Chloral–ketone condensations in acetic anhydride. Reaction of chloral with butanone, 3-pentanone, cyclohexanone, and 4-methyl-2-pentanone

EBERHARD KIEHLMANN AND PUI-WAH LOO
Department of Chemistry, Simon Fraser University, Burnaby 2, British Columbia

Received November 5, 1968

In the presence of sodium acetate as catalyst, chloral hydrate undergoes a mixed aldol condensation with aliphatic and alicyclic ketones in acetic anhydride as solvent. Contrary to previous literature reports, reaction occurs at both the methyl and the methylene group in α-position to the carbonyl group of butanone, to give a mixture of 1,1,1-trichloro-2-hydroxy-4-hexanone (**1**) and 1,1,1-trichloro-2-hydroxy-3-methyl-4-pentanone (**2***a* and **2***b*, diastereomers). 3-Pentanone, cyclohexanone, and 4-methyl-2-pentanone yield 1,1,1-trichloro-2-hydroxy-3-methyl-4-hexanone (**3***a* and **3***b*, diastereomers), 2-(1-hydroxy-2,2,2-trichloroethyl-)cyclohexanone (**4***a* and **4***b*, diastereomers), and 1,1,1-trichloro-2-hydroxy-6-methyl-4-heptanone (**5**), respectively. Compound **5** is the exclusive product formed from chloral hydrate and 4-methyl-2-pentanone since attack at the methylene group is sterically hindered. The low-melting diastereomers **2***a*, **3***a*, and **4***a* which have not been characterized before, exhibit strong intramolecular hydrogen bonding and have been assigned the *threo* configuration on the basis of nuclear magnetic resonance and molecular model studies.

Canadian Journal of Chemistry, 47, 2029 (1969)

The condensation of chloral hydrate with aliphatic and alicyclic ketones is known to give aldol addition products which do not readily undergo dehydration when the reaction is carried out in acetic anhydride in the presence of sodium acetate as catalyst. According to Caujolle and co-workers (1), acetone, butanone, 3-pentanone, cyclohexanone, benzalacetone, and camphor yield only one addition product, respectively, under these experimental conditions although two asymmetric centers are generated, i.e., two diastereomeric products are possible when reaction occurs at the α-methylene group of butanone, 3-pentanone, or cyclohexanone. It has been postulated but not experimentally verified by the same authors (1), that chloral adds preferentially at the methylene group if a ketone e.g., butanone, contains both a methyl and a methylene group in α-position to the carbonyl function. The opposite view is held by Breusch and Keskin (2), who prepared a series of fourteen 1,1,1-trichloro-2-hydroxy-4-alkanones by refluxing the appropriate ketone, $R—CH_2—CO—CH_3$, with anhydrous chloral in glacial acetic acid. They determined the structure of the condensation product of 4-methyl-2-pentanone and chloral by synthesis and mixture melting point determination of 6-methyl-4-oxoheptanoic acid by two different routes, one of which involved 1,1,1-trichloro-2-hydroxy-6-methyl-4-heptanone (**5**) as an intermediate. On the basis of this experiment, the general structure $R—CH_2—CO—CH_2—CHOH—CCl_3$ resulting from addition of chloral at the ketone methyl group was assigned to all 14 reaction products.

Although the structure of **5** was subsequently verified by spectroscopic means (3), it appeared strange to us that the site of aldol addition changes from the α-methylene to the α-methyl group of a 2-alkanone when anhydrous chloral and glacial acetic acid are used instead of chloral hydrate and acetic anhydride. Therefore, we decided to reinvestigate the reaction of chloral hydrate with ketones in acetic anhydride in the presence of sodium acetate placing particular emphasis on the number and structure of the reaction products formed. This product study which made extensive use of modern techniques (vapor phase chromatography (v.p.c.) and nuclear magnetic resonance (n.m.r.)) not available to the authors of the original papers (1, 2) was also desirable as a first step toward future kinetic investigations of the addition step in mixed aldol condensations.

Results and Discussion

Chloral (trichloroacetaldehyde) appears to be a particularly suitable aldehyde component for studying the mechanism of mixed aldol condensations since due to the absence of α-hydrogens no self-condensation products are possible; thus, the desired mixed condensation product with the ketone component is expected to be formed exclusively. However, due to the inductive effect of the three chlorine atoms, the carbonyl group of chloral surpasses that of other aldehydes

TABLE I

Reaction products from chloral hydrate and various ketones*

Ketone	Reaction time (h)	Product yield (mole %)†‡				Literature‡§ yield (%)
		A	B	C	6	
Butanone	58	10.1	13.6	13.6	6.6	55 (B)
3-Pentanone	102	12.2	14.5	—	6.3	70 (B)
Cyclohexanone	45	5.2	18.3	—	23.5	70 (B)
4-Methyl-2-pentanone	52	—	—	17.7	5.3	—
Acetone	50	—	—	33.9	5.1	50 (C)
Benzalacetone	21	—	—	Trace	43‖	65 (C)

*Equation [1]: $RCOCH_2R' + CCl_3CH(OH)_2 \rightarrow RCOCHR'—CHOH—CCl_3$.
Experimental conditions: 1.25 moles ketone, 1 mole $CCl_3CH(OH)_2$, 1 mole Ac_2O, 10% (by weight) NaOAc, 70°.
†Determined by v.p.c. of crude product mixture on a 5 ft × $\frac{1}{4}$ in. SE-30 column (120–140°).
‡A = low-melting diastereomer, B = high-melting diastereomer, C = $RCOCH_2CHOHCCl_3$, 6 = $CCl_3CH(OAc)_2$.
§Reference (1).
‖Determined by n.m.r. of crude product mixture after removal of solvent, NaOAc, and unreacted chloral hydrate.

