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REACTIONS OF ALKOXIDES WITH CERTAIN HYDROGENATED ALKALOIDS OF THE MORPHINE SERIES

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Concurrently with a study of the Oppenauer oxidation of dihydrocodeine[1], we have been engaged in an investigation of the action of alkoxides upon certain derivatives of dihydromorphine. Because our results, though incomplete, are of value for preparative purposes and may also provide a means of clarifying a number of stereochemical problems in this field, we wish to report our findings to date.

The stereochemical equilibration of an optically active alcohol has been most thoroughly investigated in the case of quinine (2). That alkaloid was converted by certain metallic alkoxides, *excluding* aluminum isopropoxide, to a mixture of four isomers: quinine, *epi*-quinine, quinidine, and *epi*-quinidine. By proper choice of experimental conditions it was possible to arrange this "partial racemization" so as to obtain satisfactory yields of one of the isomers, *e.g.*, quinidine.

We have found that treatment of dihydrocodeine with aluminum isopropoxide under anhydrous, but not completely anaerobic, conditions yielded dihydroisocodeine in *ca.* 65% crude yield, not admixed, so far as we could determine, with significant quantities of starting material. When potassium isopropoxide, in smaller molar excess, was substituted for aluminum isopropoxide, the results were less clean-cut: 30% of dihydroisocodeine was obtained and an additional 64% of the starting material was present as a mixture of the two epimeric alcohols.

The separation of dihydroisocodeine from dihydrocodeine presented considerable difficulty. Several recrystallizations from ethanol were generally required before the (less soluble) dihydroisocodeine was obtained in a satisfactory state of purity. The recovery by this procedure was poor and the refinement of successive crops became successively less satisfactory. Passage of a mixture of the epimers, dissolved in ethylene dichloride, through activated alumina followed by elutions with the same solvent yielded dihydrocodeine in the early effluents and left the bulk of the dihydroisocodeine adsorbed on the alumina from which it could be recovered by dilute acid; intermediate fractions, however, were not further resolved by additional chromatography. The picrates obtained from a mixture of the epimers would, on recrystallization from alcohol, rise (or fall) in melting point until a constant value of 217–218° was reached, which is roughly intermediate between that for dihydrocodeine picrate (208–209°) and dihydroisocodeine picrate (235–237°). The approximate composition of those epimer mixtures which could not be separated by the methods so far developed was

[1] With the appearance of the paper by Rapoport, *et al.* (1) on the identical subject, we have discontinued further work on the Oppenauer method.

gauged by reference to melting point data obtained from synthetic mixtures of the two picrates (Table I) or the alkaloids (Table II).

Dihydromorphine was recovered unchanged after 24 hours' heating with aluminum isopropoxide in boiling benzene. When the excess of aluminum isopropoxide was increased and a small quantity of cyclohexanone was added to the original reaction mixture (*cf.* Doering, Cortes, and Knox, reference 2), reaction occurred and *ca.* 25% of a substance (A) was obtained whose melting point was not raised above 207° by repeated recrystallization from ethyl acetate [reported (15) for dihydromorphine, 155–157°, for dihydro-α-isomorphine (3), 224–226°]. Recrystallized A was methylated by means of phenyltrimethylammonium hydroxide; the mixture of phenolic methyl ethers obtained was separated first by recrystallization and then by chromatography into dihydrocodeine and a component whose picrate melted at 217–218° (corr.) and at 218–219° (corr.) when mixed with a sample consisting of 50% dihydrocodeine picrate and 50% dihydroisocodeine picrate. The epimerization of dihydromorphine had therefore occurred, albeit to a very small extent.

Reduction of dihydrocodeinone by aluminum isopropoxide alone or by aluminum isopropoxide and isopropyl alcohol yielded 61–93% respectively of crude dihydroisocodeine containing only minor quantities of its epimer. When potassium isopropoxide, in smaller molar excess, was substituted for aluminum isopropoxide under otherwise similar conditions, 25% of starting material was readily recovered, and 33.3% of dihydroisocodeine was isolated together with 23.8% of a mixture of alkaloids consisting of dihydrocodeinone, dihydroisocodeine, and an unidentified component.

