[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Kishner Reduction–Elimination. II. α-Substituted Pinacolones[1,2]

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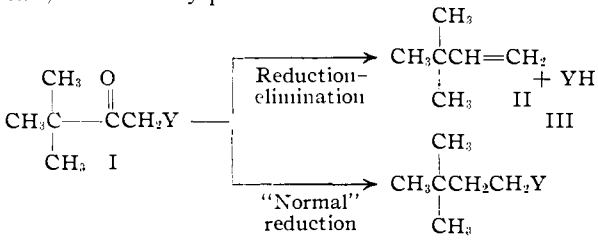
We have examined the scope of the Kishner reduction–elimination reaction by means of a series of α-substituted pinacolones I wherein it is relatively easy to determine the extent of elimination of various groups with concomitant formation of 3,3-dimethyl-1-butene (II). The Huang-Minlon modification of the Wolff–Kishner reduction conditions was employed in the reduction of the series I. The relative yields of the reduction–elimination products (II, III) and the "normal" reduction products (carbonyl to methylene) were determined for each example (I, Y = NR_2, NHAr, NRAr, OAr, SR, SAr). The extent of elimination was found to vary with the ability of the α-substituent to assume anionic character and with the hindrance provided at the bond joining the substituent group to the α-carbon.

Following our demonstration, with a series of open-chain α-aminoketones, of the generality of occurrence of the Kishner reduction–elimination reaction,[4] and, with cyclic α-aminoketones, of the dependence of this reaction upon ring size,[5] we sought to establish the relative ease of elimination of a variety of α-substituents in similarly constituted ketone models. The α-substituted pinacolone system I offered several advantages for such a study. The preparation of most of the desired ketones could be accomplished with ease from α-bromopinacolone, which presents only one reaction site. The Kishner reduction–elimination reaction of the α-substituted pinacolones would lead to a common olefin, 3,3-dimethyl-1-butene (II), readily separable from the reaction mixture and logically isomerically pure.



The synthesis of the series of α-substituted pinacolones I wherein Y was an alkylamino, dialkylamino or cyclic amino grouping was realized by bringing together α-bromopinacolone and the appropriate amine in ether solution. The combination of the bromoketone with the highly hindered 2,2,6,6-tetramethylpiperidine required refluxing xylene. The preparation of the two arylaminopinacolones (see Table IV) was effected in ethanol solution in the presence of sodium bicarbonate. The aminoketones were identified by elemental analysis of the bases or their hydrobromides and picrates.[6] If they were not rendered sufficiently pure by fractional distillation, as indicated by infrared spectra, final purification was accomplished through the hydrobromide salts. Of the other α-substituted ketones prepared in this investigation, the phenoxy-, trimethylacetoxy-, mesitoyloxy-, benzoyloxy- and *p*-toluenesulfonylpinacolones were obtained by reaction of the corresponding sodium or potassium salts with α-bromopinacolone in benzene or ethanol. 3,3-Dimethyl-1-*n*-hexylmercapto-2-butanone and 3,3-dimethyl-1-phenylmercapto-2-butanone were obtained from the corresponding mercaptans in sodium hydroxide solution.

For the Wolff–Kishner reduction of the α-substituted pinacolones, the Huang-Minlon conditions[7] were used. The details given in the experimental section for the reduction of 3,3-dimethyl-1-N-piperidyl-2-butanone are illustrative of the general method employed. Any 3,3-dimethyl-1-butene (b.p. 41.6°) formed was removed from the reaction mixture by entrainment with a slow stream of nitrogen and was collected in two Dry Ice traps connected in series to the top of the vertical take-off condenser, the jacket of which was kept at about 25°. The feasibility of this method of separation of the olefin from higher boiling condensate was indicated by a control experiment with ether. The identity and purity of the 3,3-dimethyl-1-butene collected were checked by several independent methods: refractive index, infrared absorption,[8] melting point and infrared absorption of the 2,4-dinitrobenzenesulfenylchloride derivative, and formation of 1,2-dibromo-3,3-dimethylbutane. Authentic samples of 3,3-dimethyl-1-butene and its derivatives also were available for direct comparison. We found that no olefin was formed unless hydrazine was originally present in the Wolff-Kishner reaction mixture, nor was any olefin produced after formation of the hydrazone and before addition of alkali. Thus, the formation of 3,3-dimethyl-1-butene was directly attributable to attack by alkali on the hydrazones of the α-substituted pinacolones I. In control examples where the hydrazones was first isolated and then subjected to the same experimental conditions, the yield of olefin was equivalent to that obtained from the ketone.

Any "normal" reduction product obtained from the α-substituted pinacolones was separated from the condensate removed through the take-off and from the water-diluted reaction mixture by repeated

(1) N. J. Leonard, *Chimia*, **7**, 93 (1953); see also S. Gelfand, Ph.D. Thesis, University of Illinois, 1953.

(2) N. J. Leonard and S. Gelfand, Abstracts of Papers, 124th Meeting, American Chemical Society, Chicago, Ill., September 6–11, 1953, p. 15-O.

(3) U. S. Rubber Company Fellow, 1952–1953.

(4) Designated thus because of Kishner's original observation of the formation of an olefin from an α-hydroxyketone, in contrast to the usual carbonyl-to-methylene transformation encountered with simple aldehydes and ketones (N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913)).

(5) N. J. Leonard and S. Gelfand, THIS JOURNAL **77**, 3269 (1955).

