Alkylation of Enamines with t-Propargylic Chlorides[1]

G. F. HENNION AND F. X. QUINN[2]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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The alkylation of the pyrrolidine enamines derived from cyclohexanone and cyclopentanone with *t*-propargylic chlorides produced, after hydrolysis, the corresponding 2-*t*-alkylated cycloalkanones. The alkylation was catalyzed by cuprous chloride and the yields depended not only on the substrates used but also on the reaction temperature, solvent polarity, and the presence or absence of a basic nonalkylatable amine. 2-(1,1-Dimethylpropargyl)cyclopentanone (1) formed the expected products following hydrogenation, hydration, oxidative coupling, and sodium borohydride reduction. The hydration product formed novel heterocyclic compounds by reactions with ammonia and hydrazine.

It is now well known that *t*-propargylic chlorides, $R^1R^2C(Cl)—C\equiv CH$, react in basic media to produce zwitterion carbene intermediates which behave either as ambident electrophiles or as carbenes.[1b] Tertiary amines have been found to produce *t*-propargylic and/or allenic quaternary ammonium chlorides depending on both the *t*-chloride and the amine used.[3] Enamines,[4] which are known to react both as ambident nucleophiles and as carbene acceptors,[5] constitute a special class of tertiary amines whose reactions with *t*-propargylic chlorides have not been studied previously.

The pyrrolidine enamines derived from cyclohexanone and cyclopentanone were successfully alkylated with a variety of *t*-propargylic chlorides to produce, following hydrolysis, the corresponding 2-*t*-alkynylcyclohexanones and -cyclopentanones. The optimum reaction conditions, determined for the alkylation of 1-pyrrolidino-1-cyclopentene with 3-chloro-3-methyl-1-butyne, consisted of dropwise addition of a slight excess of *t*-chloride to a cold (−10 to −15°) solution of enamine, triethylamine, and a trace of cuprous chloride in dimethylformamide (DMF) solvent maintained under a nitrogen atmosphere. Hydrolysis concomitant with steam distillation gave 2-(1,1-dimethylpropargyl)-cyclopentanone in 50–60% yields. The low reaction temperature was essential to minimize HCl elimination from the *t*-chloride. Alkylation was favored by use of polar solvents (*e.g.*, DMF) and small amounts of copper powder or cuprous chloride proved effective as a catalyst.[6] Triethylamine was used to neutralize the hydrogen chloride liberated in the reaction, thus preventing the consumption of a second mole of the parent enamine.

The reactions of a variety of enamines and *t*-propargylic chlorides were studied to determine the scope and limitations of the alkylation. The reactions employing enamines derived from pyrrolidine gave yields higher than those employing enamines derived from piperidine. This observation, previously seen by Stork,[7] has been rationalized on the basis of Brown's observation[8] that the formation of a trigonal carbon is more facile in five-membered than in six-membered rings. Since the transition state for C-alkylation involves the formation of a trigonal nitrogen, enamines in which the nitrogen is contained in a five-membered ring should be more reactive than enamines in which the nitrogen is in a six-membered ring. It was also found that enamines formed from cyclopentanone gave consistently higher yields than those from enamines formed from cyclohexanone. This result can also be explained on the basis of Brown's observation. The alkylation of enamines derived from mono- and disubstituted acetaldehydes was unsatisfactory since these reactions always gave complex mixtures of products in poor yields.

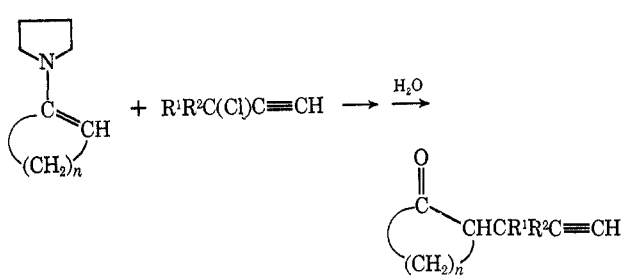
TABLE I

2-(1,1-DIALKYLPROPARGYL)CYCLOALKANONES

$(CH_2)_n—CO—CH—CR^1R^2—C\equiv CH$

Compd	n	R^1	R^2	Yield, %	Bp, °C (mm)	$n^{25}D$
1	3	CH_3	CH_3	53	64 (2.2)	1.4642
2	4	CH_3	CH_3	17	77–79 (3)	1.4742
3	3	$-(CH_2)_5-$		33	93–97 (0.5)	1.4986
4	4	$-(CH_2)_5-$		9	85–86 (0.1)	1.5050
5	3	CH_3	C_2H_5	23	63–64 (0.3)	1.4698
6	4	CH_3	C_2H_5	8	47–48 (0.1)	1.4800
7	3	C_2H_5	C_2H_5	12	55–56 (0.2)	1.4745
8	3	H	H	36	58 (2.2)	1.4700

The yield data obtained by variation of the *t*-propargylic chloride paralleled earlier amine alkylation results.[3,6] As the steric bulk of the groups attached to the tertiary carbon was increased, the yields of the alkylated products were sharply reduced. Table I lists the yields and the physical properties of the 2-*t*-alkylated ketones prepared in this work.



