[CONTRIBUTION FROM THE BRISTOL-MYERS CO., PRODUCTS DIVISION, HILLSIDE, NEW JERSEY]

Ring Openings of Substituted Cyclobutanes Induced by Grignard Reagents. I. Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate[1]

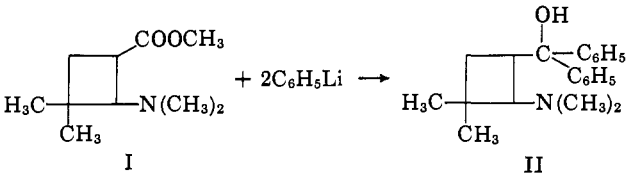
BY LEONARD WEINTRAUB, ARMIN WILSON,[2] DAVID L. GOLDHAMER, AND DONALD P. HOLLIS

RECEIVED MAY 25, 1964

Reaction of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I) with phenylmagnesium bromide does not produce the expected diphenyl(2-dimethylamino-3,3-dimethyl)cyclobutylcarbinol (II). The product is instead shown to be 1,5-diphenyl-4,4-dimethyl-5-dimethylaminopentanone-1 resulting from ring cleavage and addition of a Grignard radical to the β-carbon atom. The ring-opening reaction is completely general for I with alkyl, cycloalkyl, and aryl Grignard reagents. No carbinol formation is observed in these cases. With alkyl and cycloalkyl Grignard reagents which have a β-hydrogen, a second ring-opened product is obtained. This product results from the addition of a hydrogen atom to the carbon bearing the amino group. The ratio of the two ring-opened products is seen to have a steric dependence. The ring is also opened by magnesium bromide etherate. The mechanism of the reaction is discussed.

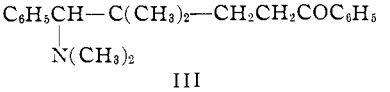
In an attempt to prepare diphenyl(2-dimethylamino-3,3-dimethyl)cyclobutylcarbinol (II) an ether solution of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I)[3] was added to 2 molar equiv. of phenylmagnesium bromide in ether. A 90% yield of a viscous oil, III, was isolated. The elemental analysis agreed perfectly with the empirical formula, $C_{21}H_{27}NO$, of the expected carbinol. However, the infrared spectrum showed no absorption above 3200 cm.$^{-1}$ and showed a strong peak at 1680 cm.$^{-1}$, indicating that the product was a conjugated ketone and not an alcohol. The presence of the keto group was verified by the ready formation of a 2,4-dinitrophenylhydrazone and an oxime. Aniline was isolated after Beckmann rearrangement of the oxime followed by hydrolysis of the resulting amide. This confirmed that III was a phenyl ketone.

Since III had the same empirical formula as the expected cyclobutylcarbinol but was instead a ketone, the ring must have opened. Ring opening did not result from rearrangement of the cyclobutylcarbinol II, since this compound could be prepared in 85% yield by addition of I to phenyllithium under essentially the same conditions as the Grignard reaction.



I II

We then considered the possibility that III was formed by normal carbonyl addition of 1 equiv. of Grignard reagent to the ester group and attack of another equivalent of reagent at one of the carbons of the cyclobutane skeleton. A reasonable compound which could arise from this reaction is 1,5-diphenyl-4,4-dimethyl-5-dimethylaminopentanone-1.



III

This was confirmed to be the structure of III by its n.m.r. spectrum which showed peaks centered at δ = 7.0–7.8, 3.2, 2.2, 2.8, 1.8, 1.1, and 0.9, with integrated intensity ratios of 10:1:6:2:2:3:3, respectively. Only the peaks from δ = 1.8 and 2.8, which are assigned to the protons on C-3 and C-2, respectively, showed spin–spin coupling. The latter two multiplets appear as a perturbed A_2B_2 pattern as would be expected. The peak at δ = 3.2 is assigned to the single proton at C-5; the δ = 2.2 is assigned to the N-methyls, and the two peaks at δ = 1.1 and 0.9 represent the two C-methyls. The latter two are nonequivalent, attributed, presumably, to hindered rotation about the C_4–C_5 bond.

The scope of the reaction was explored in an effort to determine the structural features of the ester necessary for the carbon–carbon cleavage and addition of the Grignard reagent to the β-carbon atom.

The reaction of phenylmagnesium bromide with methyl β-dimethylaminopropionate, the simplest acyclic analog of I, gave principally the normal carbinol and smaller amounts of the ketone resulting from addition of 1 equiv. of reagent. Nothing else could be detected by gas chromatography. The reaction is thus not entirely general for β-amino esters, and the cyclobutane ring is involved.

The dimethylamino group also plays a role. Methyl 3,3-dimethylcyclobutanecarboxylate, when treated with phenylmagnesium bromide, gave a quantitative yield of diphenyl(3,3-dimethyl)cyclobutylcarbinol.

These two experiments demonstrate that this extensive cleavage of the α–β bond and addition to the β-carbon atom is dependent on the presence of both the dimethylamino group and the cyclobutane ring.

The nature of the Grignard reagent was then varied to determine the generality of the reaction. In no case was a cyclobutylcarbinol isolated, although in some cases small amounts of high boiling materials were present which showed OH absorption in the infrared. In every case but one, which will be mentioned below, the major product was an acyclic ketone analogous to III. Table I lists the Grignard reagents studied, the yield of ketone, and the analysis of the product.

