

ammonia. Substitution of methyl groups on the formamide nitrogen appears to stabilize the formyl hydrogen against radical attack.

### Experimental

All melting points are corrected and were taken on a Fisher-Johns apparatus.<sup>12</sup> Infrared spectra were determined using a Perkin-Elmer Infracord 137 spectrophotometer. Analyses for ammonia nitrogen were performed by H. M. Wright of this laboratory.

**Reaction of Potassium Persulfate with Amides.**—Into a 500-ml. three-necked round-bottom flask equipped with a gas-inlet tube, reflux condenser, thermometer, and magnetic stirring bar was placed 0.1 mole of amide, 27.0 g. (0.1 mole) of potassium persulfate, 34.8 g. (0.2 mole) of dipotassium hydrogen phosphate, and 250 ml. of distilled water. In experiments using *N,N*-diisopropylacetamide, 500 ml. of water was used. The reflux condenser was fitted with a gas-outlet tube leading to a calcium chloride drying tube followed by two tubes containing Ascarite sodium hydrate asbestos absorbent. Nitrogen was bubbled through the solution for 1 hr., and the reaction system was swept with a stream of nitrogen throughout the course of the reaction. On heating to 65° with stirring, a rapid exothermic

(12) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

reaction took place, raising the temperature to 85–90° at which the reaction mixture was maintained for 30 min. The water was removed from the reaction mixture by distillation.

In experiments where an aldehyde or ketone was a product, the water distillate was treated with 2,4-dinitrophenylhydrazine dissolved in dilute sulfuric acid. The resulting 2,4-dinitrophenylhydrazone was removed by filtration and recrystallized from 95% ethanol. In each case, the purified 2,4-dinitrophenylhydrazone's melting point and infrared spectrum were compared with those of an authentic sample.

The residue in the reaction flask was extracted with several small portions of hot 95% ethanol. The ethanol was distilled to yield an oil. Distillation of this oil at 20 mm. yielded any demethylated amide and/or unreacted amide present. Each amide was characterized by comparing its boiling point and infrared spectrum with those of an authentic sample of amide. In the case of *N-t*-butylacetamide, recovery was made by sublimation.

The carbon dioxide evolved during the reaction was determined by the weight uptake of Ascarite absorbent. The yield of ammonia was determined by analyzing the crude reaction mixture for ammonia nitrogen.

Each dealkylation was performed two or more times, and the yields of products were found reproducible within a few per cent. In control experiments, recoveries of known quantities of amides and aldehydes were 70% or greater by the methods of isolation used in these dealkylations. The product yields based on starting material for the dealkylations are listed in Tables I, II, and III.

## Dissociation Constants of the Cyanohydrins of Alkylcyclohexanones

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The dissociation constants of the cyanohydrins of a series of 2-, 3-, and 4-alkylcyclohexanones and 2,6-dialkylcyclohexanones show the effect of interactions with the cyanohydrin for groups larger than methyl in the  $\alpha$ -position. The effect is smaller in the  $\beta$ - and absent in the  $\gamma$ -position.

The possible interaction between an equatorial  $\alpha$ -alkyl group and the oxygen atom of the carbonyl group in cyclohexanone has been termed the 2-alkyl ketone effect. The suggestion<sup>2</sup> that an equatorial methyl group in the 2-position interacting with the carbonyl group destabilizes the alkyl group by 1.0 kcal./mole with respect to the axial conformation has not been confirmed by recent studies.<sup>3</sup> Larger groups, such as ethyl and isopropyl, apparently show such an effect.<sup>3</sup> However, a 2-*t*-butyl group distorts the ring into a twist-chair conformation,<sup>3,4</sup> and recent data<sup>5</sup> suggest that even a 2-methyl group may produce some twisting of the ring. The origin of the increased reactivity of cyclohexanone over acyclic ketones has recently been attributed<sup>6</sup> to the stabilization by  $\alpha$ -axial carbon-hydrogen bonds, relative to carbon-carbon bonds. The amount of stabilization is estimated as 1 kcal./mole and this stabilization is lost on methyl substitution. A 3-

alkyl ketone effect has also been postulated,<sup>2,7</sup> arising from the fact that in cyclohexanone there are only two axial substituents on one side of the molecule and an alkyl substituent can be accommodated on one of these positions without greatly increasing the nonbonded interactions.