Dihydromorphinone was very slowly reduced by aluminum isopropoxide and isopropyl alcohol. After 24 hours of slow distillation insufficient reduction product was formed to permit positive identification.

Our findings on the epimerizations here reported are not at variance with the oxidation-reduction mechanism proposed by Doering, *et al.* (2) to account for the partial racemizations of other alcohols by alkoxides.

The stereo-preference shown in the aluminum isopropoxide reduction of dihydrocodeinone[2] may lend support to the hypothesis that pseudo-ring complexes of greatly different degrees of stability are involved as intermediates in both the Meerwein-Ponndorf-Verley and Oppenauer reactions (5, 6). Our data, in conjunction with this hypothesis, would at first thought lead to the conclusion that the —OH group is *cis* to the 5-oxygen bond in dihydroisocodeine and *trans* in dihydrocodeine.

On the basis of a degradation study Rapoport, *et al.* (7) reached the opposite conclusion concerning the configuration of these epimers. Their additional finding (1) that dihydrocodeine was easily oxidized in an Oppenauer-type reaction employing potassium *tert*-butoxide as catalyst whereas dihydroisocodeine was relative inert was interpreted as offering confirmation of the view that dihydroisocodeine has the *trans* structure.

[2] It is interesting to note that Small, *et al.* (4) found that catalytic reduction of dihydrocodeinone gave dihydrocodeine exclusively.

This discrepancy in conclusions, based on the one hand on Oppenauer oxidation data and on the other on Meerwein-Ponndorf-Verley reduction data cannot at present be finally resolved but may be clarified by the following considerations:

1. Since aluminum isopropoxide (acidic) and potassium *tert*-butoxide (basic) are different catalyst types, the reduction of dihydrocodeinone by the first and the oxidation of dihydrocodeine and dihydroisocodeine by the aid of the second catalyst may not proceed by strictly comparable mechanisms. Furthermore, aluminum isopropoxide should be more likely than potassium alkoxides to participate in cyclic intermediates in which the metal has an electron-acceptor role. This suggests that in an Oppenauer oxidation involving aluminum *tert*-butoxide, dihydrocodeine and dihydroisocodeine may show reactivities different from those reported (1).

2. The ring-complex hypothesis was based on the fact that a preponderance of *cis*-alcohol was formed [and, in the cases reported (5), isolated] in the aluminum alkoxide reduction of hindered ketones. It is not a necessary condition, however, that the *cis*-alcohol represent the predominant isomer finally isolated. In spite of the constant removal of acetone from the reaction mixture, some opportunity is provided in an aluminum isopropoxide reduction for the re-oxidation of the epimeric alcohols formed, and the *cis* isomer could through this series of redox reactions be converted to the *trans* end-product. A knowledge of the relative stabilities of the epimeric alcohols under the reaction conditions used in the reduction is needed before it can be definitely concluded that the major product isolated (dihydroisocodeine) was indeed the preponderant initial reduction product.

The proposal (2), recently challenged (6), that in the case of aminoalcohols and ketones acid-base reaction between nitrogen and aluminum occurs to the detriment of a desired aluminum alkoxide-catalyzed oxidation or reduction does not seem applicable to the work reported in the present paper. While a beginning has been made (6) toward an analysis of the structural conditions under which aluminum alkoxides succeed or fail in catalyzing the above mentioned reactions with amino-alcohols and ketones, it would seem that the possibility of predicting with a fair degree of certainty the outcome in a specific case is still limited, particularly for molecules of complex geometrical structure.

If the aluminum isopropoxide reduction of ketones of the morphine series proves in general to provide the alcohol epimeric with the one produced by catalytic hydrogenation, a method will be at hand for producing otherwise difficultly accessible substances. [*E.g.*, dihydroisocodeine was previously prepared by the sequences: codeine → chlorocodide (8) → isocodeine (7) → dihydroisocodeine in *ca.* 6–22% over-all yield (7); or, codeine → bromocodide → isocodeine → dihydroisocodeine (7) in 35% over-all yield]. Furthermore it will allow assignment of definite configuration, at the carbinol carbon, to isomers presently of unknown configuration, *e.g.*, the two dihydrothebainols (10).