In the last four cases another, lower boiling, ketone was obtained. The n.m.r. spectrum of the lower boiling ketone derived from reaction of cyclohexylmagnesium bromide with I indicated that the product was 1-cyclohexyl-4,4-dimethyl-5-dimethylaminopentanone-1 (IV), a reductive ring cleavage product. The analysis of IV agrees with this formula. Further, the analyses of the other similarly obtained products also agree with an empirical formula containing two

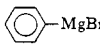
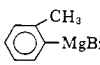
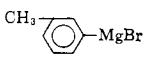
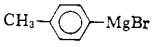
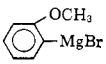
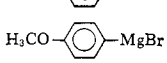
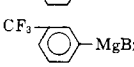
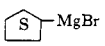
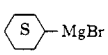
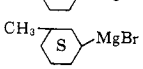
(1) Presented in part at the Third Annual Regional Meeting of the New York–North Jersey Section of the American Chemical Society, New York, N. Y., Jan. 27, 1964.

(2) To whom inquiries should be directed.

(3) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.* **26**, 625 (1961).

TABLE I

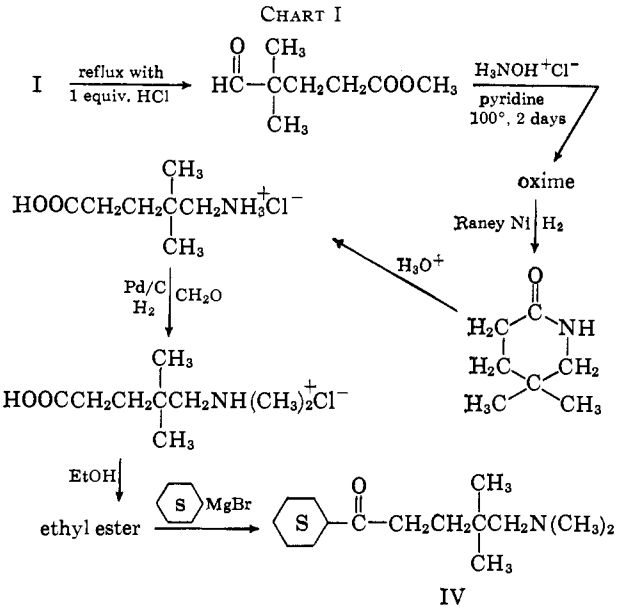
$RCHCMe_2CH_2CH_2COR$

Grignard reagent (RMgX)	NMe_2 Yield, %	M.p., °C.	B.p., °C. (mm.)	Empirical formula	Analysis, %, Calcd./Found— C	H	N
	82	42–44	178–179 (0.5)	$C_{21}H_{27}NO$	81.51	8.80	4.53
					81.37	8.87	4.64
	75		182–184 (0.5)	$C_{23}H_{31}NO$	81.85	9.26	4.15
					81.79	9.43	4.30
	60		178–180 (0.1)	$C_{23}H_{31}NO$	81.85	9.26	4.15
					82.00	9.30	4.22
	50		197 (0.3)	$C_{23}H_{31}NO$	81.85	9.26	4.15
					81.64	9.24	4.05
	37[a]	72–73		$C_{23}H_{31}NO_3$	74.76	8.46	3.79
					75.09	8.72	3.91
	40[a]	65–67		$C_{23}H_{31}NO_3$	74.76	8.46	3.79
					74.57	8.46	3.74
	49[a]		173–174 (0.1)	$C_{23}H_{26}NOF_6$	62.02	5.68	3.15
					62.13	5.66	3.15
CH_3MgI	21		97 (5.0)	$C_{11}H_{23}NO$	71.30	12.51	7.56
					71.12	12.39	7.57
CH_3CH_2MgI	53[b]		67 (0.1)	$C_{13}H_{27}NO$	73.18	12.76	6.57
					73.40	12.90	6.79
$(CH_3)_2CHMgBr$	47[b,c]		88 (0.1)	$C_{15}H_{31}NO$	74.63	12.94	5.80
					74.65	13.13	5.96
	40		149 (0.1)	$C_{19}H_{35}NO$	77.75	12.02	4.77
					77.68	11.93	4.83
	63		182 (1.0)	$C_{21}H_{39}NO$	78.44	12.23	4.36
					77.88	12.15	4.35
	59		172 (0.5)	$C_{23}H_{43}NO$	79.02	12.40	4.01
					78.41	12.33	4.15

[a] Crude yields of these products were in excess of 90%, and the infrared curves of crude products were substantially similar to those of the pure material. [b] Based on analysis of gas chromatograph of crude reaction mixture. [c] Net yield based on amount of starting ester consumed.

additional hydrogens derived from reductive ring cleavage. It was deemed essential to verify the acyclic structure of IV by an independent synthesis, which was achieved as shown in Chart 1. The ketone obtained in this way was identical by infrared and v.p.c. on two different columns with the lower boiling ketone IV obtained by reaction of I with cyclohexylmagnesium bromide.

CHART I

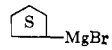
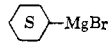
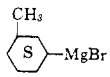


Interestingly, ethylmagnesium iodide gave no reductive ring cleavage product (henceforth called "reduction product"), whereas isopropylmagnesium bromide gave this product in a ratio of about 1:2.5 with product arising from addition of 2 equiv. of Grignard reagent (henceforth called "addition product"). In order to establish this point firmly, the gas liberated during the reaction was collected. By analogy with the reduction of ketones by the Grignard reagent, one might expect that the formation of reduction product involves the concomitant formation of the olefin corresponding to the alkyl or cycloalkyl portion of the reagent. The crude reaction mixtures were submitted to v.p.c. with the relative proportions of the various products calculated with a Disc integrator. In addition, the gas collected was passed into bromine water, and the product was examined for dibromoethane or dibromopropane. With the ethyl Grignard reagent, although a small amount of gas was evolved, no reduction product was detected, whereas the ratio of reduction to addition product of 1:2.5 was observed for the isopropyl Grignard reagent.