(1) (a) Paper No. 88 on substituted acetylenes; (b) previous paper: G. F. Hennion and J. F. Motier, *J. Org. Chem.*, **34**, 1319 (1969).

(2) Eli Lilly Company Fellow, 1967–1969; Lubrizol Corp. Fellow, 1967–1968; Du Pont Teaching Fellow, 1968–1969. Abstracted from a portion of the Ph.D. Dissertation of F. X. Q.

(3) (a) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 3696 (1965); (b) *ibid.*, **31**, 1977 (1966).

(4) For reviews of the preparations and reactions of enamines, see (a) J. A. West, *J. Chem. Educ.*, **40**, 194 (1963); (b) J. Szmuszkovicz in "Advances in Organic Chemistry," Vol. 4, E. C. Taylor, Ed., Interscience, New York, N. Y., 1963, Chapter 1; (c) K. H. Blaha and O. Cervinka in "Advances in Heterocyclic Chemistry," Vol. 6, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1966, p 147.

(5) (a) M. Ohno, *Tetrahedron Lett.*, 1753 (1963); (b) J. Wolinsky, D. Chan, and R. Novak, *Chem. Ind. (London)*, 720 (1965).

(6) Previous studies have shown that other amine alkylations with *t*-propargylic chlorides are similarly catalyzed by copper and/or cuprous chloride. See, G. F. Hennion and R. S. Hanzel, *J. Amer. Chem. Soc.*, **82**, 4908 (1960).

(7) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(8) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

TABLE II

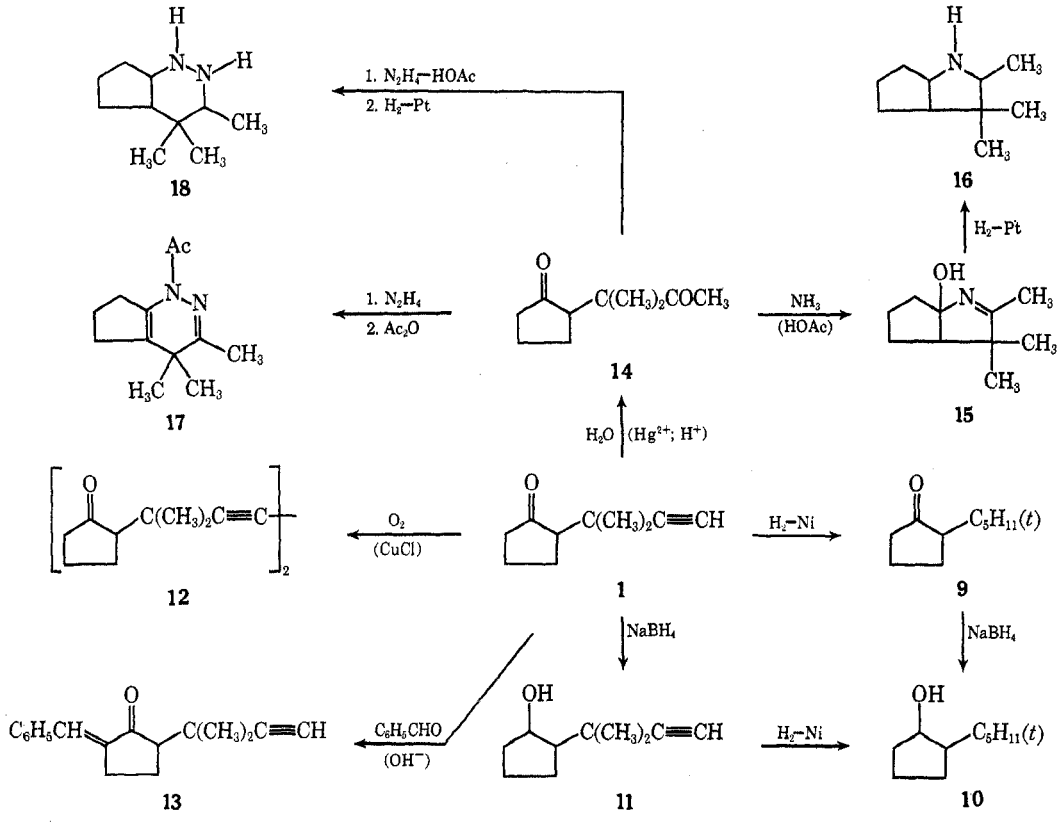
DERIVATIVES OF 2-(1,1-DIALKYLPROPARGYL)CYCLOALKANONES

