THE JOURNAL OF Organic Chemistry®

VOLUME 31, NUMBER 1

JANUARY 12, 1966

Enols in the Pyrrolidine Series. Reaction Site and Stereoselectivity in Reactions of Certain Aluminum and Boron Hydrides with α,β-Unsaturated Ketones and Their Enolic Reduction Products[1a]

PHILIP L. SOUTHWICK, NAZIH LATIF,[1b] BERENICE M. FITZGERALD, AND NORBERT M. ZACZEK

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh, Pennsylvania

Received June 25, 1965

A study of the action of several hydride reducing agents and Grignard reagents on the α,β-unsaturated ketonic structure of 4-benzylidene-2,3-dioxopyrrolidines (I) led to the following conclusions. (1) The initial reaction of diborane involves the olefinic bond and leads to formation of enols of 4-benzyl-2,3-dioxopyrrolidines (IV), as does catalytic hydrogenation. A comparison with chalcone showed that the latter substance is attacked to a considerable extent at the olefinic bond (conjugate reduction to the saturated ketone) by lithium tri-*t*-butoxyaluminohydride (LBAH) as well as by diborane. (2) The initial reaction of LBAH, sodium borohydride, phenylmagnesium bromide, methylmagnesium iodide, and presumably of lithium aluminum hydride with 4-benzylidene-2,3-dioxopyrrolidines (I) takes place at the ketonic carbonyl and produces the 4-benzylidene-3-hydroxypyrrolidine derivatives X, II, or VIII. (3) 4-Benzylidene-3-hydroxy-2-oxopyrrolidines (X) are isomerized rapidly at room temperature to enols IV by sodium hydroxide, LBAH, or sodium borohydride. At 0° the isomerization is too slow to interfere seriously with isolation of compounds of type X formed in LBAH or sodium borohydride reductions. (4) Enols of type IV are reduced by lithium aluminum hydride and sodium borohydride but not by LBAH or diborane. (5) Stereoselectivity in hydride reductions of enols of type IV favors products having the 4-benzyl *trans* to the 3-hydroxyl. The same stereoisomers are favored in reductions of 4-benzylidene-3-hydroxypyrrolidines (VIII) with lithium aluminum hydride at high temperatures.

Although reactions of α,β-unsaturated ketones with sodium borohydride usually do not involve reduction of the olefinic bond, a number of instances are known in which such reductions have produced saturated alcohols or, very rarely, saturated ketones.[2-4] Reduction of the olefinic bond was invariably encountered when sodium borohydride reacted with a series of 4-benzylidene-2,3-dioxopyrrolidines (I) having different substituents in the 1-position.[5] The observation that sodium borohydride reduced these compounds to 4-benzyl-3-hydroxy-2-oxopyrrolidines (V) in good yields suggested the operation of steric or electronic effects strongly favoring reaction in the conjugate manner. It seemed possible that a steric situation particularly conducive to conjugate addition might be implicated. The vinyl proton of the benzylidene group gives rise to a very low-field triplet in the n.m.r. spectra of compounds of type I (triplet centered at τ 2.36, $J \cong 2$ c.p.s., for compound Ia). On the basis of the correlation recently established for similar exocyclic α,β-unsaturated ketones by Kevill, Weiler, and Cromwell,[6a] the vinyl

(1) (a) This investigation was supported by a research grant (GM-04371) from the National Institutes of Health, U. S. Public Health Service. Much of the work is described in doctoral theses by N. M. Zaczek (1962) and B. M. Fitzgerald (1965). (b) Postdoctoral Research Associate, 1961–1962.

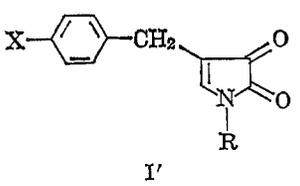
(2) For examples in which saturated ketones were obtained, see (a) M. E. Cain, *J. Chem. Soc.*, 3532 (1964); (b) O. L. Chapman, H. G. Smith, and R. W. King, *J. Am. Chem. Soc.*, **85**, 803 (1963); (c) N. W. Atwater, *ibid.*, **83**, 3071 (1961).

(3) For examples in which saturated alcohols were obtained, see (a) ref. 2a; (b) J. A. Zderic and J. Iriate, *J. Org. Chem.*, **27**, 1756 (1962); (c) D. Kupfer, *Tetrahedron*, **15**, 193 (1961); (d) A. C. Currie, J. Gillon, G. I. Newbold, and F. S. Spring, *J. Chem. Soc.*, 773 (1960); (e) F. Sondheimer and Y. Kibansky, *Tetrahedron*, **5**, 15 (1959); (f) J. Fajkős, *Collection Czech. Chem. Commun.*, **23**, 2155 (1958); (g) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957); (h) C. Djerassi, A. J. Manson, and H. Bendas, *Tetrahedron*, **1**, 22 (1957); (i) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955); (j) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind.* (London), 1482 (1954).

(4) Unlike α,β-unsaturated ketones, α,β-unsaturated esters are apparently often reduced by sodium borohydride to saturated alcohols in a slow reaction. See M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(5) P. L. Southwick and E. F. Barnas, *ibid.*, **27**, 98 (1962).

(6) (a) D. N. Kevill, E. D. Weiler and N. H. Cromwell, *ibid.*, **29**, 1276 (1964). (b) An alternative structure (I′) for these compounds, in which the olefinic bond is endocyclic and the aromatic ring is not in conjugation



I′

with the olefinic and carbonyl functions, would not be consistent with the large bathochromic shifts produced in the ultraviolet–visible spectra when the group X is methoxy or dimethylamino rather than hydrogen. [The long wave length maximum of the unsubstituted compound (Ia) in ethanol is at 327 mμ (ε 24,600), whereas that of the methoxy derivative (Ic) is at 368 mμ (ε 24,010) and that of the dimethylamino derivative (Id) is at 461 mμ (ε 35,460).] Chemical evidence also favors I rather than I′; thus, for example, heating of Ia with excess phenylhydrazine cleaves it smoothly to yield benzaldehyde phenylhydrazone and the phenylhydrazone of 1-cyclohexyl-2,3-dioxopyrrolidine (observations by N. L. to be detailed elsewhere).

TABLE I. REACTIONS OF PYRROLIDINE DERIVATIVES WITH HYDRIDE REDUCING AGENTS AND GRIGNARD REAGENTS

Expt.	Substrate	Reagent[a]	Temp., °C.	Solvent[b]	Product(s) (% yield)
1	Ia	$NaBH_4$	*Ca.* 30	Ethanol	Va (72.1)
2	Ia	$LiAlH_4$	*Ca.* 30	Ether	VIIIa (59)
3	Ia	C_6H_5MgBr	*Ca.* 35	Ether	IIa, R′ = C_6H_5 (72)
4	Ia	CH_3MgI	*Ca.* 35	Ether	IIa, R′ = CH_3 (73)
5	Ia	LBAH	*Ca.* 30	THF	IVa (74)
6	Ia	$NaBH_4$	*Ca.* 30	Pyridine	IVa (23) Va (27)
7	Ia	B_2H_6	0	THF	IVa (58)
8	Ia	$NaBH_4$	0	Ethanol	Xa (55)
9	Ia	LBAH	0	THF	Xa (87)
10	Xa	$NaBH_4$	*Ca.* 30	Ethanol	Va (74)
11	Xa	LBAH	*Ca.* 30	Ether	IVa (75)
12	IVa	$NaBH_4$	*Ca.* 30	Ethanol	Va (83)
13	Xa	B_2H_6	0	THF	Xa (*ca.* 100)
14	IVa	LBAH	*Ca.* 30	THF	IVa (*ca.* 100)
15	IVa	B_2H_6	*Ca.* 30	THF	IVa (*ca.* 100)
16	IVa	$LiAlH_4$	*Ca.* 30	Ether	VIa (44)
17	VIIa	$LiALH_4$	*Ca.* 30	Ether	VIa (50)
18	VIIIa	$LiAlH_4$	*Ca.* 140	*n*-Butyl ether	VIa (84.6)
19	Ia	$LiAlH_4$	*Ca.* 140	*n*-Butyl ether	VIa (56.2)

[a] LBAH is lithium tri-*t*-butoxyaluminohydride. [b] THF is tetrahydrofuran.

hydrogen in these compounds must be *cis* to the ketonic carbonyl and deshielded by that group.[6b] Thus, the 4-benzylidene derivatives of type I are so constituted as to permit a reagent molecule to make a relatively unhindered approach to a position bridging the ends of the conjugated system, which is fixed in a nearly planar *s-cis* configuration.[7] We were hopeful that further investigation would reveal whether or not the outcome of the sodium borohydride reductions had any such basis.

It might be supposed that an effect based on configuration in this way should extend to reactions with other reagents. Experiments have since been conducted on compounds of type I with the methyl and phenyl Grignard reagents, lithium aluminum hydride, lithium tri-*t*-butoxyaluminohydride (hereafter designated LBAH), and diborane. Much of the work was performed with the substance containing the unsubstituted benzyl group (X = H) at position 4 and a cyclohexyl group (R = cyclohexyl) at position 1. (The letter a will be appended to formula numbers to indicate specifically the 1-cyclohexyl-4-benzylidene derivative of type I and the products derived from it.[8]) Results of representative experiments with these compounds are summarized in Table I and Chart I.

As will be explained in the discussion to follow, it eventually became evident that the initial reactions of all of the reagents except diborane (and including sodium borohydride) occur in the 1,2 manner at the carbonyl group only, the apparent 1,4 reductions with sodium borohydride and LBAH being the result of exceptionally facile isomerizations of the initial reduction products (X) to enols (IV). Sodium borohydride reductions produced 4-benzyl-3-hydroxy-2-oxopyrrolidines (V) by reducing these enols (or corresponding enolates). Such reduction of the enol IVa was quite stereoselective, producing the *trans*-hydroxypyrrolidone Va in good yield. Only with diborane did compound Ia react principally in the conjugate manner, whereas chalcone was found to react to a considerable extent in this way with both diborane and LBAH, as well as with Grignard reagents.[7b,9] The discussion of the details of the investigation will be divided into two sections, the first concerned with reaction site selectivity in reactions of α,β-unsaturated ketones and enols, and the second with the stereochemistry of the reduction of endocyclic enols. Some observations on the stereochemistry of reductions of the exocyclic double bond of 4-benzylidene-3-hydroxypyrrolidines (VIII) are discussed in connection with the results considered in the second section.

