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Nonsymmetrical Bimolecular Reduction: Structure of the So-Called "Hydroxycodeine"

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The so-called "hydroxycodeine" (II), obtained on reduction of 14-hydroxycodeinone (I) with zinc and acetic acid, is shown to have twice the molecular size of a simple reduction product of I. II is a trihydroxymonoketone, and consequently results from nonsymmetrical reductive coupling of two molecules of I. Structure VIII is proposed for II.

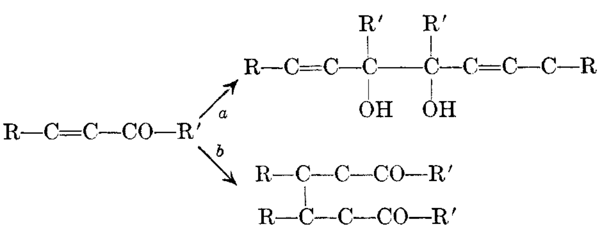
The reduction of 14-hydroxycodeinone (I) with zinc dust and acetic acid[1a] or with the zinc-copper couple and formic acid[1b] was first described by Freund and Speyer. From the reaction mixture they obtained a nonphenolic, high-melting compound (II), which they assumed to be 14-hydroxycodeine (III),[2] the secondary alcohol corresponding to I.

Subsequently, Lutz and Small[3] questioned this interpretation of Freund's compound as the normal reduction product of I: if it were correct, "dihydrohydroxycodeine A" (IV), obtained on catalytic reduction of II (platinum oxide in acetic acid), should be identical with one of the two authentic dihydrohydroxycodeines B and C (Va and b), which are formed on catalytic reduction (platinum oxide) of VI, the dihydro derivative of I. In reality, the chemical and pharmacological properties of IV differ widely from those of either Va or Vb. Hence, II can be neither III nor its 6-epimer, and Lutz and Small concluded that the zinc reduction of I had taken an irregular course; however, they did not attempt to establish the structure of II.

Further support for these doubts comes from the recent preparation[4] of authentic III, obviously different from II. The structure of III follows from the method used to prepare it (sodium borohydride reduction of I), and from the fact that it is reduced to Va,[4a] and reconverted to I by manganese dioxide.[4b] II is resistant to the latter reagent and hence should not be a *secondary* allylic alcohol.

In the course of marshalling together data relevant to the problems which the late Dr. Small[5] had under investigation, the question of the actual nature of II presented itself. That the substance might be a bimolecular species was suspected, since it is well known[6] that metal-acid reduction of ketones often results in the formation of such products. Furthermore, the melting points of II and IV (303–304° and 301–302°, respectively[3]) would be exceptionally high for simple codeine derivatives (*cf.* III, m.p. 156–157°; Va, 145°; Vb, 167°), but this would not be surprising if the compounds had twice the molecular weight. The first clue in support of this interpretation appeared as a result of a molecular weight determination (Signer) when a value *twice* that previously assigned was obtained (found, 627; calcd. for $C_{36}H_{40}N_2O_8$, 629).

In general, bimolecular reduction of α,β-unsaturated ketones[7] proceeds in a symmetrical way to yield[6] either an unsaturated 1,2-glycol (Reaction *a*) or a saturated 1,6-diketone (Reaction *b*).



In the present case, however, neither path is followed. Reaction *a* is excluded since the infrared spectrum of II shows a band at 5.78 μ (in potassium bromide), consistent with the presence of a nonconjugated carbonyl group. On the other hand, Reaction *b* seems unlikely, since the intensity of this carbonyl band, relative to other bands in the spectrum (*e.g.*. the one at 6.67 μ), is much lower than that of the corresponding band in authentic monomolecular ketones of the codeine series, *e.g.*, VI (5.8 μ). Consequently, II seemed to contain only *one* carbonyl group.

This last point was proven by the smooth formation from II of an *oxime* (in contrast to older state-

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[1] (a) M. Freund and E. Speyer, *J. prakt. Chem.* (2) **94**, 135 (1916); (b) E. Speyer, S. Selig, and M. Heil, *Ann.* **430**, 1 (1923).

[2] Compound I was interpreted by Freund and Speyer as the 7-hydroxy derivative of codeinone as formulated on the basis of the Knorr-Hörlein structure for morphine; consequently they designated II as "7-hydroxycodeine." Their formulas and nomenclature have been modified to conform with modern usage.

