TABLE II

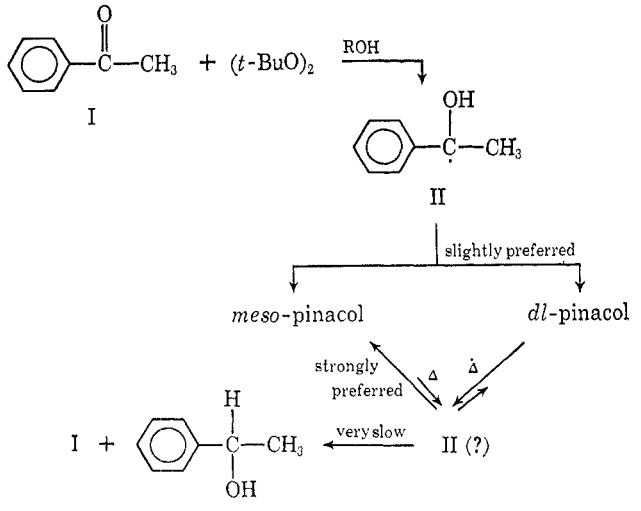
THERMAL STABILITY OF ACETOPHENONE PINACOLS[a] AT 160°

Expt	Pinacol, mg (form)	Solvent (ml)	Time, days	Product analysis[b] meso, %	dl, %	Other, % (product)
12	256 (*meso*) 257 (*dl*)	2-Pentanol (4)	4	54	46	None
13	250 (*dl*)	2-Pentanol (2)	2	17	83	None
14	250 (*dl*)	2-Pentanol[c] (2)	2	9	91	None
15	250 (*dl*)	2-Pentanol[c] (2)	5	14	86	None
16	200 (*dl*)	None	14	15	12	20 (methyl phenyl carbinol), 31 (acetophenone)
17	25 (*dl*)	2-Pentanol (4)	7	90	10	None
18	10 (*meso*) 10 (*dl*)	2-Pentanol (4)	7	95	5	None
19	25 (*meso*)	2-Pentanol (4)	7	100	0	None

[a] *meso*- and *dl*-2,3-diphenyl-2,3-butanediol. [b] Based on starting pinacol(s) as evaluated by proton integration of aromatic region (nmr) constituting 100% of invested aromatic protons; see J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968). [c] *t*-Butyl peroxide (0.5 ml) present.

report of simple *thermal* interconversion.[9] The *meso* form clearly predominates to a degree that observation of an equilibrium situation was not practical; *i.e.*, for very small samples a net conversion of 90% of the *dl* into the *meso* form, from a 50:50 mixture of the two forms, took place in 7 days (expt 18), while a net change of zero occurred for the *meso* form in a like period of time (expt 19). It may be noted that the presence of peroxide did not produce an appreciable change in results, the change, if real, being in a decelerative direction. Interconversion also took place in the absence of solvent (expt 16) but appreciably more slowly; cleavage by-products were observed. It would not be obvious, *a priori*, whether preferential cleavage of the *dl* form, or preferred recombination of the resultant ketyl radicals from both forms, or some combination of these two possibilities, would be responsible for this extreme dominance of the *meso* form over a period of time; if one makes the reasonable assumption that recombination of radicals is stereochemically unchanged from combination, preferential cleavage of the *dl* form must be invoked. A speculative alternative might consider the recombination to be from a tight pair rather than the initial freer combination.

The interrelationships involved are most simply rationalized as follows.



(9) A mechanism proposed by Neckers and Colenbrander[8] for the thermal breakdown of benzpinacol involved scission into benzhydrol radicals; these disproportionate[10] at temperatures above 100° (see ref 1, footnote 9). Interconversion of diastereomers would be implicit in this mechanism where radical stability permitted.

(10) The absence of disproportionation in the present studies (excepting only expt 16) is admittedly surprising. The products from this process—acetophenone and methyl phenyl carbinol—are readily observable in nmr analysis and were specifically sought. It may be suggested that in the related benzophenone studies, the more stable benzhydrol radical (compared with its acetophenone counterpart radical) is accordingly more readily formed and lingers longer, permitting the (slower) disproportionation reaction to become more important than recombination.

(11) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968).

The results reported suggest that stereochemical studies involving peroxides in this area may carry an important thermal component, and, further, that such interconversion may be exploited to enrich a mixture of diastereomers in the more favored isomer.

