by the NMR analysis, were as follows:

fraction	wt, g	mol % 8a	mol % 12
7	0.25	0	100
8	0.62	5	95
9	0.41	62	38
10	0.29	93	7
11	0.25	100	0
12	0.21	100	0

Fraction 7, a liquid, was pure 5-ethyl-3-phenyl-1,2,4-oxadiazole (**12**):[15] *m/e* 174.2, calcd M^+ = 174.1; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.6 Hz, 3 H, CH_3), 2.88 (q, J = 7.6, 2 H, CH_2), 7.42 (m, 3 H, Ar H), 8.10 (m, 2 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 10.5 (CH_3), 20.0 (CH_2), 126.8, 127.1, 128.5, 130.7, 168.0 (C-3), 180.4 (C-5); IR (neat) 3060, 3015, 2980, 2935, 2875, (all C-H), 1591, 1570, 1475, 1445, 1360, 1342, 1305, 902, 780, 714, 690 cm^{-1}.

Fractions 11 and 12 both formed white crystals of 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**) identical in mp, mmp, ^1H and ^{13}C NMR, and IR with an authentic sample.[10]

Fractions 7–12, comprising 88% recovery by weight of the original crude product, represented a 41% yield of **8a** and a 32% yield of **12**, for a total yield of 73% of combined oxadiazoles.

B. Reaction of Benzonitrile, Nitroethane, Ammonium Propionate, and Propionic Acid. In a parallel experiment employing 2.00 g (19 mmol) of benzonitrile, 14.2 g (156 mmol) of ammonium propionate, 52.3 g (700 mmol) of nitroethane, and 24.8 g (335 mmol) of propionic acid, refluxed (N_2) 72 h, there was obtained a 20% yield of **8a** and a 34% yield of **12**; total yield 54% of oxadiazoles.

Reaction of 1-Nitropropane with Ammonium Acetate in Acetic Acid. A. Formation of Propionic Acid. A solution of 14.2 g (184 mmol) of ammonium acetate in 62.5 g (702 mmol) of 1-nitropropane and 25 mL (436 mmol) of acetic acid was refluxed under N_2 for 72 h. The initially colorless solution gradually turned to a deep amber-yellow. Gas chromatographic analysis of the crude reaction mixture run isothermally at 30 °C on the HP 5880A capillary column showed the following fractions [retention time, (compound) relative area]: 0.75 min (HOAc) 1.09; 1.32 min (1-nitropropane) 3.97; 1.67 min (propionic acid) 1.39; 2.49 min (unknown) 0.74; 3.27 min (unknown) 0.86. Since all of the propionic acid must have originated from the 1-nitropropane, the yield of propionic acid was 26%.

B. Trapping of Hydroxylamine. A mixture of 11.11 g (61 mmol) of benzophenone, 10.45 g (136 mmol) of ammonium acetate, 17.8 g (200 mmol) of 1-nitropropane, and 26.2 g (436 mmol) of acetic acid was refluxed under N_2 for 10 h. The resulting pale yellow solution was cooled and then diluted with 150 mL of water to yield a white precipitate, which was thoroughly washed with H_2O and air-dried. One recrystallization from 95% ethanol gives 7.17 g (60% yield) of benzophenone oxime, mp 137–139 °C. One more crystallization gave pure oxime, mp 139.5–141 °C, identical (mp, mmp, and IR) with an authentic sample[16]

Acknowledgment. We are grateful to the Department of Chemistry of Lehigh University for support of this work and also thank Dr. Uli Hacksell for helpful discussions.