Deriv[a]	Mp, °C	Formula	% C		% H		% N	
			Calcd	Found	Calcd	Found	Calcd	Found
1 Sc	189–190	$C_{11}H_{17}N_3O$	63.74	63.95	8.27	8.53	20.27	20.49
1 Ph	174–176	$C_{16}H_{18}N_4O_4$	58.17	58.25	5.49	5.71	16.96	17.21
1 Ox	85–86	$C_{10}H_{15}NO$	72.69	72.45	9.15	8.94	8.48	8.28
2 Ph	140–142	$C_{17}H_{20}N_4O_4$	59.29	59.15	5.85	6.05	16.27	16.32
3 Sc	196–197	$C_{14}H_{21}N_3O$	67.99	68.05	8.56	8.38	16.99	16.86
3 Ph	162–164	$C_{19}H_{22}N_4O_4$	61.61	61.73	5.99	5.95	15.13	15.14
4 Sc	194–196	$C_{15}H_{23}N_3O$	68.93	68.97	8.87	9.02	16.08	16.24
5 Sc	176–177	$C_{12}H_{19}N_3O$	65.13	65.39	8.65	8.56	18.99	19.23
5 Ph	169–170	$C_{17}H_{20}N_4O_4$	59.29	59.27	5.85	5.77	16.27	16.37
6 Sc	146–148	$C_{13}H_{21}N_3O$	66.35	66.12	8.99	8.76	17.86	17.80
6 Ph	150–151	$C_{18}H_{22}N_4O_4$	60.32	60.59	6.19	6.26	15.63	15.83
7 Sc	156–157	$C_{13}H_{21}N_3O$	66.35	66.09	8.99	9.01	17.86	18.03
7 Ph	159–160	$C_{18}H_{22}N_4O_4$	60.32	60.34	6.19	6.28	15.63	15.85
8 Ph	131–132	$C_{14}H_{14}N_4O_4$	55.63	55.77	4.67	4.56	18.53	18.61

[a] Sc = semicarbazone; Ph = 2,4-dinitrophenylhydrazone; Ox = oxime.

SCHEME I

REACTIONS OF 2-(1,1-DIMETHYLPROPARGYL)CYCLOPENTANONE



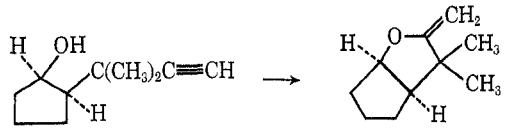
The structures of the alkylated products were established by ir and nmr spectroscopy (see Experimental Section), by the analysis of crystalline carbonyl derivatives (see Table II), and by a variety of chemical reactions characteristic of ketones and terminal ethynyl groups. Furthermore, the dialkylpropargyl moiety was firmly established to be in the position α to the carbonyl by several ring closure reactions (see below).

The reactions of the 2-*t*-alkylated cycloalkanones were then studied using 2-(1,1-dimethylpropargyl)-cyclopentanone (**1**) as a model. A summary of its reactions is presented in Scheme I. The propargylic ketone **1** displayed reactivity typical of acetylenic compounds. Hydration, hydrogenation, and oxidative coupling produced the normal 1,4 diketone **14**, saturated ketone **9**, and conjugated diyne **12** (as a mixture of diastereoisomers), respectively.

All the ketones reacted with 2,4-dinitrophenylhydrazine and semicarbazide in the typical manner. There was no evidence of any subsequent cyclization of the derivatives into the triple bond. Furthermore, ketone **1** formed the normal oxime derivative which could not be thermally cyclized by prolonged heating above its melting point. The reaction of **1** with benzaldehyde produced the normal benzal derivative **13**. There was no evidence of any product formed by reaction through the acetylide anion.

Ketone **1** was reduced by sodium borohydride to a mixture of *cis*- and *trans*-2-(1,1-dimethylpropargyl)-cyclopentanols (**11**). The *cis*/*trans* ratio could not be

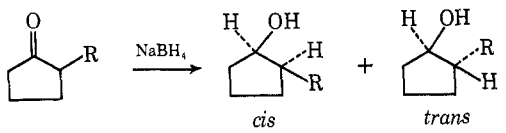
obtained directly by glpc of the reaction mixture owing to the facile cyclization of the *cis* alcohol to form a vinyl ether. However, hydrogenation to the saturated alcohols prior to glpc analysis allowed the *cis/trans* ratio to be obtained. The reaction product (**11**) on glpc analysis produced three fractions identified as vinyl ether (**19**), a mixture of **19** and *cis* alcohol, and *trans* alcohol, re-