Experimental Section

Acetophenone, *t*-butyl peroxide, and 2-pentanol were the highest grade commercial products available and were used as received. *meso*- and *dl*-acetophenone pinacols were prepared by photochemical or organometallic techniques.[2]

General Procedure.—Acetophenone, *t*-butyl peroxide (if present), and 2-pentanol were placed in a 3-oz aerosol compatibility tube (Fisher and Porter) subsequently sealed with a stainless steel cap fitted with a pressure valve and neoprene gasket. Exact amount of all reaction components are given in Tables I and II. Temperatures were controlled by use of an oil bath and variable-temperature hot plate and were held to ±2° of the reported values. Following the reaction period, the pressure was released and the sample was prepared for nmr analysis as previously reported in the related photochemical studies.[11]

Registry No.—Acetophenone, 98-86-2; *meso*-acetophenone pinacol, 4217-65-6; *dl*-acetophenone pinacol, 22985-90-6.

Preparation of 2-Heteroalkyl Substituted 2-Cyclohexen-1-ones

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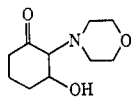
Received October 3, 1969

Because of our general interest in the chemistry of 2-cyclohexen-1-one (**1**), we wished to prepare and examine previously unreported 2-substituted derivatives

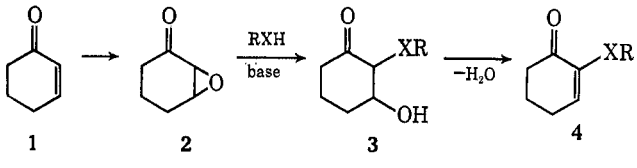
TABLE I

2-HETEROALKYL 2-CYCLOHEXEN-1-ONES (4)

XR	Registry no.	Yield, %	Mp or bp, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S	δ for C-3 proton
OCH_3	23740-37-6	25	117–119 (18)	52.46[a]	6.63	22.95	...	52.57	6.93	22.70	...	5.74
$SCH_2CH(CH_3)_2$	23740-38-7	72	122–125 (3)	65.21	8.69	...	17.39	65.33	8.83	...	17.30	6.73
$SCH(CH_3)_2$	23704-39-8	81	109–112 (3)	63.53	8.23	...	18.82	63.70	8.84	...	18.63	6.90
$SC(CH_3)_3$	23704-40-1	62	105–106 (3)	65.21	8.69	...	17.39	65.43	8.77	...	17.32	7.41
	23740-61-6	47	54–55	56.31[b]	5.45	15.16	...	56.53	5.60	15.00	...	6.40
	18543-93-6	75	83 (3)									5.37[c]
	23740-63-8	72	90 (3)	73.74	9.50	7.82	...	73.88	9.67	7.76	...	5.88
	23740-64-9	83	53–54	66.30	8.29	7.73	...	66.29	8.02	7.66	...	5.94
$N(CH_3)_2$	23740-65-0	86	55 (0.1)	69.03	9.41	...	...	69.05	9.51	...	...	5.78
$N(CH_2CH_3)_2$	13120-89-3	76	58 (0.1)	71.81	10.25	...	...	71.74	10.15	...	...	5.90
	23740-67-2	43	94–96	60.30	8.54	7.04	...	60.31	8.55	7.01	...	

[a] Analysis on semicarbazone, mp 211–212°. [b] Analysis on thiosemicarbazone, mp 186–187°. [c] Reported[4] at δ 5.44 for neat compound.

(4) of this material. Thus the following preparative scheme was adopted.



1 2 3 4

Epoxidation of 1 with either alkaline hydrogen peroxide[1] or *t*-butyl hydroperoxide[2] afforded 2,3-epoxycyclohexanone (2) in high yield. Base-catalyzed reaction of 2 with varied nucleophilic substrates (RXH) yielded 2-substituted 3-hydroxycyclohexanones (3), which generally dehydrated *in situ* or during isolation to afford the desired 2-substituted 2-cyclohexen-1-one (4).

The utility of this procedure is, however, highly dependent upon both the nucleophilicity of RXH and the stability of 2, 3, and 4 to the basicity of the reaction medium. Thus species which are both good nucleophiles and strong bases were not effective in preparing compounds of type 4, whereas strongly nucleophilic but weakly basic substrates gave very good yields of the desired products 4. For example, sodium methoxide in methanol reacted with 2 to afford a 25% yield of 2-methoxy-2-cyclohexen-1-one,[3] while both sodium isopropoxide and *t*-butoxide yielded only resinous reaction mixtures. On the other hand, primary, secondary, and tertiary alkyl mercaptans, aryl mercaptans, and both aliphatic and alicyclic secondary amines provided high yields of the 2-substituted derivatives of 1 (Table I).