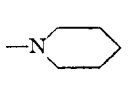
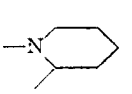
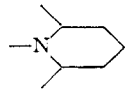
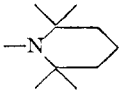
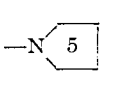
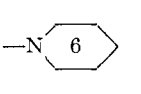
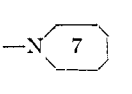
(6) The freshly distilled α-aminoketones and the α-phenoxyketone gave positive Tollens tests at room temperature. In most cases the solution began to blacken in 0.5–2 minutes and to deposit a silver mirror in 15–30 minutes. H. R. Henze and N. E. Rigler, *ibid.*, **56**, 1350 (1934), have reported that α-alkoxyketones ($RCOCH_2OCH_3$) give positive Tollens tests when heated.

(7) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(8) Catalog of Infrared Spectral Data, A. P. I. Research Project 44, National Bureau of Standards, Vol. 1, Infrared Absorption Spectrogram No. 199.

TABLE I

EFFECT OF INCREASING STERIC HINDRANCE AT THE C–Y BOND

Y							
Number	Ia	Ib	Ic[b]	Id[c]	Ie	Ia	If
Yields, % Olefin	29[a]	38	54	...	15	29	41
Yields, % "Normal" product (+29% $C_5H_{10}NH$)	64	44	...	...	65	64	42

[a] Equivalent yield from the hydrazone. [b] Probably a mixture of *meso*- and *dl*-forms. [c] The hydrazone probably was not formed. The resistance of highly hindered ketones to Wolff–Kishner reduction has been demonstrated by Ng. Ph. Buu-Hoï, Ng. Hoán and Ng. D. Xuong, *Rec. trav. chim.*, **25**, 285 (1952).

extraction with ether. Fractional distillation of the residue from the ethereal extracts allowed the separation of product from any unreacted hydrazone. In general, the sum of the yields of 3,3-dimethyl-1-butene and the "normal" reduction product accounted for 70–90% of the original ketone. The identity of the "normal" reduction product was established in most of the examples by physical properties and analysis of suitable derivatives and, in representative cases, by unequivocal synthesis.

Both "normal" reduction products and reduction–elimination products were obtained when the substituted α-aminopinacolones in triethylene glycol solution were heated with hydrazine and subsequently with potassium hydroxide, and the relative reproducible yields of these products varied with the structure of the substituted α-aminopinacolone.[9] A systematic increase in the yield of 3,3-dimethyl-1-butene was observed for the series of α-substituted pinacolones (I), in which Y was N-piperidyl, N-(α-methylpiperidyl) and N-(α,α'-dimethylpiperidyl) (Table I). The results indicate that the amount of elimination increases with increasing steric hindrance at the C_α–N bond. The same conclusion can be reached from a consideration of the relative yields of 3,3-dimethyl-1-butene obtained for the series I in which Y was N-pyrrolidyl, N-piperidyl and N-hexamethyleneimino (Table I). The influence of hindrance on the extent of elimination also was demonstrated by the predominance of the elimination reaction in the reduction of 1-N-di-*n*-butylamino-3,3-dimethyl-2-butanone, which contains an open-chain amino substituent of relatively large steric requirement (Table II) (also, compare Ie and Ii). In Table II are indicated the relative amounts of olefin and "normal" product formed upon Wolff–Kishner reduction of α-aminopinacolones in which Y consisted of representative monoalkylamino, monoarylamino, dialkylamino and arylalkylamino groupings. Although the generality of occurrence of the reduction–elimination reaction[5] was further indicated by this series, there was no obvious correlation between the extent of elimination and the basicity of the substituted amino grouping.

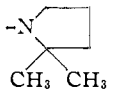
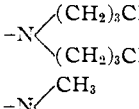
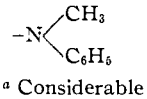
In the interest of determining which other substituents could be eliminated from the α-carbon of the model selected (I) a further series was investigated, with the results given in Table III. All of the substituent groups in these examples are capable of forming stable anions. All were effectively eliminated during the reduction process, and no "normal" reduction product was isolated from any of these α-substituted pinacolones. In fact, direct correlation between the electron-attracting ability of the group Y and the ease of elimination is not possible on the basis of the yield data presented, since the reduction–elimination reaction was in each case practically exclusive. It will be observed, however, from a comparison of the fate of the ketones listed in Tables I and II with that of the ketones in Table III, that the groups –OAr, –OOCR, –OOCAr, –SR, –SAr, which have greater capacity for assuming anionic character than do the amino groups, were more readily eliminated, while the

(9) The elimination of an α-amino group was observed first in this Laboratory,[10] and other examples have been given in the preceding paper.[5]

(10) N. J. Leonard and R. C. Sentz, THIS JOURNAL, **74**, 1704 (1952).

TABLE II

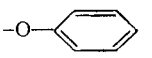
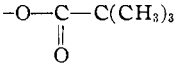
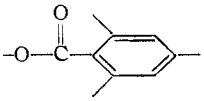
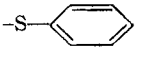
ELIMINATION OF REPRESENTATIVE α-AMINO GROUPINGS

Y		Yields, % Olefin	Yields, % "Normal" product
$-NH(CH_2)_6CH_3$	Ig	41	37
$-NHC_6H_5$	Ih	(13)[a]	(31)[a]
	Ii	24	41
	Ij	54	21
	Ik	36	48

[a] Considerable decomposition was encountered under the reaction conditions.

TABLE III

ELIMINATION OF SUBSTITUENTS CAPABLE OF ASSUMING ANIONIC CHARACTER

Y		Olefin %
	Il	80[a]
	Im	52[b]
	In	58[b]
	Io	76% (+78% C_6H_5SH)
$-S(CH_2)_5CH_3$	Ip	95% (+70% $CH_3(CH_2)_5SH$ and disulfide)

[a] Equivalent yield from the hydrazone. [b] Hydrolytic and hydrazinolytic side reactions probably account for the lower yields of olefin.

