amount of chlorine (0.078 mole for 0.308 mole of benzenesulfonyl chloride) was employed, the mixture at the end of the reaction showed no peak in the infrared spectrum at 8–9 μ, characteristic of sulfonyl chlorides, and gave 92% chlorobenzene on distillation.

Under the same conditions diphenylsulfone also gave chlorobenzene in essentially quantitative yield, but phenyl benzenesulfonate and methyl benzenesulfonate gave no chlorobenzene and good yields of starting material when treated with chlorine and light, either at 70° in carbon tetrachloride or at 150–170° in absence of solvent.

Other Attempted Displacements.—Treatment of azobenzene, azoxybenzene and N-phenylphthalimide with chlorine and light at 70° in carbon tetrachloride solution gave only starting material and no trace of chlorobenzene. Similarly no displacement was observed when iodobenzene was refluxed with sulfuryl chloride in the presence of benzoyl peroxide, or when benzenesulfonyl chloride or diphenylsulfone was illuminated in the presence of bromine.

Exchange of Br^{82}_2 with Bromobenzene.—Twenty-five ml. of bromine containing Br^{82}, 50 ml. of bromobenzene and 75 ml. of carbon tetrachloride were mixed and then divided into three equal portions placed in stoppered flasks. One flask was kept for 18 hours at room temperature while being illuminated at a distance of 8 inches by a 200 watt incandescent light, the others were stored in the dark. The contents of the illuminated flask and one other were washed with sodium bisulfite solution and then three portions of water, and the radioactivity of the organic layer determined, using a Geiger counter of the type described by Sibbett.[23] The contents of the third flask were used to determine total radioactivity. In a second experiment a similar mixture was irradiated for four hours at 50° and overnight at room temperature. The bromine was then washed out, and the radioactivity of the organic layer determined. In order to establish that the radioactivity was confined to bromobenzene, the organic layer was next carefully fractionated and the radioactivity of the bromobenzene fraction determined. Results of both experiments are shown below.

Run	Total	Activity (counts/min.) Organic	C_6H_5Br	Background
1 (light)	12,344	2272	...	50
1 (dark)	12,344	90	...	50
2 (light)	21,317	4211	4110	62

(23) D. L. Sibbett, Thesis, Columbia University, 1951, pp. 11–12.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Structure and Properties of Cyclic Compounds. IX.[1] Hemiketal Formation of Cyclic Ketones

BY OWEN H. WHEELER

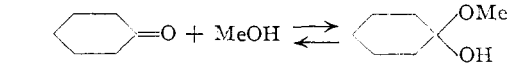
RECEIVED SEPTEMBER 20, 1956

Cyclohexanone has been found to undergo acid-catalyzed hemiketal formation with methanol in dioxane solution. The extent of hemiketal formation of a number of cyclic ketones in pure methanol is in agreement with I-strain prediction, and is reduced by steric effects. Less reaction takes place with ethanol and no reaction is observed with isopropyl alcohol or water.

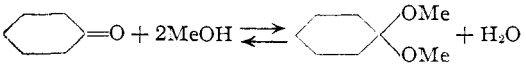
During the course of routine spectroscopic measurements,[2] it was observed that the intensity of absorption of cyclic ketones in methanol depended on the sample of methanol used as solvent. Addition of a drop of concentrated hydrochloric acid greatly reduced the intensity. The decreased absorption of aldehydes in polar solvents has been noted by many workers[3] and has been attributed to hemiacetal formation. This suggests that the above results may be due to a similar reaction. A decrease in the refractive index of solutions of acetone and cyclohexanone in methanol on the addition of acids has been noted[4] and is probably caused by the same effect.

The reaction between cyclohexanone and methanol was studied using dioxane as solvent. Solutions of cyclohexanone in dioxane showed λ_{max} 290 mμ (ϵ 15.8 ± 0.1, mean of five readings). In the presence of 0.05 *M* hydrogen chloride the absorption was unchanged. Similarly the absorption intensity of cyclohexanone in dioxane containing 0.07, 0.12 and 0.26 *M* methanol was ϵ 15.85, 15.75, 15.8, respectively, with the maxima at the same wave length. These solutions showed no change in absorption on standing. Thus the decrease in intensity in methanolic hydrogen chloride solution cannot be due to reaction between the ketone and the acid or to a non-acid-catalyzed reaction between the ketone and methanol.