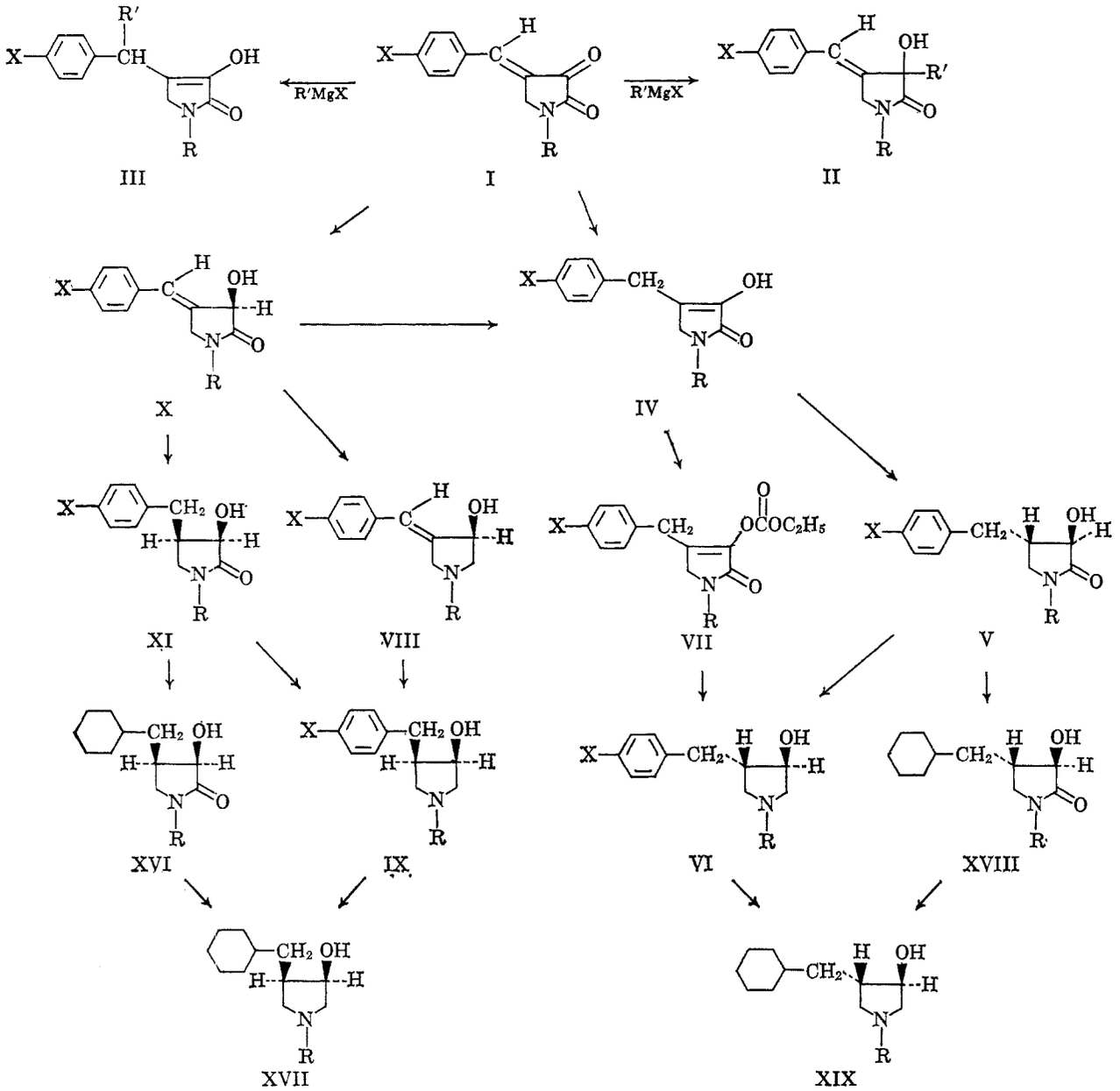
Selective Reductions of α,β-Unsaturated Ketones.—Experiments with lithium aluminum hydride and also with the phenyl and methyl Grignard reagents (expt. 2, 3, and 4 in Table I) at once disclosed that the configuration of compound Ia did not decisively influence the reactions of these reagents in the direction of conjugate addition. The products showed neither the ferric chloride colors nor the alkali solubility which are characteristic of the enols of the type IV. Infrared absorption corresponding to a ketonic carbonyl was absent from all of the products, but ultraviolet absorption characteristic of a substituted styrene structure was present. (In the lithium aluminum hydride reductions the lactam carbonyl was also removed, but in the Grignard additions there was selective reaction at the ketonic carbonyl.) It was therefore evident that the isolated products correspond to the 1,2 addition products IIa or VIIIa rather than to conjugate

(7) (a) Availability of an *s-cis* conformation was clearly not a *necessary condition* for occurrence of conjugate reduction of sodium borohydride; many of the known examples involved fixed *s-trans* α,β-unsaturated ketones which contain the 2-cyclohexen-1-one structure. A nearly planar conjugated system may favor such reductions. (b) For a concise discussion of conjugate addition of Grignard reagents, see R. C. Fuson, "Reactions of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 463, 464. Some recent investigators discount the importance of the possible six-centered cyclic processes. See H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963); J. Klein, *Tetrahedron*, **20**, 465 (1964).

(8) Substituents in individual compounds of the various structural types shown in Chart I and in the tables of compounds are indicated by letters appended to formula numbers as follows: a, R = *cyclo*-C_6H_{11}, X = H; b, R = *cyclo*-C_6H_{11}, X = Cl; c, R = *cyclo*-C_6H_{11}, X = OCH_3; d, R = *cyclo*-C_6H_{11}, X = $N(CH_3)_2$; e, R = CH_3, X = Cl; f, R = $C_6H_5CH_2$, X = Cl; g, R = $C_6H_5(CH_2)_2$, X = Cl; h, R = $C_6H_5CH_2$, X = H; and i, R = $C_6H_5(CH_2)_2$, X = H.

(9) R. E. Lutz and J. O. Weiss, *J. Am. Chem. Soc.*, **77**, 1815 (1955). This paper deals with phenylmagnesium bromide and phenyllithium additions to *cis*- and *trans*-chalcone, as well as with sodium borohydride and lithium aluminum hydride reductions.

CHART I



addition products IIIa and IVa. In the case of the lithium aluminum hydride reductions other products were present; sharp-melting samples of structure VIIIa were obtained only after considerable amounts of material had been lost in sublimation and/or recrystallization operations. It was obvious, however, that in neither the lithium aluminum hydride reductions nor the Grignard additions had conjugate addition been a favored course of reaction. (The yields of these substances given in Table I are of purified products; they represent minimum values for the amount of a given product formed in the reaction.) It is noteworthy that, although alkyl but not aryl Grignard reagents add in the conjugate manner to 4-benzylidene oxazolones,[10] no difference between the mode of reaction of the phenyl and methyl Grignard reagents was seen when they were applied to 4-benzylidene-2,3-pyrrolidinediones.

Completely contrasting results were obtained with LBAH and with diborane (expt. 5 and 7, Table I). Both of these reagents reduced the 4-benzylidene derivatives Ia to the enol IVa. LBAH had no apparent reducing action on the enol IVa (expt. 14), and this fact accounts for the difference between the outcome of expt. 5 and that of expt. 1 in which sodium borohydride was used. In ethanol the latter reagent readily reduces enols of type IV to yield the hydroxypyrrolidones V, but in pyridine (expt. 6) this type of reduction was slower and some enol survived in the final product mixture.[11a] At room temperature diborane (expt. 15) failed to reduce the enol IVa either at the enolic or the lactam function.[11b]

At this point in the investigation it was clear that at least three reagents, sodium borohydride, LBAH, and diborane, produced what was in effect a 1,4 reduction of the conjugated system of 4-benzylidene-2,3-dioxopyrrolidines. However, only in the case of the

(10) See R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 3348 (1962), and references cited therein.

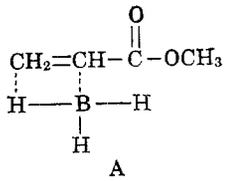
(11) (a) H. C. Brown and I. Ishikawa [*J. Am. Chem. Soc.*, **83**, 4372 (1961)] reported that in pyridine at 0° acetone is not reduced by sodium borohydride. (b) In refluxing tetrahydrofuran diborane converts many amides to corresponding amines. See H. C. Brown and P. Heim, *ibid.*, **86**, 3566 (1964).

TABLE II. REACTIONS OF CHALCONE AND RELATED COMPOUNDS WITH HYDRIDE REDUCING AGENTS

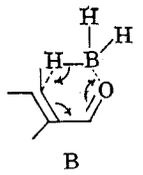
Expt.	Substrate	Reagent[a]	Temp., °C.	Solvent[b]	Product(s) (% yield)
1b	XII	LBAH	30	THF	XIII (44), XIV (49)
2b	XIV	LBAH	30	THF	XIV (*ca.* 100)
3b	XII	LBAH	0	THF	XIII (48), XIV (<30)
4b	XII	B_2H_6	0	THF	XIII (29)

[a] LBAH is lithium tri-*t*-butoxyaluminohydride. [b] THF is tetrahydrofuran.

diborane reaction is there any longer reason to suppose that the initial reaction was actually a 1,4 reduction. At a reaction temperature of 0° (expt. 8 and 9) sodium borohydride in ethanol or LBAH in THF attacked first the ketonic carbonyl group of Ia to give the unsaturated hydroxypyrrolidone Xa. At room temperature this compound isomerized rapidly in the presence of LBAH to the enol IVa. Sodium borohydride converted compound Xa to the hydroxypyrrolidone Va at room temperature, presumably *via* the enolate of IVa. Treatment of the compound Xa with sodium hydroxide in ethanol converted it into the enolate of IVa; the basic character of the reducing agents would account for the failure of compound Xa to survive in expt. 1, 5, 10, and 11. Diborane in tetrahydrofuran, on the other hand, failed to reduce or isomerize compound Xa (expt. 13). Apparently the initial reaction of Ia with diborane did involve attack at the β-carbon of the α,β double bond. Recently Brown and Keblys[12] showed that diborane reduces ethyl acrylate in part to ethyl propionate and suggested that the latter substance arose *via* an initial addition of the type indicated by formula A. However, there appears to be no reason at present to exclude a true 1,4 addition, as in formula B, at least in reduction of Ia.