cis **19**

spectively. The ir of **19** exhibited bands at 3120 cm^{-1} and 1665 and 1595 cm^{-1} typical of the >C=CH_2 and –O—C=CH_2 groups, respectively. The nmr displayed twin singlets at 1.1 and 1.2 ppm (anisochronous $(CH_3)_2C$ group), an AX pattern at 3.6 and 4.0 ppm (J = 1.5 Hz, –O—C=CH_2), and a broad multiplet centered at 4.75 ppm (–CH—O–). The vinyl ether should have only *cis*-ring fusion and was, therefore, assigned structure **19**. The isolation and the identification of **19**, coupled with the observations that the second fraction contained **19** in a mixture with its alcohol precursor and that the third fraction contained the noncyclizing alcohol, firmly established that the *cis* alcohol had the shorter retention time. This assignment of the structures was further substantiated by the nmr of the respective isomers. Though the *cis* isomer could not be obtained pure, a comparison of the nmr of the pure *trans* isomer with that of the original reduction product allowed an assignment of the *cis* peaks. The important feature of the spectra was the relative positions of the hydroxyl proton resonances. Since hydrogen bonding is known to cause a downfield shift of the proton resonance,[9] the *trans* hydroxyl proton, as expected, appeared at a significantly lower field than the *cis* proton [*e.g.*, 3.9 ppm (*trans*) *vs.* 2.8 ppm (*cis*)]. The saturated alcohols exhibited the same trends in both retention times and nmr. Thus, *cis*-2-*t*-amylcyclopentanol had the shorter retention time and its hydroxyl proton resonance appeared at a considerably higher field than that of its *trans* isomer [*e.g.*, 2.77 ppm (*cis*) *vs. ca.* 3.5 ppm (*trans*)].

2-Propargylcyclopentanone (**8**) was likewise reduced. However, no attempts were made to isolate and separate the *cis*- and *trans*-2-propargylcyclopentanols. Instead, the reduction product was hydrogenated and the 2-propylcyclopentanols were separated and identified. In addition, the saturated ketones were reduced and the *cis/trans* ratios were determined by



cis *trans*

glpc. Table III lists the product ratios for the reductions studied. It is worth noting that the ketones bearing the bulkiest groups (*e.g.*, dimethylpropargyl and *t*-amyl) produce the *cis* isomer preferentially, whereas those ketones bearing relatively small groups

(9) I. V. Aleksandrov, "The Theory of Nuclear Magnetic Resonance," Academic Press, New York, N. Y., 1966, p 149.

TABLE III

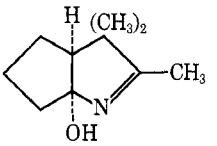
PRODUCT RATIOS FOR THE SODIUM BOROHYDRIDE REDUCTIONS OF SELECTED 2-SUBSTITUTED CYCLOPENTANONES

R	Cyclopentanol, % *cis*	Cyclopentanol, % *trans*
$-C(CH_3)_2C{\equiv}CH$	69	31
$-C(CH_3)_2CH_2{-}CH_3$	61	39
$-CH_2C{\equiv}CH$	34	66
$-CH_2CH_2{-}CH_3$	28	72
$-CH_3$[a]	26	74

[a] J. B. Umland and B. W. Williams, *J. Org. Chem.*, **21**, 1302 (1956).

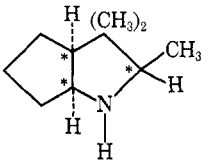
produce the *trans* isomer preferentially. This result appears to be another example of steric approach control (with bulky groups) *vs.* product development control (with the small groups).[10]

The cyclization reactions of diketone **14** with ammonia and hydrazine were also studied. The reaction of **14** with ammonium acetate in glacial acetic acid produced a stable solid identified as 1-hydroxy-3,4-4-trimethyl-2-azabicyclo[3.3.0]-2-octene (**15**). Hydrolysis of **15** regenerated the starting diketone **14**. The ir and nmr spectra of **15** were consistent with the assigned structure (see Experimental Section). The hydroxyl group was assigned to the bridgehead carbon (carbon 1) from the mass spectrum which displayed a strong peak (50%) at m/e 126 (P – 41) corresponding to the loss of CH_3CN. Since the nmr spectrum and the sharp melting point of the solid indicated that the product was not a diastereomeric pair and since the steric features favor *cis*-ring fusion, the product was assigned the structure shown below.



15

Heterocycle **15** was hydrogenated over platinum producing the amine **16** formed by the saturation of the –C=N– group and hydrogenolysis of the hydroxyl group. Though the product could have been a mixture of four diastereomeric pairs, the nmr spectrum indicated that the product consisted of only two diastereomeric pairs. This conclusion was made on the basis of the appearance of only eight peaks due to the methyl groups. Since each pair of diastereomers would be expected to give rise to four peaks, a doublet for >$CHCH_3$ and twin singlets for $(CH_3)_2C$, had the product been a mixture of the four possible *d,l* pairs, a total of 16 peaks would have been predicted.