The most probable reactions of cyclohexanone and methanol catalyzed by acids are those of hemiketal (1) and ketal (2) formation. Both reactions are first order in ketone but reaction 1 is first order



(1)



(2)

and reaction 2 second order in alcohol. The reaction was studied in dioxane containing 0.05 *M* hydrogen chloride using varying concentrations of ketone and alcohol (Table I). The concentration of unreacted ketone was calculated from the extinction coefficient of the solution and the known extinction of cyclohexanone in dioxane in the absence of acid. The concentration of the addition compound is then the difference between this and the initial ketone concentration. In the first case the final methanol concentration is the difference between the initial concentration and the concentration of addition compound and in the second the difference with twice the addition compound concentration. The dissociation constants K^1_D and

(1) Part VIII, *Chemistry & Industry*, 1388 (1956).

(2) *Cf.* O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).

(3) (a) W. Harold and K. L. Wolf, *Z. physik. Chem.*, **21**, 165 (1931); (b) A. M. Buswell, E. C. Dunlop, W. H. Rodebush and J. B. Swartz, THIS JOURNAL, **62**, 325 (1940); (c) I. L. Gaudity, *Z. physik. Chem.*, **48**, 228 (1941); (d) N. Melchior, THIS JOURNAL, **71**, 3647 (1949); (e) P. Rampf and C. Bloch, *Compt. rend.*, **223**, 1364 (1951); (f) C. D. Hurd and W. H. Saunders, THIS JOURNAL, **74**, 5324 (1952).

(4) T. Tomonari, *Angew. Chem.*, **46**, 269 (1933); *J. Soc. Chem. Ind. Japan*, **36**, 485 (1933).

TABLE I

REACTION OF CYCLOHEXANONE AND METHANOL IN DIOXANE[a]

[MeOH]I, M	[ =O]I, M	ϵ[b]	K^1_D	K^2_D
0.492	0.0169	13.2	2.46	0.957
.492	.0325	13.3	2.62	1.25
.492	.0519	13.4	2.70	1.29
1.220	.0311	11.0	2.75	3.28
1.220	.0494	10.9	2.69	3.16
2.490	.0251	7.37	2.16	5.30
2.490	.0519	7.71	2.34	5.64
2.490	.0698	7.95	2.48	5.93
		Mean	2.53 ± 0.15	

[a] In the presence of 0.05 M hydrogen chloride at 25.0 ± 0.2°. [b] ϵ at 290 mμ.

K^2_D for the first and second reactions were calculated, and it can be seen that while K^1_D is sensibly constant, K^2_D varies considerably and thus the reaction must be first order in both ketone and alcohol and is the hemiketal equilibrium (1).[5] That the only function of the hydrogen chloride is to act as an acid catalyst is shown by the fact that the dissociation constants of the hemiketals of cyclopentanone and cyclohexanone are independent of acid concentration over a range of 50-fold (Table II).

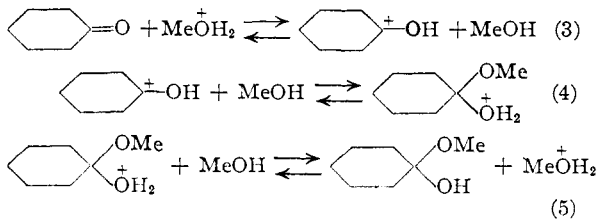
TABLE II

EFFECT OF ACID CONCENTRATION[a]

	0.002 M HCl		0.01 M HCl		0.05 M HCl		0.1 M HCl	
	ϵ	K^1_D	ϵ	K^1_D	ϵ	K^1_D	ϵ	K^1_D
Cyclopentanone	5.63	15.4	5.59	15.3	5.55	15.1	5.68	15.4
Cyclohexanone	1.01	2.35	0.93	2.13	0.98	2.16	0.99	2.30

[a] In methanol at 25.0 ± 0.2°.