A



B

Experiments with chalcone have disclosed that LBAH, as well as diborane, differs from sodium borohydride not only in a lesser tendency to reduce enolates but also, in that instance, in a greater tendency to give direct 1,4 reduction. Our experiments confirmed the observations of others that sodium borohydride reduction of *trans*-chalcone gives *ca.* 80% of the allylic alcohol XIV.[9,13] Both diborane and LBAH, on the other hand, afforded 29–48% yields of the ketone XIII (see Table II and Chart II). In the experiments with LBAH, changing the temperature from 30 to 0° made no significant difference in this outcome. An attempt to bring about isomerization of the unsaturated alcohol XIV to the saturated ketone XIII by treatment with excess LBAH in tetrahydrofuran at room temperature left the alcohol unchanged and failed to produce a detectable amount of the ketone (expt. 2b, Table II).[14]

(12) H. C. Brown and K. A. Keblys, *J. Am. Chem. Soc.*, **86**, 1795 (1964).

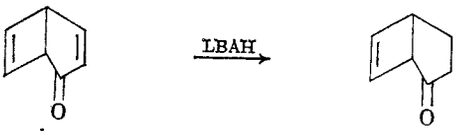
(13) (a) H. H. Wasserman and N. E. Aubrey [*ibid.*, **77**, 590 (1955)] isolated a small amount of saturated ketone XIII from a lithium aluminum hydride reduction of chalcone, however. When the carbonyl group bears a hindering substituent, larger amounts of the enolates of saturated ketones may be formed in lithium aluminum hydride reductions of α,β-unsaturated ketones. See (b) R. E. Lutz and D. F. Hinkley, *ibid.*, **72**, 4091 (1950); (c) R. C. Fuson and J. J. Looker, *J. Org. Chem.*, **27**, 3357 (1962).

This failure to demonstrate the conversion XIV → XIII under the conditions prevailing during the reduction of chalcone with LBAH suggests that the reduction may have proceeded by a direct 1,4 process, XII → XV, not by the path, XII → anion of XIV → XV. It would therefore appear that, despite its fixed *s-cis* geometry, compound Ia has less tendency than chalcone to react in the 1,4 manner with this hydride reducing agent. Whether the 1,4 reductions by diborane will be confined to conjugated systems which can assume an *s-cis* conformation is a question which merits investigation.

Apart from their applications to the preparation of particular compounds in the pyrrolidine series, these observations on hydride reductions are potentially useful as a basis for planning selective reductions in other cases. Stated in general terms, in the expectation that similar behavior may be seen in other compounds of similar functionality, the implications of these observations include the following. (1) Enols or enolates are apparently reduced much more readily by lithium aluminum hydride or sodium borohydride than by LBAH or diborane. The last two reagents evidently reduce this kind of structure relatively slowly or not at all. (2) Diborane appears more prone than lithium aluminum hydride or sodium borohydride to react in the conjugate manner with α,β-unsaturated ketones. LBAH also can react in the conjugate manner, and in certain cases (with chalcone or *cis*-bicyclo[3.2.0]hepta-3,6-diene-2-one,[15a] for example) does so to a greater extent than sodium borohydride and/or lithium aluminum hydride.[15] (3) Diborane (as well as sodium borohydride and LBAH) may reduce an α,β-unsaturated ketone function selectively in the presence of an amide function. (4) In certain instances an allylic alcohol-to-enol isomerization occurs readily under conditions used in sodium borohydride

(14) Isomerization of the vinyl alcohol XIV to the ketone XIII by heating with sodium ethoxide has been reported, however. See (a) M. H. Nomura, *Bull. soc. chim. France*, **37**, 1245 (1925); (b) W. Davey and J. A. Hearne, *J. Chem. Soc.*, 4978 (1964).

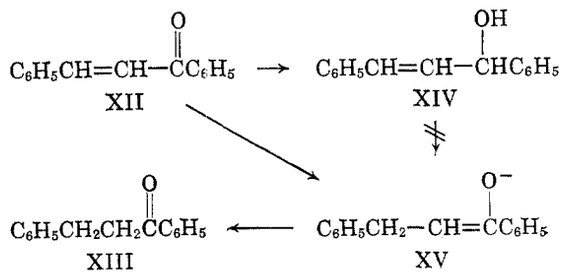
(15) (a) P. R. Story and S. R. Fahrenholtz [*J. Am. Chem. Soc.*, **87**, 1623 (1965)] attributed the conjugate reduction of *cis*-bicyclo[3.2.0]hepta-3,6-dien-2-one (i) by LBAH to the exceptional steric environment of the



i

carbonyl group. The conjugate reductions of chalcone and mesityl oxide[15b] with this reagent, while less strongly favored, demonstrate that the behavior of i is not unique. (b) M. E. Cain [*J. Chem. Soc.*, 3532 (1964)] has suggested that, when the effects of the commonly employed complex hydride reducing agents on a given α,β-unsaturated ketone are compared, conjugate reductions will be most important with sodium borohydride reductions performed in hydroxylic solvents. In the case of mesityl oxide, which Cain examined carefully, the extent of conjugate reduction by different reagents fell in this order: sodium borohydride in aqueous methanol (17.2%) > LBAH in tetrahydrofuran (7.8%) > lithium aluminum hydride in ether (0.4%). Our results show that with chalcone LBAH in tetrahydrofuran belongs first in the sequence.

CHART II



or LBAH reductions. However, use of low reaction temperatures may minimize such isomerizations.

The Stereochemistry of the Reduction of the Enol IVa.—In connection with investigation of the reduction of the enols IV, the opportunity was presented for examination of the stereochemistry of hydride reductions which create asymmetric centers from both carbons of a double bond in a nearly planar five-membered ring. Infrared[5] and n.m.r. data have indicated that compound IVa contains little or none of the ketonic tautomer in such solvents as chloroform, and the substance is acidic enough to dissolve in aqueous sodium hydroxide. Its reduction should, therefore, exemplify reduction of enols or enolates, rather than of normal carbonyl compounds, unless the reduction should occur only *via* traces of free ketonic tautomer which might be present. Reduction of the enol IVa with sodium borohydride in ethanol was, in fact, quite stereoselective; the only isomer isolated (Va) was obtained in 83% yield after full purification.

Without knowing the reduction mechanism in full detail it was not possible to predict with confidence whether this favored reduction product from the enol IVa should have the benzyl and hydroxyl groups in the *cis* or in the *trans* relationship. However, it was expected that a *cis*-hydroxypyrrolidone could be obtained by a rapid stereoselective hydrogenation of the benzylidene derivative Xa, to which addition of hydrogen should occur chiefly from the side opposite the hydroxyl group. Such had, in fact, been the result of hydrogenation of an analogous cyclopentane derivative, 2-benzylidenecyclopentanol.[16] Hydrogenation of Xa in ethanol over a platinum oxide catalyst produced an 88% yield of compound XIa, an isomer of Va. Thus, if the usual *cis* stereochemistry prevailed in the catalytic hydrogenation and XIa is the *cis* isomer, the sodium borohydride reduction of the enol IVa had proceeded stereoselectively in the *trans* manner and the product Va is the *trans* isomer. In the sodium borohydride reductions the *trans* isomer Va does not arise from initially formed *cis* isomer XIa; XIa does not isomerize under the influence of sodium borohydride solutions as used in the reduction experiments nor is it readily isomerized by sodium ethoxide in ethanol. Hydrogenation of Xa over palladium on calcium carbonate yielded the *trans* isomer Va in excellent yield; as is often the case, *cis* stereoselective addition of hydrogen was not observed with the palladium catalyst, and the more stable isomer was formed.

Further reduction of the reduction product Va with lithium aluminum hydride in ether gave the hydroxypyrrolidine VIa. The same hydroxypyrrolidine isomer was obtained directly from the enol IVa in 44% yield (expt. 16, Table I) and from the enol carbonate VIIa in 50% yield (expt. 17, Table I) by reduction with lithium aluminum hydride in ether; the stereoselectivity apparently operated in the same direction in reductions of the enol (or its carbonate ester) with lithium aluminum hydride as with sodium borohydride. Although the yields of the fully purified product were 50% or less in the lithium aluminum hydride reductions of structures IVa or VIIa, the rest of the product mixture evidently consisted of other types of compounds, not other stereoisomers. The hydroxypyrrolidine VIa has the expected *trans* configuration. The *cis* isomer IXa was obtained by lithium aluminum hydride reduction of the *cis*-hydroxypyrrolidone XIa. *cis* isomer IXa was also produced by catalytic hydrogenation of 4-benzylidene-3-hydroxypyrrolidine VIIIa but only in rather low yield (35%). Any catalyst and set of hydrogenation conditions which proved effective in hydrogenating the olefinic bond also hydrogenated the phenyl group, so that much of the product consisted of a 4-cyclohexylmethyl derivative.

The *cis*- and *trans*-1-cyclohexyl-4-cyclohexylmethyl-3-hydroxy-2-oxopyrrolidines (XVIa and XVIIIa) were readily obtained by hydrogenating the phenyl group of compounds XIa and Va using a platinum catalyst. Removal of the lactam carbonyl group from these substances by lithium aluminum hydride reduction produced the corresponding *cis*- and *trans*-1-cyclohexyl-4-cyclohexylmethyl-3-hydroxypyrrolidines (XVIIa and XIXa). Comparison of the n.m.r. spectra of the set of four compounds, IXa, VIa, XVIIa, and XIXa, provided evidence regarding the configuration of these compounds which supported the conclusions based on the hydrogenation results discussed above. In the case of one of the two compounds still containing the benzyl group, the multiplet arising from the proton at carbon 3, the carbon holding the hydroxyl group, was located upfield by about 0.2 p.p.m. from the corresponding protons in the spectra of the other three compounds (see Table III). The only structure among the four in question in which the proton on carbon 3 could experience appreciable long-range shielding due to the magnetic anisotropy of a benzene ring[17] would be VIa, in which this proton is *cis* to a neighboring benzyl group. The compound already assigned this configuration on other grounds was, in fact, the compound having the more upfield proton at carbon 3.