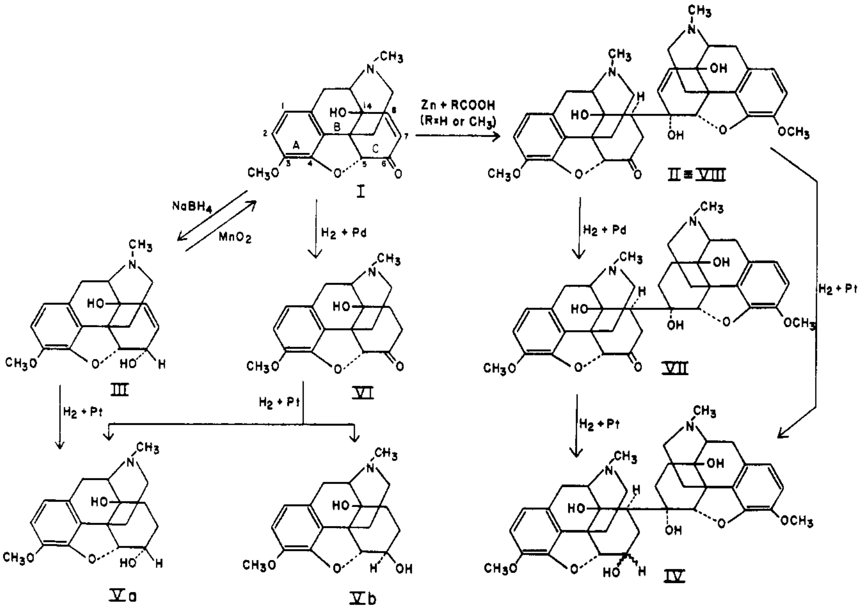
[3] R. E. Lutz and L. F. Small, *J. Org. Chem.* **4**, 220 (1939).

[4] (a) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958); (b) U. Weiss, unpublished work.

[5] Deceased, June 1957.

[6] R. C. Fuson, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) 12, 1 (1951).

[7] The conjugated system of I must be involved in the formation of II, since VI, the corresponding saturated ketone, is unaffected by zinc–acetic acid at 80–90°.[3]



ments[1b]). This derivative had the correct analysis for a *monoxime* of II.[7a] Furthermore, Zerewitinoff analysis of II showed *three* active hydrogen atoms per molecule $C_{36}H_{40}N_2O_8$. Two of these undoubtedly stem from the hydroxyl functions at C-14 originally present in I, while the third must be attributed to a hydroxyl group resulting from the reduction of the carbonyl in one of the two C_{18} moieties. II is therefore a trihydroxymonoketone.

According to Lutz and Small,[3] catalytic reduction of II over platinum oxide results in the slow uptake of *one* mole of hydrogen (per C_{18} unit) to give compound IV. Since this substance lacks the carbonyl band present in II and contains *four* active hydrogen atoms (based on a molecular weight of 629), the keto group of II has been reduced. However, the uptake of hydrogen found by Small actually corresponds to *two* moles per mole of II, $C_{36}H_{40}N_2O_8$, and consequently proves the presence of a second center of unsaturation. That this is a double bond was first indicated by the NMR spectrum,[8] which showed bands 3.62 and 4.58 p.p.m. lower in field than that of acetone, used as an internal reference (the corresponding values calculated relative to tetramethylsilane as reference are 5.7 and 6.7 p.p.m.). These bands can be ascribed to double bond and aromatic ring, respectively.

Conclusive proof for the presence of this double bond was obtained by catalytic reduction of II over palladium–barium sulfate, which proceeded with the uptake of *one* mole of hydrogen per molecular weight of 629 to give a new dihydro derivative (VII).[9] This compound retains the carbonyl group (band at 5.75 μ, *i.e.* in unaltered position). Further reduction of VII with platinum oxide as catalyst leads to IV.

On the other hand, it is also possible to reduce the carbonyl group specifically with sodium borohydride. This reaction seems to lead to the formation of two compounds in very unequal amounts; the two products are presumed to be epimers at C_6 (*cf.* the analogous hydride reduction of 8,14-dihydroxydihydrocodeinone,[4a] and the formation of much Va and little Vb on platinum-catalyzed hydrogenation of VI[3]). In the present case, neither the compounds themselves nor several of their salts were obtained crystalline, and the products were not investigated any further. However, the absence of carbonyl bands from the infrared spectra of both compounds showed that the desired reduction had taken place.