The structure of these new cyclohexenones (4) were assigned on the basis of (A) the chemical shifts and splitting patterns of the C-3 vinyl proton, which appears as a triplet (J = 4–6 Hz) at 5.37–7.41 ppm; (B) the stretching frequencies of the α,β-unsaturated carbonyl at *ca.* 5.9 and 6.2 μ; and (C) satisfactory elemental analysis. An additional proof of structure for 2-methoxy-2-cyclohexen-1-one and 2-N-pyrrolidino-2-cyclohexen-1-one was obtained by converting the former into *o*-methoxyphenol and by comparing the spectral properties of the latter with those of an authentic sample prepared from pyrrolidine and 1,2-cyclohexanedione.[4]

Experimental Section[5]

The following examples are representeative of the synthetic method used. Homologous compounds were prepared by similar procedures.

2-N,N-Dimethylamino-2-cyclohexen-1-one.—Gaseous dimethylamine was introduced through a glass frit into a solution of 5.6 g (0.05 mol) of 2, 15 ml of methanol, and 5 ml of water. The exothermic reaction was controlled by regulating the flow of amine. After the exotherm had subsided (0.5 hr), the amine addition was stopped and the solvent was removed. The residue was taken up in chloroform, and the organic layer was dried ($MgSO_4$), concentrated, and distilled, giving 6.2 g of product, bp 55° (0.1 mm).

2-N-Morpholino-2-cyclohexen-1-one.—A solution of 5.6 g (0.05 mol) of 2, 5.3 g (0.06 mol) of morpholine, 15 ml of methanol, and 5 ml of water was refluxed for 3 hr. After cooling, the solvent was removed and the residue was placed in 100 ml of saturated brine solution. Extraction with ether, drying ($MgSO_4$), and removal of the solvent yielded 7.5 g of oil which solidified slowly. Several crystallizations from hexane afforded an analytically pure sample, mp 53–54°.

2-N-Morpholino-3-hydroxycyclohexanone.—When the temperature of the exothermic reaction resulting from the combination of 2 and morpholine was kept below 40° and an identical work-up procedure with that described above used, 4.3 g of the 2,3-disubstituted cyclohexanone was isolated, mp 94–96° after several crystallizations from hexane.

2-Thioisopropyl-2-cyclohexen-1-one.—Isopropyl mercaptan, 15.7 g (0.2 mol), was dissolved in 25 ml of ethanol and added during 1.5 hr to a solution of 22.4 g (0.2 mol) of 2, 75 ml of ethanol, and 1.25 ml of 15% sodium hydroxide. The temperature of the exothermic reaction was maintained at 35–40°. After the solution had stood for 12 hr at ambient temperature, the solvent was removed and the residue was distilled, giving 27.5 g of product, bp 109–112° (3 mm).

(1) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 552.

(2) N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

(3) Direct methylation of 1,2-cyclohexanedione has been reported to produce an 11% yield of impure material: M. S. Gibson, *J. Chem. Soc.*, 681 (1962).

(4) S. Danishefsky and R. Cavanaugh, *Chem. Ind.* (London), 2171 (1967).

(5) Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected. Nuclear magnetic resonance spectra were determined with a Varian Model A-60; pertinent chemical shifts are expressed in parts per million downfield from internal tetramethylsilane.

2-Methoxy-2-cyclohexen-1-one.—A solution of 11.2 g (0.1 mol) of **2** in 50 ml of 0.1 *M* sodium methoxide was allowed to stand at 20–25° for 40 hr. Neutralization of the reaction mixture, removal of excess solvent, and distillation yielded 3.1 g (25%) of product, bp 116–119° (18 mm).

The Synthesis of Amino-Substituted α,α,α-Trifluoroacetophenones

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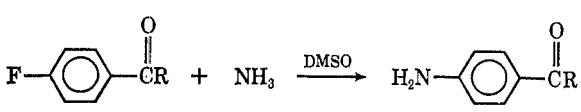
In connection with other work in our laboratory, we were in need of a series of *meta*- and *para*-substituted perfluoroacyl ketones—especially substituted trifluoroacetophenones. Normal procedures for the preparation of substituted trifluoroacetophenones involve reaction of the appropriate Grignard reagents with trifluoroacetic acid,[1,2] or bromination, nitration, etc., of the appropriate perfluoroacyl ketone to give some *meta* derivatives not available by the Grignard procedure. However, these procedures fail when substituents such as amino, dimethylamino, cyano, iodo, or bromo are present in the Grignard reagent.[3] Consequently, substituents of this type cannot be introduced into the *para* position by these normal procedures.