In a previous study<sup>8</sup> 3- and 4-methylcyclohexanone were found to have slightly smaller dissociation constants than cyclohexanone (see Table I); this was interpreted as being due to equatorial interference between the methyl group and the neighboring equatorial hydrogen atoms. The higher alkylcyclohexanones studied in the present work all had larger  $K_D$ -values than cyclohexanone itself (see Table I).

For the 2-alkyl compounds, an ethyl group had a slightly larger effect than methyl, and this increased greatly for isopropyl and *t*-butyl. However, increasing the number of methylene groups in an unbranched chain, as in *n*-propyl and *n*-butyl, resulted in little increase in the dissociation constants. Two  $\alpha$ -methyl (2,6-dimethyl) groups had little effect, although two  $\alpha$ -isopropyl groups lead to a large increase in  $K_D$ . The data for 3-alkyl substitution showed a slight increase in dissociation constant with increasing size of the sub-

(1) Operated by the University of Puerto Rico under Contract No. At-(40-1)-1833 for the Atomic Energy Commission.

(2) W. Klyne, *Experientia*, **12**, 119 (1956).

(3) (a) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); (b) B. Rickborn, *ibid.*, **84**, 2414 (1962); (c) C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, **86**, 85 (1964).

(4) C. Djerassi, E. J. Warawa, J. M. Berdahl, and E. J. Eisenbraun, *ibid.*, **83**, 3334 (1961).

(5) C. Beard, C. Djerassi, T. Elliot, and R. C. C. Tao, *ibid.*, **84**, 874 (1962); C. Beard, C. Djerassi, J. Sicker, F. Sipas, and M. Tichy, *Tetrahedron*, **19**, 919 (1963); C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).

(6) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters*, No. 26, 1833 (1963).

(7) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962).

(8) (a) O. H. Wheeler and J. Z. Zabicky, *Chem. Ind. (London)*, 1388 (1956); *Can. J. Chem.*, **36**, 656 (1958). (b) Cf. R. A. Benseker and E. W. Bennet, *J. Am. Chem. Soc.*, **80**, 5414 (1958).

TABLE I  
DISSOCIATION CONSTANTS OF ALKYL CYCLOHEXANONE  
CYANOHYDRINS<sup>a</sup>

	$K_D \times 10^3$
Cyclohexanone	0.60 <sup>b</sup>
2-Methyl-	1.07 <sup>c</sup>
2-Ethyl-	3.70
2-Isopropyl-	16.9
2- <i>t</i> -Butyl-	132
2- <i>n</i> -Propyl-	5.11
2- <i>n</i> -Butyl-	4.11
2,6-Dimethyl-	4.82
2,6-Diisopropyl-	41.7
3-Methyl-	0.55 <sup>c</sup>
3-Ethyl-	0.98
3-Isopropyl-	2.65
3- <i>t</i> -Butyl-	6.39
4-Methyl-	0.32 <sup>c</sup>
4-Ethyl-	0.65
4-Isopropyl-	0.63
4- <i>t</i> -Butyl-	0.59

<sup>a</sup> In 95% ethanol at  $23 \pm 1^\circ$ . <sup>b</sup> Ref. 8a gives  $K_D = 0.59 \times 10^{-3}$  in 95% ethanol at  $25^\circ$ . <sup>c</sup> Ref. 8a.

free-energy differences for interconversion of equatorial ethyl and isopropyl substituents to the axial conformation is about the same as for a methyl group.<sup>10,11</sup> Accordingly these groups must be largely in an equatorial conformation and the *t*-butyl group necessarily adopts the same conformation. Assuming that no alkyl group carbonyl interactions are present in the ketones, the free energies of 1,2-equatorial-equatorial interaction [from  $\Delta(\Delta F) = -RT \ln(K^1/K^2)$  at  $23^\circ$ ] between the alkyl substituent and either the cyano or hydroxyl group of the cyanohydrin are then for ethyl, isopropyl, and *t*-butyl 1.1, 2.0, and 3.2 kcal./mole, respectively. These values are probably somewhat low, since some interactions will be present in the ketones. The isopropyl and *t*-butyl groups are thus progressively bulkier when occupying an equatorial conformation. However, this does not imply that the ratio of equatorial to axial forms will be changed as has been sometimes assumed for ethyl and isopropyl substituents.<sup>12</sup> For two methyl and two isopropyl groups the  $\Delta(\Delta F)$ -values (from the 2,6-dialkylcyclohexanone) are 1.2 and 2.5 kcal./mole.