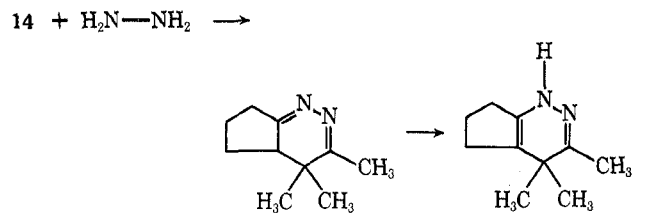


16

The reaction of **14** with hydrazine in glacial acetic acid produced an unstable oil which on distillation suffered extensive decomposition and tar formation. The

(10) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

ir and nmr spectra of the crude distillate (bp 60–90°, 1 mm) indicated that the initial reaction product tautomerized, as shown below. The ir spectrum displayed



a strong band at 1695 cm^{-1} (-C=N-) and a band of medium intensity at 1618 cm^{-1} (C=C). The nmr spectrum exhibited a broad peak (*ca.* 1, N—H) centered at 7.1 ppm, a singlet (3, CH_3C=N-) at 1.87 ppm, and a singlet [6, $(CH_3)_2C$] at 1.13 ppm. The crude product formed a stable acetyl derivative identified as 2-acetyl-4,5,5-trimethyl-2,3-diazabicyclo[4.3.0]-1(6),3-nonadiene (**17**). Hydrolysis of **17** regenerated the starting diketone **14**. The ir and nmr spectra of **17** were consistent with the assigned structure (see Experimental Section). The original reaction mixture (*i.e.*, the solution of the dihydropyridazine in acetic acid) was hydrogenated over platinum to form the hexahydropyridazine **18**.

Experimental Section

The *t*-propargylic chlorides were prepared as previously reported.[11] 1-Pyrrolidino-1-cyclopentene[7] and 1-pyrrolidino-1-cyclohexene[7] were prepared according to the procedure of Herr and Heyl.[12]

The 2-(1,1-dialkylpropargyl)cycloalkanones listed in Table I were prepared according to the procedure described below.

2-(1,1-Dimethylpropargyl)cyclopentanone (**1**).—A solution of 68.5 g (0.5 mol) of 1-pyrrolidino-1-cyclopentene, 76.5 g (0.75 mol) of triethylamine, and 0.5 g of cuprous chloride in 200 ml of DMF was cooled to −10° under nitrogen and 76.5 g (0.75 mol) of 3-chloro-3-methyl-1-butyne was added dropwise with stirring over 4 hr. The mixture was stirred at near −10° for an additional 5 hr and allowed to warm to room temperature overnight. Then 125 ml of 4 *N* hydrochloric acid was added dropwise and the mixture was steam distilled. The distillate was extracted with ten 50-ml portions of ether. The combined ethereal solution was washed with 50 ml of 10% hydrochloric acid, twice with 50-ml portions of water, with 50 ml of dilute sodium bicarbonate, and finally three times with 50-ml portions of water, and then dried over anhydrous potassium carbonate. Distillation gave 40 g (53%) of **1**: bp 64° (2.2 mm); $n^{25}D$ 1.4642; ir (neat) 3310 and 2118 (C≡C—H) and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.1 and 2.5–1.5 (singlet superimposed on a multiplet, 8, ≡C—**H** and C_4H_7 ring protons), and 1.3 and 1.4 (s, 3 each, anisochronous $(CH_3)_2C$).

2-*t*-Amylcyclopentanone (**9**) was prepared from 15.0 g (0.1 mol) of **1** dissolved in 50 ml of absolute ethanol containing 2 g of Raney nickel. The hydrogenation was carried out at room temperature for 1 hr at an initial pressure of 36 psig. Distillation afforded 13.4 g (87%) of **9**: bp 72° (2.2 mm); $n^{25}D$ 1.4523; ir (neat) 1730 cm^{-1} (strong, >C=O), but no absorption at 3330 and 2115 (C≡C—H), 3080 and 900 (=CH_2), nor 1655 cm^{-1} (C=C).

The semicarbazone had mp 177–178°.

Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.86. Found: C, 62.80; H, 9.87; N, 20.12.

The 2,4-dinitrophenylhydrazone had mp 127–129°.

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.63; H, 6.92; N, 17.02.

2-Propylcyclopentanone (**9a**) was prepared according to the procedure described above. Hydrogenation of a 12.2-g (0.1 mol) sample of 2-propargylcyclopentanone (**8**) yielded 9.56 g (76%) of **9a**: bp 60–61° (5.5 mm); $n^{25}D$ 1.4393 (lit.[13] bp 175–177°; $n^{30}D$ 1.4382).

2-*t*-Amylcyclopentanol (**10**).—A solution of 10.0 g (0.065 mol) of 2-*t*-amylcyclopentanone (**9**) in 20 ml of absolute ethanol was added to a solution of 2.0 g (0.05 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 75 ml of absolute ethanol. The reaction mixture was refluxed for 4 hr, cooled to room temperature, and then concentrated on a rotary evaporator. The residue was hydrolyzed with 70 ml of 4 *N* hydrochloric acid and extracted with ether. The extracts were washed with water, dilute sodium bicarbonate, again with water, and dried over anhydrous calcium sulfate. Distillation gave 7.8 g (78%) of **10**: bp 70–72° (0.8 mm); $n^{25}D$ 1.4654; ir (neat) 3580–3330 cm^{-1} (-OH) but no absorption at 1730 cm^{-1} (C=O).