in additive ability and is readily attacked even by weak nucleophiles. It adds water to form a stable gem-diol (chloral hydrate), and acetic anhydride (4) to form 1,1-diacetoxy-2,2,2-trichloroethane (**6**) (trichloroethylidene diacetate). The latter is a stable compound which was obtained as the exclusive product in an attempt to prepare **5** from 4-methyl-2-pentanone and anhydrous chloral in acetic anhydride as solvent.

$$\begin{tikzcd}(CH_3)_2CHCH_2COCH_3 + CCl_3CHO + Ac_2O + NaOAc \arrow[r] \arrow[d, "/" marking] & \underset{\mathbf{6}}{CCl_3CH(OAc)_2\ (71\%)} \\ \underset{\mathbf{5}}{(CH_3)_2CHCH_2COCH_2CHOHCCl_3}\ \text{(not observed)} & \end{tikzcd}$$

Chloral hydrate, on the other hand, is less reactive than anhydrous chloral as expected from its structure. It forms **6** in 5% yield when treated with acetic anhydride and sodium acetate for 52 h at 100°.

$$CCl_3CH(OH)_2 + Ac_2O \xrightarrow{NaOAc} HOAc + \underset{\mathbf{6}}{CCl_3CH(OAc)_2}$$

Thus under the experimental conditions reported in the literature (1), i.e., treatment of a ketone with chloral hydrate, acetic anhydride and sodium acetate at 70° for several hours, we expected to obtain substantial quantities of **6** in addition to the desired chloral–ketone condensation products. The experimental results reported below were essentially in agreement with these expectations.

In contrast to the results reported by Caujolle and co-workers (1), we obtained three isomeric condensation products from butanone, two diastereomeric products each from 3-pentanone and cyclohexanone, respectively, and one product each from 4-methyl-2-pentanone, acetone and benzalacetone; considerable amounts of 1,1-diacetoxy-2,2,2-trichloroethane were found in all product mixtures, but no dehydration products of the type $R—CO—CR'{=}CH—CCl_3$ or acetylation products of the type $R—CO—CHR'—CHOAc—CCl_3$ were detected. This demonstrates that in general the aldol reaction between ketones of the type $R—CO—CH_2—R'$ (except when R′ is bulky, *vide infra*) and chloral hydrate leads to the formation of all possible isomeric condensation products resulting from attack at both the α-methyl ($R = CH_3$) and the α-methylene group of the ketone. Yields and product composition data for the condensation reaction [1] are summarized in Table I.

$$[1]\quad RCOCH_2R' + CCl_3CH(OH)_2 \xrightarrow[70°]{Ac_2O,\ NaOAc} RCOCHR'—CHOH—CCl_3$$

1, R = Et, R′ = H	**5**, R = *i*-Bu, R′ = H
2, R = R′ = Me	**7**, R = Me, R′ = H
3, R = Et, R′ = Me	**8**, R = *Ph*-CH=CH, R′ = H
4, R—R′ = —$(CH_2)_4$—	

Data for acetone and benzalacetone are included for comparison.

The same products and essentially the same product ratios were obtained under reflux conditions at atmospheric pressure and under the experimental conditions described in the literature (3) for the preparation of **5**. In the latter case, i.e., when anhydrous chloral and glacial acetic acid were used instead of chloral hydrate and acetic anhydride, the desired condensation products were formed in higher yields.

The tabulated results (Table I) show that cyclohexanone and benzalacetone are less reactive than the other ketones studied, and that the α-methyl groups of acetone and 4-methyl-2-pentanone are approximately of equal reactivity toward chloral hydrate (taking into account a statistical factor of two for acetone). When two diastereomeric condensation products are possible, the high-melting isomer (**2***b*, **3***b*, **4***b*) is generally formed in higher yield than the low-melting compound (**2***a*, **3***a*, **4***a*).

The reaction between chloral hydrate and the 6 ketones listed in Table I is not accompanied by dehydration or acetylation of the condensation products. Only traces of unexpected by-products were detected by v.p.c. analysis of the slightly yellow, crude reaction mixtures; the ketone peak areas were found to correspond to 98–99% of the amount of unreacted ketone as calculated from the yield of condensation product. Thus, unreacted starting material, acetic acid, and the products listed in Table I account for more than 98% of the weight of the final reaction mixtures.

Butanone and Chloral Hydrate

Butanone reacts with chloral hydrate to form three isomeric condensation products and 1,1-diacetoxy-2,2,2-trichloroethane (**6**):

$$CH_3CH_2COCH_3 + CCl_3CH(OH)_2 \xrightarrow{Ac_2O} \underset{\mathbf{1}}{CH_3CH_2COCH_2CHOHCCl_3}$$

$$+ \underset{\mathbf{2}a \text{ and } \mathbf{2}b \text{ (diastereomers)}}{CH_3COCH(CH_3){-}CHOHCCl_3}$$

$$+ \underset{\mathbf{6}}{CCl_3CH(OAc)_2}$$

This demonstrates that contrary to a report in the literature (1), butanone undergoes condensation at both the methylene and the methyl group in α-position to the carbonyl function. Melting point and ease of crystallization indicate that the only product isolated by Caujolle and co-workers was ketol **1** and not the postulated isomeric ketol **2**. All three ketols are stable compounds which neither isomerize nor cleave to yield butanone and chloral when treated with acetic anhydride and sodium acetate under the preparative experimental conditions. The crude product mixture contains the straight-chain isomer (**1**) and the branched-chain isomers (**2***a* and **2***b*) in the approximate molar ratio 4:7 indicating that reaction occurs preferentially but not exclusively at the methylene group. However, the greater reactivity of the methylene group relative to the methyl group toward chloral hydrate appears to be specific for butanone (*vide infra*).