Equation 1 only represents the stoichiometry of the reaction. The mechanism probably will involve initial formation of the protonated ketone (3), followed by nucleophilic attack of methanol to form the protonated hemiketal (4) and subsequent



(3)

(4)

(5)

proton transfer to methanol (5).[6] The reactions 3 and 5 of proton equilibration will be rapid and reaction 4 the slow stage.

The hemiketal formation of a series of ketones (see Table IV) in pure methanol and ethanol solution in the presence of 0.05 M hydrogen chloride has been measured. The concentration of unreacted ketone [Ket.$_f$] is proportional to the extinction coefficient (ϵ_a) of the acid solution, and the concentration of hemiketal [Hemiket.] is proportional to the difference between the extinction coefficients of the neutral (ϵ_0) and acidified solutions.

The concentration of methanol and ethanol was taken as the molarity of the pure solvent.[7]

$$K_D = [\text{Ket.}_f][\text{ROH}]/[\text{Hemiket.}] = 32 \text{ (or } 46)\epsilon_a/\epsilon_0 - \epsilon_a$$

The results with cyclopentanone and cyclohexanone are in agreement with the I-strain concept of Brown.[8] Cyclohexanone is reactive since addition to the double bond relieves angle strain in the ring and the small interference of the α-hydrogen atoms with the keto group, while addition to the carbonyl grouping of cyclopentanone gives a product in which there is considerable interaction with the ring hydrogen atoms and these additions are not favored. In the case of cyclobutanone this ketone is highly strained[8c] and addition reactions will be facilitated. However, the hemiketal will be a crowded molecule, and ring hydrogen interactions will tend to decrease its stability. Thus though cyclobutanone methyl hemiketal is more stable than cyclohexanone methyl hemiketal, the reverse is true for the ethyl hemiketal where repulsion of the bulky ethoxy group decreases the stability of the cyclobutanone addition compound. Addition to the ketone groupings of cycloheptanone and cycloöctanone will also not be favored because of the hindered nature of the hemiketals, and no reaction was observed between these ketones and ethanol.

The presence of methyl groups in cyclic ketones at positions not adjacent to the ketone grouping has been found[1,9] to decrease the reactivity toward cyanohydrin formation due to steric repulsion across the ring between the methyl and cyano groups. Similarly in methyl hemiketal formation 3-methylcyclopentanone is less reactive than cyclopentanone itself, and 3,3,5,5-tetramethylcyclohexanone is very unreactive, and neither compound reacts with ethanol. Bridge ring ketones are also unreactive toward addition reactions,[10] and the methyl hemiketal of camphor is very unstable, and no reaction occurs with ethanol. Di-*n*-propyl ketone has the same number of carbon atoms as cycloheptanone, but the chains are staggered in space and not confined in a ring, and accordingly steric hindrance to addition is greater. In the case of diisopropyl ketone, the two bulky isopropyl groups prevent any reaction from taking place.

The methyl hemiketal formation of di-*n*-propyl ketone, cyclobutanone, cyclopentanone and cyclohexanone was also measured at 1.5° and the heat of formation of the hemiketals (ΔH) calculated (see Table III). Since it was difficult to measure the small amounts of unreacted ketone in the case of cyclobutanone and cyclohexanone, the results are only approximate, but addition to the ketone grouping of cyclohexanone involves less energy change than in di-*n*-propyl ketone, whereas additions to

(5) The initial rapid formation of hemiketal may be followed by slow formation of a ketal, but this could not be detected since on long standing the absorption intensity increased and the maximum was shifted to shorter wave length, the ketones probably undergoing self-condensation.

(6) *Cf.* C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955).

(7) No appreciable error is involved in this assumption since the ketone concentration was never greater than 0.1 M.

(8) (a) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951); (b) H. C. Brown, J. H. Brewster and H. Schechter, *ibid.*, **76**, 467 (1954); (c) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(9) Unpublished work with O. Chao.

(10) O. H. Wheeler, R. Cetina and J. Z. Zabicky, *J. Org. Chem.*, in press.

