

# Mono- vs. Dialkylation of Acetylacetone with Alkyl Halides through Dialkali Salts. Metallic Cation Effect<sup>1a,b</sup>

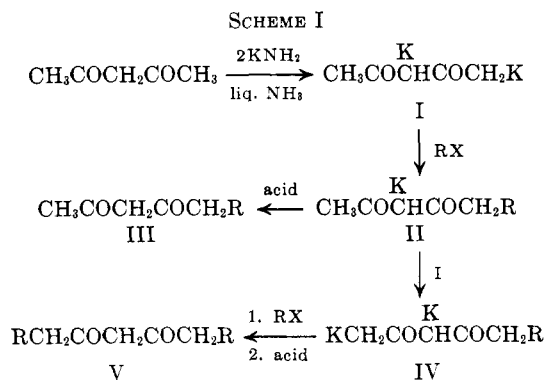
K. GERALD HAMPTON,<sup>1c</sup> THOMAS M. HARRIS, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

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Monoalkylations of dipotassioacetylacetone (I) with molecular equivalents of alkyl halides in liquid ammonia are accompanied by appreciable amounts of dialkylation, whereas those of disodio- and dilithioacetylacetone are not. The dialkylations are due to equilibration between I and the monopotassio salt of the monoalkylation product. Such equilibration does not occur with the sodio salts. Disodioacetylacetone (IX) is recommended for the synthesis of monoalkylation products.

Although treatment of dipotassioacetylacetone (I) with molecular equivalents of alkyl halides has generally afforded the monoalkyl derivatives III in good yields,<sup>2,3</sup> such treatment of I with octyl bromide was observed to afford, besides III, some of the 1,5-dialkyl derivative V, R = octyl.<sup>3</sup> The latter product presumably arose through conversion of monopotassio salt II to dipotassio salt IV by dipotassio salt I, and further alkylation of IV (Scheme I).<sup>4</sup>



Reinvestigation of such monoalkylations of I has now revealed that they are generally accompanied by some dialkylation. More significantly, corresponding monoalkylations of disodio- and dilithioacetylacetone are essentially unaccompanied by dialkylation. In this work the dialkali salts were prepared by direct addition of acetylacetone to the alkali amide in liquid ammonia at  $-78^\circ$  (see Experimental),<sup>5</sup> not through the ammonium salt of acetylacetone<sup>6</sup> employed earlier.<sup>2,3</sup>

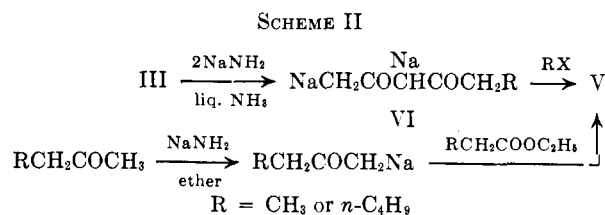
In Table I are summarized the new results obtained with dipotassio salt I and molecular equivalents of four typical alkyl halides. This table shows that each of the halides afforded not only the respective monoalkylation product III in fair to good yields (35–57%) but also a substantial amount of the corresponding dialkylation product V (14–26%).<sup>7</sup> The dioctyl and dibenzyl derivatives V were readily separated from the monoalkylation products III by distillation, and identified

TABLE I  
ALKYLATIONS OF DIPOTASSIO SALT I TO FORM MONO- AND DIALKYLATION PRODUCTS III AND V (SCHEME I)<sup>a</sup>

Alkyl halide	R	Yield, %	
		III	V
Methyl iodide	CH <sub>3</sub>	35, 46	26, 18
Butyl bromide	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	43, 53	16, 14
Octyl bromide	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	51, 57	14, 14
Benzyl chloride	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	41, 39	22, 16

<sup>a</sup> These are the results of two experiments with each alkyl halide.

as the 1,5-dialkyl derivatives.<sup>8</sup> The dimethyl and dibutyl derivatives V<sup>9</sup> were detected and identified as the 1,5-derivatives by gas chromatographic comparison with authentic samples. These samples were prepared both by appropriate further alkylations of monoalkyl derivatives III through their disodio salts VI<sup>10</sup> and by acylations of ketones with esters<sup>11</sup> (Scheme II). Also the dimethyl derivative was shown *not* to be the possible 1,1-derivative, CH<sub>3</sub>COCH<sub>2</sub>COCH(CH<sub>3</sub>)<sub>2</sub>, by gas chromatographic comparison with an authentic sample<sup>11</sup> of the compound. The v.p.c. retention times of the two compounds were substantially different.