This indicates a steric involvement in the ratio of reduction to addition product. Indeed, with *t*-butylmagnesium chloride, only reduction product was isolated. The acyclic structure of this product, 2,2,4,4-tetramethyl-7-dimethylaminoheptanone-3, was confirmed by its n.m.r. spectrum. The reduction products, their yields, and analyses are listed in Table II.

The Grignard reagent adds as a nucleophile to polarized unsaturated systems. Prior to the nucleophilic addition, the reagent behaves as an electrophile in complexing with the basic part of the unsaturated system. The ability of the Grignard reagent to bring about reactions by virtue of its electrophilic nature has

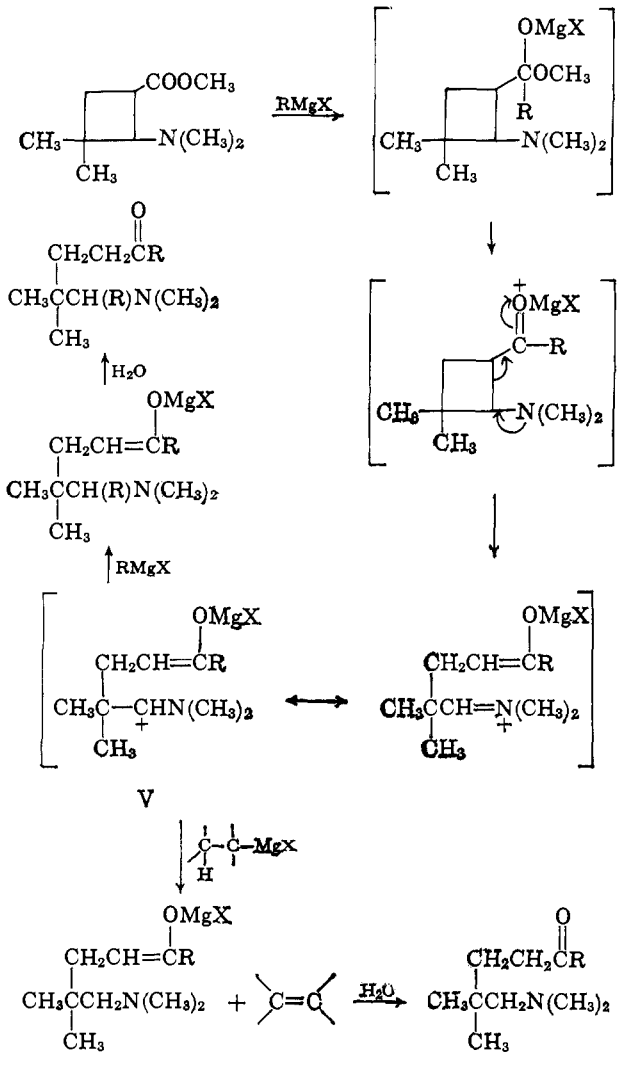
TABLE II

Grignard reagent (RMgX)	Reduction product $Me_2NCH_2CMe_2CH_2CH_2COR$ Yield,[a] %	B.p., °C. (mm.)	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$(CH_3)_2CHMgBr$	17.3[b]	71 (0.1)	$C_{12}H_{25}NO$	72.30	12.64	7.03	72.36	12.62	6.58
$(CH_3)_3CMgCl$	40	65 (0.2)	$C_{13}H_{27}NO$	73.18	12.76	6.57	72.67	11.92	6.65
	10.6	82–84 (0.1)	$C_{14}H_{27}NO$	74.61	12.08	6.22	74.59	11.73	5.96
	6.6	108 (0.8)	$C_{15}H_{29}NO$	75.25	12.21	5.85	75.88	12.57	5.41
	12.9	116–120 (0.5)	$C_{16}H_{31}NO$	75.83	12.33	5.53	75.25	11.93	5.38

[a] All yields are corrected to account for recovered starting material. [b] Calculated from quantitative v.p.c. on crude material.

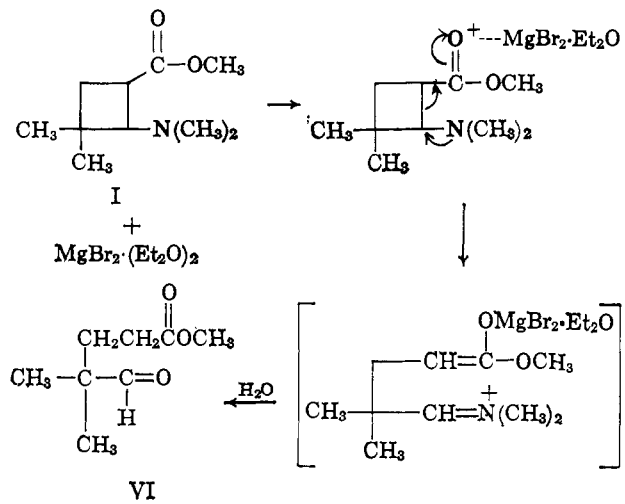
not often been emphasized.[4] Our reaction can be considered to be brought about by an electrophilic Grignard–carbonyl complex which withdraws the electrons from the α–β bond. This electron withdrawal is assisted by donation of the unshared pair on nitrogen as shown in Chart II.