If one excludes the possibility that the hydrogen atom on C-5 participates in enolization (4, 11), it may now be possible to plan additional non-degradative experiments directed toward assigning a position to the methyl group of methyl-

dihydrocodeinone, the precursor of Metopon (4, 11), for, if the methyl group is at C-5, alkoxide reduction should lead to no more than two isomers,[3] whereas if the methyl group is at C-7, thereby introducing a new center of asymmetry at that carbon atom, as many as four isomers could be produced upon reduction.[4] (Steric factors at C-5, C-6, and C-7 would in each case operate against the production of the maximum number of isomers). Similar reasoning would apply to a possible elucidation of the structure of isomethyldihydrocodeinone (11).

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EXPERIMENTAL[5]

A. Epimerization of dihydrocodeine. 1. *By aluminum isopropoxide.* A mixture of 5.00 g. (0.0166 mole) of anhydrous dihydrocodeine, 7.50 g. (0.0372 mole) of aluminum isopropoxide, and 150 cc. of dry toluene was heated for 24 hours under a reflux condenser attached to a sulfuric acid trap. The reaction mixture was cooled and extracted with one 100-cc. and two 25-cc. portions of 5% sulfuric acid. The combined acid extracts were chilled and made alkaline with 40% potassium hydroxide. The liberated alkaloid was extracted with three 100-cc. portions of chloroform. The pale yellow chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness. The residue (3.38 g., 67.6%) was crystalline and gave a picrate melting at 235° [reported (12) for dihydroisocodeine picrate, 235–237°] and a methiodide melting, after one recrystallization, at 269° [reported (12) 272°].

A sample of the crude alkaloid was dissolved in 5% sulfuric acid and reprecipitated by 40% potassium hydroxide; m.p. 192–196°. After one recrystallization from ethanol, the purified alkaloid melted at 200° and gave no depression in melting point when mixed with a reference sample of dihydroisocodeine (see below).

In another experiment, the reaction mixture contained the quantities of alkaloid, alkoxide, and solvent given above and in addition 25 cc. of cyclohexanone. The crude product obtained as a residue from chloroform was dissolved in 90 cc. of ethylene dichloride and the solution passed through a column of activated alumina. After two elutions with 50-cc. portions of the same solvent, the alkaloid remaining on the column was removed by 5% sulfuric acid and precipitated, m.p. 182–187°. Three recrystallizations from absolute ethanol provided our reference sample of dihydroisocodeine: m.p. of alkaloid 199–200° [reported (12) 199–200°], of picrate, 235–236° [reported (12) 235–237°], of the methiodide, 268–269° [reported (12) 272°], of the acetyl derivative, 166–168° [reported (12) 166°].

2. *By potassium isopropoxide.* A mixture of 5.00 g. (0.0166 mole) of anhydrous dihydrocodeine, 2.50 g. (0.026 mole) of potassium isopropoxide, and 150 cc. of dry benzene was heated for 24 hours as in *A*1. The preliminary isolation procedure was similar to that described in *A*1. The residue obtained upon the evaporation of the chloroform was dissolved in ethylene dichloride and passed by gravity through a column of activated alumina 3.5 in. high and 0.75 in. in diameter. The original solution was followed by ethylene dichloride washes; the effluents were collected in three fractions, each of which was evaporated to dryness: (a) 2.23 g., (b) 0.79 g., (c) 0.18 g. Fraction (a) was converted to picrates whose melting point was not raised above 217–218° by repeated recrystallization. Fractions (b) and (c) were converted to picrates, combined, and fractionally crystallized. The first

[3] One of these would be the known methyldihydrocodeine (4).

[4] The stereochemistry at C-6 and C-7 would then be analogous to that at C-8 and C-9 in quininone.

[5] Optimum conditions for each transformation described were not determined.

three crops removed melted at 217–218°, the fourth crop at 214–215° and the fifth crop at 209–210°; the latter gave the melting point 208–209° when mixed with dihydrocodeine picrate (m.p. 208–209°).

The alkaloid remaining on the alumina was removed by 5% sulfuric acid and precipitated by alkali (1.50 g., 30%). After recrystallizations from alcohol, it melted at 196–198°; no depression with the reference sample of dihydroisocodeine.