That partial conversion of monopotassio salt II to dipotassio salt IV is readily effected by dipotassio salt I (see Scheme I) was demonstrated by preparing a mixture of molecular equivalents of II, R = butyl, and I (mixture A, Scheme III) and adding ethyl bromide<sup>12</sup> after 6 min. Ethylation products VII and VIII were obtained in the ratio of 83:17; when the halide was

(7) It was reported previously that dioctylation of I could be essentially avoided by very slow addition of the octyl halide to the reaction mixture.<sup>3</sup> We have been unable to repeat this observation and, in fact, have obtained slightly more dioctylation on very slow addition of the alkyl halide than on rapid addition. This is consistent with Scheme III.

(8) See ref. 3 and T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

(9) The butyl derivative III, which could not be separated quantitatively by distillation, was not detected in the earlier work<sup>3</sup> where v.p.c. was not used.

(10) These further alkylations probably could have been effected equally well through the dipotassio salts IV, as such alkylations have been carried out previously.<sup>3</sup>

(11) J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).

(12) The use of a halide in which the alkyl group differed from the R group of III and V provided a sensitive method by which even small amounts of proton exchange could be detected.

(1) (a) Supported in part by the National Science Foundation (GP 2274). (b) For a communication on part of this work, see K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 1946 (1963); (c) National Science Foundation Cooperative Fellow, 1961–1962.

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(3) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960).

(4) It is possible that part of the dialkylation product might have arisen through the 1,5-dianion,  $\bar{\text{C}}\text{H}_2\text{COCH}_2\text{CO}\bar{\text{C}}\text{H}_2$ .

(5) Direct addition of acetylacetone to the alkali amide in liquid ammonia at  $-33^\circ$  is not feasible because of the violence of the reaction.

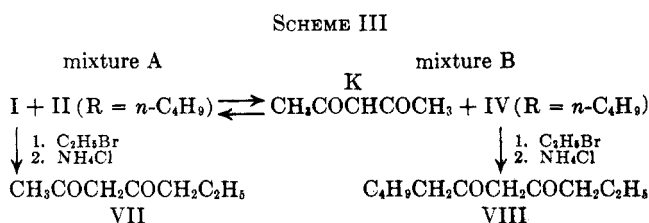
(6) This ammonium salt is deliquescent and reverts to acetylacetone and ammonia on standing at room temperature, making it difficult to store or handle.

TABLE II  
 ALKYLATIONS OF DISODIO SALT IX TO FORM MONOALKYLATION PRODUCTS III (Eq. 1)

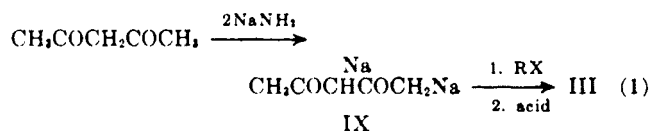
Alkyl halide	R	Yield, %	Diketone III		Copper chelate	
			Obsd.	Lit.	Obsd.	Lit.
Methyl iodide	CH <sub>3</sub>	59, 65	63-66 (36)	155-158 (760) <sup>a</sup>	196-198	197-198 <sup>a</sup>
Ethyl bromide	CH <sub>3</sub> CH <sub>2</sub>	70	79-81 (36)	67.5-70 (20) <sup>a</sup>	167-168	164-165 <sup>a</sup>
Isopropyl bromide	(CH <sub>3</sub> ) <sub>2</sub> CH	66	77-80 (21)	77-80 (21) <sup>b</sup>	155-156	154-155 <sup>b</sup>
Butyl bromide	n-C <sub>4</sub> H <sub>9</sub>	67, 73	100-103 (19)	101-102 (19) <sup>b</sup>	139-140	139-140 <sup>b</sup>
Isobutyl bromide	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	78	97-99 (20)	...	119.5-120.5	...
sec-Butyl bromide	CH <sub>3</sub> CH <sub>2</sub> (CH <sub>3</sub> )CH	78	95-97 (20)	...	105-106.5	...
Benzyl chloride	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	73	158-161 (15)	162-165 (16) <sup>b</sup>	158-160	158.5-160 <sup>b</sup>
Octyl bromide	n-C <sub>8</sub> H <sub>17</sub>	66, 79	154-156 (16)	155-160 (16) <sup>b</sup>	117-118	117-118 <sup>b</sup>