CHART II



This mechanism suggests that the ring opening should take place in the absence of a nucleophile if a strongly electrophilic group is added to remove the electrons from the α–β bond. We felt that magnesium bromide etherate could form a complex of sufficient electron-withdrawing power to give some ring cleavage by the pathway shown in Chart III.

CHART III



This was borne out by the isolation of a 15% yield of methyl 4,4-dimethylglutaraldehydate (VI) from the reaction of I with magnesium bromide etherate.

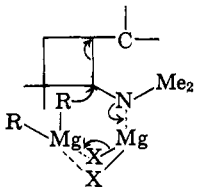
Thus, an electrophilic mechanism can account for product formation. However, the steric dependence of the addition:reduction ratio is not too easily explained in this way. A Stuart model of carbonium ion V fails to reveal hindrance to attack even by a tertiary butyl group.

Another possibility which may be considered is that the ring is cleaved by addition of the nucleophilic Grignard radical to the amino carbon. This carbon atom might be activated by complexing the amino group with the Grignard reagent. Although the structure of the Grignard reagent is once again in doubt, there is good evidence for a dimeric reagent,[5] particularly in the concentrated ether solutions used in synthesis. It is appealing to regard the complex formed as an amine–dimeric reagent complex which reacts through a six-membered transition similar to that suggested by Mosher[5a] for ketone addition and reduction.

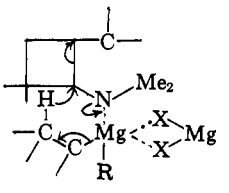
Steric factors would obviously determine whether addition through complex VII or reduction through VIII takes place. Structural features which could stabilize the developing carbanion would facilitate ring cleavage. The electrophilic complex postulated previously could do so, and would also help to activate

(4) The possibility that the Grignard reagent might function here as an electrophile was pointed out by a referee who reviewed a portion of this paper.

(5) (a) D. O. Cowan and H. S. Mosher, *J. Org. Chem.*, **27**, 1 (1962); (b) S. Storfer and E. I. Becker, *ibid.*, **27**, 1868 (1962); (c) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1963); (d) J. Miller, G. Gregoriou, and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 3966 (1961).

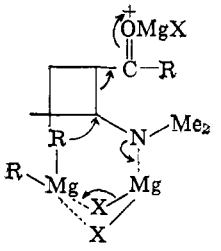


VII, addition



VIII, reduction

the amino carbon. This combination of electron withdrawal and nucleophilic addition as shown in IX fits the observed requirements of the reaction.



IX

There are few reports in the literature of Grignard addition to an amino carbon.[6] The closest analogy to this case is the cleavage of hindered α,β-dimorpholino ketones upon reaction with the Grignard reagent.[6a] This reaction can be interpreted in the same way as ours. The largest yield of cleavage product in this case is 23%. The differences in yield reflect the drive of the cyclobutane ring to open and relieve ring strain.

We are investigating this interesting type of fragmentation reaction in other cyclobutanes.

Experimental

Melting points are uncorrected. Microanalyses were performed by Geller Microanalytical Laboratory, Charleston, W. Va.

Magnesium turnings were cut on a lathe from a rod of magnesium of minimum 99.80% purity obtained from Fisher Scientific Co. Alkyl and aryl halides were highest purity grades obtained from Eastman or Matheson. Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate was obtained from Tennessee Eastman Co. and redistilled prior to use. A Varian A-60 spectrometer was used to determine n.m.r. spectra. Infrared spectra were recorded on a Beckman IR-7 spectrophotometer. Gas chromatographic analyses were performed with an F & M Model 500. In all v.p.c. runs reported, the carrier (helium) flow rate was 64 ± 2 cc./min., and the injection port temperature was 350°. Columns were 0.25-in. diameter and 6 ft. long. The solid support was Chromosorb W.

Reaction of Aryl Grignard Reagents and of Methylmagnesium Iodide with Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate (I).—A solution of 0.24 mole of Grignard reagent in 50–75 ml. of anhydrous ether was prepared in the usual fashion. A solution of 18.5 g. (0.1 mole) of I in 35 ml. of anhydrous ether was added dropwise to the Grignard reagent at a rate which maintained gentle reflux. After addition was complete, the mixture was refluxed 2 hr. In some cases a grey precipitate appeared during addition or reflux. The reaction mixture was cooled and poured into cold ammonium chloride solution. The aqueous phase was extracted with ether. The ether extracts were extracted with 1 *N* hydrochloric acid. The acid solution was made basic with solid sodium bicarbonate and then brought to pH 10 with 5 *N* sodium hydroxide. The alkaline mixture was extracted with ether. The ether extract was dried over sodium sulfate, filtered, and the ether was removed *in vacuo*. Infrared curves of the crude residues were substantially similar to those of the purified products. In all cases except the two anisyl Grignard reagents, the products were distilled at the pressures and temperatures indicated in Table I. The products from the anisyl Grignard reagents separated as solids after removal of the ether. These two were recrystallized from ethanol.

Beckmann Rearrangement of 1,5-Diphenyl-4,4-dimethyl-5-dimethylaminopentanone-1 (III).—The oxime of III was prepared according to Shriner, Fuson and Curtin[7]; m.p. 131–132°

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63. Found: C, 77.16; H, 8.72; N, 8.86.

Seventeen grams of the oxime was stirred overnight with 17 g. of phosphorus pentachloride in 1500 ml. of anhydrous ether. The mixture was poured into ice–water, and, after separation of the ether, the aqueous solution was brought to pH 10. The amide was extracted into ether, which was dried and removed *in vacuo*.