Registry No. **1a**, 100-52-7; **1b**, 93-02-7; **4a**, 100-47-0; **4b**, 5312-97-0; **8a**, 1198-98-7; **8b**, 95124-65-5; **8c**, 69792-78-5; **8d**, 95124-66-6; **8e**, 81386-30-3; **8f**, 95124-67-7; **8g**, 95124-68-8; **9**, 1199-00-4; **12**, 10364-68-8; benzamidoxime, 613-92-3; acetamidoxime, 22059-22-9; *O*-benzoylacetamidoxine, 22046-72-6; 4-methylbenzaldehyde, 104-87-0; ammonium propionate, 17496-08-1; ammonium acetate, 631-61-8; nitroethane, 79-24-3; benzoyl chloride, 98-88-4; 2,4-dichlorobenzaldehyde, 874-42-0; 3-chlorobenzaldehyde, 587-04-2; 3,5-dimethoxybenzaldehyde, 7311-34-4; 4-formylbenzoic acid, 619-66-9; 1-nitropropane, 108-03-2; benzophenone, 119-61-9; benzophenone oxime, 574-66-3.

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(16) Lackman, A. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 70.

2,4-Dinitrophenylhydrazones: A Modified Method for the Preparation of These Derivatives and an Explanation of Previous Conflicting Results

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Conventional methods for forming 2,4-dinitrophenylhydrazones (2,4-DNPH's) usually leave traces of acids complexed with the derivatives and cause variable melting points. A bicarbonate wash of the 2,4-DNPH crystals removes the acid and reproducibly gives derivatives with previously reported or higher melting ranges. 2,4-DNPH's of hydroxy ketones previously unattainable by the standard methods were prepared by this method. NMR studies showed that traces of acids catalyze the syn–anti isomerization or the dehydration of the products and thus cause the melting point anomalies.

Characterization of aldehydes and ketones through their 2,4-dinitrophenylhydrazone (2,4-DNPH) derivatives, one of the most important qualitative methods in organic analyses, was first introduced by Allen[2] and Brady.[3] Although some minor modifications[4-6] have been reported, Allen and Brady's procedures are still the standard methods used for the preparation of these derivatives.[7-10] Brady's method has been used more widely because of the greater solubility of 2,4-dinitrophenylhydrazine in sulfuric acid. However, this method often gives derivatives with low and ambiguous melting ranges and several recrystal-

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(2) Allen, C. F. H. *J. Am. Chem. Soc.* **1930**, *52*, 2955.
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(8) Shriner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. "The Systematic Identification of Organic Compounds", 6th ed.; Wiley: New York, 1980.
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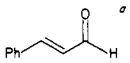
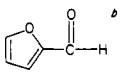
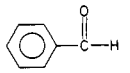
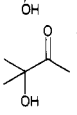
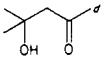
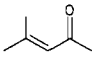
Table I. 2,4-Dinitrophenylhydrazones of Aldehydes

		mp, °C				
		lit. method		modified method		
entry	aldehyde	crude	recryst	crude	recryst	lit. mp, °C
1		125–132	145–148	160–164	166–169	168.5
2		128–132	144–147	141–142	148–150	154
3		109–111	113–116	120–123	125–126	117
4	 [a]	171–173	246–247	200–202	251–254	255
5	 [b]	169–171	198–200	206–207	214–215	214
6		185–190	231–232	237–238	237–238	237

[a,b] The solvent of recrystallization was ethanol except acetonitrile for entry 4 and 1,4-dioxane for entry 5.

Table II. 2,4-Dinitrophenylhydrazones of Ketones

		mp, °C				
		lit. method		modified method		
entry	ketones	crude	recryst	crude	recryst	lit. mp, °C
1		119–120	124–125	124–125	125–126	126
2		136–138	141–142	140–141	144–145	145
3		111–114	120–121	120–122	123–124	120
4		190–192	237–238	242–243	243–244	240
5		138–141	143–145	140–142	143–145	146
6	 [a]	245 dec	>322	105–245 dec	101–102	318 (bis)
7	 [b]	165–170	183–186	144–146	145–147	140[c]
8	 [d]	137–140	140–142	147–148	156–158	157–159
9		143–150	200–203	192–197	202–203	203

[a-d] The solvent of recrystallization was 95% ethanol except an aqueous solution of ethanol was used for entries 7 and 8. For *a*, *b*, and *d* see ref 20, 21, and 23. For *c* see ref 22.