TABLE III. CHEMICAL SHIFTS FOR THE PROTON AT CARBON 3

Compd.		Midpoint of multiplet, τ scale
VIa	*trans*	6.08
XIXa	*trans*	5.86
IXa	*cis*	5.87
XVIIa	*cis*	5.87

The results of hydride reductions with compounds IVa and VIIa imply a preference for *trans* reduction of β-substituted endocyclic enols or enolates by the hydride reducing agents, at least when the ring is nearly planar and the two sides of the ring are equally acces-

(16) A. P. Philips and J. Mentha, *J. Am. Chem. Soc.*, **78**, 140 (1956).

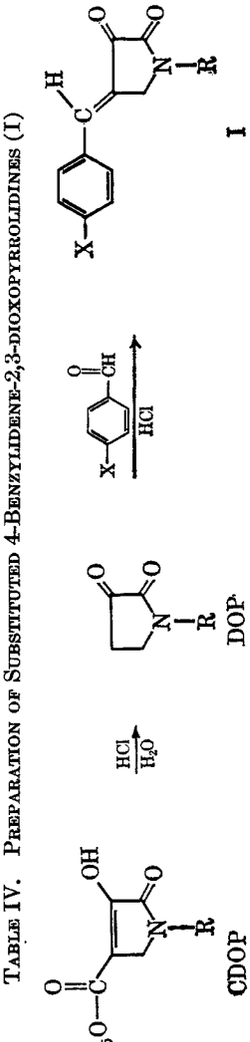
(17) See (a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London 1959, pp. 51, 52; (b) J. B. Hyne, *J. Am. Chem. Soc.*, **81**, 6058 (1959); (c) P. L. Southwick, J. A. Fitzgerald, and G. E. Milliman, *Tetrahedron Letters*, 1247 (1965).

sible. It must be noted that the stereochemical result would probably be similar if the compounds were ketonic; 2-benzylcyclopentanone, which is presumed to exist largely in the keto form, yielded principally *trans*-2-benzylcyclopentanol when reduced with lithium aluminum hydride.[16] However, in several experiments with sodium borohydride the possibility that the unknown ketonic tautomer could be involved to any significant extent was excluded by conducting the reduction on the preformed sodium enolate of IVa in dry diglyme. Reduction occurred readily and the principal product was again the *trans* reduction product Va. It is believed that the observed stereoselectivity in favor of *trans* reduction of IVa must reflect the mode of reaction of the enol or enolate.[18,19]

Results of deuterium labeling experiments reported by Dauben and Eastham[19] have indicated that, in lithium aluminum hydride reductions of enol acetates derived from 3-cholestanone and 3-coprostanone, the reduction proceeds by way of the transfer of a hydride ion to the carbon linked to oxygen and the formation of an intermediate having an organometallic bond to the other (β) carbon of the original enolic double bond. If that mechanism applies to the cases studied here, the *cis* or *trans* configuration of the product would be set on the basis of the *cis* or *trans* orientation assumed in formation of the organometallic bond at position 4 and/or the direction of a subsequent protonation. Thus, for example, it is quite possible that reduction of the enol carbonate VII with lithium aluminum hydride may have yielded an intermediate of the type C, having a *cis* ring fusion. Further reduction would remove the lactam carbonyl. Protonation in the work-up procedure of the organometallic bond with retention of configurations would then have yielded the *trans* isomer VI. If the reduction of the enol itself (IV) or of an enolate formed from IV involved an intermediate D (analogous in structure and configuration to intermediate C), then preferential formation of a *trans* reduction product would again result if protonation of the organometallic bond on carbon 4 occurred without inversion of the configuration of that atom. Formula E represents a possible alternative to D as a suggested structure for the unhydrolyzed reduction product of the enol IV. It is hoped that projected deuterium labeling experiments may elucidate the nature of this intermediate. (See Chart III.)

Unlike a number of other alcohols structionally related to cinnamyl alcohol, the 4-benzylidene-3-hydroxypyrrolidines (VIII) are not reduced at the olefinic bond by lithium aluminum hydride in ethyl ether solu-

TABLE IV. PREPARATION OF SUBSTITUTED 4-BENZYLIDENE-2,3-DIOXOPYRROLIDINES (I)



Product	R	X	M.p., °C.	Yield,[a] %	Reaction mixture: Aldehyde, mole	CDOP or DOP,[b] mole	Ethanol, ml.	HCl, ml. (strength, %)	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ie	CH_3	Cl	210–212	34 (A)	0.119	0.108	80	400 (10)	$C_{12}H_{10}ClNO_2$	61.15	4.28		61.15	4.16	
If	$PhCH_2$	Cl	228–231	58 (A)	0.152	0.115	290	1160 (20)	$C_{18}H_{14}ClNO_2$	69.34	4.53	4.49	69.15	4.81	4.26
Ig	$Ph(CH_2)_2$	Cl	167–168	37 (A)	0.102	0.073	200	1000 (10)	$C_{19}H_{16}ClNO_2$	70.05	4.92		69.74	4.92	
Ib	Cyclohexyl	Cl	198–200	54 (A)	0.16	0.16	320	800 (20)	$C_{17}H_{18}ClNO_2$	67.21	5.97	4.61	67.22	5.76	4.53
Ic	Cyclohexyl	CH_3O	187–188[c]	40 (A)	0.4	0.4	800	2000 (20)	$C_{18}H_{21}NO_3$	72.22	7.07		71.86	6.97	
Id	Cyclohexyl	$(CH_3)_2N$	228–229[d]	32 (A)	0.2	0.2	400	1000 (20)	$C_{19}H_{24}N_2O_2$	73.04	7.74	8.97	72.97	7.78	9.06
				67 (B)	0.132	0.12	...	800 (20)							

[a] Letters (A or B) following yield figures identify the preparative procedure (Experimental Section). [b] DOP = 1-substituted 2,3-dioxopyrrolidine; CDOP = 1-substituted 4-carbethoxy-2,3-dioxopyrrolidine. [c] Ultraviolet spectrum (95% ethanol): maxima at 244 mμ (ε 7410), 368 mμ (ε 24,010); minima at 222 mμ (ε 4260), 272 mμ (ε 1830). [d] Ultraviolet spectrum (95% ethanol): maximum at 461 mμ (ε 35,460).

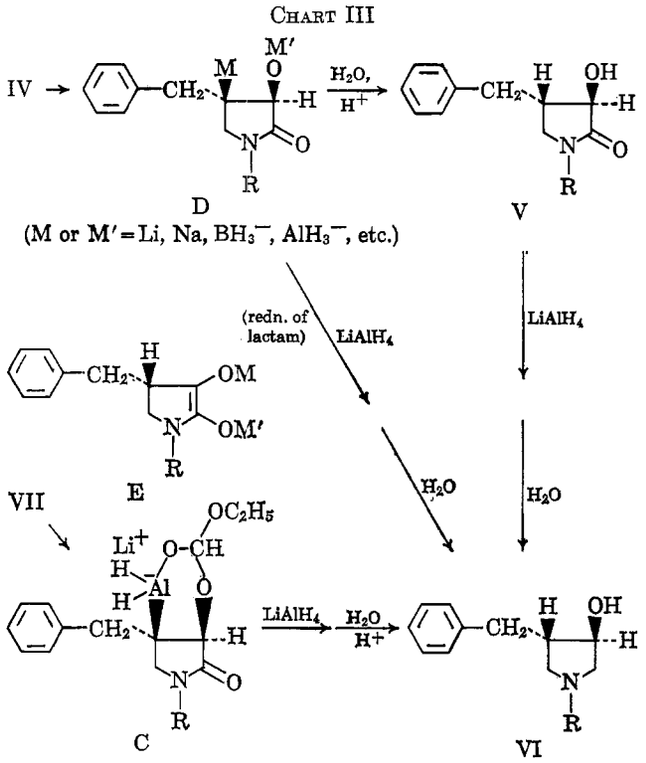
(18) It would not seem reasonable to attribute the preferential formation of *trans*-2-benzylcyclopentanol in the lithium aluminum hydride reduction of 2-benzylcyclopentanone[16] to equilibration of the *cis* and *trans* configurations of the alkoxide anion after that anion is formed in the reduction; such equilibration is not normally observed under the conditions of a lithium aluminum hydride reduction in ether. It appears that the formation of the stable *trans* isomer has been kinetically favored, and that "product development control" analogous to that suggested for certain similar hydride reductions of substituted cyclohexanones may be in evidence here. *Cf.* W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(19) It can probably be assumed that reductions of enolates by lithium aluminum hydride or sodium borohydride would normally be slower than reductions of corresponding carbonyl compounds, and there is experimental evidence supporting this assumption. See ref. 13 and also W. G. Dauben and J. F. Eastham, *ibid.*, **75**, 1718 (1953). Whether an enolate will be fully immune to attack by a given hydride reducing agent probably depends upon relationships of the enolate function to other groups in the molecule, and upon the reaction conditions prevailing in the reduction experiment.

TABLE V. PREPARATION OF 1,3-DISUBSTITUTED 4-BENZYLIDENE-3-HYDROXYPYRROLIDINES

Product	R	R'	M.p., °C.	Yield, %	λ_{max}, mμ (ε)	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa-A	Cyclohexyl	Ph	144–145	72	258 (20,590)	$C_{23}H_{25}NO_2$	79.50	7.23	4.03	79.23	7.00	4.36
IIi	$Ph(CH_2)_2$	Ph	158–159			$C_{25}H_{23}NO_2$	81.26	6.28	3.79	81.02	6.06	3.93
IIh	$PhCH_2$	Ph	184–186			$C_{24}H_{21}NO_2$	81.10	5.96	3.94	80.90	5.75	4.44
IIa-B	Cyclohexyl	CH_3	150–151	73	255 (20,520)	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.83	8.28	4.84

CHART III



tion. However, when the reaction temperature was raised to *ca.* 140° by use of *n*-butyl ether as the solvent, reduction occurred. When applied to the reduction of compound VIIIa, for example, the procedure yielded the *trans* isomer VIa of 1-cyclohexyl-4-benzyl-3-hydroxypyrrolidine in 84.6% yield (expt. 18). The same compound was obtained in 56.2% yield by treatment of the 4-benzylidene-2,3-dioxopyrrolidine (Ia) with excess lithium aluminum hydride in *n*-butyl ether. Other 1-substituted 4-benzyl-3-hydroxypyrrolidines [VI, R = methyl, benzyl, β-phenylethyl; X = Cl, OCH_3, $N(CH_3)_2$] were also conveniently prepared in one step by reduction of the corresponding 4-benzylidene-2,3-dioxopyrrolidine (I) in *n*-butyl ether.[20]

Because the conditions required for reductions of compounds of type VIII were quite severe, whereas reductions of cinnamyl alcohol and related compounds often occur under very mild conditions, it would be hazardous to assume that the mechanism of reduction is the same in both cases. It is quite possible that, at the high temperatures required for reduction of compounds of type VIII, the reduction step itself may be preceded by the isomerization of an allylic alcohol anion to an enolate anion, as was observed with compound Xa under milder conditions. It is noteworthy that, in a case in which the steric situation was very similar, the reduction of 2-benzylidenecyclopentanol by lithium aluminum hydride, the reaction occurred in ethyl ether at room temperature.[16] Probably the ring nitrogen is responsible for this difference in reactivity, but how the effect is exerted is not clear.