<sup>a</sup> R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945). <sup>b</sup> See ref. 3. <sup>c</sup> These are new compounds (see Experimental).

added after 120 min., the ratio of VII to VIII was 80:20 (Scheme III). Evidently an equilibrium involving the mono- and dipotassio salts is readily established, as similar ratios of VII to VIII resulted when a mixture of molecular equivalents of monopotassioacetylacetone and dipotassio salt IV, R = butyl (mixture B, Scheme III), was treated with ethyl bromide; after 6 and 120 min., these ratios were 73:27 and 81:19, respectively (see Scheme III). Such equilibration appears to account for the relative yields of the mono- and dialkylation products obtained in Table I.



In Table II are summarized the results obtained with disodioacetylacetone (IX) and molecular equivalents of various alkyl halides, including the four that had been employed with dipotassioacetylacetone (I). In contrast to I, disodio salt IX underwent monoalkylation almost exclusively to form the monoalkyl derivatives III in good yields (59-79%). That the monoalkyl derivatives III were essentially free of the corresponding dialkyl derivatives was indicated by v.p.c. Therefore, the disodio salt is clearly to be recommended for the synthesis of monoalkylation products III by this method (eq. 1).

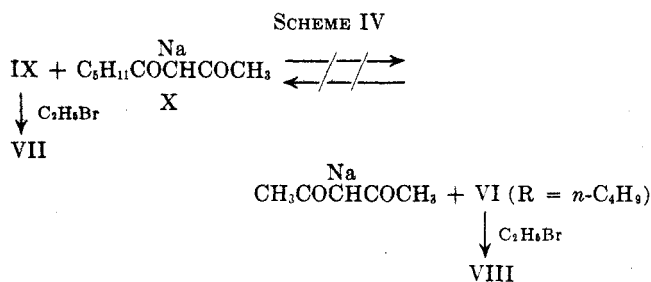


The yields of diketones III by this procedure are often superior to those of Claisen-type acylations of ketones (see Scheme II). Moreover, the products from the latter are sometimes difficult to purify.<sup>13</sup>

It was readily demonstrated that the lack of formation of dialkylation products V in the sodio cases was not caused by any large nucleophilicity difference between disodioacetylacetone (IX) and the disodio salts VI of alkylation products by treatment of an equal molar mixture of IX and VI (R = butyl) with one-half the theoretical amount of ethyl bromide. V.p.c. indi-

cated that the two salts had been alkylated approximately to the same extent.<sup>14</sup>

The possibilities remained that either the sodio salts equilibrated in a manner similar to the potassio salts in Scheme III but that the equilibrium point lay too far on the left for dialkylation to occur significantly, or that equilibrium between the sodio salts was never achieved during the reaction period. That the latter was, in fact, the case was shown by alkylation of a mixture of disodio salt IX and monosodio salt X with ethyl bromide (Scheme IV). Regardless of whether the sodio salt mixture was stirred 6 or 120 min. before treatment with ethyl bromide, only product VII arising from IX was obtained. Moreover, when disodio salt VI, R = butyl, and monosodioacetylacetone were treated similarly, only product VIII arising from VI was observed, even after 120 min. of attempted equilibration (see Scheme IV). Thus, no equilibration of the sodio salts could be demonstrated under these conditions.