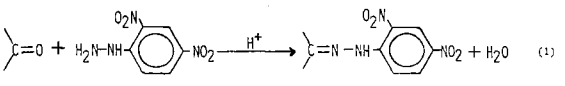
lizations are necessary to reach the reported melting ranges. Moreover, standard methods usually cannot be used for the preparation of derivatives of hydroxy carbonyl compounds.

In reviewing the literature we found that for a given compound different investigators employing these methods often obtained derivatives with varying melting ranges and other physical properties. For example, three melting points, 148 °C, 154 °C, and 156 °C, are reported for the 2,4-DNPH of propanal.[7-9] Six different melting ranges have been reported for acetaldehyde.[11-18] This paper reports a modified method for the preparation of these derivatives which overcomes the aforementioned limitations.

(11) Karabatsos, G. J.; Shapiro, B. L.; Vane, F. M.; Fleming, J. S.; Ratha, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 2784 and references therein.

Results and Discussion

Brady's method, the most commonly used procedure, involves treatment of the carbonyl compound with a solution of 2,4-dinitrophenylhydrazine in ethanol and sulfuric acid followed by recrystallization of the precipitate (eq 1).

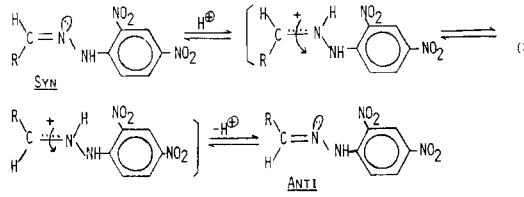


In the modified method, the precipitate is collected on a fritted glass funnel, washed with a 5% sodium bicarbonate solution and water, and then recrystallized. Vigorous foaming occurs when base is added, indicating the presence of an appreciable amount of acids in the crystals. A number of aldehyde and ketone derivatives were made by the modified as well as by the literature method by using either freshly prepared or 2-month-old reagents. The

melting range of each derivative was recorded before and after one recrystallization. Tables I and II show the data for aldehydes and ketones, respectively.

As is shown, the modified method gives higher melting derivatives than the literature procedure, and the melting ranges of the products are nearly the same or higher (entry 3 in Table I and entries 3, 4, and 7 in Table II) than those reported in the literature. It should be noted that the literature melting ranges are usually recorded on samples which have been recrystallized more than once. The differences between the melting ranges are much more pronounced when they are determined on the crude products, i.e., 35°, 29°, 37°, and 52° for entries 1, 4, 5, and 6, respectively, in Table I and 52° for entry 4 in Table II.

We believe that the low and variable melting ranges of the derivatives obtained by the literature method are mainly due to syn–anti isomerizations of the products. Traces of acids remain even in the recrystallized samples and catalyze the syn–anti isomerization reactions (see eq 2) before or during the melting process and thus change



(2)

the melting behaviors of the derivatives. When the acid is removed by a base wash, no interconversion of the isomers occurs during melting (or in the solutions) and the melting point is stabilized.

It was also found that the use of freshly prepared reagents is not necessary as suggested in some reports.[8] The melting ranges of derivatives were nearly the same whether using 2-month-old or freshly prepared reagents.

