the major product was phenalanone (3). While small amounts of 3 can be obtained from the $LiAlH_4/AlCl_3$ reduction of 2,[3] the best known synthesis is the cyclization of β-1-napthylpropionic acid using anhydrous hydrogen fluoride.[2] The latter route is inconvenient and limited to small scale reactions because of the precautions necessary when using anhydrous HF. This cyclization procedure also gives the isomeric mixture, phenalanone/4,5-benzhydrindone.

We have prepared 3 in ~30% yield using 2 equiv of TMDS and 2 in acidified 95% ethanol in the presence of catalytic amounts of palladium. Although the yield is modest, the simple reaction conditions, ready availability of these inexpensive reagents and ease of product isolation make this an attractive synthesis of 3. PMHS was found to be less effective than TMDS, giving yields of ~20%. No improvement in this yield was observed over the range of 1.1 to 4.4 equiv[9] of PMHS to 2.

Experimental Section

Phenalenone was prepared by the method of Fieser and Hershberg.[10] Benzene and hexane were stirred over H_2SO_4, distilled, and stored in brown bottles until needed. Tetrahydrofuran was refluxed over sodium metal and benzophenone until the blue color of benzophenone ketyl was observed, and then it was distilled just before use. NMR spectra were recorded on a Varian EM-390 spectrometer and correspond to those reported in the literature.[11] Melting points were obtained on a Thomas-Hoover Mel-Temp melting point apparatus and are uncorrected. All glassware was oven-dried, assembled hot, and cooled under a stream of dry nitrogen. The reactions were run under a dry nitrogen atmosphere unless otherwise noted. Florisil was placed in a round-bottom flask, put under vacuum, and purged with N_2. This cycle was repeated several times just before use.

DIBAL-H Reduction of Phenalenone. Excess DIBAL-H (11.2 mL, 1 M in hexane; Aldrich Chemical Co.) was added to a benzene solution (~20 mL) of 2 (1.0 g, 5.5 mmol) over a 30-min period at room temperature. The resulting dark red solution was heated to reflux overnight and cooled to room temperature, and excess DIBAL-H was quenched by the dropwise additon of 2 mL of a saturated NH_4Cl solution. Hexane (50 mL) was added and the mixture filtered. The salts were washed with 1 × 50 mL of hexane. The hexane layers were combined, washed with 1 × 50 mL of the NH_4Cl solution, and dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The oil was deposited on Florisil (100–200 mesh; Matheson, Coleman and Bell) and placed atop a 10 × 5 cm column of Florisil. Elution was with 250 mL of hexane; 50-mL fractions were collected. Fractions 2–4 contained 1 (0.40 g, 2.41 mmol), mp 70–75 °C (lit. mp 85 °C).[2] The column was then eluted with 50 mL of 1:1 hexane/ether, and 2 (0.52 g, 2.88 mmol) was recovered. The isolation of 2 from the product mixture was confirmed by comparison of its melting point and IR and NMR spectra with those of an authentic sample.

9-Borabicyclononane (9-BBN) Reduction of Phenalenone. Excess 9-BBN (6 mL, 0.5 M in THF; Aldrich Chemical Co.) was added slowly to a THF solution (~15 mL) of 2 (0.50 g, 2.8 mmol) at 0 °C. The solution was stirred overnight at room temperature. Excess 9-BBN was quenched with 0.5 mL of methanol.[12] NaOH (3 M, 1 mL) and 2 mL of 30% H_2O_2 were added, and the mixture was heated to reflux for 1 h. Anhydrous K_2CO_3 was added to saturate the aqueous phase; the organic layer was decanted, and the K_2CO_3 was extracted with 3 × 20 mL of ether. The organic layers were combined, washed with 4 × 30 mL of H_2O, and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the oil was deposited on Florisil. This was placed atop a 10 × 2 cm Florisil column. Elution was with 100 mL of hexane. This fraction contained 1 (0.20 g, 1.20 mmol) as pale yellow crystals, mp 65–75 °C. The column was then eluted with 50 mL of 1:1 hexane/ether, and crude 2 (0.26 g, 1.4 mmol, 52%) was obtained.

Purification of Phenalene. Analysis of the chromatographed samples of 1 from the above reductions by NMR spectroscopy showed that the impurities were saturated hydrocarbon residues. However, if 1 must be further purified, the following procedure[13] is recommended.