The n.m.r. and infrared (i.r.) spectra of the three isomeric condensation products exhibit a number of special features which permit conclusions to be drawn with respect to hydrogen-bonding and conformational interactions in these compounds. At a mole fraction of 0.08 in deuteriochloroform, the hydroxylic proton of **1**, **2***a*, and **2***b* appears as a sharp doublet at τ 5.83, 4.30, and 6.23, respectively. The coupling of this proton with the geminal proton (4.9–8.5 c.p.s.) suggests hydrogen-bonding association in $CDCl_3$ solution and a slow rate of proton exchange. Middleton and Lindsey (6) have reported similar retention of OH—H coupling for certain hydrogen-bonded solute–solvent complexes of 2*H*-hexafluoro-2-propanol.

The n.m.r. dilution shift data and i.r. absorption bands summarized in Table II provide evidence for different types of hydrogen bonds in the isomeric condensation products of butanone and chloral. Decreasing the mole fraction of the product in $CDCl_3$ from 0.25 to 0.04 results in an upfield shift of 36, 0, and 54 c.p.s. for the hydroxylic proton of **1**, **2***a*, and **2***b*, respectively. All three isomers exhibit an i.r. absorption band at 3600 cm^{-1} ("free" OH).[1] The "bonded" OH peak for **1** and **2***b* appears at 3470 to 3480 cm^{-1} (Δ_v between "free" and "bonded" OH 120–130 wavenumbers) while the corresponding band for **2***a* is found at 3380 cm^{-1} ($\Delta_v = 220$ wavenumbers). The effect of concentration changes on the relative intensities of these i.r. absorption peaks is markedly different for **2***a* on one hand and **1** and **2***b* on the other hand. The "free" OH band of **2***a* is much less intense than the bonded OH band, and the ratio of peak intensities of the two bands remains essentially constant over the concentration range 0.5 *M* to 0.04 *M* in CCl_4. In contrast, dilute solutions (0.04 *M* in CCl_4) of **1** and **2***b* show a sharp, intense "free" OH band at 3600 cm^{-1} and a weak "bonded" OH band at 3475

---

[1] This band may be due to weakly hydrogen-bonded OH involving Cl as acceptor site, see ref. 9.

TABLE II

Nuclear magnetic resonance chemical shift and infrared absorption bands of OH group in R—CO—CHR′—CHOH—CCl_3*

Compound	Chemical shift mole fraction:†				Infrared absorption (cm^{-1})‡	
	0.25	0.15	0.08	0.04	"free" OH	"bonded" OH
1	273	260	250	237	3600	3470
2*a*	342	342	342	342	3600	3380
2*b*	265	243	226	211	3600	3480
3*a*	345	345	345	345	3600	3395
3*b*	268	250	230	215	3605	3490
4*a*		381	381		3600	3380
4*b*	248	232	218	206	3605	3500
5		252	238		3600	3450

*See eq. [1] for definition of R and R′.
†In c.p.s. downfield from TMS in $CDCl_3$ at 60 Mc.p.s.
‡0.5 *M* in CCl_4 (Beckman IR-12 or Perkin-Elmer 457) using NaCl window.

cm^{-1}. As the concentration is increased, the intensity of the bonded OH band increases at the expense of the "free" OH band. The absorption peak at 3600 cm^{-1} is entirely absent from the i.r. spectrum of a pure liquid (melt) film of **1** and **2***b* on sodium chloride plates.

It is apparent from these data that **2***a* is intramolecularly hydrogen-bonded involving the hydroxyl group as donor and the carbonyl oxygen as acceptor site (7, 8), while the isomeric ketols **1** and **2***b* form intermolecular hydrogen bonds at high concentrations. The possibility of weak Cl . . . . HO hydrogen bond interactions (9, 10) cannot be entirely excluded.

Molecular models show that only a limited number of conformations will satisfy the hydrogen-bonding requirements of the three isomeric condensation products **1**, **2***a*, and **2***b* if these assumptions are correct. These considerations prompted a conformational analysis of the two diastereomeric products **2***a* and **2***b*.

It is well known (11) that the coupling constant J_{ab} for the H_a—C—C—H_b fragment of ethane derivatives depends on the dihedral angle ϕ between the H_a—C—C and C—C—H_b planes. Although indiscriminate application of the theoretically derived correlation curve between J_{ab} and ϕ may lead to incorrect structural assignments (12), it may be used to estimate bond angles and conformations of organic molecules. Stiles and co-workers (13) investigated hydrogen bonding and conformational interactions in the diastereomeric condensation products of butanone with aromatic aldehydes by i.r. spectroscopy and measurement of the coupling constant J_{ab} between the tertiary hydrogens of CH_3—CO—$CH_a(CH_3)$—CH_bOH—Ar. They found intramolecular hydrogen bonding for both diastereomers and coupling constants of 8.0 and 3.0 c.p.s. for the *threo* (tertiary hydrogens *trans*) and *erythro* structure (tertiary hydrogens *gauche*), respectively.

After deuterium exchange, the n.m.r. spectrum of CH_3—CO—$CH_b(CH_3)$—CH_aOD—CCl_3 (**2***a* or **2***b*) exhibits a simple doublet due to the tertiary proton (H_a) of the —CH_aOD— group and a multiplet due to the tertiary proton (H_b) of the methyl-substituted carbon. Measurement of the H_b-methyl coupling in the methyl doublet and the H_a—H_b coupling in the H_a doublet allowed a satisfactory interpretation of the H_b signal, based upon simple splitting rules. The chemical shifts of the tertiary hydrogens and the coupling constants are summarized in Table III.