TABLE IV

α-SUBSTITUTED PINACOLONES

Compound	Yield, %	B.p., or m.p., °C.	Mm.	N_D^t	t, °C.	d^{20}_4	Infrared C=O max., cm.$^{-1}$[a]	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd	Found
3,3-Dimethyl-1-1-N-piperidyl-2-butanone[d] (Ia)	88	49–50	0.4	1.4593	20	0.910	1713 1712[b]	$C_{11}H_{21}NO$	72.08	71.73	11.55	11.47	7.64	7.92
3,3-Dimethyl-1-1-N-(α-methylpiperidyl)-2-butanone (1b)	72	65–67	0.5	1.4570	27		1718[b]	$C_{12}H_{23}NO$						
3,3-Dimethyl-1-1-N-(α,α′-dimethylpiperidyl)-2-butanone (1c)	55	72.5–73.5	0.5	1.4598	23.5	0.919		$C_{13}H_{25}NO$						
3,3-Dimethyl-1-1-N-(α,α,α′,α′-tetramethylpiperidyl)-2-butanone (1d)	10	63	0.1[c]				1720	$C_{15}H_{29}NO$	75.25	75.29	12.21	12.21	5.85	5.62
3,3-Dimethyl-1-1-N-pyrrolidyl-2-butanone[d] (1e)	74	81.5	8	1.4534	23	0.915	1712 1712[b]	$C_{10}H_{19}NO$						
3,3-Dimethyl-1-1-N-hexamethyleneimino-2-butanone[d] (1f)	86	97	1.7	1.4659	22	0.914	1720[b]	$C_{12}H_{23}NO$						
3,3-Dimethyl-1-1-*n*-heptylamino-2-butanone (1g)	58	79–80	0.1	1.4423	20	0.859	1720[b]	$C_{13}H_{27}NO$						
1-N-Anilino-3,3-dimethyl-2-butanone (1h)	70	M. 72–73					1705	$C_{12}H_{17}NO$	75.35	75.42	8.96	8.91	7.32	7.04
3,3-Dimethyl-1-1-N-(α,α-dimethylpyrrolidyl)-2-butanone (1i)	86	80–81	3	1.4535	23		1707[b]	$C_{12}H_{23}NO$						
1-N-Di-*n*-butylamino-3,3-dimethyl-2-butanone (1j)	88	84.5–85	1.5	1.4379	23		1715	$C_{14}H_{29}NO$	73.95	73.82	12.86	12.29	6.16	6.64
3,3-Dimethyl-N-(N-methylanilino)-2-butanone (1k)	70	116	0.7	1.5299	25	0.988	1717 1725[b]	$C_{13}H_{19}NO$	76.05	75.73	9.33	9.17	6.82	7.10
3,3-Dimethyl-1-phenoxy-2-butanone[d] (II)	81	77	0.2	1.5077	20	1.013	1721	$C_{12}H_{16}O_2$	74.97	74.87	8.39	8.46		
3,3-Dimethyl-2-ketobutyl trimethylacetate (Im)	75	81–83	1.5–2.0[e]					$C_{11}H_{20}O_3$	65.97	65.50	10.07	9.96		
3,3-Dimethyl-2-ketobutyl mesitoate (In)	81	M. 59.5–60.5[f]					1720	$C_{16}H_{22}O_3$	73.25	73.39	8.45	8.71		
3,3-Dimethyl-1-phenylmercapto-2-butanone (Io)	86	92–92.5	0.3	1.5453	20.5	1.043		$C_{12}H_{16}OS$	69.19	69.39	7.74	7.94		
3,3-Dimethyl-1-*n*-hexylmercapto-2-butanone (Ip)	88	70	0.25	1.4654	20	0.904	1706	$C_{12}H_{24}OS$	66.63	65.41	11.18	11.27		
3,3-Dimethyl-2-ketobutyl benzoate (Iq)	73	M. 87–88[g]					1716	$C_{13}H_{16}O_3$	70.89	71.00	7.32	7.62		
3,3-Dimethyl-1-*p*-toluenesulfonyl-2-butanone (Ir)	76	M. 114–115[g]					1712	$C_{13}H_{18}O_3S$	61.39	61.11	7.13	7.23		

[a] Determined on the pure liquid or in Nujol mull when solid. [b] For hydrobromide salt in Nujol mull. [c] M.p. 77.5–80°, prisms from aqueous ethanol. [d] Positive Tollens test: R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 145. [e] M.p. 49–50°, hygroscopic. [f] Colorless prisms from aqueous ethanol. [g] Colorless needles from ethanol.

amino groups permitted appreciable competition of the "normal" reduction process.

The Wolff–Kishner reduction of 3,3-dimethyl-1-phenoxy-2-butanone and of the preformed hydrazone took place at a lower temperature (80–90°) than that required for any of the other α-substituted pinacolones. The 3,3-dimethyl-1-butene was formed rapidly, in excellent yield (87% from the hydrazone), and with a high degree of purity. The ease of preparation of the hydrazone and the high yield of olefin obtained suggest that this reaction may constitute a generally useful and convenient method for the preparation of olefins from ketones. The elimination of an α-phenoxy group also has been observed by Perrine and Small[11] in the conversion of dihydrocodeinone to dihydrodesoxycodeine-C under Wolff–Kishner conditions. Reduction with elimination of the α-trimethylacetate and mesitoate groups is similar to that observed with several α-acetoxyketones in the steroid series, where olefins were found in the mixture of Wolff–Kishner products.[12,13] Inconclusive results were obtained in the attempted reduction of 3,3-dimethyl-2-ketobutyl benzoate and its semicarbazone, and no appreciable amount of olefin was produced. That the results with the carbonyl-hindered esters (Im,n) were more satisfactory than with the benzoyloxy ketones (Iq, Table IV) is considered to be due to the greater resistance of the sterically hindered esters to basic hydrolysis or hydrazinolysis.