The crude amide, 14.5 g., was recrystallized from 50% ethanol with Darco to give 7 g., m.p. 111–113°.

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63. Found: C, 77.95; H, 8.60; N, 8.60.

The amide, 14 g., was refluxed with 100 ml. of 3 *N* hydrochloric acid for 3 hr. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of water, and the solution was made basic with solid sodium bicarbonate. The 6.5 g. of oil which was extracted into ether was identified as aniline by its infrared spectrum and conversion to the phenylthiourea and benzenesulfonamide.

Diphenyl(2-dimethylamino-3,3-dimethyl)cyclobutylcarbinol (II).—Phenyllithium was prepared from 33.0 g. (0.21 mole) of bromobenzene in ether and 2.95 g. (0.42 g.-atom) of lithium. A solution of 18.5 g. (0.1 mole) of I in 100 ml. of anhydrous ether was added at a rate to maintain gentle reflux. A tan precipitate settled during addition. After addition was complete, the mixture was refluxed 1 hr., cooled, and poured into cold ammonium chloride solution. The product was extracted into ether and back into 2 *N* hydrochloric acid as described previously. It was then precipitated as a brown solid by the addition of 5 *N* sodium hydroxide to the acid solution. There was 28 g. of product. This was recrystallized from large volumes of petroleum ether with Darco to give 20 g. of diphenyl(2-dimethylamino-3,3-dimethyl)cyclobutylcarbinol, m.p. 104–105°. Pertinent infrared peaks (CCl_4) are: 3620 m (sharp), 3360 (broad), 3080 w, 3060 m, 3020 m, 2780 m, 1600 w, 1500 w, 1382 w, 1367, 705 s (cm.$^{-1}$); n.m.r.: singlet (6H) at 0.93 and 1.1 p.p.m. (*gem*-dimethyl); singlet (6H) at 2.1 p.p.m. (N-$(CH_3)_2$); doublet (1H) at 2.5 p.p.m. (C-H-NMe_2), quartet (1H) at 3.3 p.p.m. (-C*H*-C(OH)-$(C_6H_5)_2$); multiplet (2H) at 1.0–1.9 p.p.m. (ring CH_2); multiplet (10H) at 7.27 p.p.m. (aryl protons).

Anal. Calcd. for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.34; H, 8.52; N, 4.65.

Reaction of Methyl β-Dimethylaminopropionate with Phenylmagnesium Bromide.—A solution of methyl β-dimethylaminopropionate[8] (13.1 g., 0.1 mole) in 30 ml. of anhydrous ether was added to phenylmagnesium bromide (from 35.4 g., 0.225 mole, of bromobenzene and 5.4 g. of magnesium in 70 ml. of anhydrous ether). After addition was complete, the mixture was refluxed 2 hr., cooled, and poured into cold ammonium chloride solution. A white solid separated. The mixture was extracted with chloroform and the chloroform extracts were extracted with 2 *N* hydrochloric acid. The combined acid extracts were brought to pH 10, and the basic solution was again extracted with chloroform After removal of the solvent, 19.4 g. of a semisolid residue remained. This was extracted with 25 ml. of ether leaving 15 g. of insoluble solid, m.p. 159–161°. After one recrystallization from absolute ethanol, 13 g. of 1,1-diphenyl-3-dimethylaminopropanol was obtained, m.p. 164–165° (lit.[9] m.p. 166°). Evaporation of the ether left 3.5 g. of oil which had carbonyl peaks in the infrared at 1745 cm.$^{-1}$ attributed to starting ester and 1685 cm.$^{-1}$ attributed to conjugated ketone. The mixture was distilled *in vacuo*, and 2 g. of β-dimethylaminopropiophenone, b.p. 103° at 3 mm. (lit.[9] b.p. 100° at 2.5 mm.) was obtained.

Diphenyl(3,3-dimethyl)cyclobutylcarbinol.—Methyl 3,3-dimethylcyclobutenecarboxylate[10] (14.0 g., 0.1 mole) was hydrogenated in methanol in a Parr apparatus at 3 atm. at

(6) (a) N. H. Cromwell, *J. Am. Chem. Soc.*, **69**, 1857 (1947); (b) G. F. Wright in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 417; see also H. H. Wasserman, *ibid.*, p. 374; (c) V. Migrdichian, "Organic Synthesis," Vol. 1, Reinhold Publishing Corp., New York, N. Y., 1957, p. 598.

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 255, Method B.

(8) I. N. Nazarov and R. I. Kruglikova, *Zh. Obshch. Khim.*, **27**, 346 (1957); *Chem. Abstr.*, **51**, 15521*i* (1957).

(9) D. W. Adamson, *J. Chem. Soc.*, 5144 (1949).

(10) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

room temperature with 50 mg. of 10% palladium-on-charcoal catalyst. Hydrogen was taken up rapidly, the reaction being complete in 20 min. The catalyst was filtered and the methanol was removed at atmospheric pressure through an 18-in. Vigreux column. The residue was distilled to give 10.4 g. of methyl 3,3-dimethylcyclobutanecarboxylate, b.p. 161–164°. This had no olefinic infrared absorption, and the carbonyl peak was shifted to 1745 cm.$^{-1}$ as opposed to the conjugated carbonyl peak at 1725 cm.$^{-1}$ of the starting material.