The data presented prove that II is formed from I by bimolecular reduction, that it contains a nonconjugated carbonyl, one reducible double bond, and three hydroxyls. Consequently, it must have been formed by a nonsymmetric reductive coupling of two molecules of I.

To account for these findings, we wish to propose formula VIII for II. This formulation seems in agreement with all observations made so far,[10,11]

[7a] NOTE ADDED IN PROOF: The infrared spectrum of this derivative (Nujol) lacked the characteristic carbonyl band at 5.8 μ.

[8] Kindly taken by Dr. E. D. Becker and Mr. R. B. Bradley of this Institute, using a Varian NMR spectrometer operating at 60 mc., and deuterium oxide plus hydrochloric acid as solvent.

[9] *Cf.*, however, the statement[1b] that II is not reduced by hydrogen-on-palladium.

[10] One apparent exception is the failure of II to give the pink color with *m*-dinitrobenzene and alkali characteristic of a methylene group activated by an adjacent carbonyl (von Bittó–Zimmermann reaction). However, this reaction is known to be negative for many compounds containing the grouping —CO—CH_2—, *e.g.*, the 6, 7, and 12-ketosteroids, (K. Kaziro and T. Shimada, *Z. physiol. Chem., Hoppe-Seyler's* **249**, 220 (1937).

[11] The earlier literature[1b,3] contains references to various acetylated derivatives of II. These compounds have not been reinvestigated by us.

and formation of a substance of this constitution can be explained by a plausible mechanism. Structure VIII would result from reduction of the carbonyl of one molecule of I, followed by attack upon position 8 of another molecule by the intermediate reduced species, which could be either a carbanion or a free radical.[12] The susceptibility of position 8 in I and its analogs, particularly to nucleophilic attack, is well known.[13] Alternatively, conjugate reduction of one molecule of I with subsequent attack of the resulting carbanion upon the carbonyl carbon of another molecule would likewise yield VIII.

While formation of necessarily nonsymmetrical products by reductive coupling of two *different* substances is well known,[6,12a] reductive coupling of *like* molecules generally leads to symmetrical products.[6] Formation of a nonsymmetrical structure under the latter conditions seems to be quite uncommon, and we have been unable to find in the literature a case sufficiently close to the one described here to serve as a model for the reduction of I to II. Formation of compounds with nonsymmetrical structures has been observed by Fuson and coworkers[14] on reduction of *p*-anisyl duryl and mesityl ketones with sodium; however, neither course nor products of this reaction are analogous to ours. More closely related to the present case is an instance of heterogeneous bimolecular reduction: formation of compound IX either from the disodio salt of benzhydrol and benzalacetophenone, or from dipotassiobenzalacetophenone and benzophenone.[15] While here two *different* molecules are

$$\begin{tikzcd}
(C_6H_5)_2\,CNa{-}ONa + C_6H_5CH{=}CHCOC_6H_5 \arrow[d] \\
(C_6H_5)_2\,C(OH)CH(C_6H_5)CH_2COC_6H_5 \quad \text{IX} \\
(C_6H_5)_2\,CO + C_6H_5CHKCHKCOC_6H_5 \arrow[u]
\end{tikzcd}$$

reductively combined in either case, the resulting product is a saturated γ-hydroxy ketone just like VIII, and it arises through a mechanism quite similar to the one postulated by us for the bimolecular reduction of I. We believe, therefore, that the formation of IX constitutes a valid analogy to that of VIII. Some other instances of nonsymmetric bimolecular reduction have been described which, while less closely related to our case, similarly proceed by attack of an intermediate reduced species upon the conjugated double bond of another molecule. Examples of such reactions are the reductive dimerization of α-nitroalkenes,[16a] and of α,β-unsaturated amides.[16b]

No direct exper.mental evidence is available on the stereochemistry of the juncture of the two moieties in VIII. However, either one of these moieties constitutes a very bulky substituent on ring C for the other one, and since the underside of this ring is very strongly hindered, it seems unlikely that the other ring system should have become attached to it from that side. Hence, we feel that the configuration can hardly be other than the one indicated in formula VIII.