(20) A number of the compounds described in this paper and a previous one[5] have been screened for biological activity by the Smith, Kline and French Laboratories and the Lilly Research Laboratories. The only activity observed which seems of possible significance was a rather weak hypotensive effect of certain compounds of types VIII or VI in hypertensive (Goldblatt) rats, an effect which was most definitely established in the case of compound VIj.[5] (Tests on blood pressure effects carried out in the Lilly Research Laboratories under the supervision of Dr. Francis Henderson.)

Experimental Section[21]

Substituted 4-Benzylidene-2,3-dioxopyrrolidines.[5] Procedure A.—To a solution of hydrochloric acid and 95% ethanol were added a substituted 4-carbethoxy-2,3-dioxopyrrolidine and an aromatic aldehyde. The mixture was refluxed for 3 hr., cooled in an ice bath, and filtered to collect the product which had precipitated. In the case of the *p*-dimethylamino compound, 40% aqueous sodium hydroxide was added to the cooled reaction mixture to precipitate the product. The products were recrystallized from 95% ethanol. Yields and melting points quoted in Table IV are for fully purified products. All of the compounds were obtained as bright yellow needles, except for *p*-dimethylamino compound, which formed orange-red plates.

Procedure B.—A solution of 1-cyclohexyl-2,3-dioxopyrrolidine and *p*-dimethylaminobenzaldehyde in hydrochloric acid was heated on a steam cone until it had turned bright red (*ca.* 30 min.). After cooling, solid sodium carbonate was added until the solution was slightly basic, precipitating the product. The orange solid was collected by filtration, air dried, and recrystallized from 95% ethanol. The yield of Id quoted in Table IV is for the purified product.

1,3-Disubstituted 4-Benzylidene-3-hydroxy-2-oxopyrrolidines.—The 1-substituted 4-benzylidene-2,3-dioxopyrrolidines (I) were treated with phenylmagnesium bromide or methylmagnesium iodide in ether solution, as illustrated in the procedure which follows. To a solution of the methyl or phenyl Grignard reagent prepared from 0.31 mole of methyl iodide or bromobenzene and the equivalent weight of magnesium turnings in *ca.* 30 ml. of anhydrous ether was added 7.0 g. (0.026 mole) of 1-cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia) in 300–350 ml. of warm benzene. (In some experiments the 4-benzylidene derivatives were added as solids.) The mixture was stirred at room temperature for 3 hr. and then poured into a mixture of ice and 10%

(21) Melting points are corrected. Microanalyses were by Drs. G. Weiler and F. B. Strauss, Oxford, England; Galbraith Laboratories, Knoxville, Tenn.; Geller Microanalytical Laboratories, Charleston, W. Va.; and A. Bernhardt, Mülheim (Ruhr), Germany. Ultraviolet spectra were determined with a Cary recording spectrophotometer in 95% ethanol; infrared spectra were obtained from Nujol mulls with Perkin-Elmer Model 21 or Infracord spectrophotometers. N.m.r. spectral determinations were made at 60 Mc. with a Varian A-60 spectrometer. All spectra were obtained from deuteriochloroform solutions at ambient temperature, using tetramethylsilane as an internal reference.

hydrochloric acid. The aqueous layer was extracted with benzene. The benzene solutions were combined, washed with water until free of acid, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to yield orange oils which crystallized (usually as fluffy white needles) upon the addition of a benzene–Skellysolve B mixture. The yields quoted for compounds IIa-A and IIa-B in Table V were obtained following two recrystallizations from the same mixture. The compounds of this type could also be crystallized from benzene–cyclohexane or benzene–ether mixtures. They give no color tests with ferric chloride.

Enols of Substituted 4-Benzyl-2,3-dioxopyrrolidines (IV). A. Hydrogenation of Substituted 4-Benzylidene-2,3-dioxopyrrolidines (I).—The 4-benzylidene derivative I and the catalyst in 95% ethanol were shaken in a Parr hydrogenation apparatus at an initial pressure of 60 p.s.i.g. at ambient temperature. The catalysts employed were platinum oxide (Adams catalyst) or 10% palladium on calcium carbonate. In the case of the *p*-chlorobenzylidene derivatives, 1 ml. of concentrated hydrochloric acid was also added to the initial reaction mixture. After hydrogen was no longer absorbed at an appreciable rate, the catalyst was filtered from the solution and the filtrate was evaporated to dryness under reduced pressure. The solid products were recrystallized from 95% ethanol. The yields quoted in Table VI are for the purified products.

B. Reduction of 1-Cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia) with LBAH.—Lithium tri-*t*-butoxyaluminohydride (LBAH)[22] (5.69 g., 0.02 mole) was added to a solution of 1-cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia, 2.69 g., 0.01 mole) in 100 ml. of ether. This mixture was stirred for 1 hr. at room temperature and then acidified with 50 ml. of 10% sulfuric acid. The ether was removed by evaporation. The aqueous slurry was extracted with chloroform, and the combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give a white solid. Recrystallization from ethanol afforded 2.6 g. (92%) of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine (IVa), m.p. 194–196° (lit.[5] m.p. 196–197°). Similar results were obtained in an experiment in which the solvent was tetrahydrofuran (50 ml.). Recrystallization from 95% ethanol raised the melting point to 196–197°.

Treatment of compound Ia (5.38 g., 0.02 mole) by a similar procedure with sodium borohydride (1.51 g., 0.04 mole) in 75 ml. of dry pyridine for 10 hr. at room temperature yielded 1.25 g. (23%) of the enol IVa, m.p. 196–197°, and 1.50 g. (27.5%) of the hydroxypyrrolidone Va, m.p. 128–130°.

C. Reduction of 1-Cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia) with Diborane.—A solution of diborane (5.0 mmoles), prepared by the dropwise addition of 1.42 g. (10 mmoles) of boron trifluoride etherate in 50 ml. of tetrahydrofuran to a stirred slurry of 0.29 g. (7.7 mmoles) of sodium borohydride in 50 ml. of tetrahydrofuran, was filtered and added dropwise to a cold, stirred solution of 2.69 g. (0.01 mole) of 1-cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia) in 75 ml. of tetrahydrofuran through a pressure-equilibrated dropping funnel. After the addition was complete (*ca.* 30 min.), the reaction mixture was warmed to room temperature gradually and absolute ethanol was added to destroy the excess hydride. The solution was then evaporated to dryness under reduced pressure to yield an oily yellow solid. Recrystallization from ethyl acetate afforded 1.08 g. of the enol of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine (IVa), m.p. 185–194°. The mother liquor was extracted with dilute sodium hydroxide solution. The alkaline extracts were acidified with dilute hydrochloric acid and extracted with chloroform. The combined chloroform extracts were dried and upon evaporation under reduced pressure yielded an additional 0.5 g. of product to bring the total yield of compound IVa to 1.58 g. (58%).

D. Isomerization of Substituted 4-Benzylidene-3-hydroxy-2-oxopyrrolidines (X).—The procedure is illustrated by the following example. 1-Cyclohexyl-4-benzylidene-3-hydroxy-2-oxopyrrolidine (Xa, 0.5 g., 1.8 mmoles) was suspended in 25 ml. of 40% sodium hydroxide solution, and then 95% ethanol was added until all of the solid dissolved. The resulting solution, which had turned yellow immediately upon the addition of ethanol, was swirled for a few minutes, acidified with concentrated hydrochloric acid, cooled to room temperature, and filtered to collect the enol of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine (IVa), yield 0.40 g. (80%), m.p. 195–197°. Treatment of compound Xa with LBAH in ether for 1 hr. at room temperature likewise yielded IVa. Data regarding this and other isomerizations are recorded in Table VI.

Preparation of Substituted 1-Cyclohexyl-4-benzylidene-3-hydroxy-2-oxopyrrolidines (X). A. Reduction of Compounds of Type I with LBAH.—In the usual procedure LBAH was added with stirring to a slurry of a 4-benzylidene-2,3-dioxopyrrolidine (I) in anhydrous tetrahydrofuran cooled in a methanol–ice bath. The mixture was stirred at this temperature during the reaction period and then treated with dilute sulfuric acid. (Sulfuric acid was 10% by weight; 25 ml. was used for each 0.01 mole of LBAH.) The organic solvent was removed by evaporation in a stream of air and the resulting aqueous slurry was extracted with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. The solid products of type X recrystallized from anhydrous ethyl acetate. The yields quoted in Table VII are for the purified products.

B. Reduction of Ia with Sodium Borohydride.—Sodium borohydride (1.0 g., 0.026 mole) was added to a cold solution of 1-cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (2.70 g., 0.011 mole) in 100 ml. of 95% ethanol. The mixture was stirred for 1 hr. at 0° in an ice bath, made acidic with dilute hydrochloric acid while still cold, and then evaporated to dryness under reduced pressure. Water (75 ml.) was added and the resulting slurry was extracted with ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to give a light yellow oil which crystallized upon standing. Recrystallization from ethyl acetate afforded 1.63 g. (55%) of 1-cyclohexyl-4-benzylidene-3-hydroxy-2-oxopyrrolidine, m.p. 100–101°.