Like disodioacetylacetone (IX), dilithioacetylacetone underwent exclusively monoalkylation with butyl bromide; however, the yield of the monoalkyl derivative III, R = butyl, was only 25% even though twice the normal alkylation period was employed. The sluggishness of the butylation of the dilithio salt is rather surprising, since this dilithio salt has been employed successfully in condensation reactions with aliphatic esters<sup>15</sup> and ketones.<sup>16</sup>

In summary, a remarkable cation effect has been observed among the dialkali salts of acetylacetone. Dipotassio salt I has afforded substantial dialkylation, while the dilithio salt was found to be quite unreactive. However, the disodio salt IX afforded excellent yields

(13) See K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

(14) A similar study of the relative nucleophilicities of dipotassio salts I and IV (R = butyl) could not be made because they lacked sufficient solubility in the reaction medium.

(15) S. D. Work and C. R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).

(16) R. J. Light and C. R. Hauser, *ibid.*, **26**, 1716 (1961).

of the monoalkylation derivatives III, uncontaminated by higher alkylation products.

### Experimental<sup>17</sup>

**Alkylations of Dialkali Salts of Acetylacetone.**—A 1-l. three-necked flask containing potassium,<sup>2</sup> sodium,<sup>18</sup> or lithium<sup>19</sup> amide in 700 ml. of liquid ammonia was cooled to  $-78^\circ$  in a Dry Ice-acetone bath while nitrogen was passed over the reaction mixture. A solution of acetylacetone in 20 ml. of ether was added in small portions from a pressure-compensating addition funnel. The cooling bath was removed, the temperature of the reaction mixture allowed to return to normal, and the nitrogen flow stopped. The dipotassio and dilithio salts were partially precipitated while the disodio salt was in solution. After 20 min. (60 min. with dilithioacetylacetone), the alkyl halide in 30 ml. of ether was added dropwise over 10 min. The reaction mixture was stirred for 30 min. (60 min. with dilithioacetylacetone), 250 ml. of ether was added, and the ammonia was evaporated on the steam bath. The ethereal suspension was cooled in ice and a mixture of 100 g. of ice and 30 ml. of cold, concentrated hydrochloric acid was added. The ether layer was separated and the aqueous layer was extracted three times with ether. The combined ethereal solution was dried with anhydrous magnesium sulfate and filtered; the ether was evaporated.

The reactions were carried out with 0.10 to 0.30 mole of acetylacetone. The mole ratios of acetylacetone, alkali amide, and alkyl halide were 1.0:2.0:1.0 with ethyl, isopropyl, isobutyl, and *sec*-butyl bromides, 1.0:1.83:0.83 with benzyl chloride, butyl bromide and octyl bromide, and 1.0:2.25:1.25 with methyl iodide. The yields were based on the dialkali salt or the alkyl halide, which ever was present in the limiting amount.

With dipotassio salt I, some dialkylation was observed in every case (Table I). The mono- and dimethylation products were determined by v.p.c. The butylation products were partially separated by distillation, some of the monobutyl derivative III being obtained pure. The product ratio was determined by v.p.c. The mono- and dibenzylation products were separated by distillation [monobenzyl III distilled at  $158-161^\circ$  (15 mm.) and dibenzyl V at  $188-191^\circ$  (1 mm.)]. The composition of an intermediate fraction was determined by v.p.c. The octylation products were completely separated by distillation, the dioctyl derivative being obtained as a residue product.

In the sodio (Table II) and lithio cases the monoalkylation products III were isolated by distillation. No more than a trace (<2%) of the dialkylation products V was observed although all crude mixtures and distilled products were examined by v.p.c.

The copper chelates were formed by adding a filtered, aqueous solution of copper acetate to about 1.0 g. of diketone. The blue-gray chelates were recrystallized from methanol (see Table II).

7-Methyl-2,4-octanedione [III, R = CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>] from isobutylation of disodio salt IX and its copper chelate were new (see Table II).

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.19.

*Anal.* Calcd. for C<sub>18</sub>H<sub>30</sub>CuO<sub>4</sub>: C, 57.80; H, 8.09; Cu, 16.95. Found: C, 58.09; H, 8.00; Cu, 16.83.

6-Methyl-2,4-octanedione [III, R = CH(CH<sub>3</sub>)C<sub>2</sub>H<sub>5</sub>] from *sec*-butylation of disodio salt IX and its copper chelate were also new (see Table II).