B. Reduction of dihydrocodeinone. 1. *By aluminum isopropoxide.* A mixture of 5.00 g. (0.0167 mole) of dihydrocodeinone, 7.50 g. (0.0372 mole) of aluminum isopropoxide, and 150 cc. of dry toluene was heated for 24 hours as in *A*. The reaction mixture was cooled and extracted with 80-, 50-, and two 35-cc. portions of 10% hydrochloric acid. The combined acid extracts were made alkaline with 40% sodium hydroxide and extracted with four 100-cc. portions of chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to dryness. The residue (4.75 g., largely crystalline) was dissolved in 60 cc. of ethylene dichloride and passed by gravity through a column of activated alumina 6 in. high and 0.75 in. in diameter. The original solution was followed by three rinses with 50-cc. portions of ethylene dichloride. The effluents were collected in 50-cc. fractions each of which was evaporated to dryness: (a) 0.07 g. of glassy material, which was discarded; (b) 0.60 g. of a mixture of dihydroisocodeine and dihydrocodeinone, identified through the picrate and oxime respectively; (c) 0.30 g., ketonic; and (d) 0.15 g., ketonic. The bulk of the alkaloid remained adsorbed on the alumina and was removed with 5% sulfuric acid; the

TABLE I

DIHYDROCODEINE PICRATE—DIHYDROISOCODEINE PICRATE MIXTURES

DIHYDROCODEINE PICRATE, %	DIHYDROISOCODEINE PICRATE, %	MELTING RANGE, °C.
100	0	208–209
75	25	214–216
50	50	221–222
25	75	226–227
0	100	235–237

acid solution was made alkaline, extracted with chloroform, etc. The residue (3.05 g., 61%) after recrystallization from alcohol, melted at 195–198°, gave a picrate melting at 235–236°, and an acetyl derivative melting at 165–166°, and was therefore identified as dihydroisocodeine.

2. By aluminum isopropoxide and isopropyl alcohol. The reaction mixture, consisting of 5.00 g. (0.0167 mole) of dihydrocodeinone, 150 cc. of dry toluene, 7.50 g. (0.0372 mole) of aluminum isopropoxide, and 50 cc. of anhydrous isopropyl alcohol, was heated in the usual apparatus. The acetone-isopropyl alcohol mixture, which was allowed to distill slowly (13), was tested periodically by the sodium nitroprusside method (14). About 60 cc. of isopropyl alcohol was added in portions during the reaction. When no more acetone appeared in the receiver (*ca.* two hours), the mixture was heated until a vapor temperature of 107° was reached. It was then cooled and extracted with 50-, 20-, and 10-cc. portions of 10% hydrochloric acid. The combined acid extracts were chilled and made alkaline with 40% sodium hydroxide. The precipitated alkaloid was removed, washed with water, and oven-dried at 60°; yield: 4.38 g. (87.6%), m.p. 180–193°. The alkaline liquor was extracted thoroughly with chloroform, the extracts washed, dried, and distilled to dryness; residue, 0.71 g.

A portion of the main crop after two recrystallizations from alcohol melted at 194–199° gave no depression in melting point when mixed with a reference sample of dihydroisocodeine, and a large depression when mixed with dihydrocodeinone. The alcoholic mother liquors obtained in these recrystallizations were reduced to dryness. The residue formed no oxime, indicating that no unchanged dihydrocodeinone was present.

A 2-g. sample of the main crop was dissolved in 30 cc. of ethylene dichloride and passed through a column of activated alumina 2 in. high and 0.75 in. in diameter. The original solution was followed by two 20-cc. washes with ethylene dichloride. The effluents were collected separately and reduced to dryness: (a) 0.01 g., discarded; (b) 0.91 g., m.p. 175–192°; (c) 0.25 g., m.p. 178–192°. The alkaloid remaining on the alumina was removed by 5% sulfuric acid and precipitated: 0.77 g., m.p. 196–199°. One gram of fractions (b) and (c) was re-chromatographed. Ethylene dichloride eluted 0.07 g. of glassy alkaloid and the alumina retained 0.91 g., m.p. 178–190°.