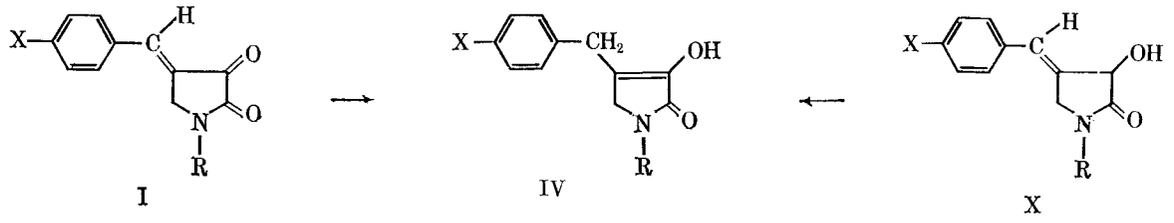
Preparation of Substituted *cis*- and *trans*-4-Benzyl- or -4-Cyclohexylmethyl-3-hydroxy-2-oxopyrrolidines (XI, V, XVI, and XVIII). A. Reductions of Compounds of Types I or IV with Sodium Borohydride.—Sodium borohydride was added to a slurry of a substituted 4-benzylidene-2,3-dioxopyrrolidine (I) or the enol of a substituted 4-benzyl-2,3-dioxopyrrolidine (IV) in 95% ethanol at room temperature. The mixture was stirred for 1 hr., acidified by the addition of 20% hydrochloric acid, filtered to remove the precipitated sodium chloride, and evaporated to dryness under reduced pressure. Water was added to the residue and the resulting oily slurry was extracted with ether or chloroform. The combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The oily solid was triturated with anhydrous ether and the residue was recrystallized from *n*-heptane or a *n*-heptane–absolute ethanol mixture. The yields quoted in Table VIII are for the purified products.

B. Hydrogenations of Compounds of Types V, X, and XI.—A mixture of a substituted 4-benzylidene- or 4-benzyl-3-hydroxy-2-oxopyrrolidine (X, XI, or V) and a catalyst (Adams platinum oxide or 10% palladium on calcium carbonate) in 95% ethanol was shaken in a Parr hydrogenation apparatus at an initial pressure of 60 p.s.i. at room temperature. At the end of the reaction period the catalyst was then filtered from the solution and the filtrate was evaporated to dryness under reduced pressure. The solid products were recrystallized from 95% ethanol. The yields quoted in Table VIII are for the purified products.

Preparation of Substituted 4-Benzylidene-3-hydroxypyrrolidines (VIII).—The substituted 4-benzylidene-2,3-dioxopyrrolidine (I) was added with stirring to a cold slurry of excess lithium aluminum hydride in anhydrous ether. The mixture was refluxed for 2 to 6 hr. and then cooled in an ice bath. Aqueous sodium potassium tartrate (20%) or, in the case of the last two compounds listed in Table IX, saturated sodium sulfate solution, was added with stirring to decompose the lithium and aluminum salts. When the sodium potassium tartrate solution was used in the decomposition, the ether layer was separated and the aqueous layer was extracted four times with ether. When a saturated sodium sulfate solution was used, the mixture was filtered and the inorganic filter cake was washed well with ether. The ether solutions were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The 1-methyl- and 1-benzyl-4-*p*-chlorobenzylidene derivatives were oils which were isolated as the *p*-toluenesulfonate salts by dissolving the oil and a slightly less than equivalent amount, based on starting material, of *p*-toluenesulfonic acid monohydrate in minimum amounts of absolute ethanol and mixing the two solutions. The salt, which separated immediately, was

(22) H. C. Brown and R. R. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

TABLE VI. PREPARATION OF ENOLS OF SUBSTITUTED 4-BENZYL-2,3-DIOXOPYRROLIDINES (IV)



I IV X

Product	R	X	Appearance, m.p., °C.	Yield, %	Reaction mixture: Starting material (g.)	Reagent or catalyst	Solvent (ml.)	Reaction period, hr.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IVb	Cyclohexyl	Cl	Plates 190–192 dec.	59	I (10)	PtO_2 (50 mg.)	95% ethanol (300)	0.5	$C_{17}H_{20}ClNO_2$	66.76	6.59		66.44	6.72	
IVg	Ph(CH_2)$_2$	Cl	Plates, 175–176 dec.	45	I (10)	PtO_2 (50 mg.)	95% ethanol (300)	1.0	$C_{19}H_{18}ClNO_2$	69.92	5.53		70.12	5.68	
IVc	Cyclohexyl	CH_3O	Rods, 171–173 dec.	80	I (5)	Pd on $CaCO_3$ (500 mg.)	95% ethanol (200)	0.33	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.78	7.57	4.63
				80	X (0.5)	40% NaOH (15 ml.)	Aq. ethanol	0.25							
IVd	Cyclohexyl	$(CH_3)_2N$	Needles, 200–202 dec.	74	I (5)	Pd on $CaCO_3$ (500 mg.)	95% ethanol (200)	1.0	$C_{19}H_{26}N_2O_2$	72.58	8.34	8.91	72.85	8.44	8.70
				90	X (0.25)	40% NaOH (15 ml.)	Aq. ethanol	0.25							
IVa[a]	Cyclohexyl	H	Rods, 196–197 dec.	74	I (2.69)	LBAH (5.96 g.)	THF (50)	1.0	$C_{17}H_{21}NO_2$						
				58	I (2.69)	B_2H_6 (0.14 g.)	THF (175)	1.0							
				80	X (0.5)	40% NaOH (25 ml.)									
				75	X (2.4)	LBAH (1.94 g.)	Ether (100)	1.0							

[a] Described previously in ref. 5.

TABLE VII. PREPARATION OF SUBSTITUTED 4-BENZYLIDENE-1-CYCLOHEXYL-3-HYDROXY-2-OXOPYRROLIDINES

I X

Product	X	Appearance, m.p., °C.	Yield, %	Reaction mixture: Mole of I	Reducing agent, (mole)	Solvent (ml.)	Reaction period, hr.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Xa	H	White needles,[a,b] 100–101	55	0.011	$NaBH_4$ (0.026)	95% ethanol (100)	1	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.06	7.68	5.22
			44	0.025	$NaBH_4$ (0.007)	Diglyme (75)	1							
			87	0.01	LBAH (0.02)	THF (100)	2							
Xc	CH_3O	Pale yellow needles, 160–161	93	0.03	LBAH (0.06)	THF (300)	0.75	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.48	7.55	4.35
Xd	$(CH_3)_2N$	Yellow powder, 177–179	56	0.0125	LBAH (0.025)	THF (100)	2	$C_{19}H_{26}N_2O_2$	72.58	8.34	8.91	72.46	8.59	9.04

[a] Xa oxidized to starting material upon exposure to light and upon standing in solution. [b] Ultraviolet spectrum (95% ethanol): λ_{max} 254 mμ (ε 16,640), 285 mμ (ε 790) (shoulder), 293 mμ (ε 360); λ_{min} 225 mμ (ε 4535), 289 mμ (ε 290).

TABLE VIII. PREPARATION OF SUBSTITUTED *cis*- AND *trans*-4-BENZYL- OR -4-CYCLOHEXYLMETHYL-3-HYDROXY-2-OXOPYRROLIDINES

V (*trans*) XI (*cis*) XVIII (*trans*) XVI (*cis*)

Product	R	X	M.p., °C.	Yield, %	Reaction mixture: Starting material (mole)	NaBH4, mole	Catalyst (mg.), reaction period, hr.	Ethanol, ml.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Va	Cyclohexyl	H	128–130	72	Ia (0.018)	0.027		75	$C_{17}H_{23}NO_2$	74.69	8.48	5.12	74.89	8.42	5.23
				83	IVa (0.021)	0.054		200							
				74	Xa (0.006)		Pd (200), 0.5	150							
Ve[a]	CH_3	Cl	132–133	65	Ie (0.05)	0.07		200	$C_{12}H_{14}ClNO_2$	60.20	5.88	5.84	60.08	5.81	5.56
Vc	Cyclohexyl	CH_3O	95–96	62	Ic (0.04)	0.067		250	$C_{18}H_{25}NO_3$	71.25	8.31		71.36	8.41	
Vd	Cyclohexyl	$(CH_3)_2N$	132–134	70	Id (0.016)	0.027		100	$C_{19}H_{28}N_2O_2$	72.11	8.92	8.85	72.25	8.90	8.78
XIa	Cyclohexyl	H	134–135	88	Xa (0.003)		PtO_2 (100), 0.25–0.5	100	$C_{17}H_{23}NO_2$	74.69	8.48		74.86	8.44	
XIc	Cyclohexyl	CH_3O	138–139	80	Xc (0.016)		PtO_2 (500), 0.33	200	$C_{18}H_{25}NO_3$	71.25	8.31	4.62	71.37	8.58	4.74
XId	Cyclohexyl	$(CH_3)_2N$	163–164	73	Xd (0.006)		PtO_2 (190), 0.33	100	$C_{19}H_{28}N_2O_2$	72.11	8.92	8.85	71.99	8.70	9.03
XVI	Cyclohexyl		161–162	88	Xa (0.0184)		PtO_2, (500), 24	200	$C_{17}H_{29}NO_2$	73.07	10.46	5.01	72.90	10.55	4.81
XVIII	Cyclohexyl		138–139	88	Va (0.0183)		PtO_2 (500), 25	200	$C_{17}H_{29}NO_2$	73.07	10.46	5.01	72.98	10.24	5.30

[a] Configuration not established; *trans* configuration assigned tentatively on the basis of the method of preparation.

filtered out and recrystallized from absolute ethanol. The other products, as the crude free bases, were colored solids, mixed with oils. They were purified by sublimation and recrystallization. The yields and melting points quoted in Table IX are for the purified products.