EXPERIMENTAL[17]

"14-Hydroxycodeine" (II). Samples from Dr. L. F. Small's collection were used.

Anal. Calcd. for $C_{36}H_{40}N_2O_8$: Mol. wt. 629; active H, 3.0. Found: Mol. wt. 627 (Signer, in chloroform); active H, 3.0.

The test with diazotized sulfanilic acid was negative, confirming the older statements[1,3] that the compound is nonphenolic. It gives strong melting point depressions with IV and VII.

Oxime of II. A suspension of 0.19 g. of finely powdered II in a mixture of 73 ml. of 95% ethanol and 2 ml. of water was heated (reflux) for 20 hr. with 0.028 g. (1.3 equiv.) of hydroxylamine hydrochloride and 0.032 g. (1.3 equiv.) of fused sodium acetate. The clear solution was concentrated to small volume (*in vacuo*), diluted with 50 ml. of water and made basic with a slight excess of concd. ammonium hydroxide. The white precipitate was collected and recrystallized twice from 95% ethanol; small colorless prisms, m.p. 275–277° (evac. tube).

Anal. Calcd. for $C_{36}H_{41}N_3O_8$: C, 67.2; H, 6.42; N, 6.53. Found: C, 67.3; H, 6.44; N, 6.39.

Palladium-barium sulfate reduction of II to VII. A solution of 0.6 g. of II in 20 ml. of 10% acetic acid was shaken in hydrogen with 0.15 g. of 5% palladium on barium sulfate during 10 hr., (1 mole of hydrogen absorbed). The product was recovered from the filtered solution (chloroform/ammonium hydroxide) and obtained as a colorless foam which crystallized when triturated with a little warm ethanol. Recrystallization from this solvent afforded small rectangular plates, m.p. 307–309° dec. (evac. tube). Mixed melting points with both II and IV were strongly depressed. The infrared spectra of these three compounds are significantly different.

Anal. Calcd. for $C_{36}H_{42}N_2O_8$: C, 68.6, H, 6.71. Found: C, 68.3; H, 6.86. $[\alpha]^{20}_{D}$ $-94.6°$ ($c = 0.975$, *in* 10% *acetic* acid).

Further reduction of VII to IV. A solution of 0.3 g. of VII in 8 ml. of 10% acetic acid absorbed 1.2 moles of hydrogen in 1 hr. when shaken with 25 mg. of platinum oxide. The product, isolated as above, was recrystallized from ethanol, m.p. 301–303° (evac. tube), undepressed when mixed with a sample prepared by Small directly from II.[3] A Zerewitinoff analysis showed *four* active hydrogens.

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[12] (a) *Cf.* G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.*, **22**, 1296 (1957), and literature quoted there; (b) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 701.

[13] Examples, *inter alia:* addition of hydroxyl: S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **72**, 3247 (1950); **73**, 4001 (1951) (in *acidic* medium); U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957) (in *alkaline* medium); of morpholine: U. Weiss, unpublished observations; of thioethyl D. E. Morris and L. Small, *J. Am. Chem. Soc.*, **56**, 2159 (1934).

[14] R. C. Fuson, G. W. Parshall, and E. H. Hess, *J. Am. Chem. Soc.*, **77**, 3776 (1955).

[15] P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 493 (1959).

[16a] H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Am. Chem. Soc.*, **78**, 4984 (1956); (b) H. R. Snyder and R. E. Putnam, *J. Am. Chem. Soc.*, **76**, 33 (1954).

[17] Analyses are by the Analytical Service Laboratory of this Institute under the supervision of Dr. W. C. Alford. Melting points are corrected.

Hydride-reduction of II. A suspension of 0.6 g. sodium borohydride in 5 ml. methanol was added to 0.19 g. II suspended in 5 ml. methanol. After 20 hr. at room temperature, 10 ml. 10% aqueous sodium hydroxide was added to the slightly opalescent solution, and the mixture was heated over a free flame for 5 min. The milky liquid was cooled, diluted with water, and extracted six times with chloroform. The combined extracts were washed three times with small amounts of water, dried (sodium sulfate), and evaporated (*in vacuo*). The white residue was brought into solution by refluxing with six successive portions of hexane, which deposited noncrystalline solids on cooling. Additional material was obtained by evaporation of the filtrates. Infrared spectroscopy showed the presence of two different nonketonic products having very similar but definitely nonidentical spectra. One of these was present in the first three hexane filtrates, while all other fractions consisted of the other compound. All fractions were noncrystalline and melted over a wide temperature range (approx. 155–175°). Numerous attempts to convert the bases or a variety of their salts to well characterized, crystalline products were unsuccessful.