Acetaldehyde 2,4-DNPH and Its NMR and Differential Scanning Calorimetric (DSC) Analyses. More than six different melting ranges have been reported for the 2,4-DNPH of acetaldehyde:[11-18] Bryant[12] reported two derivatives, mp 149 °C and 168.5 °C; Ingold[13] prepared two forms, mp 146 °C and 165 °C; Allen[15] reported one derivative, mp 157 °C; and Clark[17] obtained two modifications, mp 165 °C and 166 °C. Van Duin[18] was the first to assign anti and syn geometries to two modifications with mp 93–94 °C and 167–168 °C, respectively. Karabatsos[11] prepared several forms of 2,4-dinitrophenylhydrazone derivatives of acetaldehyde, mp 145–146 °C, 157–158 °C, 160–161 °C, and 165–166 °C, studied them by nuclear magnetic resonance spectroscopy, and found that they are all the syn isomer except the product of 145–146 °C which has 5% of the anti isomer. He concluded that the formation of the syn isomer is highly kinetically favored. Thermodynamically the syn isomer is also favored but in a ratio of 2 to 1. Prolonged standing or the addition of acid affected the syn–anti equilibration in solutions.

In our hands the 2,4-DNPH of acetaldehyde prepared in the conventional way and recrystallized once from ethanol (A) had mp 145–148 °C. Crystals obtained by the modified method and recrystallized once (B) had mp 165–168 °C. The NMR of sample A showed two CH_3 doublets (δ 2.1, 2.04[11]) in a ratio of 2 to 1 for the syn and anti isomers, respectively. B proved to be the pure syn isomer (δ 2.1). The NMR of sample A after melting showed nearly the same ratio of syn to anti (2 to 1) but that of melted B showed no change (pure syn). As expected, on the basis of Karabatsos' work,[11] addition of a small amount of sulfuric acid to sample B caused the isomerization to occur, giving a 2 to 1 ratio of syn to anti. When crystals of sample A were washed with the bicarbonate solution, the melting range rose to 165–168 °C and the NMR showed it to be the syn isomer as observed for sample B. Differential scanning calorimetric analysis gave a single peak with a melting range of 145–148 °C for sample A and a single peak with a melting range of 164.4–167.9 °C for base-washed A. Based on these results, it appears that both of the methods produce the syn isomer, but since there is no acid present in samples B and base-washed A, the isomerization to the anti form does not take place in their melts or in their $CDCl_3$ solutions. While in sample A traces of acid present catalyze the syn–anti equilibrations. The results also indicate that traces of acids remain even in the recrystallized samples of A as shown by the NMR and melting data. It should also be noted that the melting behavior of sample A is similar to that of a pure single compound. This may be due to the fast equilibration of the isomers before melting and then their aggregation as a eutectic mixture.

2,4-DNPH Derivatives of Hydroxy Ketones. It has been reported that due to side reactions the standard method is not applicable to the preparation of hydroxy carbonyl 2,4-DNPH's.[5,7,19] We found that the 2,4-dinitrophenylhydrazone of 3-hydroxy-3-methyl-2-butanone prepared by the conventional method (A) gave mp 183–186 °C and that prepared by the modified method (B) had mp 145–147 °C. TLC and NMR showed A and B to be the same. A bicarbonate wash of A lowered its melting range to that of B. The NMR spectrum of melted A showed it to be a mixture of the hydroxy ketone 2,4-DNPH and its dehydrated product. Differential scanning calorimetric analysis (DSC) gave two peaks for sample A; one at 127–134 °C due to the dehydration process, and another at 184–191 °C corresponding to the melting range of the dehydrated product. Sample B gave only a single peak at 143–147 °C, showing no dehydration reaction. These observations point out that samples A and B are the same except for the presence of a small amount of acid in A which causes the dehydration reaction during melting and consequently changes the melting range.