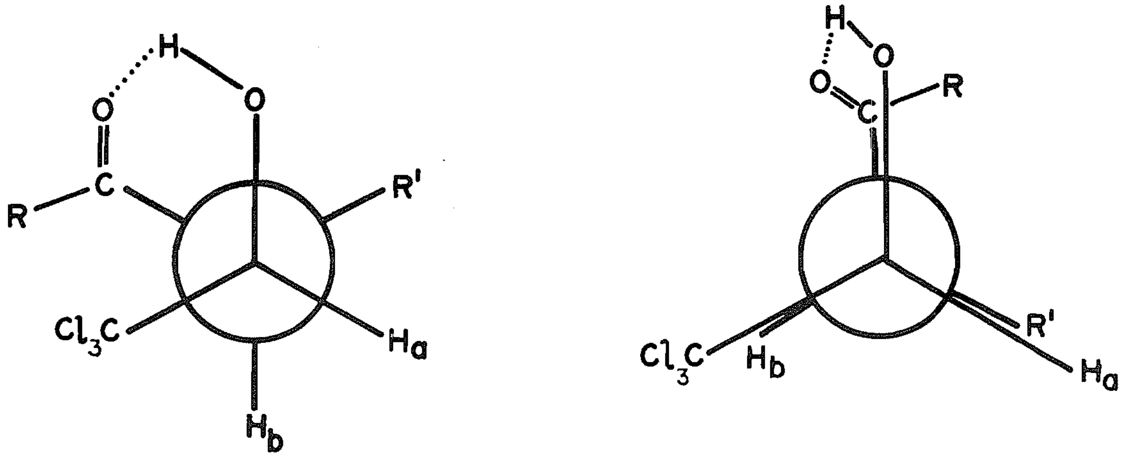
It is concluded from the magnitude of the splitting and from the inspection of molecular models that the H_a—C—C—H_b dihedral angle ϕ in the preferred conformation of **2***a* is close to 60 or 120° (Fig. 1, structures T-1 and T-2) while

TABLE III

Nuclear magnetic resonance chemical shifts and coupling constants J_{ab} of $RCOCH_bR'$—CH_aOD—CCl_3

Compound	Chemical shift (c.p.s.)*		J_{ab} (c.p.s.)
	H_a	H_b	
2*a*	246	207	1.9
2*b*	282	193	5.5
3*a*	247	208	2.0
3*b*	282	193	5.5
4*a*	238	183	2.0
4*b*	301	184	2.5

*Downfield from TMS in $CDCl_3$.

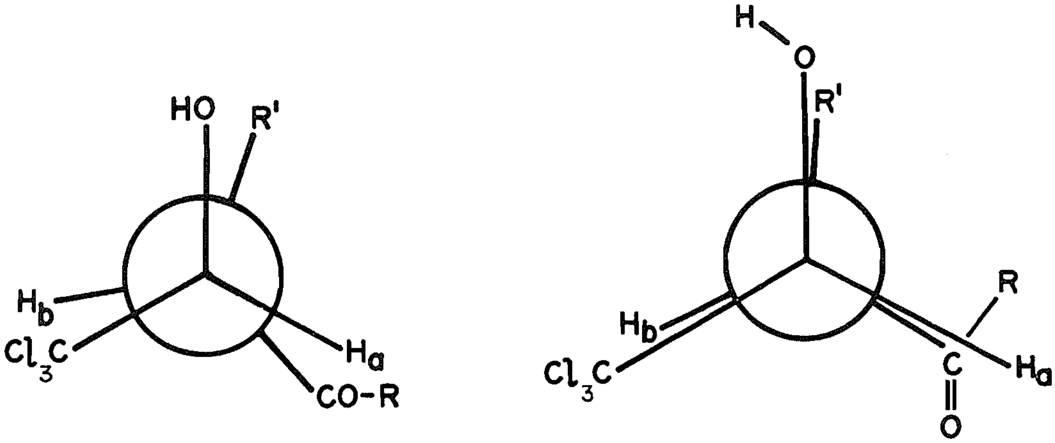


T-1 (threo)

2a, R = R' = Me
3a, R = Et, R' = Me

T-2 (threo)

2a, R = R' = Me
3a, R = Et, R' = Me
4a, R–R' = $-(CH_2)_4-$



E-1 (erythro)

2b, R = R' = Me
3b, R = Et, R' = Me

E-2 (erythro)

4b, R–R' = $-(CH_2)_4-$

FIG. 1. Conformational assignments for R—CO—CHR'—CHOH—CCl_3.

2*b* (and **1**) prefers a conformation with ϕ close to 140° (Fig. 1, structure E-1). Based on these results and the hydrogen-bond studies, the *threo* configuration has been assigned to **2*a*** and the *erythro* configuration to **2*b***.[2]

The *erythro* configuration has been ruled out for the hydrogen-bonded structure **2*a*** because molecular models of the two conformers obtained by 80° counterclockwise or 160° clockwise rotation of the rear carbon of structure E-1 (Fig. 1) indicate serious steric hindrance due to the eclipsing effect of the methyl and the trichloromethyl group, and all other conformers with an H_a—C—C—H_b dihedral angle of 60 or 120° (corresponding to the observed coupling constant J_{ab} = 1.9 c.p.s.) do not permit intramolecular hydrogen bonding. To minimize steric interaction between the R—CO— and the bulky trichloromethyl group of **2*b*** (structure E-1, Fig. 1), a dihedral angle of 140° between the tertiary hydrogens is preferred to a 180° angle corresponding to a completely staggered conformation. For the same reason, the alternative *erythro* conformation with ϕ 140° (obtained by 80° clockwise rotation of the rear carbon of the structure E-1, Fig. 1) and all conformers with the alternative dihedral angle of 35° (corresponding to the observed coupling constant J_{ab} = 5.5 c.p.s.) are unfavorable for ketol **2*b***. It is therefore concluded that in contrast to the flat aryl groups of the compounds studied by Stiles and coworkers (13), the bulkiness of the trichloromethyl group prevents intramolecular hydrogen bonding in the *erythro* structure **2*b***, and in the straight-chain isomer **1** (see Table II).

It is hoped that high-resolution i.r. and n.m.r. spectral studies of very dilute solutions of **1**, **2*a***, and **2*b*** in nonpolar solvents (presently in progress) will permit a quantitative estimate of the relative contribution of Cl . . . . H—O hydrogen-bonded structures and of conformational energy differences.