In another experiment the reduction was carried out as described above. The alkaloid isolated by precipitation (B) weighed 4.64 g. (92.8%), m.p. 174–187°, and by extraction (C) 0.37 g. (7.2%). B was slurry-washed with four 13-cc., three 7-cc., and two 5-cc. portions of absolute ethanol, which treatment left undissolved 1.52 g. (30.4%) of dihydroisocodeine, m.p. 196–199°, no depression with the reference sample. From the alcoholic washes three crops of alkaloid, totalling 2.98 g. were removed by concentration and combined with C. Three recrystallizations from absolute ethanol yielded 1.20 g. (24.0%) of product, m.p. 190–197°, mixture m.p. 196–200°. The alcoholic mother liquors were reduced to dryness. The residue was dissolved in ethylene dichloride and chromatographed over alumina. From the effluents 0.69 g. (13.8%) of alkaloid was isolated whose picrate melted at 208–209° and gave no depression with dihydrocodeine picrate. The alkaloid remaining on the alumina was removed by 5% sulfuric acid and precipitated. After three recrystallizations, there

TABLE II

DIHYDROCODEINE—DIHYDROISOCODEINE MIXTURES

DIHYDROCODEINE, %	DIHYDROISOCODEINE, %	BEHAVIOR ON HEATING AT °C.		
		Softens	Forms turbid melt	Clear melt
100	0			112–115
75	25	113	115–118	170
50	50	118	128–144	175
25	75	157	172–184	188
10	90	177	184–194	200
0	100			200

remained 0.35 g. (7%) of dihydroisocodeine, m.p. 190–196°, when mixed with dihydroisocodeine, m.p. 193–196°. The alkaline liquor extract was combined with the alcoholic mother liquors and reduced to dryness. The residue, 0.60 g. (12%) yielded a picrate which after recrystallization melted at 219°.

3. *By potassium isopropoxide.* The reaction mixture consisted of 5.00 g. (0.0167 mole) of dihydrocodeinone, 150 cc. of dry benzene, and 2.50 g. (0.026 mole) of potassium isopropoxide. The reaction time was 24 hours and the preliminary isolation procedure the same as described above in the first reduction experiment. The residue obtained upon evaporation of the chloroform was dissolved in 75 cc. of benzene and shaken for one hour with 7.5 cc. of 38% aqueous sodium bisulfite. Addition of a little water caused crystallization of the dihydrocodeinone-sodium bisulfite addition compound, which was removed and converted to alkaloid (1.10 g., 22%) melting at 190–193°; the oxime, m.p. 256–258°.

The remaining alkaloid was recovered from the mother liquors (aqueous and benzene) obtained in the above treatment, dissolved in ethylene dichloride, and passed by gravity through a column of activated alumina 3.5 in. high and 0.75 in. in diameter. The original solution was followed by fresh ethylene dichloride washes; the effluents were collected in separate fractions and dried: (a) 0.15 g., which yielded a picrate melting (after two recrystallizations) at 234–235° and giving no depression in melting point when mixed with dihydrocodeinone picrate; (b) 0.74 g.; (c) 0.32 g.; and (d) 0.13 g.

[Fractions (b), (c), and (d) were combined and re-chromatographed. Dihydrocodeinone was identified in the first effluent and dihydroisocodeine remained on the alumina. Intermediate fractions yielded inseparable mixtures melting in the range 185–205°.]

The alkaloid remaining on the alumina was removed by 5% hydrochloric acid and precipitated by sodium hydroxide: 1.66 g. (33.3%). After two recrystallizations from alcohol it melted at 199–201° (no depression with reference dihydroisocodeine) and gave an acetyl derivative melting at 169–170° obs. (no depression with acetyldihydroisocodeine.)

SUMMARY

1. Dihydroisocodeine has been prepared by epimerization of dihydrocodeine or reduction of dihydrocodeinone using potassium isopropoxide or aluminum isopropoxide as catalyst.

2. Dihydromorphine and dihydromorphinone are relatively unreactive under conditions sufficient to bring about the transformations noted above in their respective phenolic methyl ethers.

3. The bearing of these results upon the question of the stereoisomerism of dihydrocodeine and dihydroisocodeine at C-6 is discussed.

4. The potential usefulness, for synthesis and structure determination, of the alkoxide reduction of hydrogenated ketones of the morphine series is indicated.

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