The product was shown by glpc to consist of 67% *cis* and 33% *trans* isomer. The isomers were separated by preparative gas chromatography (15% Hyprose on Chromosorb W at 140°; 15 ft × 0.25 in. (OD); helium flow rate, 60 ml/min; retention times *cis* 33 min, *trans* 44 min). The isolated isomers exhibited the following properties: *cis* $n^{25}D$ 1.4651; ir (neat) 3610 (w, nonbonded -OH) and 3580–3100 cm^{-1} (bonded -OH); nmr (neat) δ 4.17 (broad m, 1, CHOH), 2.77 (broad m, 1, -**OH**), and 2.0–0.5 (overlapping m, 18); *trans* $n^{25}D$ 1.4639; ir (neat) 3600 (w, nonbonded -OH) and 3580–3060 cm^{-1} (bonded -OH); nmr (neat) δ 4.4–3.3 (broad overlapping m, 2, **CHOH**) and 2.0–0.4 (overlapping m, 18).

The original mixture gave a 3,5-dinitrobenzoate, mp 109.5–111°, and the alcohol recovered by saponification was found by glpc to consist of 94% *cis* and 6% *trans* isomer. Crystallization of the 3,5-dinitrobenzoate from 95% ethanol gave an analytical sample, mp 112.5–114.5°.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.27; H, 6.35; N, 7.87.

2-Propylcyclopentanol (**10a**).—A 4.2-g (0.03 mol) sample of 2-propylcyclopentanone (**9a**) was reduced according to the procedure described above using 1.0 g (0.03 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 75 ml of absolute ethanol. Distillation gave 3.0 g (70%) of **10a**: bp 69–72° (4 mm); $n^{25}D$ 1.4519.

The product was shown by glpc to be a mixture of the *cis* and *trans* alcohols. These were separated by preparative gas chromatography and exhibited the following properties: *cis* $n^{25}D$ 1.4533 [lit.[14] $n^{8}D$ 1.4600, bp 79–80° (12 mm), lit.[15] $n^{22}D$ 1.4540]; ir (neat) 3610 (w, nonbonded -OH) and 3580–3060 cm^{-1} (bonded -OH); nmr (neat) δ 4.4–3.4 (broad overlapping m, 2, **CHOH**) and 2.2–0.4 (broad overlapping m, 14); *trans* $n^{25}D$ 1.4509 [lit.[14] $n^{8}D$ 1.4565; bp 78–79° (10 mm)]; ir (neat) 3600 (shoulder, nonbonded -OH) and 3580–3040 cm^{-1} (bonded -OH); nmr (neat) δ 4.7 (m, 1, -**OH**), 3.6 (broad m, 1, **CHOH**), and 2.2–0.5 (broad overlapping m, 14).

2-(1,1-Dimethylpropargyl)cyclopentanol (**11**).—A solution of 2.0 g (0.05 mol) of sodium borohydride, 0.5 ml of 10% sodium hydroxide, and 15.0 g (0.1 mol) of acetylenic ketone **1** in 100 ml of absolute ethanol was allowed to stand at room temperature overnight. The reaction mixture was then concentrated on a rotary evaporator. The residue was cooled in an ice bath, diluted with 50 ml of water, and hydrolyzed with 75 ml of 4 *N* hydrochloric acid. The acidic solution was extracted with ether and the extracts were washed with water, dilute sodium bicarbonate, and again with water, and finally dried over anhydrous calcium sulfate. Distillation afforded 11.4 g (75%) of **11**: bp 62–67° (2.2 mm). Redistillation gave bp 61–65° (2 mm); $n^{25}D$ 1.4697; ir (neat) 3600–3510 (-OH), 3333 and 2110 cm^{-1} (C≡C—H), but no absorption at 1730 cm^{-1} (C=O).

Hydrogenation of a 3.15-g (0.02 mol) sample of **11** with either Raney nickel (1.5 g) or platinum oxide (0.05 g) in absolute ethanol gave 2.5 g (75%) of 2-*t*-amylcyclopentanol (**10**): bp 47–48° (0.8 mm); $n^{25}D$ 1.4660; ir (neat) corresponded to a mixture of *cis*- and *trans*-2-*t*-amylcyclopentanol (**10**), described above; glpc showed the isomer ratio to be 87% *cis* and 13% *trans*.

1,6-Di(2-ketocyclopentyl)-1,1,6,6-tetramethyl-2,4-hexadiyne (**12**).—A solution of 5 g (0.03 mol) of **1** in 25 ml of absolute ethanol was added to a solution of 8 g (0.08 mol) of cuprous chloride, 13.2 g (0.25 mol) of ammonium chloride, 0.5 ml of concentrated hydrochloric acid, and 40 ml of water. The solution was shaken

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mechanically (5 hr) under a slight positive oxygen pressure, diluted with 50 ml of cold water, and filtered. The solid was washed with 75 ml of 10% hydrochloric acid followed by 75 ml of water to yield 4.5 g (91%), mp 103–110°. Crystallization from 60% aqueous methanol gave 4.2 g (85%): mp 107–117°; ir (KBr) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.5–1.5 (overlapping m, 7) and 1.36 and 1.29 (s, 6, anisochronous $(CH_3)_2C$).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.29; H, 8.60.