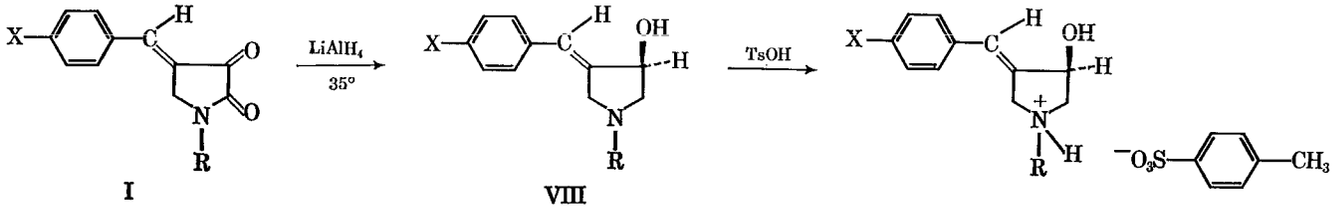
Preparation of Substituted *cis*- or *trans*-4-Benzyl- or -4-Cyclohexylmethyl-3-hydroxypyrrolidines (VI, IX, XVII or XIX).—Compounds of types I, V, VII, VIII, or XI were added with stirring to a slurry of excess lithium aluminum hydride in anhydrous ethyl or *n*-butyl ether. The mixture was heated at the reflux temperature for 2–6 hr., then cooled in an ice bath. Aqueous sodium potassium tartrate (20%) or, in the case of compounds VIc, VId, IXa, IXc, IXd, XIIIa, and XVa, saturated sodium sulfate solution, was added with stirring to decompose the lithium and aluminum salts. When the sodium potassium tartrate solution was used, the ether layer was separated and the aqueous layer was extracted four times with ether. When saturated sodium sulfate was used, the mixture was filtered and the inorganic filter cake was washed well with ethyl ether. The combined ether solutions were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The 1-cyclohexyl derivatives were obtained as solids and purified by sublimation and/or recrystallization, but the other compounds were oils which were converted into salts of *p*-toluenesulfonic acid in the same manner as the 4-benzylidene-3-hydroxypyrrolidines (VIII) described above. Anhydrous ether acetate was added to the ethanol solutions of these salts, which were cooled overnight in a refrigerator to induce crystallization. The salts were collected and recrystallized from absolute ethanol or absolute ethanol–ethyl acetate mixtures with Norit decolorization. Several recrystallizations were sometimes necessary. The yields and melting points quoted in Table X are for fully purified products.

Sodium Borohydride Reductions of Enolates of 1-Cyclohexyl-4-benzyl-2,3-dioxopyrrolidine (IVa) in Dry Diglyme.—Enolates derived from the enol IVa could be obtained by the action of sodium ethoxide on the enol IVa and would also be intermediates (following isomerization of the initial reduction product Xa) in the reduction of the benzylidene derivative Ia to the hydroxypyrrolidones Va (*trans*) or XIa (*cis*) by sodium borohydride. The experiments recorded below indicate that enolates produced in either manner are reduced in diglyme even under anhydrous conditions to yield principally the *trans* reduction product Va. In the experiment with compound Ia the reaction mixture was treated with excess propionaldehyde to destroy the sodium borohydride prior to treatment with water and thus establish that the enolate was being reduced during the reaction period in dry diglyme, and not merely during the work-up procedure, after water had been added.

Sodium borohydride (0.75 g., 0.02 mole) was added to 2.69 g. (0.01 mole) of 1-cyclohexyl-4-benzylidene-2,3-dioxopyrrolidine (Ia) in 70 ml. of dry diglyme (distilled from lithium aluminum hydride). The reaction mixture was stirred at room temperature for 2 hr. and then mixed rapidly with 9.29 g. (0.16 mole) of propionaldehyde. A mildly exothermic reaction was evident. The mixture was stirred at room temperature for 1 hr., acidified with 10% hydrochloric acid (no hydrogen evolution was observed), and poured into *ca.* 750 ml. of water. To complete the precipitation of the product the resulting cloudy white suspension was allowed to stand at room temperature overnight. Filtration afforded 1.7 g. of crude *trans*-1-cyclohexyl-4-benzyl-3-hydroxy-2-oxopyrrolidine (Va), m.p. 120–124°. Ether extraction of the filtrate gave an oil from which an additional 0.55 g. of Va, m.p. 124–126°, was obtained following crystallization from an absolute ethanol–Skellysolve B mixture. The total yield of Va was thus 2.25 g. (83%). The infrared spectra of both portions of the product were indistinguishable from that of pure samples of Va, and the prominent bands of the *cis* isomer at 8.36, 10.40, and 13.45 μ were absent. Recrystallization from absolute ethanol–Skellysolve B raised the melting point to that of pure Va (m.p. 128–130°).

In another experiment the enol IVa (2.0 g., 7.4 mmoles) was added to a sodium ethoxide solution prepared by the addition of 0.17 g. (7.4 mg.-atoms) of sodium metal to 50 ml. of absolute ethanol. The solution was evaporated to dryness under reduced pressure over a steam cone. The enolate, a sticky yellow solid, was taken up in 50 ml. of anhydrous diglyme to yield a cloudy orange solution. Sodium borohydride (0.56 g., 14.8 mmoles) was added and the mixture was stirred for 3 hr. at room temperature, acidified with 10% hydrochloric acid, and

TABLE IX. PREPARATION OF SUBSTITUTED 4-BENZYLIDENE-3-HYDROXYPYRROLIDINES AND THEIR *p*-TOLUENESULFONATES

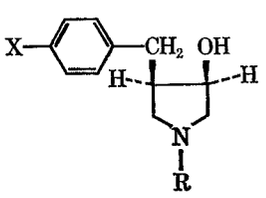


I VIII

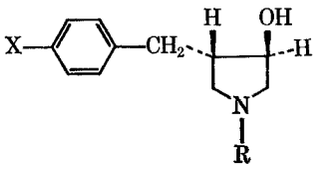
Product	R	X	Appearance, m.p.[a] °C.	Yield, %	Reaction mixture: I, mole	Reaction mixture: $LiAlH_4$, mole	Reaction mixture: Ether, ml.	Reaction time, hr.	λ_{max}, mμ (ϵ)	Formula	Calcd., %: C	Calcd., %: H	Calcd., %: N	Found, %: C	Found, %: H	Found, %: N
VIIIa	Cyclohexyl	H	Colorless needles, 131–133 (B)	59[b]	0.05	0.28	200	2	257 (19,200)	$C_{17}H_{23}NO$	79.34	9.01	5.44	79.25	9.40	5.62
VIIIj	CH_3	H	Colorless needles, 109–110 (B)	24[c]	0.09	0.52	500	2		$C_{12}H_{15}NO$	76.15	7.99	7.40	76.20	8.14	7.41
VIIIi	$Ph(CH_2)_2$	H	Colorless needles, 141–142 (B)	38[d]	0.045	0.27	300	4		$C_{19}H_{21}NO$	81.68	7.58	5.01	81.53	7.62	5.12
VIIIh	$PhCH_2$	H	Colorless needles, 99–101 (B)	42[e]	0.06	0.34	400	4		$C_{18}H_{19}NO$	81.47	7.22	5.28	81.68	7.31	5.31
VIIIb	Cyclohexyl	Cl	Colorless needles, 151–152 (B)	45.5[b]	0.045	0.27	300	2	263 (26,400)	$C_{17}H_{22}ClNO$	69.96	7.60	4.80	69.99	7.68	4.72
VIIIe	CH_3	Cl	Colorless needles, 177–179 (T)	38[f]	0.07	0.41	450	2		$C_{19}H_{22}ClNO_4S$	57.89	5.60	3.54	57.85	6.04	3.47
VIIIg	$Ph(CH_2)_2$	Cl	Colorless crystals, 88–90 (B)	51[e]	0.06	0.36	400	6		$C_{19}H_{20}ClNO$	72.71	6.42	4.45	72.54	6.85	4.28
VIIIf	$PhCH_2$	Cl	Colorless needles, 195–197 (T)	70[g]	0.06	0.35	400	4		$C_{25}H_{26}ClNO_4S$	63.61	5.55	2.97	63.34	5.63	2.92
VIIIc	Cyclohexyl	CH_3O	Colorless needles, 126–127 (B)	71[h]	0.045	0.27	300	2	265 (25,800)	$C_{18}H_{25}NO_2$	75.22	8.77	4.87	75.51	8.59	5.01
VIIId	Cyclohexyl	$(CH_3)_2N$	Pale yellow needles, 159–160 (B)	52[h,i]	0.032	0.16	250	2	301 (28,100)	$C_{19}H_{28}N_2O$	75.96	9.36	9.33	75.73	9.26	9.46

[a] Melting points followed by T are of *p*-toluenesulfonate salts; melting points followed by B are of free bases. [b] Sublimed at 135–145° (<10 μ). Recrystallized from *n*-heptane. [c] Sublimed at 80–90° (<10 μ). Recrystallized from *n*-hexane. [d] Sublimed at 125–135° (<10 μ). Recrystallized from *n*-heptane. [e] Sublimed at 125–135° (<10 μ). Recrystallized from *n*-hexane. [f] *p*-Toluenesulfonic acid monohydrate (12.05 g., 0.064 mole) added. [g] *p*-Toluenesulfonic acid monohydrate (10.33 g., 0.054 mole) added. [h] Recrystallized from anhydrous ethyl acetate. [i] Very sensitive to light.

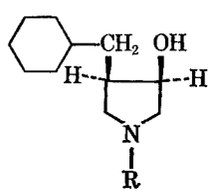
TABLE X. PREPARATION OF *cis*- AND *trans*-SUBSTITUTED 4-BENZYL- OR 4-CYCLOHEXYLMETHYL-3-HYDROXYPYRROLIDINES



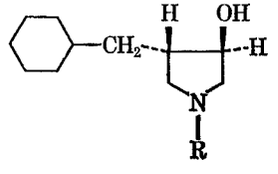
IX (*cis*)



VI (*trans*)



XVII (*cis*)



XIX (*trans*)