TABLE III

HEMIKETAL FORMATION WITH METHANOL AND ETHANOL

	25°		1.5°		25°		K_D^{MeOH}		25°	
	MeOH[a]	MeOH/HCl[b]	MeOH	MeOH/HCl	EtOH	EtOH/HCl	25°	1.5°	K_D^{EtOH}	ΔH[c]
Di-*n*-propyl ketone	282:24.6	18.1	23.9	12.3	23.4	23.7	89.0	34.0		6.7
Diisopropyl ketone	284:19.5	19.5			19.6	19.4	∞			
Cyclobutanone	278:16.95	0.57	16.55	0[d]	15.0	13.15	1.11	0[e]	327	..[f]
Cyclopentanone	288:17.3	5.55	16.7	2.17	17.65	16.7	15.1	4.79	810	8.0
Cyclohexanone	282:14.9	0.98	14.1	0.49	16.6	13.9	2.16	1.15	237	4.3
Cycloheptanone	284:19.5	12.2			18.55	18.65	53.5		∞	
Cyclooctanone	282:19.2	17.15			21.8	21.9	268		∞	
3-Methylcyclopentanone	288:19.45	11.30			21.7	21.7	23.3		∞	
3,3,5,5-Tetramethylcyclohexanone	288:50.2	39.5			46.8	46.5	118		∞	
Camphor	290:30.8	29.9			30.5	31.5	1060		∞	

[a] All measurements at 25.0 ± 0.2° unless otherwise stated. 0.05 *M* hydrogen chloride in all cases. [c] ΔH, kcal. in MeOH at 25°. [d] ϵ 0.05. [e] $K < 0.2$. [f] ΔH *ca.* 11.9 kcal.

cyclobutanone and cyclopentanone are more difficult due to the steric repulsions produced in the hemiketals.

The spectra of di-*n*-propyl ketone, cyclopentanone and cyclohexanone were measured in water and 2-propanol containing 0.05 *M* hydrogen chloride (Table IV). In neither case was there

TABLE IV

SPECTRA IN WATER AND ISOPROPYL ALCOHOL

	Water		Isopropyl alcohol	
	−	+ 0.05 *M* HCl	−	+ 0.05 *M* HCl
Di-*n*-propyl ketone	275:28.2	28.4	283:24.0	23.8
Cyclobutanone	273:19.7	19.6	.....	..
Cyclopentanone	280:20.4	20.2	298:18.8	19.2
Cyclohexanone	278:18.6	18.8	284:16.8	17.2

any decrease in absorption intensity as compared with the spectra in neutral solution.[11] This difference in the behavior of methanol and ethanol, on the one hand, and water and 2-propanol on the other, cannot be due to the differing nucleophilic properties of the solvents since water is a stronger nucleophile than methanol. The unreactivity of water probably is due to its high self-solvation and the high free energy necessary for its "desolvation," before solvation of a ketone can take place. In the case of 2-propanol, steric hindrance to the formation of a bulky isopropoxide derivative probably prevents reaction. The non-reactivity of cyclobutanone is interesting in that cyclopropanone is known only as its hydrate,[12] but in the latter case I-strain in the ketone is so great that hydrate formation is favored.

The closest analogous addition reaction to that of hemiketal formation is the cyanohydrin reaction, and it is interesting to compare the results for the two series (Table V). Comparing di-*n*- and diisopropyl ketone and cycloheptanone and cyclooctanone in the two reactions, the hemiketal appears to have larger steric requirements, and this is to be expected since the methoxy group with the lone pair of electrons on the oxygen atom and the hydrogen atoms of the methyl group will be larger than the linear cyano group. The cyclization of open chain hydroxyaldehydes to form intramolecular cyclic hemiketals has been investigated.[13] In this case the stabilities will depend on both the ease of ring closure and the resulting I-strain in the ring,

TABLE V

COMPARISON WITH OTHER DATA

	K_D^{MeOH}[a]	$K_D^{HCN} \times 10^2$	K^{ketals}[d]
Di-*n*-propyl ketone	89.0	13.4[b]	...
Diisopropyl ketone	∞	19.3[b]	...
Ring size, $n = 4$	1.11		
$n = 5$	12.1	2.1[c]	0.13
$n = 6$	2.1	0.1[c]	0.065
$n = 7$	53.5	13[c]	5.7
$n = 8$	268	86[c]	...