1 was dissolved in sufficient pentane (~6 mL/g) so that when the resulting solution was chilled to dry ice temperature, a filterable slurry was formed. During the chilling period (~30 min), a Büchner funnel wrapped in aluminum foil and a stoppered flask containing pure solvent were chilled in powdered dry ice. Immediately before use, a conventional filtration assembly was set up using the chilled funnel. The slurry of 1 was filtered and washed with the chilled solvent. An inverted funnel connected to a dry N_2 source was placed over the Büchner funnel, and suction was continued until the apparatus reached room temperature. Phenalene was obtained as a white powder (mp 83–84 °C), and no hydrocarbon residue was visible in the NMR spectrum. The structure was confirmed by comparison of its NMR spectrum [(in $CDCl_3$) δ 2.5–4.1 (m, 8 H), 6.1 (s, 2 H)] with published data.[11]

We have carried out this procedure many times, including runs on as much as 5 g of 2, and in all cases the net yields of 1 exceeded 80% based on recovered 2.

TMDS Reduction of Phenalenone. Palladium on charcoal (5%) (10 mg; Matheson, Coleman and Bell) and a few drops of 12 M HCl were added to a solution of 2 (5.0 g, 27.7 mmol) in 95% ethanol, and the mixture was heated to reflux. TMDS (11.1 mL, 62.3 mmol) was added by syringe through the condenser at a rate to maintain the reflux, which was continued for 1 h after the addition was complete. The mixture was filtered, and the volatile products were removed by rotary evaporation to give ~3 mL of an orange-brown oil. This was dissolved in 50 mL of ether and washed with 3 × 50 mL of H_2O. The H_2O layers were combined and washed with 1 × 50 mL of ether. The ether layers were combined, washed with 1 × 50 mL of a saturated NaCl solution, dried (Na_2SO_4), and filtered, and the ether was removed by rotary evaporation. The residual oil was deposited on alumina (neutral, Alcoa F-20) and placed atop a 25 × 5 cm column of alumina. The product was eluted with 1:1 hexane/ether; 100-mL fractions were collected. Fractions 4 and 5 contained 3 (1.4 g, 7.9 mmol, 28%), mp 80–81 °C (lit.[2] mp 82.6–83.2 °C). No phenalenone was detected in the product mixture. The structure of 3 was confirmed by its NMR [(in $CDCl_3$) δ 1.9–2.7 (m, 6 H), 6.5–7.2 (m, 4 H)] and IR [(in CCl_4) 1700 cm^{-1} (C=O)] spectra, which compare well with the published spectra.[11]

Acknowledgment. Financial support from the Research Corporation is gratefully acknowledged.

Registry No.—1, 203-80-5; 2, 548-39-0; 3, 518-85-4.

References and Notes

(1) D. H. Reid, *Q. Rev., Chem. Soc.*, **19**, 274 (1965).
(2) V. Boekelheide and C. E. Larrabee, *J. Am. Chem. Soc.*, **72**, 1245 (1950); L. F. Fieser and M. D. Gates, Jr., *Ibid.*, **62**, 2335 (1940).
(3) R. M. Pagni and C. R. Watson, Jr., *Tetrahedron*, **29**, 3807 (1973).
(4) E. C. Ashby and J. Prather, *J. Am. Chem. Soc.*, **88**, 729 (1966).
(5) L. R. Snyder, *J. Chromatogr.*, **12**, 488 (1963).
(6) R. Pettit, *Chem. Ind. (London)*, 1306 (1956).
(7) H. Felkin, E. Jampel-Costa, and G. Swierczewski, *J. Organomet. Chem.*, **134**, 265 (1977).
(8) E. Dunkelblum, *Tetrahedron*, **28**, 3879 (1972).
(9) J. Lipowitz and S. A. Bowman, *Aldrichimica Acta*, **6**, 1 (1973).
(10) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 1658 (1938).
(11) H. Prinzbach, V. Freudenberg, and V. Scheidegger, *Helv. Chim. Acta*, **50**, 1087 (1967).
(12) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **42**, 1197 (1977).
(13) I. A. Kaye, *J. Chem. Educ.*, **46**, 696 (1969).

Studies with Amino Acids. 1. Synthesis of Valine

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The synthesis of amino acids by the Strecker[1] method is well known and offers one of the best routes available for the preparation of these important compounds. Several modifications have been introduced which increase the yields and safety of the preparation. The method has been of great value in the preparation of carboxyl-labeled amino acids starting with ^{13}C and ^{14}C cyanide, but difficulties arise when synthesizing amino acids labeled with ^{11}C. Compounds labeled with this isotope have great potential for in vivo metabolism studies using nuclear medicine techniques. The short half-life of ^{11}C (20 min) requires considerable modification in existing procedures. The method presented here proceeds smoothly and rapidly without the production of any interfering byproducts. The procedure is described for the synthesis of valine (Scheme I), but may be used for the preparation of other amino acids.