TABLE II  
PHYSICAL CONSTANTS OF CYCLOHEXANONES

	B.p., °C. (mm.)	Lit. b.p., °C. (mm.)	$n_D^{20}$	Lit. $n_D$ (°C.)
2-Ethyl-	83 (28)	73.5-74.5 (35) <sup>a</sup>	1.4488	1.4530 (16) <sup>b</sup>
2-Isopropyl-	79 (18)	72 (15) <sup>c</sup>	1.4570	1.4526 (24) <sup>c</sup>
2- <i>t</i> -Butyl-	98 (28)	75-79 (12) <sup>d</sup>	1.4566	1.4570 (17) <sup>d</sup>
2- <i>n</i> -Propyl-	97 (25)	86 (22) <sup>e</sup>	1.4506	1.4504 (24) <sup>e</sup>
2- <i>n</i> -Butyl-	105-106 (17)	76-78 (7) <sup>f</sup>	1.4525	
2,6-Dimethyl-	81.5-82 (40)	60 (20) <sup>g</sup>	1.4456	1.4470 (20) <sup>g</sup>
2,6-Diisopropyl-	142 (38) <sup>h</sup>		1.4544	
3-Ethyl-	78-80 (21)	38-41 (0.8) <sup>i</sup>	1.4515	1.4537 (20) <sup>i</sup>
3-Isopropyl-	85-86 (20)	50-51 (1) <sup>j</sup>	1.4520	1.4540 (20) <sup>j</sup>
3- <i>t</i> -Butyl-	95-96 (18)	92-95 (10) <sup>k</sup>	1.4614	1.4611 <sup>l</sup>
4-Ethyl-	87 (18)	109-112 (50) <sup>k</sup>	1.4525	1.4533 <sup>k</sup>
4-Isopropyl-	73.5-76 (18)	90-91 (13) <sup>l</sup>	1.4510	1.4560 (20) <sup>l</sup>
4- <i>t</i> -Butyl-	M.p. 47-48	M.p. 47.5-48.5 <sup>j</sup>	...	...

<sup>a</sup> F. E. King, J. A. Baltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945). <sup>b</sup> J. R. Dice, L. E. Loveless, Jr., and H. L. Cates, Jr., *J. Am. Chem. Soc.*, **71**, 3546 (1946). <sup>c</sup> R. Filler, B. R. Camara, and S. M. Naqvi, *ibid.*, **81**, 658 (1959). <sup>d</sup> Ref. 18. <sup>e</sup> C. Weizmann, E. Bergmann, and E. Haskelberg, *Chem. Ind. (London)*, 587 (1937). <sup>f</sup> M. Ogawa and G. Tanaka, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 696 (1955). <sup>g</sup> H. Conroy and R. A. Firestone, *J. Am. Chem. Soc.*, **78**, 2290 (1956). <sup>h</sup> *Anal. Calcd. for C<sub>12</sub>H<sub>20</sub>O: C, 79.94; H, 11.18. Found: C, 79.76; H, 11.25.* <sup>i</sup> G. F. Woods, P. H. Griswold, Jr., B. H. Armbrrecht, D. I. Blumenthal, and R. Plapinger, *J. Am. Chem. Soc.*, **71**, 2028 (1949). <sup>j</sup> Ref. 12. <sup>k</sup> Ref. 15. <sup>l</sup> R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Am. Chem. Soc.*, **71**, 3889 (1949).

stituent, but the differences for 4-alkylation were not significant.

To consider the individual dissociation constants in more detail, it must be remembered that these measure the relative stabilities of the ketones and their cyanohydrins.

The 2- and 3-alkyl ketone effects<sup>7</sup> result from the differences in stability of the alkylcyclohexanone and the corresponding alkylcyclohexane with the substituent occupying an equatorial or axial position. However, these effects are small and the cyclohexanone ring can relieve any strain due to substitution by adopting a twist-chair conformation.<sup>3,4</sup> The differences found in the dissociation constants of the cyanohydrins are probably largely due to differences in the stability of the cyanohydrins themselves, and these are subject to interactions not present in the parent ketones.

Measurements of the Raman spectra of the cyanohydrins of 2-<sup>9a</sup> and 3-methylcyclohexanone<sup>9b</sup> show that the methyl group is predominantly equatorial and the cyano group is about 75% axial in both cases. The

However, both alkyl groups are probably not equatorial. This same treatment applied to 2-*n*-propyl and *n*-butyl substituents shows that they have the same effectiveness in shielding the ketone group as does an ethyl group; *i.e.*, increasing the carbon chain beyond two atoms has no further effect. Undoubtedly the chain is spatially staggered away from the ring.