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>: C, 69.19; H, 10.32. Found: C, 68.96; H, 10.27.

*Anal.* Calcd. for C<sub>18</sub>H<sub>30</sub>CuO<sub>4</sub>: C, 57.80; H, 8.09; Cu, 16.95. Found: C, 57.57; H, 7.79; Cu, 16.84.

**Preparation According to Scheme II.**—6,8-Tridecanedione (V, R = butyl) was prepared by adding 14.0 g. (0.09 mole) of 2,4-

nonanedione in ether to 0.18 mole of sodamide in 400 ml. of liquid ammonia and, after 30 min., introducing 12.3 g. (0.09 mole) of butyl bromide in ether. The reaction mixture was worked up as above to afford 12.9 g. (68%) of the diketone, b.p.  $149-152^\circ$  (17 mm.). Its copper chelate, after recrystallization from methanol, melted at  $117-119^\circ$ . A mixture melting point with chelate of the diketone prepared by condensation of ethyl hexanoate and 2-heptanone with sodamide was undepressed.<sup>11</sup>

Similarly, alkylation of disodio-2,4-hexanedione with methyl iodide afforded largely 3,5-heptanedione (V, R = methyl), b.p.  $76-79^\circ$  (30 mm.). Its identity was demonstrated by v.p.c. comparison with the diketone prepared by condensation of ethyl propionate and 2-butanone with sodamide.<sup>11</sup> A detailed description of this dianion reaction, which afforded a small amount of another product, will be presented in a future paper.

**Equilibration of Monopotassio and Dipotassio Salts (Scheme III).**—To a solution of 0.10 mole of potassium amide in 400 ml. of liquid ammonia in an inverse addition flask<sup>20</sup> was added 5.0 g. (0.05 mole) of acetylacetone in 10 ml. of ether. After 30 min., the slurry of dipotassio salt I was stirred and added to a solution of 0.05 mole of monopotassio-2,4-nonanedione (prepared from 7.8 g. of the diketone and 0.05 mole of potassium amide) in liquid ammonia. After the mono- and dipotassio salts had equilibrated for 6 min., 5.5 g. (0.05 mole) of ethyl bromide in ether was added rapidly. The reaction mixture was worked up as above. Gas chromatography indicated that 2,4-heptanedione (VII) and 4,6-undecanedione (VIII) had been formed in a ratio of 83:17. The procedure was repeated, except 2 hr. was allowed for the anions to equilibrate before ethyl bromide was added. Gas chromatography showed that VII and VIII had been formed in a ratio of 80:20.

The equilibrium was approached from the other side by adding dipotassio-2,4-nonanedione (0.05 mole) to monopotassioacetylacetone (0.05 mole). When the mixture of anions was stirred 6 min., alkylation with 0.05 mole of ethyl bromide afforded VII and VIII in the ratio of 73:27, while when the mixture was stirred for 2 hr. the ratio was 81:19.

**Independent Preparation of  $\beta$ -Diketones VII and VIII.**—Diketone VII was prepared above and was designated III, R = ethyl, in Table II.

Diketone VIII was prepared by adding 42 g. (0.27 mole) of 2,4-nonanedione in ether to 0.55 mole of sodium amide in 700 ml. of liquid ammonia and, after 30 min., introducing 30.0 g. (0.28 mole) of ethyl bromide in ether. The reaction mixture was worked up as above to afford 34.5 g. (70%) of VIII, b.p.  $123-126^\circ$  (19 mm.). Its copper chelate, after recrystallization from methanol, melted at  $104-105^\circ$ . A mixture melting point with chelate of the diketone prepared by acylation of 2-heptanone with butyric anhydride using boron fluoride<sup>21</sup> was undepressed.