3-Pentanone and Chloral Hydrate

3-Pentanone reacts with chloral hydrate in acetic anhydride to form 1,1-diacetoxy-2,2,2-trichloroethane (**6**) and 1,1,1-trichloro-2-hydroxy-3-methyl-4-hexanone (**3*a***, m.p. 37–38°, and **3*b***, m.p. 57.5–58.5°). Pure samples of the two diastereomeric condensation products were obtained by partition chromatography of selected fractions of the high vacuum distillate on silicic acid using benzene as eluent.

Apparently Caujolle *et al.* (1) isolated only the high-melting isomer of this diastereomeric pair (m.p. 58.5°). We found that **3*a*** and **3*b*** are formed in the approximate molar ratio 5:6. The composition data of Table I show that the two methylene groups of 3-pentanone and cyclohexanone (*vide infra*) are less reactive toward chloral hydrate than the two methyl groups of acetone which is attributed to decreased nucleophilicity of the alkyl-substituted α-carbons.

The n.m.r. and i.r. spectra of the two diastereomers (Tables II and III) exhibit the same general features as the spectra of **2*a*** and **2*b***, i.e. coupling of the hydroxylic proton with the geminal proton of the CHOH group, downfield position of the OH chemical shift of **3*a*** relative to **3*b***, upfield shift of the OH proton signal of **3*b*** (but not **3*a***) on dilution, concentration dependence of the i.r. absorption intensity ratio "free" OH: "bonded" OH for **3*b*** only, and largely different coupling constants J_{ab} for the tertiary protons of **3*a*** (2.0 c.p.s.) and **3*b*** (5.5 c.p.s.), respectively. Applying arguments analogous to those advanced for the structural analysis of 1,1,1-trichloro-2-hydroxy-3-methyl-4-pentanone (**2*a*** and **2*b***), it is concluded from these spectral data that **3*a*** is an intramolecularly hydrogen-bonded *threo* structure (Fig. 1, conformer T-1 or T-2), and **3*b*** is the *erythro* isomer existing predominantly in a conformation with ϕ close to 140° (Fig. 1, conformer E-1).

Cyclohexanone and Chloral Hydrate

The reaction between cyclohexanone and chloral hydrate in acetic anhydride has been reported (1) to give a 70% yield of a condensation product melting at 105°. Under the same reaction conditions we obtained a product mixture (47% yield) containing 1,1-diacetoxy-2,2,2-trichloroethane (**6**) as major component, and the two diastereomers of 2-(1-hydroxy-2,2,2-trichloroethyl-)cyclohexanone (**4*a*** and **4*b***) in the approximate molar ratio 2:7. Ketol **4*b*** (m.p. 101–102°) crystallized readily from the high-vacuum distillate of the crude product mixture but the isolation and purification of **4*a*** (m.p. 43–44.5°) was found to be extremely difficult.

In close similarity to the structural features

---

[2] The *erythro*/*threo* nomenclature is used in this paper with reference to the two adjacent tertiary hydrogen atoms considering CCl_3—CH_a—CH_b—R′ as the main chain of the molecule and —OH and —CO—R as substituents.

observed for 1,1,1-trichloro-2-hydroxy-3-methyl-4-pentanone (**2***a* and **2***b*) and 1,1,1-trichloro-2-hydroxy-3-methyl-4-hexanone (**3***a* and **3***b*), i.r. and n.m.r. spectral data (Tables II and III) indicate strong intramolecular hydrogen bonding in **4***a* with the OH proton signal (381 c.p.s.) appearing considerably downfield from the position of the corresponding proton in **2***a* and **3***a* (342 and 345 c.p.s., respectively), and intermolecular hydrogen bonding in concentrated solutions of the more stable *erythro* structure **4***b*. The coupling constant J_{ab} between the two tertiary hydrogens was found to be 2.0 c.p.s. for **4***a* and 2.5 c.p.s. for **4***b* suggesting dihedral angles close to 60 or 120°. In order to satisfy these conformational requirements and to permit intramolecular C=O . . . H—O hydrogen bonding in **4***a*, the two diastereomers are believed to exist predominantly in the eclipsed conformations T-2 and E-2 (Fig. 1), respectively.

The rigidity of the cyclohexane ring prevents free rotation about the CHR′—CO single bond thus forcing the molecule into an eclipsed conformation in order to minimize steric interaction of the bulky CCl_3CHOH group with axial ring hydrogens or with the carbonyl group.

4-Methyl-2-pentanone and Chloral Hydrate

4-Methyl-2-pentanone yields only one condensation product, 1,1,1-trichloro-2-hydroxy-6-methyl-4-heptanone (**5**), when treated with chloral hydrate and acetic anhydride at 70°. In addition, 1,1-diacetoxy-2,2,2-trichloroethane is formed in low yield. It was not possible to detect any isomeric product by v.p.c. analysis using three different analytical columns. This finding, in conjunction with the experimental observation that 4,4-dimethyl-2-pentanone also undergoes condensation with chloral at the methyl group only, is indicative of steric factors being predominant in determining the product structure in crossed aldol condensations of unsymmetrical aliphatic ketones with chloral. Assuming that the reaction proceeds through an enol-like transition state rather than through an enolate intermediate, these results are in qualitative agreement with recent literature reports on the rate and orientation of the acid- and base-catalyzed deuteration of methyl ketones (5, 14, 15). The unusually high reactivity of the methylene group of butanone (see Table I) as compared to other methyl ketones of the general structure CH_3—CO—CH_2—R has been attributed by Warkentin and Barnett (15) to a rate-accelerating polar effect of the alkyl group which "opposes the steric effect and is swamped by it in all the ketones except butanone". The same authors have shown that in the base-catalyzed deuteration of 4-methyl-2-pentanone in aqueous dioxane, enolization toward the methyl group is favored over enolization toward the methylene group by a factor of 2.38. The exclusive formation of **5** from chloral hydrate and 4-methyl-2-pentanone therefore indicates that this reaction cannot be simply interpreted in terms of two competitive rate-determining enolization steps, and that indiscriminate quantitative comparison of results obtained in different reaction media leads to incorrect predictions.