The small increases in  $K_D$  for the 3-alkyl cyclohexanones are probably due to a combination 1,3-diequatorial interactions<sup>8a</sup> in both the cyclohexanones and their cyanohydrins and to the adoption of twist-chain conformations in the isopropyl- and *t*-butyl-substituted ketones. However, the absence of such an effect for the 4-alkyl ketones supports the assumption that

(9) (a) M. I. Batuev, A. A. Akhrem, A. D. Matveeva, A. V. Kamernitskii, and I. N. Nazarov, *Dokl. Akad. Nauk. SSSR*, **120**, 179 (1958); (b) A. V. Kamernitskii and A. A. Akhrem, *Zh. Obshch. Khim.*, **30**, 1511 (1960).

(10) (a) N. L. Allinger and S. E. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962); (b) N. L. Allinger, L. A. Freiberg, and S. E. Hu, *ibid.*, **84**, 2836 (1962).

(11) M. Mori and F. Suda, *Bull. Chem. Soc., Japan*, **36**, 227 (1963).

(12) Cf. A. R. H. Coles and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956); B. C. Lawes, *J. Am. Chem. Soc.*, **84**, 239 (1962).

equatorial substituents in a 4-position have no effect on reaction rates<sup>13a</sup> at least for those reactions that involve a change of hybridization from  $sp^2$  to  $sp^3$ .

### Experimental<sup>14</sup>

**Cyclohexanols.**—4-*t*-Butylcyclohexanol (*cis-trans*) was a gift from the Dow Chemical Co. 2-Ethyl-, 2-*n*-propyl- and 2-*n*-butylcyclohexanols were purchased from the Aldrich Chemical Co.

2-Isopropyl-, 2-*t*-butyl-, 4-ethyl- (b.p. 80–83° at 10 mm.), 2,6-dimethyl- (b.p. 58–62° at 10 mm.), and 2,6-diisopropylcyclohexanol were prepared by hydrogenation of the corresponding phenols over Raney nickel catalyst at 100° and 100 atm.<sup>15</sup>

**Cyclohexanones.**—4-Isopropylcyclohexanone was a commercial sample (Frinton Laboratories). 3-Ethyl-, 3-isopropyl-, and 3-*t*-butylcyclohexanone were synthesized by reaction of cyclohex-2-enone with the appropriate Grignard reagent in the presence of cuprous chloride.<sup>16a</sup> Better yields were obtained using cuprous acetate in tetrahydrofuran.<sup>16b</sup>

(13) (a) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955); (b) L. Munday [*J. Chem. Soc.*, 1413 (1964)] has recently measured the  $K_D$  values of the cyanohydrins of 4-alkylcyclohexanones in 94% ethanol and finds a small decrease in  $K_D$  with increasing size of the alkyl group.

(14) Analyses were by Dr. C. Janssen, Beerse, Belgium.

(15) H. E. Ungnade and A. D. McLaren, *J. Am. Chem. Soc.*, **66**, 118 (1944).

(16) (a) F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941); (b) A. H. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962).

The other cyclohexanones were prepared by chromium trioxide oxidation of the corresponding cyclohexanols.<sup>17</sup>

The ketones were fractionally distilled and then redistilled through an 18-in. spinning-band column. Only center fractions which gave single sharp peaks on gas chromatography using a Craig polyester succinate column at 100–130° were used. (The *cis-trans* mixtures of 2,6-dimethyl- and 2,6-diisopropylcyclohexanone were not completely resolved.) The physical constants are given in Table II. Some of the ketones were characterized by preparing their 2,4-dinitrophenylhydrazones which were purified by chromatography on alumina from benzene: 2-*t*-butyl, m.p. 161° (lit.<sup>18</sup> m.p. 162–162.5°); 2-isopropyl, m.p. 138° (*Anal.* Calcd. for  $C_{15}H_{19}N_4O_4$ : C, 56.40; H, 6.01. Found: C, 56.17; H, 6.20); and 2,6-dimethyl, m.p. 150° (lit.<sup>19</sup> m.p. 149–150°). 2,6-Diisopropylcyclohexanone did not form a 2,4-dinitrophenylhydrazone.