The 2,4-DNPH of 3-methyl-3-butenone (the dehydrated product) was independently prepared in 82% yield as a

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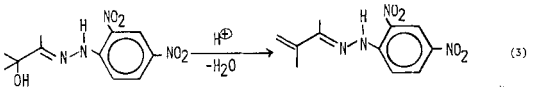
(17) Clark, G. L.; Kaye, W. J.; Parks, T. O. *Ind. Eng. Chem., Anal. Ed.* **1946**, *18*, 310.
(18) Van Duin, H. Thesis, Free University of Amsterdam, 1961.
(19) Braddock, L. I.; Garlow, K. Y.; Grim, L. I.; Kirkpatrick, A. F.; Pease, S. W.; Pollard, A. J.; Price, E. F.; Reismann, T. L.; Rose, H. A.; Willard, M. L. *Anal. Chem.* **1953**, *25*, 301.
(20) The reagent and ketone were mixed, water was added to cloudiness, and the solution was allowed to stand overnight. The precipitate was filtered off and the general procedure was followed: ^1H NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 7 Hz), 2.06 (s, 3 H), 2.7 (b, 1 H disappeared with D_2O), 4.5 (q, 1 H, J = 7 Hz), 7.8 (d, 1 H, J = 10 Hz), 8.26 (dd, 1 H, J = 10 and 3 Hz), 9.0 (d, 1 H, J = 3 Hz).
(21) To precipitate the product, water was added to the reaction mixture, and the solution was stirred for 45 min and then filtered: ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H), 2.1 (s, 3 H), 3.1 (b, 1 H), 7.73 (d, 1 H, J = 10 Hz), 8.25 (dd, 1 H, J = 10 and 3 Hz), 9.0 (d, 1 H, J = 3 Hz).
(22) Vartanyan, S. A.; Badamyan, S. O.; Agababyan, R. G. *Izv. Akad. Nauk. Arm. SSR, Khim. Nauki* **1964**, *17(2)*, 191 (Russian).
(23) The product was precipitated as in ref 21: ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H), 1.57 (s, 1 H disappeared with D_2O), 1.96 (s, 1 H disappeared with D_2O), 2.2 (s, 3 H), 2.6 (s, 2 H), 7.8 (d, 1 H, J = 10 Hz), 8.5 (dd, 1 H, J = 10 and 3 Hz) and 9 (d, 1 H, J = 3 Hz). When the mixture of 4-methyl-4-hydroxy-2-pentanone was heated at 60 °C for 15 min, the dehydrated product, 2,4-DNP of mesityl oxide, was obtained as a red crystalline material.

red crystalline material, mp 183–185 °C by refluxing an ethanolic solution of 2,4-DNP of the hydroxy ketone in the presence of sulfuric acid for 1 h (eq 3): ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 2.2 (s, 3 H), 5.44 (s, 1 H), 5.54 (s, 1 H), 7.91 (d, 1 H, J = 10 Hz), 8.28 (dd, 1 H, J = 10 and 3 Hz), 9.07 (d, 1 H, J = 3 Hz).



We were also able to prepare the 2,4-DNPH of 4-hydroxy-4-methyl-2-pentanone by the modified method as a yellow crystalline compound which upon one recrystallization gave a pure product with a melting range of 156–158 °C. Shine[5] has prepared this derivative as orange crystls by a method using acetic acid in a diglyime solution and obtained a pure sample but by four successive recrystallizations.

The 2,4-DNPH of 3-hydroxy-2-butanone could be obtained as orange crystals, mp 101–102 °C, only by the modified method. The crude product also contained a small amount of a high-melting (>322 °C) material. The standard method gave only the high-melting product.

Conclusion

The 2,4-dinitrophenylhydrazone crystals of a carbonyl compound are the same whether they are made by the conventional or the modified method. The discrepancies observed in the melting ranges, nuclear magnetic resonance spectra, etc., are due to transformations which occur during the measurements of these physical properties. Without the base wash, traces of acids remain in the crystals and catalyze transformations such as syn–anti isomerization or dehydration.

Experimental Section

2,4-Dinitrophenylhydrazine was purchased from Eastman Kodak. Aldehydes and ketones were available from Aldrich and Fisher. Melting ranges are uncorrected and were recorded on a Thomas-Hoover melting point apparatus. Differential scanning calorimetric (DSC) data was obtained on a Perkin-Elmer DSC-2 instrument. ^{1}H NMR spectra were recorded on a Varian T-60 instrument. Infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer.