The reduction–elimination reactions encountered with 3,3-dimethyl-1-phenylmercapto-2-butanone (Io) and 3,3-dimethyl-1-*n*-hexylmercapto-2-butanone (Ip) provide the first examples of the elimination of mercapto groupings during Wolff–Kishner reduction and substantiate an earlier prediction.[10] By contrast, cyclic α-thiaketones having a five-membered ring undergo normal carbonyl-to-methylene reduction.[14] When 3,3-dimethyl-1-*p*-toluenesulfonyl-2-

(11) T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1540 (1952).

(12) W. P. Long and T. F. Gallagher, *J. Biol. Chem.*, **162**, 511 (1946).

(13) D. H. R. Barton, N. J. Holness and W. Klyne, *J. Chem. Soc.*, 2456 (1949).

(14) H. Schmid and E. Grob, *Helv. Chim. Acta*, **31**, 360 (1948).

TABLE V

DERIVATIVES OF α-SUBSTITUTED PINACOLONES

Compd.	M.p., °C.	Crystal form	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
			A. Hydrobromides[a]						
Ia	257–259	Prisms	$C_{11}H_{22}BrNO$	50.00	50.28	8.32	8.32	5.30	5.28
Ib	167–169	Needles	$C_{12}H_{24}BrNO$	51.80	51.80	8.69	8.70	5.03	5.07
Ie	239–242	Plates	$C_{10}H_{20}BrNO$	48.00	47.95	8.07	7.94	5.60	5.44
If	234–236	Needles	$C_{12}H_{24}BrNO$	51.80	52.20	8.69	8.83	5.04	4.99
Ig	234–235[b]	Needles	$C_{13}H_{26}BrNO$	53.05	53.02	9.59	9.42	4.76	4.68
Ii	209–210.5	Prisms	$C_{12}H_{24}BrNO$	51.80	51.81	8.69	8.57	5.04	4.91
Ik	193	Needles	$C_{13}H_{20}BrNO$	54.55	54.64	7.04	7.04	4.89	4.89
			B. Picrates[c]						
Ia	128–129	Needles	$C_{17}H_{24}N_4O_8$	49.51	48.92	5.86	5.86	13.59	13.48
Ib	133–134	Prisms	$C_{18}H_{26}N_4O_8$	50.70	50.94	6.15	5.83	13.14	13.17
Ic	123–124	Prisms	$C_{19}H_{28}N_4O_8$	51.81	52.22	6.41	6.34	12.72	12.77
Ie	128–129	Prisms	$C_{16}H_{22}N_4O_8$	48.24	48.52	5.57	5.56	14.07	14.22
If	129–130	Plates	$C_{18}H_{26}N_4O_8$	50.70	50.85	6.15	6.54	13.14	12.87
Ii	156–158[b]	Needles	$C_{18}H_{26}N_4O_8$	50.70	50.90	6.15	6.31	13.14	13.08
			C. Hydrazones[d]						
Ia	86–88	Prisms	$C_{11}H_{23}N_3$	66.95	66.60	11.75	11.60	21.30	21.12
Ib	81–83	Plates	$C_{12}H_{25}N_3$	68.19	67.74	11.92	11.80	19.88	20.51
Il	55–57[e]	Needles	$C_{12}H_{18}N_2O$	69.87	70.00	8.80	8.86	13.58	13.72
			D. Semicarbazones[f]						
Im	154–155	Prisms	$C_{12}H_{23}N_3O_3$	56.01	55.98	9.01	9.00	16.33	16.56
Iq	155–156	Plates	$C_{14}H_{19}N_3O_3$	60.63	60.53	6.91	6.95	15.15	15.03
			E. Picrolonate[c]						
Ic	189–191	Prisms	$C_{23}H_{33}N_5O_6$	58.09	85.43	7.00	7.03	14.73	14.66

[a] Recrystallized from ethanol–ether, all colorless. [b] With decomposition. [c] Recrystallized from ethanol, yellow to orange. [d] Prepared by heating a solution of the ketone with excess 85% hydrazine hydrate in ethanol at the reflux for 2 hours. The solution was cooled, poured into water, and the product was worked up from the ether extracts and purified by recrystallization from aqueous ethanol. [e] Infrared maximum at 1641 cm.$^{-1}$ in chloroform solution. [f] Prepared by heating an aqueous ethanolic solution of semicarbazide hydrochloride, potassium acetate and the ketone on the steam-bath for 8 hours, and recrystallized from aqueous ethanol.

butanone (Ir, Table IV) was subjected to alkaline hydrazine reduction conditions, the only product isolated was methyl *p*-tolyl sulfone.[15] In an attempt to clarify the behavior of α-hydroxyketones under Wolff–Kishner conditions, we sought to include 3,3-dimethylbutan-1-ol-2-one[16] in our studies, but we were unable to prepare a pure hydrazone. Examples of the conversion of α-hydroxyketones[4,17–24] and α-methoxyketones[25] to olefins[5] have been noted previously, mainly in the steroid series.

A discussion of the possible mechanism or mechanisms of the Kishner reduction–elimination should be dependent, first of all, upon the present state of knowledge concerning the course of the alkaline decomposition of a hydrazone in the normal Wolff–Kishner reduction.[26–30] While a radical process is not excluded, it is generally agreed that the first step involves the removal of a proton from the β-nitrogen, followed by a step involving a hydrogen-shift to the carbon.[29–32] Approximately the same originating sequence has been used in all of the postulates made thus far to account for the reduction–elimination reaction of the α-substituted ketones.[33] It is altogether possible that this reaction can proceed by several paths, but any mechanism, to be satisfactory, must be consistent with our findings on the effects of the electronic and steric nature of the α-substituent and of ring size[5,10] upon the extent of elimination. Furthermore, it is important to consider the possible mechanisms[10] in greater detail, including an examination of their stereochemical requirements. Thus, the Kishner reduction–elimination can be considered as a member of the general class of base-catalyzed elimina-

(15) The instability to alkali of α-ketosulfones is well known; see, for example, H. Kloosterziel and H. J. Backer, *Rec. trav. chim.*, **71**, 373 (1952).