**Attempted Equilibration of Monosodio and Disodio Salts (Scheme IV).**—To 0.10 mole of sodamide in 350 ml. of liquid ammonia was rapidly added 7.8 g. (0.05 mole) of 2,4-nonanedione in 20 ml. of ether. After 30 min., 6.1 g. (0.05 mole) of monosodioacetylacetone (prepared by reaction of the diketone with metallic sodium) was added from an Erlenmeyer flask through Gooch tubing. After the mixture had stirred 6 min., 5.5 g. (0.05 mole) of ethyl bromide in ether was rapidly added. The reaction mixture was worked up as above. Gas chromatography indicated the presence of acetylacetone and 4,6-undecanedione (VIII) plus a trace of 2,4-nonanedione. No 2,4-heptanedione (VII) was observed. Repeating the procedure, except allowing the mono- and dicarbanions to stir for 2 hr., afforded 68% of VIII but no indication of VII.<sup>22</sup>

Similarly, to 0.05 mole of disodioacetylacetone (IX) in 350 ml. of liquid ammonia was added 8.9 g. (0.05 mole) of monosodio-2,4-nonanedione (prepared from the diketone and sodamide). After 6 min., 5.5 g. (0.05 mole) of ethyl bromide in ether was added and the reaction mixture was worked up as above. Gas chromatography indicated that 2,4-heptanedione (VII) had been formed in 86% yield, but no trace of 4,6-undecanedione (VIII).<sup>23</sup> Repeating this procedure, except allowing the mixture to stir for 2 hr., gave 79% of VII, but again no trace of VIII.<sup>23</sup>

**Relative Nucleophilicity of Disodio Salts IX and VI (R =**

(20) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(21) J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1945).

(22) The yield of VIII was calculated from the relative peak areas of VIII and 2,4-nonanedione.

(23) The yield of VII was calculated from the relative peak areas of VII and nonanedione since the recovery of acetylacetone was incomplete.

(17) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Analyses were by Dr. Ing. A. Schoeller Mikro-Labor, Kronach, West Germany. Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids, and neat liquid between sodium chloride plates for liquids. Vapor phase chromatograms were obtained on an F and M Model 500 gas chromatograph using a 2-ft. silicone gum rubber and a 5-ft. Apiezon L column.

(18) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(19) See W. R. Dunnivant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

**Butyl.**—A solution of acetylacetone (0.10 mole) and 2,4-nonanedione (0.10 mole) in 30 ml. of tetrahydrofuran was added to a suspension of 0.40 mole of sodamide in 600 ml. of ammonia to form disodio salts IX and VI (R = butyl), respectively. The solution was stirred 30 min. and 100 ml. of tetrahydrofuran was added.

After 5 min., 9.2 g. (0.09 mole) of ethyl bromide in 10 ml. of tetrahydrofuran was added over 10 min. After 30 min., 6 g. of ammonium chloride was added and the reaction was worked up as above. V.p.c. of the product showed that the ratio of VII to VIII was 50:50.

## Peptide Synthesis via Oxidation of N-Acetyl- $\alpha$ -amino Acid Phenylhydrazides<sup>1</sup>

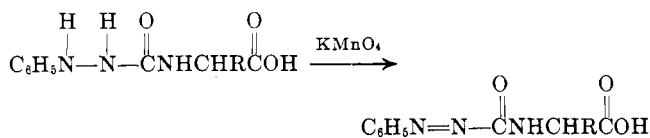
H. BAYARD MILNE AND WARREN KILDAY

Department of Chemistry, Washington State University, Pullman, Washington

Received December 4, 1964

Several N-acyl- $\alpha$ -amino acid phenyldiimides have been prepared by an N-bromosuccinimide oxidation of N-acyl- $\alpha$ -amino acid phenylhydrazides. These amino acid phenyldiimides are strong acylating agents, and may be used in peptide synthesis. A new method for the synthesis of peptides based on the oxidative activation of N-acyl- $\alpha$ -amino acid phenylhydrazides has been developed. The method causes little racemization. Several dipeptides have been prepared by this method.