Treatment of II with manganese dioxide. Thirty milligrams of II, dissolved in 10 ml. chloroform, was stirred at room temperature with 100 mg. active manganese dioxide[18] for 20 min. The mixture was filtered with suction, and the dioxide was washed several times with chloroform. Evaporation of the combined filtrates left a residue which crystallized on treatment with a few drops of ethanol. The crystalline product did not depress the melting point of an authentic sample of II, and had the same infrared spectrum. Complete evaporation of the mother liquors gave an additional amount of this material.

Parallel treatment of 0.5 g. of III in 50 ml. chloroform with 1.5 g. of the same batch of manganese dioxide gave, after purification *via* the crystalline perchlorate, 0.35 g. (70%) of pure I, m.p. and mixed m.p. 272–273°.

BETHESDA 14, MD.

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[18] T. Attenburrow *et al.*, *J. Chem. Soc.*, 1094 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Synthesis of Several Fluorinated Cyclobutanes and Cyclobutenes

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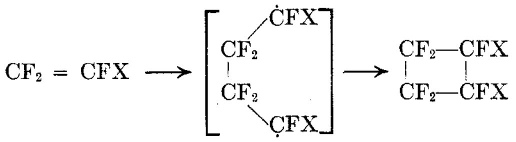
The synthesis of several fluorinated cyclobutanes by cyclization of $CF_2{=}CX_2$ olefins with themselves, and other olefins is reported. It appears that this cycloaddition takes place quite readily and easily only when X is halogen. The direction of addition of the unsymmetrical haloolefins can be rationalized and predicted by the assumption that in the product-determining transition state, the diradical of the lowest energy is preferentially formed with free (or nearly so) rotation about each single bond in the end positions (Equation 1). The physical properties of the fluorinated cyclobutanes and fluorinated cyclobutanes are described.

Many examples of the cyclization of $CF_2 = CX_2$-type olefins with themselves, alkenes and alkynes to form cyclobutanes and cyclobutenes are found in the literature. This cycloaddition appears to occur easily only when X is halogen.

Attempts to homocyclize trifluoroethylene, 2-bromo-1,1-difluoroethylene, and 2-chloro-1,1-difluoroethylene were unsuccessful. Propargyl chloride and tetrafluoroethylene also failed to cocyclize. Other studies have been carried out in this laboratory, but thus far all attempts to homocyclize fluoro-olefins of the type $CF_2 = CHX$ (where X is H, F, Cl, or Br) have been unsuccessful.

Recent work carried out in this laboratory has shown that chlorotrifluoroethylene dimerizes to give a product which is 50–50 (or nearly so) *cis-trans* 1,2-dichlorohexafluorocyclobutane. No differences in the distribution of the *cis-trans* isomers were observed when the dimerization reactions were carried out at temperatures ranging from 130 to 225°. This may be explained on the following basis. If the activated complex which forms when chlorotrifluoroethylene dimerizes has a rigid structure similar to the product molecules, then one would expect to get two parts of *cis* and one part of *trans*. The fact that the product is 50% of each suggests that the activated complex is a diradical with free (or nearly so) rotation, about each carbon single bond in the end position.

The direction of addition of unsymmetrical haloethylenes to themselves and to other unsymmetrical olefins can be rationalized and predicted by the assumption that in the product-determining transition state, the diradical of the lowest energy is preferentially formed. For example, in homocyclization:


(1)

cis and *trans* isomers
X = Cl, Br or I

The relative abilities of the halogens to stabilize free radicals appears to be: I>Br>Cl>F. The latter was determined by Haszeldine from the magnitudes of the bathochromic shifts in the ultraviolet spectra of halogenated alkyl iodides.[2]

The direction of cross-cyclization of haloethylenes with different alkenes or alkynes can likewise

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[1] From the Ph.D. dissertation submitted to the University of Colorado, August, 1957.

[2] R. N. Haszeldine, *J. Chem. Soc.*, 1764 (1953).