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(33) The reaction sequence included in ref. 24 is a modification of that suggested in ref. 13; see also refs. 10, 11, 13, 24 and 25.

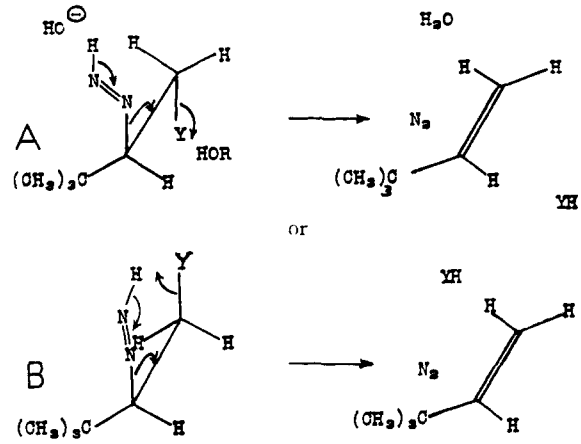

Fig. 1.

tion reactions, as shown in Fig. 1. The decomposition of the intermediate diimine, as represented in 1-A, is analogous to other planar four-center eliminations, differing only in that the proton is removed from a group attached to the β-carbon rather than from the β-carbon itself. *trans*-Elimination would be favored in such a case, whereas elimination involving an intramolecular cyclic transition (1-B) would be *cis*.[34] A decision is not yet possible between these alternative mechanisms, but the order observed for the elimination of various groups (compare Table III with Tables I and II) appears to favor the former (1-A) if the same process applies in all cases. The concept of a process which does not involve the intermediate shift of a proton to carbon (Fig. 2) also should be retained for consideration and testing. In this scheme, cleavage of the H–N and C–Y bonds, formation of a new N–N (double) bond, and shift of the original double bond could occur concurrently or consecutively.

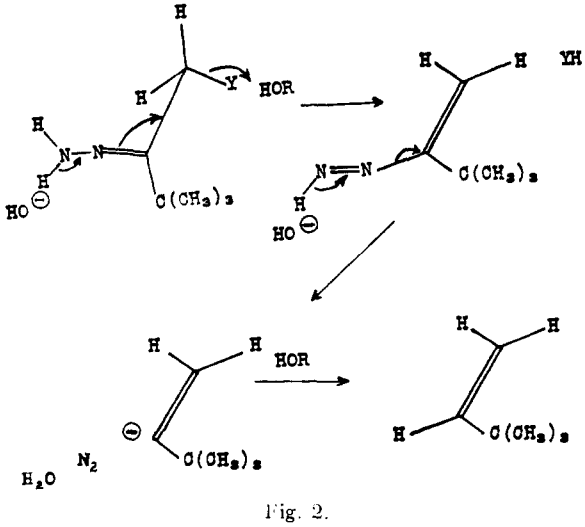

Fig. 2.

(34) The cyclic mechanism bears similarity to that suggested by Jeger and his coworkers to account for the shift of the double bond during Wolff–Kishner reduction of α,β-unsaturated carbonyl compounds: R. Fischer, "I. Über die Reduktion von α,β-ungesättigen Carbonylverbindungen nach der Methode von Wolff–Kishner. II. Beitrag zur Kenntnis des Cafestols," Dissertation, Eidgenossische Technische Hochschule, Zürich, 1952; G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949); R. Fischer, G. Lardelli and O. Jeger, *ibid.*, **33**, 1335 (1950); R. Fischer, G. Lardelli and O. Jeger, *ibid.*, **34**, 1577 (1951).

Experimental[35]

α-Bromopinacolone.—The bromoketone, b.p. 68–69° (8 mm.), was prepared essentially by the method of Widman and Wahlberg[36] in yields averaging 78%.

3,3-Dimethyl-1-N-piperidyl-2-butanone and Other Substituted Aminopinacolones.—To a solution of 16.5 g. (0.092 mole) of α-bromopinacolone in 150 ml. of commercial anhydrous ether was added dropwise with stirring a solution of 23.4 g. (0.276 mole) of piperidine in 50 ml. of ether. The mixture was stirred for 14 hours at room temperature followed by one-half hour under vigorous reflux. The precipitated piperidine hydrobromide was removed, and the filtrate was washed with water. The ethereal solution was dried, the ether was removed, and the residue was fractionally distilled *in vacuo*. The purity of the 3,3-dimethyl-1-N-piperidyl-2-butanone (Ia) was checked by conversion to the hydrobromide and reconversion to the base, with boiling point and refractive index unchanged. In the preparation of the closely related compounds, the main variation was in the reflux time, *e.g.*, for Ib, 10 hours; Ic, 10 hours, then 12 hours at 25°; Ie, Ii, 2 hours, then 15 hours at 25°; If, 3 hours; Ig, 5 hours; Ij, 7 hours. For the preparation of Id, 48 hours reflux in xylene was employed.

For the synthesis of 1-N-anilino-3,3-dimethyl-2-butanone (Ih) and 3,3-dimethyl-N-(N-methylanilino)-2-butanone (Ik), the method used by Verkade and Janetzky[37] for 1-phenyl-1-anilinoacetone was adapted. As an example, a mixture of 20.0 g. (0.112 mole) of α-bromopinacolone, 10.5 g. (0.112 mole) of aniline and 19.3 g. of sodium bicarbonate in 150 ml. of 95% ethanol was heated under reflux with stirring for 2 hours and then stirred for 4 hours at 25°. The mixture was filtered and the solvent was removed. The residue was taken up in ether, and the ether soluble material was worked up in the usual manner.