Further work will be needed to establish whether the transition state resembles ketone, enol or enolate, and to assess the importance of solvent effects and catalyst structure in determining the orientation of enolization of unsymmetrical aliphatic ketones and the rate of chloral addition. We are presently investigating the rate of acetate-catalyzed deuteration of ketones in acetic acid-d_4 and the kinetics of the reaction of anhydrous chloral with various methyl ketones in glacial acetic acid in order to gain further insight into the mechanism of this crossed aldol condensation.

On the basis of closely similar i.r. and n.m.r. spectra of **5** and **1**, intramolecular hydrogen bonding is believed to be weak or absent in straight-chain compounds of the type R—CO—CH_2—CHOH—CCl_3. In contrast to the spectral properties of the condensation products of butanone, 3-pentanone, and cyclohexanone with chloral hydrate, the OH proton signal of **5** appears as a broad singlet in the n.m.r. spectrum.

Experimental

Melting points are uncorrected. Analyses were performed by A. Bernhardt, Microanalytical Laboratory, Mülheim, Germany.

Infrared spectra were recorded on a Beckman IR-12 or a Perkin–Elmer 457 spectrometer using a CCl_4 solution or a thin film of neat liquid (melt) between sodium chloride plates. Ultraviolet (u.v.) spectra were run in 95% ethanol using a Unicam SP-200 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian A56/60 spectrometer using TMS as internal standard and $CDCl_3$ as solvent (unless specified otherwise). Chemical shifts are reported in c.p.s. downfield from TMS or in τ units. All spectral measurements were performed at room temperature.

Vapor-phase chromatographic analyses were carried out on a Varian Aerograph Model 1200-1 HY-FI III gas chromatograph using a 5 ft × $\frac{1}{8}$ in. column packed with 5% SE-30 on Aeropak 30 (column temperature 120–140°) and nitrogen as carrier gas (35 ml/min). All quantitative estimates of the composition of product mixtures by gas–liquid chromatographic (g.l.c.) analysis (Table I) are based on comparison of integrated peak areas obtained for the various components of a crude product mixture with those obtained for standard mixtures prepared from the pure components. The v.p.c. peak areas were measured planimetrically. For the purpose of analysis and identification, pure samples of all components of a product mixture were isolated by fractional distillation, crystallization and/or liquid partition chromatography on silica (Mallinckrodt, Silicic Acid A.R. 100 Mesh, Chromatographic Grade).

Butanone, 3-pentanone, cyclohexanone, and 4-methyl-2-pentanone (Matheson, Coleman, and Bell) were purified by fractional distillation; chloral hydrate (Matheson, Coleman, and Bell) and acetic anhydride (Baker and Adamson, Reagent grade) were used without further purification.

Reaction of Chloral Hydrate with Butanone

A mixture of 22.5 g (0.31 moles) of butanone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 9.9 g (0.12 moles) of anhydrous sodium acetate was heated in a 200-ml pressure bottle at 70° for 58 h. Solvent, unreacted starting materials, and acetic acid were removed by distillation under reduced pressure. The yellow distillation residue was dissolved in 100 ml of ether, washed with water and sodium bicarbonate solution, and dried ($MgSO_4$). Evaporation of the ether gave 24.7 g of crude product (yellow) containing 30% (by weight) of ketol **1**, 23% of ketol **2***a*, 30% of ketol **2***b*, and 17% of 1,1-diacetoxy-2,2,2-trichloroethane (**6**) (analysis by v.p.c.). No dehydration or acetylation products and only trace amounts of other by-products were detected in the gas chromatogram. To separate **6** from the condensation products, the crude product mixture was distilled in high vacuum; ketols **1**, **2***a*, and **2***b* (total weight 15.4 g) were collected at 75–90°/0.02 mm (lit. (16), 135–138°/17 mm). Small samples of the pure components were isolated by liquid partition chromatography on silica using 20% (by volume) petroleum ether (30–60°) in benzene as eluent. Larger quantities of pure **2***a* and **2***b* were obtained by redistillation of the product mixture through a Vigreux column at high vacuum, v.p.c. analysis of each of the 15 fractions collected, seeding of selected fractions with **2***a* and **2***b*, respectively, filtration, and recrystallization from cyclohexane. Crystallization of **2***a* was extremely slow and inhibited by small amounts of impurities.

Characterization of **1**: m.p. 56–56.5° (lit. (1) 57°), b.p. 88–89°/0.02 mm.

Anal. Calcd. for $C_6H_9O_2Cl_3$: C, 32.83; H, 4.13; Cl, 48.46. Found: C, 32.78; H, 4.10; Cl, 48.38.

Ultraviolet: ν_{max}(EtOH) 212 mμ (ε 49), 276 mμ (ε 24); n.m.r. ($CDCl_3$): τ 8.91, triplet (3 protons, $\mathrm{C}H_3\mathrm{CH}_2$); 7.47, quartet (2, $\mathrm{CH_3C}H_2$); 7.01, multiplet (2, $\mathrm{C}H_2$-CHOH); 5.85, doublet (1, OH); 5.35, multiplet (1, C*H*OH).

Characterization of **2***a*: m.p. 33.5–34.5°, b.p. 69–71°/ 0.02 mm (estimated).

Anal. Calcd. for $C_6H_9O_2Cl_3$: C, 32.83; H, 4.13; Cl 48.46. Found: C, 32.72; H, 4.05; Cl, 48.33.