Addition of 7.0 g., 0.05 mole, of the ester in 40 ml. of anhydrous ether to the Grignard reagent from 17.2 g. (0.11 mole) of bromobenzene and 2.6 g. of magnesium yielded 13 g. of solid residue. This was recrystallized from 95% ethanol to give 9.6 g. of diphenyl(3,3-dimethyl)cyclobutylcarbinol, m.p. 81–82°. Pertinent infrared peaks (CCl_4) are: 3620 m, 3080 w, 3060 m, 3022 m, 1600 w, 1585 w, 1492 m, 1366 m, 1380 w, 768 m, 700 s (cm.$^{-1}$).

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.27; H, 8.35.

Reaction of I with Isopropylmagnesium Bromide.—The Grignard reagent was prepared from 12.2 g. (0.5 g.-atom) of magnesium and 61.5 g. (0.5 mole) of isopropyl bromide in ether. After the reagent was prepared, the drying tube was replaced with a vacuum take-off adapter leading through a trap cooled in a salt–ice bath to a calibrated tube filled with water. To the Grignard solution was added dropwise a solution of 37.0 g. (0.2 mole) of I in ether. Gas evolution began immediately, and during the 1.5-hr. ester addition 750 cc. of gas was evolved. The reaction mixture was refluxed 1.5 hr. during which time an additional 50 cc. of gas evolved. The gas was forced through a series of traps containing bromine water. The bromine water was poured into excess sodium thiosulfate solution, and the colorless mixture was extracted with ether. After the ether was removed, the 5.2 g. of residue was distilled at 136°. It was identical with 1,2-dibromopropane by infrared spectrum, retention time on 10% silicone gum rubber at 50°, and refractive index ($n^{25}D$ 1.5146).

The usual work-up of the ethereal reaction mixture gave 36.5 g. of oil. A sample of this crude oil was retained for quantitative gas chromatography. The remainder was distilled *in vacuo* through a 6-in. Vigreux column. Three main fractions were collected. The first, 3.6 g., b.p. 65–71° at 0.1 mm., was mostly starting material as shown by infrared spectrum and gas chromatography. The second fraction, 5.6 g., b.p. 71° at 0.1 mm., was the reduction product 2,6,6-trimethyl-7-dimethylaminoheptanone-3. Analyses are given in Table II. Pertinent infrared peaks (smear) are: 2820 s, 2780 s, 1715 s, 1382 m, 1362 m, 1264 m, 1045 s, 845 m, 807 s (cm.$^{-1}$).

Maleate salt: *Anal.* Calcd. for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.70; H, 9.12; N, 4.49.

The third fraction, 15.3 g., b.p. 88° at 0.1 mm., was the addition product 2,6,6,8-tetramethyl-7-dimethylaminononanone-3. Analysis is given in Table I. Pertinent infrared peaks (smear) are: 2820 m, 2780 m, 1715 s, 1382 m, 1365 m, 1055 m (cm.$^{-1}$).

The sample of crude product mixture was submitted to v.p.c. on a 10% silicone gum rubber column at 155°. The ratios of peak areas were read from a Disc integrator. There were five peaks identified as: starting material at 2.3 min., an unidentified peak at 2.7 min., reduction product at 4.25 min., addition product at 15.0 min., and a peak similar to the pot residue from the distillation at 24.7 min. The relative amounts of reduction product and addition product in the 36.5 g. calculated from the peak areas are 6.2 and 20.6 g., respectively. Corrected for unreacted starting material, this gives yields of 17.3 and 47.4%, respectively. The yield of reduction product based on 800 cc. of propylene collected is 19.6%.

Reaction of I with Ethylmagnesium Iodide.—As in the previous experiment, the Grignard reagent was prepared from 12.2 g. (0.5 g.-atom) of magnesium and 78 g. (0.5 mole) of ethyl iodide in ether. The gas collecting system described in the previous experiment was connected, and 37 g. (0.2 mole) of I in ether was added over 1.5 hr. The mixture was refluxed 1.5 hr. after addition. Only 85 cc. of gas was collected. This gas was passed into bromine as described, but no dibromoethane could be detected.

The Grignard reaction was worked up as described to give 25.6 g. of oil. A sample was chromatographed on a 10% silicone gum rubber column at 150°. Peak area ratios were read with a Disc integrator. Aside from a very small amount of starting material with a retention time of 3 min. and another small amount of slow moving material with a retention time of 19.5 min., over 95% of the material was the addition product, 6,6-dimethyl-7-dimethylaminononanone-3 with a retention time of 10 min. The oil was distilled, and after a very small forerun there was collected 22.7 g. of pure product, b.p. 67° at 0.1 mm. Analysis is given in Table I. Pertinent infrared peaks (smear) are: 2820 m, 2780 s, 1718 s, 1377 s, 1365 w, (cm.$^{-1}$).