3,3-Dimethyl-1-phenoxy-2-butanone (Il).—A mixture of 2.7 g. (0.12 g. atom) of sodium, 10.5 g. (0.16 mole) of phenol and 300 ml. of dry benzene was stirred at the reflux temperature until all of the sodium had reacted. After cooling to 25°, 20.0 g. (0.11 mole) of α-bromopinacolone was added. The resulting mixture was stirred under reflux for 3 hours, cooled and washed successively with water, 10% aqueous sodium hydroxide solution and water. The benzene solution was dried, the solvent was removed, and the residue was fractionated *in vacuo*. Table IV incorporates the properties of this and the other α-substituted pinacolones. **3,3-Dimethyl-2-ketobutyl trimethylacetate** (Im) was obtained by heating equimolar quantities of sodium trimethylacetate and α-bromopinacolone in absolute ethanol at the reflux for 4 hours, followed by dilution with water, ether extraction, and normal work-up. Similar conditions were used for the preparation of **3,3-dimethyl-2-ketobutyl mesitoate** (In) and **3,3-dimethyl-2-ketobutyl benzoate** (Iq), with the exception that the potassium salts were used. **3,3-Dimethyl-1-phenylmercapto-2-butanone** (Io) was prepared from α-bromopinacolone and thiophenol in aqueous sodium hydroxide under the conditions used by Werner[38] for α-phenylmercaptoacetone.

3,3-Dimethyl-1-*n*-hexylmercapto-2-butanone (Ip) was formed in a similar manner using *n*-hexyl mercaptan, 50% aqueous ethanol as the solvent, and employing a brief heating period. **3,3-Dimethyl-1-*p*-toluenesulfonyl-2-butanone** (Ir) was obtained by refluxing a mixture of sodium *p*-toluenesulfinate dihydrate and α-bromopinacolone in 95% ethanol for 1.5 hours.

3,3-Dimethyl-1-butene (II).—A sample of the olefin was prepared by the method of Wibaut and Gitsels,[39] n^{20}D 1.3764 (reported[39] 1.3766, and for the olefin prepared by the Chugaev reaction on pinacolyl alcohol,[40] n^{18}D 1.37667).

(35) Melting points are corrected and boiling points are uncorrected. We are indebted to Miss Helen Miklas for determination of the infrared spectra and to Mrs. Katherine Pih, Mrs. Esther Fett, Mrs. Lucy Chang and Mr. Joseph Nemeth for the microanalyses.

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TABLE VI

DERIVATIVES OF "NORMAL" REDUCTION PRODUCTS OF α-SUBSTITUTED PINACOLONES

From	Compound	M.p., °C.	Crystal form	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	A. Hydrobromides[a]									
Iq	N(-3,3-Dimethylbutyl)-*n*-heptylamine (?)	253–254	Plates	$C_{13}H_{30}BrN$	55.70	54.70	10.79	11.84	5.00	5.78
Ik	N-(3,3-Dimethylbutyl)-N-methylaniline	179–180	Needles	$C_{13}H_{22}BrN$	57.35	57.19	8.15	8.02	5.15	5.12
	B. Picrates									
Ia	N-(3,3-Dimethylbutyl)-piperidine	172–173.5	Prisms[b]	$C_{17}H_{26}N_4O_7$	51.25	51.10	6.58	6.48	14.06	14.09
Ib	N-(3,3-Dimethylbutyl)-α-methylpiperidine	151–152	Prisms[b]	$C_{18}H_{28}N_4O_7$	52.41	52.75	6.84	6.47	13.59	13.75
(Ic)[d]	N-(3,3-Dimethylbutyl)-α,α'-dimethylpiperidine	161–162	Needles[c]	$C_{19}H_{30}N_4O_7$	53.51	53.46	7.09	7.02	13.14	13.06
Ie	N-(3,3-Dimethylbutyl)-pyrrolidine	192–193	Needles[c]	$C_{16}H_{24}N_4O_7$	49.99	50.09	6.29	6.27	14.58	14.40
If	N-(3,3-Dimethylbutyl)-hexamethyleneimine	186–187	Needles[c]	$C_{18}H_{28}N_4O_7$	52.41	52.50	6.84	6.54	13.59	13.52
Ii	N-(3,3-Dimethylbutyl)-α,α-dimethylpyrrolidine	126.5–127.5	Needles[c]	$C_{18}H_{28}N_4O_7$	52.41	52.53	6.84	6.86	13.59	13.69
Ik	N-(3,3-Dimethylbutyl)-N-methylaniline	126.5–128[e]	Prisms[c]	$C_{19}H_{24}N_4O_7$	54.28	54.67	5.75	5.78	13.33	13.55
	C. *p'*-Hydroxyazobenzene-*p*-sulfonate									
Ij	N-(3,3-Dimethylbutyl)-di-*n*-butylamine	191.5–193.5	Prisms[c]	$C_{26}H_{41}N_3O_4S$	63.52	63.59	8.41	8.62	8.55	8.35
	D. Phenylthiourea derivative									
Ih	N-(3,3-Dimethylbutyl)-aniline	118–119.5	Needles[c]	$C_{19}H_{24}N_2S$	73.03	73.23	7.74	7.67	8.97	9.00

[a] Recrystallized from ethanol–ether. [b] Methanol. [c] Ethanol. [d] Prepared by an unequivocal synthesis. Normal product could not be isolated in pure form from the Wolff–Kishner reduction. [e] With decomposition.