Therefore, we have devised a new method for the introduction of such substituents. This procedure introduces a *p*-amino group into the appropriately substituted *p*-fluoro perfluoroacyl ketone (available *via* the Grignard method[1]). The introduction of the amino group allows the preparation of other *para* substituents (such as CN, I, Br, etc.) *via* diazotization followed by a Sandmeyer reaction. Since all of the synthetic reactions of the amino-substituted ketones are carried out in acid solution, no haloform-type reaction of the ketones are observed. Similar substituents can be introduced into the *meta* position *via* diazotization of the *meta*-amino ketone (available *via* nitration of the parent ketones). For the sake of completeness these substituted ketones are also included.



R = CF_3, CF_3CF_2, $CF_3CF_2CF_2$

Aryl carbon–fluorine bonds are significantly activated by the introduction of an electron-withdrawing group into the aromatic nucleus. In addition, fluorine atoms are relatively susceptible to displacement by nucleophilic species, much more so than other halogens.[4] Bader and coworkers[5] have found that dimethylamine displaces activated aryl fluorine atoms in both dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF) solvents. Therefore, we considered the displacement of activated fluorine by ammonia feasible. Indeed, it was found that in DMSO the conversion of *p*-fluorotrifluoroacetophenone (I)[2] into *p*-aminotrifluoroacetophenone (II) could be carried out by bubbling ammonia into the hot, well-stirred solution. The trifluoroacetyl group creates an activated aryl carbon–fluorine bond.[6] The *p*-chloro ketone did not react under the same conditions. In addition, the conversion did not occur in other solvents such as dimethoxyethane, formamide, or DMF.

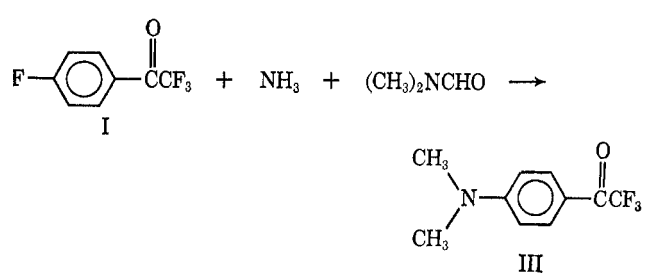
TABLE I

SUBSTITUTED TRIFLUOROACETOPHENONES *via* THE REACTIONS OF *m*- AND *p*-AMINOTRIFLUOROACETOPHENONE[a]

Starting trifluoroacetophenone	Product trifluoroacetophenone	Yield, %	Reagents[b]
p-NH_2	*p*-Cl	50	CuCl, HCl
p-NH_2	*p*-Br	70	CuBr, HBr
p-NH_2	*p*-I	74	KI, I_2
p-NH_2	*p*-CN	59	CuCN, KCN
m-NH_2	*m*-I	71	KI, I_2
m-NH_2	*m*-CN	62	CuCN, KCN

[a] Normal diazotization procedures which have been described in a general manner by Vogel[9] were employed. [b] The cuprous salts used were freshly prepared. Best results were obtained if dilute sulfuric acid was used as the diazotization medium.

The use of DMF as solvent, ammonia, and I enabled the preparation of *p*-dimethylaminotrifluoroacetophenone (III). Apparently, when ammonia is bubbled into DMF, dimethylamine is produced. Dimethylamine is a stronger base than ammonia and must react much more rapidly to displace the aryl fluorine. Thus, as dimethylamine is consumed more is produced, and good yields of III are obtained.



(1) K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, **78**, 2268 (1956).

(2) F. E. Herkes and D. J. Burton, *J. Org. Chem.*, **32**, 1311 (1967).

(3) F. E. Herkes, Ph.D. Thesis, University of Iowa, 1966.

(4) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benajmin, Inc., New York, N. Y., 1965, p 847.

(5) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

(6) The trifluoroacetyl group is not a specific activator for this reaction, and the same aryl fluorine displacement by ammonia has been carried out with 1-(*p*-fluorophenyl)pentafluoropropanone and 1-(*p*-fluorophenyl)heptafluorobutanone (these ketones were prepared by the method of Dishart and Levine[1] using *p*-fluorophenylmagnesium bromide with pentafluoropropionic acid and heptafluorobutyric acid, respectively). The *p*-amino ketones produced (V and VI, respectively) showed ir, ^1H nmr, and ^{19}F nmr spectra consistent with the expected structures. Data for V follow: ir 5.93 μ (C=O); ^1H nmr δ 4.40 (broad singlet, 2 H) and 6.67 and 7.95 (doublets, 4 H); ^{19}F nmr 82.1 (singlet, 3 F) and 115.2 ppm (singlet, 2 F). Data for VI follow: ir 5.94 μ (C=O); ^1H nmr δ 4.38 (broad singlet, 2 H) and 6.67 and 7.92 (doublets, 4 H); ^{19}F nmr 80.0 (3 F), 112.6 (2 F), and 125.1 ppm (2 F).