[a] Present work. [b] In 96% ethanol at 35°; C.P. Evans and J. R. Young, *J. Chem. Soc.*, 1310 (1954). [c] In 96% ethanol at 22–23°. V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949). [d] Dissociation constants of cyclic ketals, in 75% dioxane at 25°. Calculated from the results of C. D. Hurd and W. H. Saunders, ref. 13.

and the large dissociation constant of the seven-membered cyclic hemiketal probably is due to an unfavorable combination of these effects.

Experimental

The ketones used were specimens which had been fractionally distilled or purified through their semicarbazones.

Methanol and ethanol were dried by refluxing with and distilling from their magnesium alkoxides[14] and isopropyl alcohol by distilling with sodium. Dioxane was refluxed with potassium hydroxide and fractionated from a fresh quantity and this treatment repeated with metallic sodium. The first fraction contained traces of aromatic hydrocarbons which made it unsuitable for spectroscopic work.[15]

Hydrogen chloride was generated by dropping A. R. hydrochloric acid into A. R. sulfuric acid and was absorbed in the required solvent. The solutions were standardized with carbonate-free sodium hydroxide and used immediately after preparation.

The spectroscopic measurements were made using a Beckman DU spectrophotometer fitted with thermospacers, through which water was circulated at 25.0 ± 0.2° from a constant temperature bath or at 1.5 ± 0.2° from an ice-water-bath.

The solvents were kept in the constant temperature baths until needed; 1-cm. quartz cells were used and the comparison cell contained solvent of the same composition. Readings were taken after 10 min. and again after 0.5 hr., but no differences were noted. However, after about 1 hr. the readings began to increase. The determinations were carried out in duplicate or triplicate using different solu-

(11) The hydration of acetone has been shown to be less than 1% in aqueous solution; R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952).

(12) P. Lipp, J. Buchkremer and H. Seeles, *Ann.*, **499**, 1 (1932).

(13) C. D. Hurd and W. H. Saunders, THIS JOURNAL, **74**, 5324 (1952).

(14) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(15) *Cf.* C. A. Kraus and R. A. Vingee, THIS JOURNAL, **56**, 511 (1934).

tions, and the mean of the values is reported in the tables. No departures from Beer's law were observed except in the cases of cyclobutanone and cyclohexanone in methanolic hydrogen chloride solution, when only inflections or very broad maxima were observed.

Acknowledgment.—This work was made possible by generous grants from the Rockefeller Foundation, New York.

MÉXICO 20, D.F.

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

3α-(2-Diethylaminoethyl)-aminotropane and Related Compounds[1,2]

BY S. ARCHER, T. R. LEWIS AND M. J. UNSER

RECEIVED, FEBRUARY 20, 1957

Tropinone was reductively aminated in the presence of diethylaminoethylamine and the resulting triamine was quaternized to furnish a bismethiodide in which the secondary amine function was still present. The compound is a tropane and not a pseudotropane as was shown by converting 3α-benzylaminotropane to the known 3α-aminotropane. The corresponding triamine derived from pseudopelletierine was prepared by catalytic reduction of the Schiff base. Evidence is presented which lends additional support to the view that in the reductive amination process it is the Schiff base and not the carbinolamine which is hydrogenated. The triamines in the pseudo series were prepared by sodium–alcohol reduction of the Schiff bases from diethylaminoethylamine and tropinone or pseudopelletierine.