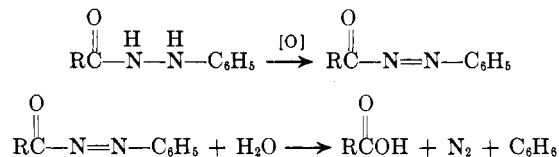
N-Acyl- $\alpha$ -amino acid phenylhydrazides have been prepared in the papain-catalyzed resolution of amino acids<sup>2</sup> and as intermediates in the enzymatic synthesis of dipeptides.<sup>3</sup> We have recently shown that carbobenzoxy (Cbzo) amino acid phenylhydrazides react with alcoholic potassium hydroxide to give N-carboxyphenylhydrazido amino acids.<sup>4</sup> These N-carboxyphenylhydrazido amino acids were oxidized to N-phenylazocarbonyl amino acids (I) by the method Pieroni used to prepare phenylazoformamide.<sup>5</sup>



The N-phenylazocarbonyl amino acids were stable under conditions that promote free-radical reactions. The ultraviolet spectra of their ethanol solutions remained unchanged after 24 hr. of refluxing in the presence of oxygen and after being irradiated 24 hr. with ultraviolet light. On the other hand, they did react with dilute sodium hydroxide solutions giving the amino acids, benzene, and a small amount (5%) of *trans*-azobenzene. The above evidence indicated that the N-carboxyphenylazido amino acids reacted by a heterolytic reaction rather than by a free-radical reaction and suggested the possibility that amino acid phenylhydrazides may be oxidized by the same mechanism.

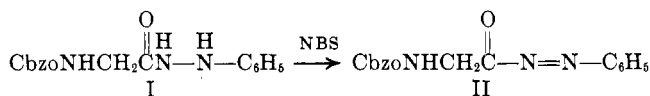
There have been several procedures reported for the removal of the phenylhydrazide group from N-acyl- $\alpha$ -amino acid phenylhydrazides. These all consist of oxidizing the phenylhydrazides in aqueous solutions to give essentially quantitative yields of nitrogen, benzene, and the acylated amino acids or dipeptides.<sup>3,6</sup> The high yields obtained in these oxidations have led to the suggestion<sup>6</sup> that the phenylhydrazides are oxidized first

to the azo compounds and that this is followed by the heterolytic elimination of nitrogen and the addition of water to give the carboxylic acids and benzene.



We now wish to report the isolation of N-acyl- $\alpha$ -amino acid phenyldiimides from the oxidation of N-acyl- $\alpha$ -amino acid phenylhydrazides, by a modification of the method Carpino used to prepare *t*-butyl *p*-bromophenylazoformate.<sup>7</sup> These diimides are acylating agents which can be used in a number of reactions including the synthesis of peptides.

Carbobenzoxyglycylphenylhydrazide (I) was oxidized in dichloromethane with N-bromosuccinimide (NBS) to give a red solution. From this solution was isolated a 83% yield of carbobenzoxyglycylphenyldiimide (II).



That compound II was in fact carbobenzoxyglycylphenyldiimide was indicated by the ultraviolet spectrum:  $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$  450.0 m $\mu$  ( $\epsilon$  112) and 302.5 m $\mu$  ( $\epsilon$  12,800). Also, the infrared spectrum of II was similar to that of the starting carbobenzoxyglycylphenylhydrazide (I): the N-H absorption at 3.08  $\mu$  was reduced, there was a shift in the amide carbonyl peak from 5.43 to 5.85  $\mu$ , and the peak at 6.23  $\mu$  (which has been attributed to an anilino group) disappeared.<sup>6</sup>

Carbobenzoxyglycylphenyldiimide was very unstable. The infrared spectrum, the ultraviolet spectrum, and the melting point changed after standing a few hours at room temperature. Analysis indicated a loss of nitrogen during the spontaneous decomposition. However, for 3 days carbobenzoxyglycylphenyldiimide was stored at *ca.* -80° without noticeable changes in the spectra or the melting point; a satisfactory analysis was obtained for this sample. The ultraviolet spectra of dilute solutions of carbobenzoxyglycylphenyldiimide in dichloromethane remained unchanged

(1) This investigation was supported in part by funds provided for biological and medical research by the State of Washington Initiative Measure No. 171. Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963.

(2) H. B. Milne and C. M. Stevens, *J. Am. Chem. Soc.*, **72**, 1742 (1950); E. L. Bennett and C. Niemann, *ibid.*, **72**, 1800 (1950); H. B. Milne and C. H. Peng, *ibid.*, **79**, 645 (1957).

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