**Dissociation Constants.**—The cyanohydrin dissociation constants were measured in purified 95% ethanol ( $d_{25}^4$  0.805) at  $23 \pm 1^\circ$  as previously described.<sup>20</sup>

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(17) A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960); H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(18) H. L. Goering, R. L. Reeves, and H. H. Espy, *ibid.*, **78**, 4926 (1956).

(19) A. J. Birch, *J. Chem. Soc.*, 1642 (1947).

(20) O. H. Wheeler and E. E. G. de Rodriguez, *J. Org. Chem.*, **26**, 718 (1964).

## N-Nitroamides and N-Nitrocarbamates. II. Amino Acid Derivatives<sup>1</sup>

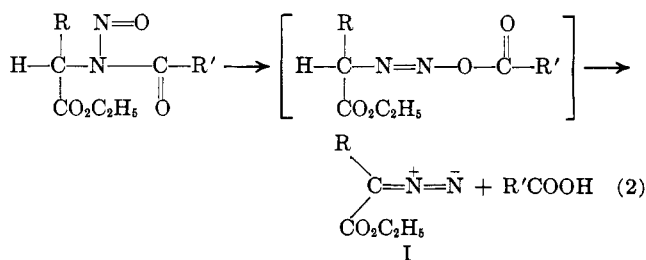
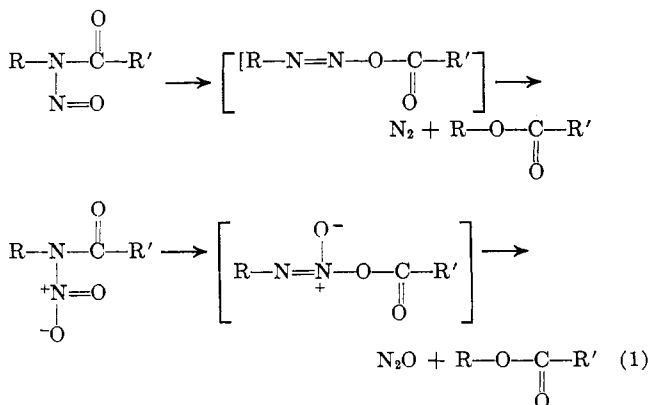
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Nitration of N-carboxy and N-acyl derivatives of ethyl glycinate and ethyl alanate yielded the corresponding N-nitro compounds (II and VI) accompanied in the acyl case by the solvolysis products, ethyl  $\alpha$ -nitratoglycinate and -alanate (V). A better method for the preparation of the N-nitro-N-acyl derivatives (VI) proved to be the reaction of acid chlorides with salts (XI and XII) of ethyl N-nitro glycinate and ethyl N-nitro alanate. These reactions of ambident ions proceed with surprisingly high per cents of N-acylation; only traces of products attributable to O-acylation were formed. Attempts to prepare N-nitrosoimines (III) by the pyrolysis of these N-nitroamide (VI) and N-nitrocarbamate (II) derivatives were unsuccessful.

N-Nitrosoamides and N-nitroamides decompose thermally under similar conditions to give the corresponding esters as products (eq. 1).<sup>2,3</sup> N-Nitrosoamides of amino acid esters, however, decompose to



yield  $\alpha$ -diazo esters I (eq. 2).<sup>4</sup> The present work was designed to find out whether an analogous reaction occurs during the decomposition of N-nitrocarbamates and N-nitroamides of amino acid esters II (eq. 3); it was hoped that nitrosoimines (III) would be formed in this reaction.

### Preparation of the Nitroamides and Nitrocarbamates.

—The N-nitrocarbamates IIa and b were readily prepared by nitration of the parent carbamates with fuming or with 100% nitric acid.<sup>2,5</sup> This procedure, when applied to the corresponding amides IV, on the other hand, yielded only the nitrate esters (Va and b)

(1) Taken in part from a thesis submitted by R. J. Baumgarten to the Faculty of the Graduate School, The Johns Hopkins University, in partial fulfillment of the requirements for the Ph.D. degree.

(2) Paper I: E. H. White and D. W. Grisley, Jr., *J. Am. Chem. Soc.*, **83**, 1191 (1961).

(3) E. H. White, *ibid.*, **77**, 6011 (1955); E. H. White and C. A. Aufdermarsh, Jr., *ibid.*, **83**, 1181 (1961).

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(5) A. Hantzsch and W. V. Metcalf, *Ber.*, **29**, 1683 (1896).