2-(1,1-Dimethylpropargyl)-5-benzalacyclopentanone (13) was prepared in the usual manner.[16] To a solution of 2.2 g (0.06 mol) of sodium hydroxide in 40 ml of 50% aqueous ethanol was added 5.0 g (0.03 mol) of **1** and 5.0 g (0.05 mol) of benzaldehyde. The yellow solid was collected and washed with water, yield 7.6 g (96%). The product was crystallized from 95% ethanol: mp 122.5–124.5°; ir (KBr) 3330 (≡C—H), 1700 (C=O), 1620 (C=C), and 764 and 690 cm^{-1} (C_6H_5–); nmr ($CDCl_3$) δ 8.0–7.5 (m, 6, olefinic and aromatic protons), 2.13 and 3.3–1.6 (singlet superimposed on overlapping m, 6, C≡C—**H** and C_4H_5 ring protons), and 1.51 and 1.44 (s, 3 each, anisochronous $(CH_3)_2C$).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.88; H, 7.76.

2-(1,1-Dimethylacetonyl)cyclopentanone (14) was prepared from an 11.25-g (0.075 mol) sample of **1** by treatment with a mixture of 3.5 ml of water, 8 ml of methanol, 0.25 g of red mercuric oxide, and 0.5 ml of concentrated sulfuric acid at 55–60° following the procedure of Hennion and Watson.[17] Distillation gave 10.15 g (81%) of **14**: bp 93–94° (2 mm); $n^{25}D$ 1.4665; ir (neat) 1740 (ring >C=O) and 1710 cm^{-1} (chain >C=O); nmr ($CDCl_3$) δ 2.14 and 2.7–1.4 (singlet superimposed on overlapping m, 10, CH_3CO and C_4H_7 ring protons) and 1.19 and 1.15 (s, 3 each, anisochronous $(CH_3)_2C$).

The bis-semicarbazone had mp 222–223°.

Anal. Calcd for $C_{12}H_{22}N_6O_2$: C, 51.05; H, 7.85; N, 29.76. Found: C, 50.85; H, 7.74; N, 29.67.

The bis-2,4-dinitrophenylhydrazone had mp 233–235° dec.

Anal. Calcd for $C_{22}H_{24}N_8O_8$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.26; H, 4.74; N, 21.30.

2-(1-Acetylcyclohexyl)cyclopentanone (14a) was prepared according to the procedure described above. The hydration of a 14.3-g (0.075 mol) sample of 2-(1-ethynylcyclohexyl)cyclopentanone (**3**) afforded 13.0 g (83%) of **14a**: bp 99–102° (0.05 mm); $n^{25}D$ 1.4982; ir (neat) 1740 (ring >C=O) and 1710 cm^{-1} (chain >C=O).

The bis-2,4-dinitrophenylhydrazone had mp 222–223° dec.

Anal. Calcd for $C_{25}H_{28}N_8O_8$: C, 52.81; H, 4.96; N, 19.71. Found: C, 52.79; H, 5.00; N, 19.80.

1-Hydroxy-3,4,4-trimethyl-2-azabicyclo[3.3.0]-2-octene (15).—To a solution of 5.15 g (0.067 mol) of ammonium acetate and 15 g (0.25 mol) of glacial acetic acid was added 6.7 g (0.04 mol) of diketone **14**. The reaction mixture was stirred at 50° for 6 hr, cooled to room temperature, and added slowly to 25 ml (0.38 mol) of cold concentrated ammonium hydroxide. The solid was collected and air dried to yield 5.2 g (78%), mp 120–134°. Crystallization from cyclohexane gave 4.6 g (69%), mp 134–137°. Sublimation provided an analytical sample: mp 134–136.5°; ir (KBr) 3230–3070 (–OH) and 1645 cm^{-1} (>C=N–); nmr ($CDCl_3$) δ 6.8 (broad s, 1, –O**H**), 1.98 and 2.3–1.2 (singlet superimposed on overlapping m, 10, CH_3—C=N– and C_4H_7 ring protons) and 1.27 and 1.07 (s, 3 each, anisochronous $(CH_3)_2C$). Mass spectrum calcd for $C_{10}H_{17}NO^+$: 167. Found: 167.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.79; H, 10.13; N, 8.17.

3,4,4-Trimethyl-2-azabicyclo[3.3.0]octane (16) was prepared by hydrogenation of an 11.0-g (0.07 mol) sample of **15** dissolved in 65 ml of absolute ethanol containing 0.66 g of platinum oxide. The reaction was carried out at room temperature for 15 hr at an initial pressure of 50 psig. Distillation gave 8.18 g (81%) of **16** (as a mixture of diastereoisomers): bp 65–66° (4 mm); $n^{25}D$ 1.4719; ir (neat) 3306 (m, –NH–) and 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 4.0–3.7 (broad m, 1, bridgehead proton adjacent to nitrogen), 2.7 (overlapping q, J = 6.5 Hz, 1, CH_3CH), 2.5–1.1 (overlapping m, 9, ring protons and –N**H**–), 1.0–0.7 (complex pattern corresponding to two pairs of doublets and four singlets, 9, CH_3CH and $(CH_3)_2C$).