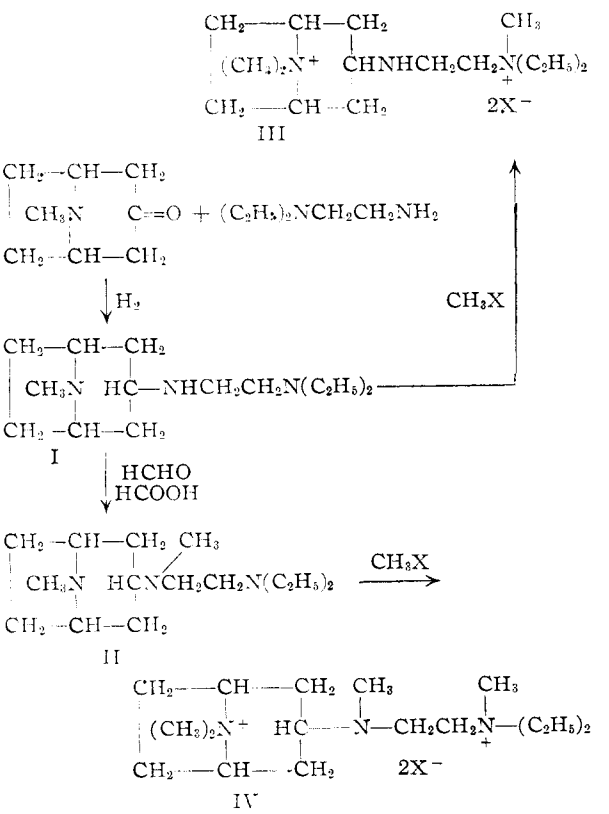
The proven clinical utility of "hexamethonium" in the control of malignant hypertension has stimulated further investigation of many bis 'onium types of peripheral ganglionic blocking agents.[3] More recently it has been shown by Cavallito and his co-workers[4] that by appropriate manipulation of the length of the chain separating the 'onium centers and the groups attached to the quaternary nitrogen atoms, it was possible to prepare hypotensive agents whose action was predominantly central rather than peripheral.

As a part of a chemical–pharmacological program, we have prepared a series of compounds of which the prototypes are the quaternary salts III and IV. Since the pharmacological aspects of this work already have been published,[5] we will confine our discussion to the more interesting chemical features of the joint endeavor.

The general method of synthesis is shown in the equation chart.

Since isomerism is possible at C-3 in the triamine I, it became necessary to establish which stereoisomer was formed in the reductive amination. Willstätter[6] prepared 3β-aminotropane by sodium–alcohol reduction of tropinone oxime. The same oxime furnished 3α-aminotropane upon reduction with sodium amalgam. We were able to obtain 3α-aminotropane by catalytic reduction of tropinone oxime. After our work was completed, a similar preparation was reported by Stoll.[7]

Hydrogenation of tropinone affords tropine[8] which has been isomerized to pseudotropine under alkaline conditions.[9] Similarly, 3α-aminotropane was isomerized to 3β-aminotropane with the aid of



sodium amoxide.[6] The configuration of the tropines has been established,[10] and in view of the marked similarities in preparation and isomerization of the two aminotropanes, it seems clear that

(1) A portion of this paper was presented at the XIV Congress for Pure and Applied Chemistry, Zurich, July, 1955.

(2) The configurations of the tropanes are designated according to the convention proposed by Fodor (ref. 10).

(3) *Inter alios, cf.* A. Marxer and K. Miescher, *Helv. Chim. Acta*, **34**, 924 (1951); J. Fakstorp, J. Christiansen and J. G. A. Pedersen, *Acta Chim. Scand.*, **7**, 184 (1953); F. Bergel, *Chimia*, **6**, 190 (1952); D. D. Libman, D. L. Pain and R. Stack, *J. Chem. Soc.*, 2305 (1952).

(4) C. J. Cavallito, A. P. Gray, T. B. O'Dell, *Arch. Internat. Pharmacodyn.*, **101**, 38 (1955); T. B. O'Dell, C. Luna and M. D. Napoli, *J. Exp. Pharm. and Therapeutics*, **114**, 306, 317 (1955).

(5) H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).

(6) R. Willstätter and W. Moller, *Ber.*, **31**, 1202 (1898).

(7) A. Stoll, E. Jucker and A. Ebnöther, *Helv. Chim. Acta*, **38**, 559 (1955).

(8) L. R. Keagle and W. H. Hartung, THIS JOURNAL, **68**, 1608 (1946).

(9) R. Willstätter, *Ber.*, **29**, 930 (1896).

(10) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).