Reaction of *t*-Butylmagnesium Chloride with I.—The Grignard reagent was prepared from 0.8 g.-atom of magnesium by slow addition of 0.8 mole of *t*-butyl chloride in anhydrous ether.[11] The reaction mixture was kept under an atmosphere of argon overnight. A titration[12] indicated that there was a total of 0.655 mole of Grignard reagent (82% yield). A solution of 55.5 g. (0.3 mole) of I in ether was added over 45 min. The mixture was refluxed 2.5 hr. after addition was complete. After the usual work-up there remained 43 g. of oil. A sample of the crude mixture was submitted to v.p.c. on a 10% silicone gum rubber column at 150°. Peak areas were recorded with a Disc integrator. There were four peaks: starting material (34.7% of total), retention time 2.9 min.; an unidentified peak[13] (17.4% of total), retention time 3.6 min.; reduction product (45.6% of total), retention time 7.2 min.; and a small peak which came off on raising the column temperature to 315° (2.3% of total). This last peak was the only one that could have contained addition product. The mixture could not be separated by distillation. Accordingly, the entire crude fraction was refluxed 3 hr. with 250 ml. of 3 *N* hydrochloric acid. The solution was cooled and brought to pH 10 with 5 *N* sodium hydroxide. The oil was extracted into ether, and, after evaporation of the ether, there was 19.2 g. of oil, which had no infrared absorption at 1745 cm.$^{-1}$ and contained over 95% reduction product by v.p.c. This was distilled *in vacuo* to give 18.0 g. of 2,2,6,6-tetramethyl-7-dimethylaminoheptanone-3, b.p. 65° (0.2 mm.). Analysis is given in Table II. Pertinent infrared peaks (smear) are: 2815 m, 2760 m, 1707 s, 1392 w, 1383 w, 1362 m, 1045 s, 843 m (cm.$^{-1}$); n.m.r.: singlet (6H) at 0.9 p.p.m. (*gem*-dimethyl); singlet (9H) at 1.15 p.p.m. ($(CH_3)_3C$); A_2B_2 (4H) at 1.5 and 2.5 p.p.m. (CH_2–CH_2–CO); singlet (2H) at 2.22 p.p.m. (N–CH_2); singlet (6H) at 2.40 p.p.m. ($N(CH_3)_2$).

Reaction of Cyclopentylmagnesium Bromide with I.—From the reaction of 0.1 mole of I with 0.22 mole of cyclopentylmagnesium bromide as described, there was obtained 23 g. of crude oil. Distillation gave 3 g. of starting material, 3.5 g. of reduction product, and 13 g. of addition product. Redistillation of the latter two gave 2.1 g. of 1-cyclopentyl-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 82–84° at 0.1 mm., and 10.5 g. of 1,5-dicyclopentyl-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 149° at 0.1 mm. Analyses are given in Tables II and I, respectively.

Reaction of 3-Methylcyclohexylmagnesium Bromide with I.—From the reaction of 0.6 mole of I with 1.5 moles of 3-methylcyclohexylmagnesium bromide, there was obtained 183 g. of crude oil. Upon distillation, there was obtained 15.9 g. of starting ester, 16.8 g. of reduction product, 1-(3-methylcyclohexyl)-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 116–120° at 0.5 mm., and 105.1 g. of addition product, 1,5-di(3-methylcyclohexyl)-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 172° at 0.5 mm. Analyses are in Tables II and I, respectively.

Reaction of I with Cyclohexylmagnesium Bromide.—From the reaction of 0.5 mole of I with 1.1 moles of cyclohexylmagnesium bromide, there was obtained 131 g. of crude oil. Distillation yielded 10.2 g. of starting material, 7 g. of reduction product, 1-cyclohexyl-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 108° at 0.8 mm., and 90 g. of addition product, 1,5-dicyclohexyl-4,4-dimethyl-5-dimethylaminopentanone-1, b.p. 182° at 1.0 mm. Analyses are in Tables II and I, respectively.

Methyl-4,4-dimethylglutaraldehydate Oxime.—A mixture of 0.2 mole of hydroxylamine hydrochloride, 0.2 mole of methyl-4,4-dimethylglutaraldehydate,[10] 90 ml. of pyridine, and 140 ml. of absolute ethanol was heated at 100° in a sealed tube for 50

(11) S. V. Puntambeker, and E. A. Zoellner in "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 524.

(12) H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

(13) This substance was isolated by quantitative gas chromatography and identified as $(CH_3)_2NCH_2C(CH_3)_2CH_2CH_2COOCH_3$ (infrared, elemental analysis, n.m.r.). In this case then, the ring-opening reaction takes precedence over the Grignard reaction with the carbonyl group. This is probably also the structure of the unidentified peak observed in the gas chromatograph of the mixture from the reaction of isopropylmagnesium bromide with I. We were unable to separate sufficient quantities from the other components of that mixture.

hr. The mixture was evaporated to near dryness *in vacuo* and treated with 300 ml. of water. The oil which separated was extracted into ether. After the ether was removed *in vacuo* there was 27.3 g. This was distilled *in vacuo* through a 6-in. Vigreux column, and 14.7 g. of oxime was collected, b.p. 98–100° at 0.5 mm., $n^{26}D$ 1.4563.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.84; H, 8.82; N, 8.06.

4,4-Dimethylvalerolactam.—A mixture of 14.7 g. (0.085 mole) of the oxime above, 1 ml. of 28% ammonium hydroxide, 25 ml. of ethanol, and a teaspoonful of Raney nickel W6 was shaken with hydrogen in a Parr apparatus overnight at an initial pressure of 50 p.s.i. The uptake of hydrogen was 95% of theory. The mixture was filtered free of catalyst and evaporated to dryness *in vacuo* leaving 10.2 g. of solid residue, m.p. 121–124°. This was recrystallized from hexane to give 7.8 g. of 4,4-dimethylvalerolactam, white needles, m.p. 123.5–125°.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.07. Found: C, 65.88; H, 9.81; N, 10.97.

4,4-Dimethyl-5-aminovaleric Acid Hydrochloride.—Hydrolysis of the lactam with 4 *N* hydrochloric acid gave, after recrystallization from isopropyl alcohol, 4,4-dimethyl-5-aminovaleric acid hydrochloride, m.p. 146.5–151°.