The hydrochloride salt had mp 187–189°.

Anal. Calcd for $C_{10}H_{20}NCl$: C, 63.01; H, 10.63; N, 7.38. Found: C, 63.49; H, 10.73; N, 7.49.

2-Acetyl-4,5,5-trimethyl-2,3-diazabicyclo[4.3.0]-1(6),3-nonadiene (17).—A 6.7-g (0.04 mol) sample of diketone **14** was added to a solution of 4.12 g (0.07 mol) of 85% hydrazine hydrate in 20 g of glacial acetic acid. The reaction mixture was stirred at 40–50° under nitrogen for 8 hr. Then 30 g (0.29 mol) of acetic anhydride was added slowly. The solution was stirred at 90° for 1 hr and poured over crushed ice. The white solid which precipitated was collected, washed with water, and air dried to yield 6.4 g (78%), mp 66–71°. Sublimation provided an analytical sample: mp 72–73°; ir (KBr) 1690–1660 (strong, broad, CH_3C=O and >C=N–) and 1615 cm^{-1} (>C=C<); nmr ($CDCl_3$) δ 3.3–2.8 (broad m, 2, –CH_2—C(N)=C<), 2.30, 2.00, and 2.6–1.6 (two singlets superimposed on overlapping m, 10, CH_3C=O, CH_3C=N–, and CH_2CH_2), and 1.20 (s, 6, $(CH_3)_2C$).

Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.59; H, 8.85; N, 13.31.

4,5,5-Trimethyl-2,3-diazabicyclo[4.3.0]nonane (18).—A 6.7-g (0.04 mol) sample of diketone **14** was added to a solution of 4.12 g (0.07 mol) of 85% hydrazine hydrate in 20 g of glacial acetic acid. The reaction mixture was stirred at 45–50° for 6 hr under nitrogen, cooled to room temperature, and added to 25 ml of glacial acetic acid containing 0.4 g of platinum oxide. The resulting mixture was hydrogenated at roon temperature under an initial hydrogen pressure of 50 psig for a period of 8 hr. The solution was filtered and added slowly to 150 ml of cold concentrated ammonium hydroxide. The product was extracted into ether and the extract was washed twice with water and dried over anhydrous potassium carbonate. Distillation gave 2.6 g (38%) of **18**: bp 65° (0.2 mm); $n^{25}D$ 1.4970; ir (neat) 3360–3180 cm^{-1} (–NH–NH–), but no absorption between 1700 and 1600 cm^{-1}; nmr ($CDCl_3$) δ 3.2 (broad m, 3, –NH–N**H**–CH), 2.41 (q, J = 7 Hz, 1, CH–CH_3), 2.0–1.2 (overlapping m, 7, ring protons), 1.11 (d, J = 7 Hz, 3, CH_3–CH), and 1.00 and 0.90 (s, 3 each, anisochronous $(CH_3)_2C$). After treatment with deuterium oxide the multiplet (3, –NH–NH–C**H**) centered at 3.15 ppm reduced to a multiplet (1, –ND–ND–C**H**) centered at 3.24 ppm.

Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 72.27; H, 12.14; N, 15.99.

Registry No.—**1**, 25111-16-4; **1** Sc, 25111-17-5; **1** Ph, 25111-18-6; **1** Ox, 25111-19-7; **2**, 25111-20-0; **2** Ph, 25111-21-1; **3**, 25111-22-2; **3** Sc, 25158-31-0; **3** Ph, 25111-23-3; **4**, 25111-24-4; **4** Sc, 25111-25-5; **5**, 25111-26-6; **5** Sc, 25184-15-0; **5** Ph, 25184-16-1; **6**, 25184-17-2; **6** Sc, 25184-18-3; **6** Ph, 25184-19-4; **7**, 25184-20-7; **7** Sc, 25184-21-8; **7** Ph, 25184-22-9; **8**, 19842-40-1; **8** Ph, 25184-24-1; **9**, 25184-25-2; **9** Sc, 25184-26-3; **9** Ph, 25184-27-4; **10** *cis*, 25172-39-8; **10** *cis* (3,5-dinitrobenzoate), 25172-40-1; **10** *trans*, 25172-41-2; **10a** *cis*, 25172-42-3; **10a** *trans*, 25172-43-4; **11**, 25184-28-5; **12**, 25184-29-6; **13**, 25150-10-1; **14**, 25184-30-9; **14** bis-Sc, 25184-31-0; **14** bis-Ph, 25150-11-2; **14a**, 25184-32-1; **14a** bis-Ph, 25184-33-2; **15**, 25184-34-3; **16**, 25184-35-4; **16** HCl, 25184-36-5; **17**, 25184-37-6; **18**, 25183-62-4.

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