The 2,4-dinitrobenzenesulfenyl chloride derivative[41] crystallized as pale yellow prisms from ethanol, m.p. 97.5–98.5°.

Anal. Calcd. for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.74; N, 8.79. Found: C, 45.21; H, 4.72; N, 8.70.

1,2-Dibromo-3,3-dimethylbutane.—Bromination of 3,3-dimethyl-1-butene was effected in chloroform solution cooled in a Dry Ice–acetone-bath. The reaction mixture was washed with dilute sodium thiosulfate solution, then with water. The chloroform was removed and the residue was fractionally distilled through a Holzman column,[42] b.p. 73° (3 mm.) (reported[43] 91–92° (14 mm.)), $n^{20}D$ 1.5054, d^{20}_4 1.604, yield 78%.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.53; H, 4.96; MR_D, 45.44. Found: C, 29.79; H, 5.07; MR_D, 45.46.

N-*t*-Butylacetylpiperidine.—A mixture of 4.0 g. (0.035 mole) of *t*-butylacetic acid,[44] b.p. 88–91° (18 mm.), $n^{24}D$ 1.4088, and 5.2 g. of thionyl chloride was heated under reflux for one hour. After the addition of 40 ml. of dry benzene heating was resumed, and benzene and excess thionyl chloride were distilled until the volume was 10 ml. To the residue cooled in an ice-bath was added cautiously 6.0 ml. (0.07 mole) of piperidine in 25 ml. of dry benzene. When the addition was complete, the mixture was heated under reflux for one hour. Upon cooling, the mixture was washed twice with water and the washings were extracted with ether. The combined organic layers were dried and the solvents were removed. The residue was distilled through a Holzman column, b.p. 73° (0.3 mm.), $n^{24}D$ 1.4737, yield 4.2 g. (67%), infrared maximum 1639 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.90; H, 11.62; N, 7.70.

N-(3,3-Dimethylbutyl)-piperidine.—The amide described above was reduced by lithium aluminum hydride in ether,[45] and the amine thus formed was distilled at 82° (15 mm.), $n^{27}D$ 1.4460, yield 48%. **The picrate** is described in Table VI.

N-(3,3-Dimethylbutyl)-α,α'-dimethylpiperidine.—N-*t*-Butylacetyl-α,α'-dimethylpiperidine, b.p. 89–91° (0.5 mm.), was reduced in the same way to N-(3,3-dimethylbutyl)-α,α'-dimethylpiperidine, b.p. 99–100° (10 mm.), $n^{20}D$ 1.4560.

Attempted Preparation of 3,3-Dimethyl-2-ketobutyl Benzoate Hydrazone.—A mixture of 1.0 g. (4.5 millimoles) of the keto ester Iq, 1.0 ml. of 85% hydrazine hydrate and 3 ml. of triethylene glycol was heated at 110–115° for one hour. The reaction mixture was cooled and diluted with 10 ml. of water. Ether extraction followed by evaporation and recrystallization of the residue from absolute ethanol furnished a small quantity of colorless plates, m.p. 212–214° with decomposition and gas evolution. The elemental analysis indicated an absence of oxygen and suggested a molecular formula of $C_{12}H_{24}N_6$. The structure was not determined.

Anal. Calcd. for $C_{12}H_{24}N_6$: C, 57.11; H, 9.59; N, 33.30. Found: C, 57.20; H, 9.89; N, 32.83.

Wolff–Kishner Reduction of 3,3-Dimethyl-1-N-piperidyl-2-butanone.—The general method employed is illustrated by this specific case. The reaction was carried out in a 100-ml. standard-taper side-arm flask equipped with a take-off condenser having a thermometer suspended inside. The take-off condenser jacket was kept at about 25°, and the top of the condenser was connected by Tygon tubing to two Dry Ice traps in series. Purified nitrogen was bubbled slowly in through the side-arm of the flask (approximately one bubble every 2–3 seconds).

The flask was charged with 9.0 g. (0.049 mole) of aminoketone, 10 ml. of hydrazine hydrate and 30 ml. of triethylene glycol, and the mixture was heated at 120–130° for 1.5 hours. (No olefin was present in the Dry Ice traps after formation of the hydrazone and before addition of alkali.) The flask was cooled to room temperature and 8.4 g. (0.15 mole) of potassium hydroxide pellets was added. The bath temperature was raised carefully until the temperature inside the flask had reached 200° and most of the volatile material had distilled. The temperature was maintained at 200–210° for 2 hours. The condensate removed through the take-off and the water-diluted reaction mixture were each extracted with four portions of ether. The combined extracts were dried and the ether was removed. The residue was subjected to fractional distillation. Piperidine (1.2 g., 29%) was obtained by distillation at atmospheric pressure and the "normal" reduction product, N-(3,3-dimethylbutyl)-piperidine (5.3 g., 64%), at reduced pressure, b.p. 99–101° (25 mm.), $n^{20}D$ 1.4500. The 3,3-dimethyl-1-butene collected in the Dry Ice trap was separated by decantation at low temperature from the small amount of higher boiling material that had been carried over; yield 1.2 g. (29%). The identity and purity of the olefin were checked by refractive index, melting point and infrared absorption spectrum (Nujol mull) of the 2,4-dinitrobenzenesulfenyl chloride derivative, and formation of 1,2-dibromo-3,3-dimethylbutane.

The other α-substituted pinacolones were reduced in the same manner, with attendant characterization of the reduction–elimination and "normal" reduction products and determination of the relative yields (see tables in Discussion section). Where some unchanged hydrazone was recovered, the yields are adjusted to the amount of hydrazone which was unrecovered. Derivatives used to identify the "normal" products are given in Table VI, and the physical properties observed for these reduction products were also useful:

N-(3,3-Dimethylbutyl)-α-methylpiperidine (from Ib), b.p. 100–102° (20 mm.), $n^{25}D$ 1.4488; N-(3,3-dimethylbutyl)-pyrrolidine (from Ie), b.p. 75–76° (22 mm.), $n^{25}D$ 1.4414; N-(3,3-dimethylbutyl)-hexamethyleneimine (from

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(42) G. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(43) M. F. Claessens, *Bull. soc. chim.*, **5**, 113 (1908).