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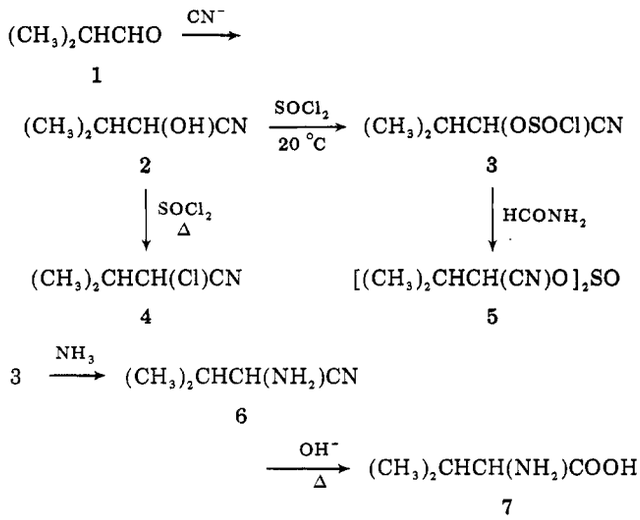
Scheme I



The preparation of the cyanohydrin **2** was carried out using anhydrous ether as solvent, although no special precautions were used to exclude traces of water. Under these conditions the aldehyde is quantitatively converted to a colorless product of very high purity. It distills without decomposition at 0.1-mm pressure. Water is undoubtedly involved in the reaction, but only trace amounts seem necessary to drive it forward. The potassium cyanide contains some moisture, leading to the reaction:

$$CN^- + H_2O = HCN + OH^-$$

$$OH^- + HAc = Ac^- + H_2O$$

Under the conditions described the acetate ion is removed as KAc and the reaction goes to completion. The presence of 1 molar equiv of water did not affect the yield, but the formed potassium acetate became heavy and pasty, making stirring difficult. A large volume of ether facilitates stirring and isolation of the product. The IR spectra of the cyanohydrin before and after distillation were identical, showing a weak band at 2260 cm^{-1} (CN), a broad intense band at 3440 cm^{-1} (OH), and an intense, rather broad band at 1056 cm^{-1} (OH deformation vibrations).

In the preparation of the chlorosulfinyl nitrile **3** from **2** it is desirable that the latter be anhydrous even though water has little effect on the yield if an excess of thionyl chloride is used. In a rapid but smooth reaction **2** is converted to **3** in over 90% of theory. Upon fractionation the product is obtained as a colorless oil. The IR spectra indicates that the presence of the sulfinyl group suppresses considerably the nitrile band at 2260 cm^{-1}, although it is still detectable. A very intense rather broad band appears at 1213 cm^{-1} (SO), indicating a shift to a higher frequency due to the presence of additional oxygen attached to the SO group.

In addition to the formation of **3** by the action of thionyl chloride on **2** two other compounds are formed. The residue remaining after the distillation of **3** from the reaction mixture consists almost entirely of **5**, the sulfite. It distills without decomposition at 0.1 mm, but cannot be freed from a trace of color even by repeated distillations of an analytically pure sample. On the other hand, a colorless sample can be prepared by treating **3** with an excess of formamide and washing the ether-extracted oil several times with water, drying, and distilling. Microanalysis and IR indicate that both products are of the same compound. Here, too, the nitrile band is present (2260 cm^{-1}), but greatly suppressed. The characteristic band (SO) at 1213 cm^{-1} is intense and rather broad. This sulfite may be reconverted to **3** by refluxing with $SOCl_2$ for 5–10 min.

The third compound formed by the action of $SOCl_2$ on **2** is the chloronitrile **4**. The latter is formed quantitatively from **2** by refluxing the reaction mixture 4–5 h. After the removal of excess $SOCl_2$ it is distilled at atmospheric pressure. For a sample free of sulfur the oil was dissolved in ether and the solution was washed with water until free of chloride. On drying and removal of solvent a sulfur-free product was obtained. The infrared spectrum of this compound shows a band at 2260 cm^{-1} (CN) which is somewhat less intense than the same band in the cyanohydrin. In addition to this, another band appears at 2230 cm^{-1} which is sharper and about three times as intense as that at 2260 cm^{-1}. This band persists after several distillations. There is also a very weak band at 1213 cm^{-1} which still appears after the sulfur content of the sample has been reduced to <0.02%. This band is absent in the cyanohydrin, although the latter does show a weak band at 1247 cm^{-1}. The band at 3440 cm^{-1} (OH) is absent.