Product	R	X	M.p.,[a] °C.	Yield, %	Reaction mixture: Starting material (mole)	Reaction mixture: $LiAlH_4$, moles	Reaction mixture: Solvent (ml.)	Reaction period, hr.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
VIa[b]	Cyclohexyl	H	94–95 (B)	56	Ia (0.06)	0.28	$(C_4H_9)_2O$ (200)	4	$C_{17}H_{25}NO$						
				85	VIIIa (0.014)	0.079	$(C_4H_9)_2O$ (100)	2							
VIj[b,c]	CH_3	H	131–133 (T)	29	Ij (0.03)	0.174	$(C_4H_9)_2O$ (200)	4	$C_{19}H_{25}NO_4S$						
VIi[b,c]	$Ph(CH_2)_2$	H	134–135 (T)	55	Ii (0.023)	0.174	$(C_4H_9)_2O$ (200)	4	$C_{26}H_{31}NO_4S$						
VIh[b,c]	$PhCH_2$	H	132–134 (T)[d]	63	Ih (0.03)	0.174	$(C_4H_9)_2O$ (200)	4	$C_{25}H_{29}NO_4S$						
VIc	Cyclohexyl	CH_3O	110 (B)[e]	76	Ic (0.05)	0.14	$(C_4H_9)_2O$ (150)	2	$C_{18}H_{27}NO_2$	74.70	9.40	4.84	74.81	9.67	4.90
				70	Vc (0.033)	0.132	$(C_2H_5)_2O$ (250)	2							
VId	Cyclohexyl	$(CH_3)_2N$	129–131 (B)[f]	19	Id (0.032)	0.13	$(C_4H_9)_2O$ (150)	2	$C_{19}H_{30}N_2O$	75.45	10.00	9.30	75.54	9.84	9.25
				81	Vd (0.011)	0.14	$(C_2H_5)_2O$ (100)	2							
VIe[c]	CH_3	Cl	171–172 (T)[g]	70	Ve (0.037)	0.20	$(C_2H_5)_2O$ (200)	2	$C_{19}H_{24}ClNO_4S$	57.60	6.08	3.52	57.88	6.11	3.37
VIf[c]	$PhCH_2$	Cl	196–198 (T)	20	If (0.06)	0.35	$(C_4H_9)_2O$ (400)	4	$C_{25}H_{28}ClNO_4S$	63.34	5.95	2.96	63.15	6.16	2.98
IXa	Cyclohexyl	H	100–101 (B)[h]	91	XIa (0.011)	0.044	$(C_2H_5)_2O$ (1000)	18	$C_{17}H_{25}NO$	78.71	9.72		78.84	9.75	
IXc	Cyclohexyl	CH_3O	79–80 (B)[h]	71	XIc (0.0115)	0.046	$(C_2H_5)_2O$ (1000)	25	$C_{18}H_{27}NO_2$	74.70	9.40	4.84	74.67	9.39	4.97
IXd	Cyclohexyl	$(CH_3)_2N$	99–101 (B)[h]	88	XId (0.0043)	0.0172	$(C_2H_5)_2O$ (250)	11.5	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	75.30	10.01	9.00
XVII	Cyclohexyl		121–122 (B)[h]	81	XVI (0.0118)	0.048	$(C_2H_5)_2O$ (1000)	4.75	$C_{17}H_{31}NO$	76.92	11.72	5.28	76.95	11.90	5.07
XIX	Cyclohexyl		100–101 (B)[i]	87	XVIII (0.0125)	0.05	$(C_2H_5)_2O$ (1000)	5.5	$C_{17}H_{31}NO$	76.92	11.72	5.28	77.16	11.96	5.08

[a] Melting points followed by T are of *p*-toluenesulfonates; melting points followed by (B) are for free bases. [b] Described previously in ref. 5. [c] Configuration not established; *trans* configuration assigned tentatively on the basis of the method of preparation. [d] A sample described in ref. 5, produced in low yield by lithium aluminum hydride reduction of the crude hydroxypyrrolidone Vh, melted at 142.5–144° and may have represented the other isomer. [e] Recrystallized from *n*-heptane–acetone mixture. [f] Sublimed at 135–145° (<10 μ) and recrystallized from ethyl acetate. [g] Recrystallized from an *n*-heptane–absolute ethanol mixture. [h] Recrystallized from Skellysolve B. [i] Sublimed under reduced pressure and recrystallized from Skellysolve B.

poured into *ca.* 500 ml. of water. After the mixture had been kept overnight at room temperature, it was filtered to collect 0.7 g. of light yellow powder. Concentration of the mother liquor afforded an additional 1.10 g. of product [total yield 1.8 g. (89%) of material melting at *ca.* 126°]. Recrystallization gave *trans*-1-cyclohexyl-4-benzyl-3-hydroxy-2-oxopyrrolidine (Va) as white needles, m.p. 128–130°. In a similar experiment carried out on a smaller scale, the sodium enolate was precipitated and obtained as a dry powder by addition of Skellysolve B to a highly concentrated ethanol solution of the enolate. This solid lacked the enolic hydroxy absorption at 3.12 μ and melted with decomposition above 300°. A 0.1-g. (0.34-mmole) portion was reduced with 0.1 g. (2.6 mmoles) of sodium borohydride in 10 ml. of dry diglyme for 1 hr. at room temperature. The reaction mixture was acidified and diluted with water in the manner described above, and the product was taken up in ether. The ether solution was dried over magnesium sulfate and evaporated to leave an oil which crystallized upon addition of a mixture of absolute ethanol and Skellysolve B. Recrystallization from the same mixture afforded 0.06 g. (67%) of pure *trans*-1-cyclohexyl-4-benzyl-3-hydroxy-4-oxopyrrolidine (Va), m.p. 128–130°.

Reductions of Chalcone. Reduction with LBAH.—Solid LBAH (11.38 g., 0.04 mole) was added to a stirred suspension of 4.17 g. (0.02 mole) of chalcone in 100 ml. of tetrahydrofuran at room temperature. After the mixture had been stirred for 2 hr. it was acidified with 100 ml. of 10% sulfuric acid and most of the tetrahydrofuran was removed by evaporation. The resulting aqueous slurry was extracted several times with chloroform, and the combined chloroform extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a yellow oil which partly crystallized when allowed to stand. This product was recrystallized from absolute ethanol to yield 1,3-diphenyl-1-propanone (XIII, 1.37 g., 44%) as fluffy white needles: m.p. 69–71°; $\lambda_{max}^{95\%\ EtOH}$ 242 mμ (ϵ 12,560) and 284 mμ (ϵ 710).[23] The 2,4-dinitrophenylhydrazone melted at 182–186° and the oxime at 79–81°, in agreement with reported values.[24,13a]

The mother liquor from the recrystallization yielded an oil which was identified from spectroscopic data as crude 1,3-diphenyl-2-propen-1-ol: (XIV): $\lambda_{max}^{95\%\ EtOH}$ 254 and 293 mμ; infrared hydroxyl bands at 2.78 and 2.90 μ, no carbonyl absorption at 6.00 μ). Estimation of the amount of this compound from the ultraviolet data indicated a yield of 1.53 g. (49%).

Slightly higher yields of the saturated ketone were obtained with smaller amounts of LBAH and a lower temperature or shorter reaction period. Treatment of chalcone (0.01 mole) with 0.0165 mole of LBAH in 125 ml. of tetrahydrofuran for 3 hr. at 0° or 1 hr. at room temperature yielded 0.75 g. (48%) of 1,3-diphenyl-1-propanone (XIII), m.p. 68–71°. Treatment of crude 1,3-diphenyl-2-propen-1-ol with LBAH in tetrahydrofuran at room temperature for 2 hr. produced no isomerization; the infrared spectrum showed no carbonyl absorption and was essentially unchanged.

Reduction with Diborane.—A solution of diborane (0.0125 mole), prepared by the dropwise addition of 3.55 g. (0.025 mole) of boron trifluoride etherate in 50 ml. of tetrahydrofuran to a stirred suspension of 0.72 g. (0.019 mole) of sodium borohydride in 50 ml. of tetrahydrofuran, was filtered and added dropwise to a cold, stirred solution of 5.21 g. (0.025 mole) of chalcone in 100 ml. of tetrahydrofuran through a pressure-equilibrated dropping funnel. After the addition was complete (*ca.* 1 hr.), the reaction mixture was warmed to room temperature gradually and absolute ethanol was added to destroy the excess hydride. The solution was then evaporated to dryness under reduced pressure to yield a yellow oil which was found to contain an amount of 1,3-diphenyl-1-propanone (XIII) equivalent to a 29% yield by comparison of the extinction coefficient (ϵ 3590) at 242 mμ of the oil with that of a pure sample of the compound (ϵ 12,560). Treatment of a portion of the product mixture with 2,4-dinitrophenylhydrazine afforded a 27% yield of 1,3-diphenyl-1-propanone dinitrophenylhydrazone, m.p. 178–182°, the infrared spectrum of which was identical with that of a pure sample. The infrared spectrum of the oil showed strong hydroxyl absorption at 3.01 μ, but the ultraviolet spectrum showed no absorption characteristic of a substituted styrene compound at 254 mμ. Therefore, it is believed that the other component of the oil was the saturated alcohol, 1,3-diphenyl-1-propanol.

Preparation of 4-Benzyl- and 1-Cyclohexyl-4-*p*-chlorobenzyl-3-ethoxycarbonyloxy-2-oxo-3-pyrrolines (Enol Carbonates VIIa and VIIb).—Enols of type IV (0.02 mole) were added to solutions of triethylamine (3.2 ml., 0.022 mole) in 50 ml. of chloroform kept below 0° in a methanol–ice bath. Ethyl chloroformate (2.1 ml., 0.022 mole) was added slowly enough to allow the temperature to remain at 0° or below. The reaction mixtures were allowed to stand at 0° for 30 min. and the solvent was then removed under reduced pressure with warming from a water bath. The residues were extracted with boiling *n*-hexane, leaving a residue of triethylamine hydrochloride. Concentration of the extracts by evaporation of the solvent under reduced pressure yielded the products which were recrystallized from *n*-hexane. The two compounds prepared are described separately below.

1-Cyclohexyl-4-benzyl-3-ethoxycarbonyloxy-2-oxo-3-pyrroline (VIIa), 5.48 g. (80.0%) of colorless needles, m.p. 95–96°, was obtained from 5.42 g. (0.02 mole) of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33. Found: C, 70.11; H, 7.62.

1-Cyclohexyl-4-*p*-chlorobenzyl-3-ethoxycarbonyloxy-2-oxo-3-pyrroline (VIIb), 5.55 g. (75.0%) of colorless needles, m.p. 89–91°, was obtained from 5.60 g. (0.02 mole) of 1-cyclohexyl-4-*p*-chlorobenzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.56; H, 6.40. Found: C, 63.99; H, 6.31.

Acknowledgment.—The authors are much indebted to Dr. George E. Milliman and to James A. Fitzgerald for n.m.r. measurements and to John W. Kersting, a National Science Foundation Undergraduate Research Participant (1960), for valuable aid in the synthesis of several pyrrolidine derivatives.

(23) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

(24) (a) G. S. Fonken and W. S. Johnson, *J. Am. Chem. Soc.*, **74**, 831 (1952); (b) R. M. Dodson and J. K. Seyler, *J. Org. Chem.*, **16**, 461 (1951).