(44) A. H. Homeyer, F. C. Whitmore and V. H. Wallingford, THIS JOURNAL, **55**, 4209 (1933).

(45) R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1938).

If), b.p. 107–108° (20 mm.); N-(3,3-dimethylbutyl)-*n*-heptylamine (from Ig), b.p. 118° (8 mm.), $n^{20}D$ 1.4377; N-(3,3-dimethylbutyl)-aniline (from Ih), b.p. 138–139° (17 mm.); N-(3,3-dimethylbutyl)-α,α-dimethylpyrrolidine (from Ii), b.p. 81–85° (18 mm.); N-(3,3-dimethylbutyl)-di-*n*-butylamine (from Ij), b.p. 116–118° (18 mm.), $n^{20}D$ 1.4291–1.4310 and di-*n*-butylamine, b.p. 53–56° (18 mm.), $n^{24}D$ 1.4181, phenylthiourea derivative, m.p. 84–85° (reported 86°)[46]; N-(3,3-dimethylbutyl)-N-methylaniline (from Ik), b.p. 77–79° (0.2 mm.), $n^{20}D$ 1.5180; thiophenol (from Io), b.p. 87° (60 mm.), $n^{20}D$ 1.5840 (also identified by odor); *n*-hexyl mercaptan (from Ip), b.p. 70–72° (60 mm.), $n^{20}D$ 1.4460. No olefin could be detected from Iq or its semicarbazone. No olefin could be detected from Ir, but colorless prisms (from ethanol) were collected, m.p. 86–87.5°, which did not depress the melting point of an authentic sample of methyl-*p*-tolylsulfone (69% yield). The hydrazones of 3,3-dimethyl-1-N-piperidyl-2-butanone (Ia) and 3,3-dimethyl-1-phenoxy-2-butanone (Il) furnished the same yields of olefin as did the ketones.

URBANA, ILLINOIS

(46) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 174, 234.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE UNIVERSITY]

Enol Esters of α-Haloketones

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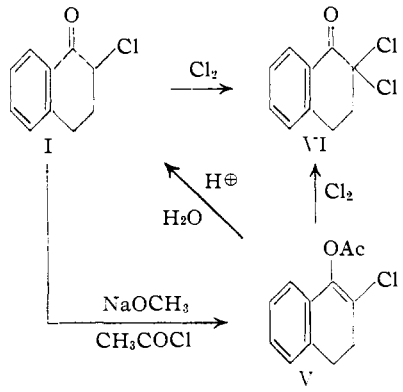
The preparation of enol esters from the following cyclic α-haloketones is reported: 2-chloro-α-tetralone (I), 2-bromo-α-tetralone (II), 2-bromo-1-indanone (III) and 2-chlorocyclohexanone (IV). Stable enolate ions, obtained at low temperatures from the reactions of I, II, III and IV with anhydrous, powdered sodium methoxide in anhydrous ether, were acylated to obtain enol acetates from I, II and III, and an enol caproate from IV.

While the preparation of enol acetates from ketones which contain an enolizable α-hydrogen atom has long been known, a practical preparation for such enol esters from α-haloketones has not been reported. Lyle[2] recently described the isolation of an enol acetate from 2,2-diphenyl-7-bromocycloheptanone, but the yield was poor (9%).

While investigating the reaction of 2-chloro-α-tetralone (I) with anhydrous, powdered sodium methoxide in anhydrous ether at −80°, it was noted that the heterogeneous sodium methoxide–ether slurry became homogeneous at once upon the addition of I. The solution became greenish-yellow in color and this color, coincident with homogeneity, was thought to have arisen from the formation of an enolate ion produced by the action of the base on the α-proton of I. This belief was confirmed upon the addition of acetyl chloride. A precipitate of sodium chloride appeared immediately and 1-acetoxy-2-chloro-3,4-dihydronaphthalene (V) was isolated from the ethereal portion in 65% yield.

The elemental analyses and infrared spectrum were compatible with structure V, and chemical evidence for O-acylation rather than C-acylation was obtained by hydrolysis to the parent α-haloketone I. Also, chlorination of V gave 2,2-dichloro-α-tetralone (VI).



This reaction constitutes another useful procedure involving the enolate ion of an α-haloketone, the ion being relatively stable at low temperature. Previously, the enolate ion has been proposed as an intermediate in the glycidic-ester type self-condensation of phenacyl halides.[3] The reaction has added significance in view of the profusion of reactions involving the action of bases on α-haloketones: epoxy-ether formation,[4] Favorski-type rearrangement,[5] elimination,[6] substitution,[7] carbon skeleton rearrangement not of the Favorski-type,[8] and functional group rearrangement.[9]

The scope of this type of O-acylation was extended and shown to be practical for α-bromoketones as well as for α-chloroketones. 1-Acetoxy-2-bromo-3,4-dihydronaphthalene (VII) was obtained from 2-bromo-α-tetralone (II) in 47% yield and 1-acetoxy-2-bromoindene (VIII) from 2-bromo-1-indanone (III) in 23% yield. Bromination of VII and VIII gave 2,2-dibromo-α-tetralone (IX) and 2,2-dibromo-1-indanone (X), respectively, in excellent yields. Both IX and X were prepared independently by bromination of II and III, respectively.

Attempts to prepare the enol acetate of α-chlorocyclohexanone (IV) in a pure state were unsuccessful because of difficulties encountered in separating

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