Ultraviolet: ν_{max}(EtOH) 210 mμ (ε 98), 278 mμ (ε 33); n.m.r.: τ 8.61, doublet (3, $\mathrm{C}H_3\mathrm{CH}$); 7.71, singlet (3, $\mathrm{C}H_3\mathrm{CO}$); 6.55, multiplet (1, $\mathrm{CH_3C}H$); 5.90, multiplet (1, C*H*OH); 4.27, doublet (1, OH).

Characterization of **2***b*: m.p. 59.5–60.5°, b.p. 80–82°/ 0.02 mm.

Anal. Calcd. for $C_6H_9O_2Cl_3$: C, 32.83; H, 4.13; Cl, 48.46. Found: C, 32.95; H, 3.99; Cl, 48.36.

Ultraviolet: ν_{max}(EtOH) 214 mμ (ε 50), 276 mμ (ε 26); n.m.r.: τ 8.65, doublet (3, $\mathrm{C}H_3\mathrm{CH}$); 7.71, singlet (3, $\mathrm{CH_3CO}$); 6.79, multiplet (1, $\mathrm{CH_3C}H$); 6.25, doublet (1, OH); 5.31, multiplet (1, C*H*OH).

Reaction of Chloral Hydrate with 3-Pentanone

Following the procedure described in the preceding experiment (reaction time 102 h), 19.3 g of crude product (yellow) was obtained from 26.9 g (0.31 moles) of 3-pentanone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 9.81 g (0.12 moles) of anhydrous sodium acetate. The crude product was found by v.p.c. analysis to contain 37% (by weight) of ketol **3***a*, 43% of ketol **3***b*, and 20% of **6**. High-vacuum distillation gave 13.4 g of a mixture of **3***a* and **3***b*, b.p. 79–89°/0.07 mm. Pure samples of the two diastereomers were obtained by fractional high-vacuum distillation and liquid partition chromatography with benzene as eluent (see preceding experiment for procedural details).

Characterization of **3***a*: m.p. 37–38°, b.p. 79–83°/0.07 mm.

Anal. Calcd. for $C_7H_{11}O_2Cl_3$: C, 36.00; H, 4.75; Cl, 45.55. Found: C, 36.05; H, 4.57; Cl, 45.45.

Ultraviolet: ν_{max}(EtOH) 213 mμ (ε 59), 279 mμ (ε 34); n.m.r. ($CDCl_3$): τ 8.95, triplet (3, $\mathrm{C}H_3\mathrm{CH}_2$); 8.61, doublet (3, $\mathrm{C}H_3\mathrm{CH}$); 7.33, quartet (2, $\mathrm{CH_3C}H_2$); 6.53, multiplet (1, $\mathrm{CH_3C}H$); 5.89, multiplet (1, C*H*OH); 4.17, doublet (1, OH).

Characterization of **3***b*: m.p. 57.5–58.5° (lit. (1) 58.5°), b.p. 85–89°/0.07 mm.

Anal. Calcd. for $C_7H_{11}O_2Cl_3$: C, 36.00; H, 4.75; Cl, 45.55. Found: C, 36.09; H, 4.70; Cl, 45.43.

Ultraviolet: ν_{max}(EtOH) 213 mμ (ε 51), 280 mμ (ε 31); n.m.r.: τ 8.93, triplet (3, $\mathrm{C}H_3\mathrm{CH}_2$); 8.71, doublet (3, $\mathrm{C}H_3\mathrm{CH}$); 7.37, quartet (2, $\mathrm{CH_3C}H_2$); 6.78, multiplet (1, $\mathrm{CH_3C}H$); 5.55, doublet (1, OH); 5.33, multiplet (1, C*H*OH).

Reaction of Chloral Hydrate with Cyclohexanone

Following the procedure described before, 28.9 g of crude product (yellow) was obtained by heating a mixture of 30.7 g (0.31 moles) of cyclohexanone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 10.8 g (0.132 moles) of anhydrous sodium acetate at 70° for 45 h. The crude product mixture was found by v.p.c. analysis to contain 11% (by weight) of ketol **4***a*, 39% of ketol **4***b*, and 50% of **6**. High-vacuum distillation gave 10.4 g of a mixture of the two diasteromeric condensation products **4***a* and **4***b*. A pure sample of **4***b* was isolated by recrystallization of the solidified portion of the distillate from carbon tetrachloride. Purification of **4***a* was accomplished by liquid partition chromatography on silica using 20% (by volume) petroleum ether in benzene as eluent.

Characterization of **4***a*: m.p. 43–44.5°, b.p. 110–111°/0.04 mm.

Anal. Calcd. for $C_8H_{11}O_2Cl_3$: C, 39.13; H, 4.52; Cl, 43.32. Found: C, 39.22; H, 4.37; Cl, 43.28.

Nuclear magnetic resonance ($CDCl_3$): τ 6.03, multiplet (1, C*H*OH); 3.62, doublet (1, OH).

Characterization of **4***b*: m.p. 101–102° (lit. (1) 105°), b.p. 119–120°/0.04 mm.

Anal. Calcd. for $C_8H_{11}O_2Cl_3$: C, 39.13; H, 4.52; Cl, 43.32. Found: C, 39.22; H, 4.68; Cl, 43.23.

Ultraviolet: ν_{max}(EtOH) 214 mμ (ε 49), 283 mμ (ε 21); n.m.r.: τ 6.93, multiplet (1, C*H*—CHOH); 6.40, doublet (1, OH); 4.99, multiplet (1, C*H*OH).

1,1,1-Trichloro-2-hydroxy-6-methyl-4-heptanone (*5*)

Following the procedure outlined before (reaction time 52 h), 14.23 g of crude product (light yellow, partially solidified) was obtained from 31.25 g (0.31 moles) of 4-methyl-2-pentanone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 10.9 g (0.133 moles) of anhydrous sodium acetate. The crude product mixture was found by v.p.c. analysis to contain 77% (by weight) of **5** and 23% of **6**. The residue left after removal of **6** by high vacuum distillation was recrystallized from carbon tetrachloride and cyclohexane to give 8.0 g of pure 1,1,1-trichloro-2-hydroxy-6-methyl-4-heptanone (**5**), m.p. 86–87° (lit. (3) 86–87°). Ketol **5** was shown by mixed melting point determination to be identical with a sample of the same compound prepared by the procedure described in the literature (3).