Preparation of 2,4-Dinitrophenylhydrazine Solution. This reagent was made according to the procedure of Shriner et al.[8] 2,4-Dinitrophenylhydrazine, 10 g, was dissolved in 50 mL of concentrated sulfuric acid and then added to a solution of 70 mL of water in 250 mL of 95% ethanol. A portion of the reagent was used immediately and another portion was allowed to stand for about 2 months and used as the old reagent.

Preparations of 2,4-Dinitrophenylhydrazones–General Procedures. The 2,4-DNPH derivatives for most of the aldehydes and ketones were prepared according to the procedure described for 3-methylbutanal. Slight variations in the general procedure for the preparations of derivatives of hydroxy ketones and enones and NMR data are given in the footnotes.

2,4-Dinitrophenylhydrazone of 3-Methylbutanal. A solution of 3-methylbutanal, 1.0 g, in 40 mL of 95% ethanol was added to 35 mL of the freshly prepared reagent. The product precipitated immediately as a yellow crystalline material which was filtered off by suction on a fritted disk glass funnel. About half the material was removed and treated according to the literature (standard) method by allowing part of the material to dry at room temperature (mp 109–111 °C, crude) and part was recrystallized from 95% ethanol (113–116 °C, recrystallized). The remainder of the material on the funnel was washed with about 20 mL of a 5% aqueous solution of sodium bicarbonate (modified method), stirred with a glass rod or a spatula, and when foaming was subsided, filtered and then washed with 20 mL of distilled water. Part of the crystals were allowed to dry (mp 113–116 °C, crude), and the remainder was recrystallized from 95% ethanol (mp 125–126 °C, recrystallized).

Acknowledgment. We are indebted to professor B. N. Storhoff, Chairman of the Department of Chemistry, for his support and to professors T. L. Kruger, L. R. Sousa, and Dr. N. C. Cook for their encouragement and suggestions in the course of this investigation. We also thank Mary E. R. Potter of RCA, Indianapolis, IN, for the DSC analyses.

Registry No. CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $(CH_3)_2CHCH_2CHO$, 590-86-3; PhCH=CHCHO, 104-55-2; PhCHO, 100-52-7; CH_3COCH_3, 67-64-1; $CH_3CH_2COCH_3$, 78-93-3; $(CH_3)_2CHCOCH_3$, 563-80-4; $C_6H_5COCH_3$, 98-86-2; $CH_3CH(OH)COCH_3$, 513-86-0; $(CH_3)_2C(OH)COCH_3$, 115-22-0; $(CH_3)_2C(OH)CH_2COCH_3$, 123-42-2; $(CH_3)_2C$=CHCOCH$_3$, 141-79-7; (2,4-dinitrophenyl)hydrazine, 119-26-6; sodium bicarbonate, 144-55-8; 2-furancarboxaldehyde, 98-01-1; cyclohexanone, 108-94-1; acetaldehyde DNP, 1019-57-4; propanal DNP, 725-00-8; cinnamaldehyde DNP, 1237-69-0; 2-furancarboxaldehyde DNP, 2074-02-4; acetone DNP, 1567-89-1; 2-butanone DNP, 958-60-1; 3-methyl-2-butanone DNP, 3077-97-2; acetophenone DNP, 1677-87-8; cyclopentanone DNP, 2057-87-6; cyclopentanone, 120-92-3; 3-methylbutanal DNP, 2256-01-1; benzaldehyde DNP, 1157-84-2; 3-hydroxy-2-butanone DNP, 35015-94-2; 3-hydroxy-3-methyl-2-butanone DNP, 52123-60-1; 4-hydroxy-4-methyl-2-cyclopentanone DNP, 95122-53-5; 4-methyl-3-penten-2-one DNP, 964-83-0.