Anal. Calcd. for $C_7H_{16}ClNO_2$: neut. equiv., 90.8; Cl, 19.5. Found: neut. equiv., 90.7; Cl, 18.8.

4,4-Dimethyl-5-dimethylaminovaleric Acid Hydrochloride.[14]—A mixture of 7.8 g. (0.043 mole) of 4,4-dimethyl-5-aminovaleric acid hydrochloride, 14.3 g. of 37% formaldehyde solution (0.176 mole of formaldehyde), and 7 g. of 10% palladium-on-charcoal catalyst in 200 ml. of water was shaken with hydrogen overnight in a Parr apparatus at an initial pressure of 50 p.s.i. The solution was evaporated to dryness *in vacuo* after filtration of the catalyst. The residue was re-evaporated several times after additions of water to remove formaldehyde, leaving 7.2 g. of solid residue. This was recrystallized from absolute ethanol to give 5.6 g., m.p. 138–139°, m.m.p. with starting material 101–139°.

Anal. Calcd. for $C_9H_{20}ClNO_2$: neut. equiv., 104.9; Cl, 16.91. Found: neut. equiv., 111; Cl, 16.95.

Ethyl 4,4-Dimethyl-5-dimethylaminovalerate.—The ethyl ester was prepared from the above amino acid hydrochloride by refluxing with absolute ethanolic hydrogen chloride solution. The free amino ester was distilled *in vacuo* through a 6-in. Vigreux column to give 6.8 g. of ethyl 4,4-dimethyl-5-dimethylaminovalerate, b.p. 87° at 2.8 mm. Pertinent infrared peaks (smear) are: 2820 s, 2780 s, 1740 s, 1387 s, and 1372 s ($cm.^{-1}$); n.m.r.: singlet (6H) at 0.88 p.p.m. (*gem*-dimethyl); triplet (3H) at 1.25 p.p.m. ($CO_2CH_2CH_3$); A_2B_2(4H) at 1.6 and 2.2 p.p.m. ($CH_2CH_2CO_2C_2H_5$); singlet (2H) at 2.1 p.p.m. ($N-CH_2-$); singlet (6H) at 2.3 p.p.m. ($N(CH_3)_2$); quartet (2H) at 4.15 p.p.m. ($CO_2CH_2CH_3$).

Anal. Calcd. for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.72; H, 11.35; N, 6.77.

Reaction of Ethyl 4,4-Dimethyl-5-dimethylaminovalerate with Cyclohexylmagnesium Bromide.—The Grignard reagent was prepared from 22.8 g. (0.14 mole) of cyclohexyl bromide and 3.4 g. of magnesium in ether. To the reagent was added a solution of 7.1 g. (0.035 mole) of ethyl 4,4-dimethyl-5-dimethylaminovalerate in ether. After addition, the mixture was refluxed 4 hr., cooled, and poured into cold ammonium chloride solution. After the usual extraction procedure, there was obtained 6.8 g. of oil showing no OH stretching infrared absorption and two strong carbonyl peaks at 1740 and 1712 $cm.^{-1}$. The mixture was distilled *in vacuo* through a 6-in. Vigreux column and 2.6 g., b.p. 100° at 0.5 mm., was collected. The infrared spectrum was identical with that of the reduction product from the reaction of I with cyclohexylmagnesium bromide. Also, the retention times were identical on 10% silicone gum rubber at 150° (12.3 min.) and on 10% Apiezon L with 5% potassium hydroxide at 215° (16.1 min.); n.m.r.: singlet (6H) at 0.9 p.p.m. (*gem*-dimethyl); multiplet (15H) at 1.0–2.0 p.p.m. ($C_6H_{11}-COCH_2CH_2$); singlet (2H) at 2.1 p.p.m. (CH_2-N); singlet (6H) at 2.33 p.p.m. ($N-(CH_3)_2$).

Reaction of I with Magnesium Bromide Etherate.—Magnesium bromide etherate was prepared from 30.5 g. of magnesium and 235 g. of 1,2-dibromoethane in a total of 2250 ml. of ether.[5b] The lower layer (pale yellow) was found by Volhard titration to contain 5.1 mg. of bromide per ml. An equivalent of acetophenone was refluxed 3 hr. in ether with 2 equiv. of magnesium bromide etherate. The mixture was cooled and poured into 2 *N* hydrochloric acid solution. Acetophenone was recovered quantitatively, indicating that there was no bromoethylmagnesium bromide in the magnesium bromide etherate.

A mixture of 125 ml. (0.31 mole) of magnesium bromide etherate and 27.8 g. (0.15 mole) of I in 100 ml. of anhydrous ether was refluxed for 3 hr. during which time a gummy mass formed. The mixture was cooled and poured into ice and concentrated hydrochloric acid. The aqueous solution was extracted with ether, and the combined ether extracts were dried over sodium sulfate. In the manner described in previous experiments, 19 g. of starting ester was isolated from acidic solution. The ether was removed from the ether extract of the acidic solution by distillation at 760 mm. through an 18-in. Vigreux column leaving 5.8 g. of thin oil. This was distilled to give 3.2 g. of methyl-4,4-dimethylglutaraldehydate, b.p. 58 at 0.5 mm., $n^{26}D$ 1.4278. The infrared curve was identical with that of the compound prepared by refluxing I with an equivalent of hydrochloric acid.

Acknowledgment.—We gratefully acknowledge the inspired technical assistance of Mr. Stanley R. Oles.

(14) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).