Characterization of **5**: u.v.: ν_{max}(EtOH) 213 mμ (ε 47), 239 mμ (ε 33), 280 mμ (ε 27); n.m.r. ($CDCl_3$): τ 9.07, doublet (6, $(CH_3)_2C$); 7.60, multiplet (3, $CHCH_2CO$); 7.05, multiplet (2, C*H*$_2$CHOH); 5.97, broad singlet (1, OH); 5.37, multiplet (1, C*H*OH).

1,1,1-Trichloro-2-hydroxy-4-pentanone (*7*)

Following the procedure outlined before (reaction time 50 h), 20.5 g of crude product (yellow, partially solidified) was obtained from 18.1 g (0.31 moles) of acetone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 9.4 g (0.114 moles) of anhydrous sodium acetate. The crude product mixture containing 85% (by weight) of the desired ketol (**7**) and 15% of **6** was distilled at high vacuum to give 14.4 g of **7**, b.p. 100–105°/0.4 mm (lit (3) 100–105°/1 mm), m.p. 73.5–75° (lit. (1, 3, 17) 75–76°) after recrystallization from cyclohexane.

Characterization of **7**: u.v.: ν_{max}(EtOH) 219 mμ (ε 41), 275 mμ (ε 17); n.m.r. ($CDCl_3$): τ 7.75, singlet (3, CH_3CO); 7.00, multiplet (2, $COCH_2$); 5.90, doublet (1, OH); 5.35, multiplet (1, C*H*OH).

Reaction of Benzalacetone with Chloral Hydrate

Only trace amounts of 1,1,1-trichloro-2-hydroxy-6-phenyl-5-hexen-4-one (**8**) were obtained when a mixture of 45.6 g (0.31 moles) of benzalacetone, 41.1 g (0.25 moles) of chloral hydrate, 25.5 g (0.25 moles) of acetic anhydride, and 12.5 g (0.152 moles) of anhydrous sodium acetate was heated at 70° for 21 h. The usual work-up procedure (see before) gave a crude product mixture which was found by n.m.r. analysis (methyl peaks) to contain approximately 75 mole-% of benzalacetone and 25 mole-% of 1,1-diacetoxy-2,2,2-trichloroethane (**6**).

1,1-Diacetoxy-2,2,2-trichloroethane (**6**)

Compound **6** was obtained as the exclusive reaction product (71% yield) when a mixture of 31.25 g (0.31 moles) of 4-methyl-2-pentanone, 36.8 g (0.25 moles) of anhydrous chloral,[3] 25.5 g (0.25 moles) of acetic anhydride, and 5.2 g (0.063 moles) of anhydrous sodium acetate was heated at 100° for 52 h and worked up as described before. None of the desired 1,1,1-trichloro-2-hydroxy-6-methyl-4-heptanone (**5**) was detected by n.m.r. and v.p.c. analysis of the crude product mixture (44.4 g).

Characterization of **6**: b.p. 217–218°/750 mm, (lit. (18) 225°/750 mm); n.m.r. ($CDCl_3$): τ 7.81, singlet (6, CH_3); 2.28, singlet (1, CH); n_D^{23} 1.4570 (lit. (14), n_D^{20} 1.4567).

Acknowledgment

The support of this work by a grant from the National Research Council of Canada is gratefully acknowledged.

1. F. Caujolle, P. Couturier, and C. Dulaurans. Bull. Soc. Chim. France, **17**, 19 (1950).
2. F. L. Breusch and H. Keskin. Arch. Biochem. Biophys. **18**, 305 (1948).
3. W. Reeve and E. Kiehlmann. J. Org. Chem. **31**, 2164 (1966).
4. S. Mamedov and F. Gadshisade. Zh. Obshch. Khim. **32**, 799 (1962).
5. J. Warkentin and O. S. Tee. J. Am. Chem. Soc. **88**, 5540 (1966).
6. W. J. Middleton and R. V. Lindsey, Jr. J. Am. Chem. Soc. **86**, 4948 (1964).
7. M. Oki, H. Iwamura, J. Aihara, and H. Lida. Bull. Chem. Soc. Japan, **41**, 176 (1968).
8. L. Joris and P. von R. Schleyer. J. Am. Chem. Soc. **90**, 4599 (1968).
9. P. J. Krueger and H. D. Mettee. Can. J. Chem. **42**, 340 (1964).
10. T. M. Connor and C. Reid. J. Mol. Spectry. **7**, 32 (1961).
11. M. Karplus. J. Chem. Phys. **30**, 11 (1959).
12. M. Karplus. J. Am. Chem. Soc. **85**, 2870 (1963).
13. M. Stiles, R. Winkler, Y. Chang, and L. Traynor. J. Am. Chem. Soc. **86**, 3337 (1964).
14. C. Rappe and W. H. Sachs. J. Org. Chem. **32**, 3700, 4127 (1967).
15. J. Warkentin and C. Barnett. J. Am. Chem. Soc. **90**, 4629 (1968).
16. G. M. Baluja, A. M. Municio, and S. Vega. Anales. Real Soc. Espan. Fis. Quim. Madrid, Ser. B, **60**, 639 (1964).
17. W. Koenigs. Chem. Ber. **25**, 729 (1892).
18. N. A. D. Parlee, J. R. Dacey, and C. C. Coffin. Can. J. Res. B, **15**, 254 (1937).

---

[3] Anhydrous chloral was prepared from the commercially available material (chloral, practical, stabilized; Matheson Coleman and Bell) by distillation from phosphorus pentoxide.