11) (a) *Cf.* Weinstein and Boschan, *ibid.*, **72**, 4669 (1950); (b) McCasland, Clark and Carter, *ibid.*, **71**, 637 (1949).

(12) All melting points are "corrected." Microanalyses were by Mrs. R. L. McConnell, Mrs. J. M. Wilgus and the Clark Microanalytical Labs.

(13) Suter and Milne, THIS JOURNAL, **63**, 3473 (1940).

under an atmosphere of nitrogen for 20 hours. It was extracted with water and then with dilute sulfuric acid. The acid extract was made basic with dilute potassium hydroxide and extracted with ether. This ether extract was dried over sodium sulfate and the product was precipitated by ethereal hydrogen chloride; 1.5 g. (60%). The hydrochloride (m.p. 219–220°) was converted to the free base which melted at 87–88°.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 5.59. Found: N, 5.74.

Aluminum isopropoxide reduction of a solution of 2.5 g. of the hydrochloride (0.01 mole) and 5.0 g. (0.025 mole) of the reagent was carried out in isopropyl alcohol under reflux for 1.5 hr. The excess solvent was distilled under reduced pressure, dilute sodium hydroxide was added and the solution was extracted with ether. The ether was extracted with dilute hydrochloric acid and the free amino alcohol was liberated by the addition of dilute sodium hydroxide; m.p. 164–166° (a mixture melting point with authentic Vc gave no depression); yield 1.0 g. (46%).

erythro-2-[**N-Ethyl-N-(β-hydroxyethyl)-amino**]-1,2-**diphenylethanol** (**VII**) (known[14]), m.p. 82–84° (base, recrystallized from dil. ethanol), on recovery from the attempted Oppenauer oxidation gave a sample of hydrochloride of m.p. 182–183°. This product gave no mixture melting point depression when admixed with starting material of m.p. 176–178°. The base when isolated crystallized in a polymorphic form of m.p. 91–92°. The original base, of m.p. 82–84° on fusion and resolidification, subsequently melted at 91–92°; no melting point depression was observed upon admixture with the recovered sample of this melting point.

Anal. (base, m.p. 91–92°). Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12. Found: C, 76.09; H, 8.34. *Anal.* (hydrochloride, m.p. 181–182°). Calcd. for $C_{18}H_{23}NO_2 \cdot HCl$: C, 67.59; H, 7.47. Found: C, 66.96; H, 7.34.

threo-2-[**N-Ethyl-N-(β-hydroxyethyl)-amino**]-1,2-**diphenylethanol** (**VII**) was prepared by heating under reflux a mixture of 5 g. of *cis*-stilbene oxide, 0.6 g. of ethylethanolamine and 2.9 g. of its hydrochloride for 2 hours. After treatment with water, extraction of the base with ether and crystallization from dilute ethanol, 4.1 g. (69%) was obtained, m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12. Found: C, 75.60; H, 8.45.

(14) Lutz, Freek and Murphey, *ibid.*, **70**, 2015 (1948).

CHARLOTTESVILLE, VA. RECEIVED SEPTEMBER 25, 1950

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Cyanoethylation of α-Amino Acids. II. Dicyanoethyl and Tricyanoethyl Derivatives[2]

BY L. L. MCKINNEY, E. H. UHING, E. A. SETZKORN AND J. C. COWAN

A series of N-dicyanoethyl derivatives of α-amino acids has been prepared by treating aqueous solutions of the alkali metal salts with acrylonitrile. N-Dicyanoethyl derivatives of the following amino acids are reported: glycine, DL-alanine, DL-valine, L-leucine, DL-methionine, L-tyrosine, DL-aspartic acid and L-glutamic acid. The difficulty with which the second cyanoethyl group added increased in the order: glycine, alanine, aspartic acid, glutamic acid, leucine, methionine, valine, tyrosine. Tyrosine reacted very slowly in aqueous alkaline solution to form the O-cyanoethyl derivative. The dicyanoethyl derivatives exhibited true melting points and were soluble in organic solvents. The second cyanoethyl group was labile to heat, alkali and acid.

A previous communication[3] described the preparation of monocyanoethyl derivatives of α-amino acids. The present paper describes the preparation of dicyanoethyl derivatives of the type

$$\begin{array}{l} N(CH_2—CH_2—CN)_2 \\ | \\ R—CH—COOH \end{array}$$

Tricyanoethyl derivatives of histidine and tyrosine are also described.

and aspartic acid were readily prepared by heating aqueous solutions of the alkaline salts of the amino acids with 2 equivalents of acrylonitrile. Preparation of the corresponding derivatives of valine, leucine, methionine, tyrosine and glutamic acid required prolonged refluxing.

All the N-dicyanoethyl derivatives were soluble in organic solvents and exhibited true melting points (see Table I) in contrast to the monocyano-

TABLE I

N-DICYANOETHYL DERIVATIVES OF α-AMINO ACIDS

Amino acid	M.p., °C.	Solubility,[b] g./100 ml. solvent: Water	Ether	Acetone	Molecular formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Glycine	77.8–78.8	52	0.7	34	$C_8H_{11}O_2N_3$	53.0	52.8	6.11	5.96	23.2	23.2
DL-Alanine	75.5–76.8	13	1.3	61	$C_9H_{13}O_2N_3$	55.4	55.5	6.71	6.50	21.5	21.4
DL-Valine	54–55	2.3[c]	>100	>100	$C_{11}H_{17}O_2N_3$	59.2	59.8	7.67	7.75	18.8	18.8
L-Leucine	64–65	1.7[d]	29	>100	$C_{12}H_{19}O_2N_3$	60.7	60.1	8.07	8.02	17.7	17.7
DL-Methionine	65–66	1.2[e]	4.3	>140	$C_{11}H_{17}O_2N_3S$	51.7	51.8	6.71	6.66	16.5	16.5
L-Tyrosine	123–124	0.6[f]	0.7	43	$C_{15}H_{17}O_3N_3$	62.7	62.5	5.96	5.83	14.6	14.5
DL-Aspartic acid	136–137	0.7[g]		7.5[h]	$C_{10}H_{13}O_4N_3$	50.1	50.0	5.48	5.11	17.5	17.5
L-Glutamic acid[a]	71.5–72.8	15	1.1	>100	$C_{11}H_{17}O_5N_3$	48.7	49.0	6.32	6.29	15.5	15.5

[a] Monohydrate. [b] Room temperature, 25–27° except as shown otherwise. [c] At 5°. [d] 2.8 g. at 80°. [e] 0.6 g. at 7°. [f] 11 g. at 100°. [g] 100 g. at 80°. [h] At 50°.

N,N-Dicyanoethyl derivatives of glycine, alanine ethyl derivatives[3] which retained the dipolar character of the amino acid.

The electrometric titration curves for DL-alanine, DL-methionine and L-glutamic acid and their mono- and di-cyanoethyl derivatives are shown in Fig. 1. Curves 1 in each case are for the unreacted amino acid and curves 2 are for the monocyanoethyl

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented before the Division of Biological Chemistry at the 117th Meeting of The American Chemical Society, Chicago, Illinois, September 3–8, 1950.

(3) McKinney, *et al.*, THIS JOURNAL, **72**, 2599 (1950).