The chlorosulfinyl nitrile **3** is rapidly converted to the amino nitrile **6** by the action of liquid ammonia.[2] On removal of excess ammonia the residue is converted to valine (**7**) by refluxing with sodium hydroxide.[3] Hydrochloric acid may be used in this hydrolysis, but base is preferred for this amino acid since there is no apparent tar formation and a chromatographically pure sample is obtained.

Experimental Section

Isobutyraldehyde was purified by distillation just before use. A purified grade of thionyl chloride was further purified by distillation from about 10% of its weight of boiled linseed oil. A colorless product is thus obtained. The ammonia was dried by distillation from a small quantity of clean sodium. All other materials were reagent grade. All boiling points are uncorrected. Analyses are by V. Tashinian Micro Lab, U. C. Berkeley. The infrared spectra were determined on a Perkin Elmer IR 421 (liquid film between KBr plates). The preparation should be carried out in a good fume hood.

2-Hydroxyisovaleronitrile (2). A well stirred suspension of 50 g of potassium cyanide in 800 mL of anhydrous ether was cooled in an ice–water bath and 36.5 g of isobutyraldehyde (**1**) in 45 mL of glacial acetic acid was added dropwise during 1 h. A light voluminous precipitate of potassium acetate began to form immediately, which eventually filled the whole volume. After stirring for another hour the acetate was removed by filtration and the filter cake was washed several times with small portions of anhydrous ether. The ether was removed from the combined filtrate and washings using a rotary evaporator at room temperature and reduced pressure. The remaining oil weighed approximately 50 g. It distilled without decomposition at 66–67 °C (0.1 mm).

Anal. Calcd for C_5H_9ON: C, 60.60; H, 9.09; N, 14.14. Found: C, 60.62; H, 9.04; N, 14.12.

2-Chlorosulfinyloxyisovaleronitrile (3). The cyanohydrin from the above preparation (50 g) was added to 118 g of thionyl chloride over a period of 30 min while the mixture was stirred and kept at room temperature by means of a water bath. When the evolution of HCl had ceased, the excess thionyl chloride was removed under reduced pressure and the residue was fractionated, yielding almost colorless oil, bp 40–41 °C (0.1 mm).

Anal. Calcd for $C_5H_8O_2NSCl$: C, 33.06; H, 4.40, S, 17.63; Cl, 19.53; N, 7.71. Found: C, 33.36; H, 4.48; S, 17.56; Cl, 19.51; N, 7.70.

The yield for a number of runs varied between 80 and 86 g. The residue which remained was distilled and consisted almost entirely of the higher boiling sulfite **5**, bp 97–98 °C (0.1 mm).

Anal. Calcd for $C_{10}H_{16}O_3N_2S$: C, 49.18; H, 6.56; N, 11.47; S, 13.11. Found: C, 49.52; H, 6.63; N, 11.61; S, 12.86.

2-Chloroisovaleronitrile (4). The chlorosulfinyl nitrile **3** (50 g) as prepared above was refluxed with 60 g of thionyl chloride for 5 h, after which the excess thionyl chloride was removed at atmospheric pressure. The residue distilled at 149–150 °C at atmospheric pressure. The colorless oil weighed 30 g.

Anal. Calcd for C_5H_8NCl: C, 51.08; H, 6.81; N, 11.91; Cl, 30.18. Found: C, 51.31; H, 6.85; N, 12.15; Cl, 29.86.

Isobutyronitrile Sulfite (5). The chlorosulfinyl nitrile **3** (30 g) was added to 30 mL of formamide and the mixture was shaken for several minutes until the exothermic reaction was complete. The mixture was poured into water (100 mL) and the oil was extracted with ether. The ether solution was washed twice with two 20-mL portions of water and dried over anhydrous sodium sulfate. Upon removal of ether and

distillation of the residue there was obtained 18 g of a colorless oil, bp 97–98 °C (0.1 mm).

Anal. Calcd for $C_{10}H_{16}O_3N_2S$: C, 49.18; H, 6.56; N, 11.47; S, 13.11. Found: C, 49.09, H, 6.62; N, 11.59; S, 13.15.

Valine (7). To approximately 35 mL of anhydrous ammonia cooled in a dry ice–acetone bath was added dropwise 18 g of **3**. A vigorous reaction occurs and when complete, the cooling bath was removed and the ammonia was allowed to evaporate. To the residue was added 75 mL of absolute ethyl alcohol and the mixture was heated to reflux. On cooling, 20 g of NaOH in 100 mL of water was added and the temperature increased to above 90 °C, allowing the alcohol to distill off. The mixture was refluxed for 24 h. After cooling, 100 mL of 6 N HCl was added and the mixture was taken to dryness under reduced pressure. A few milliliters of water was added to the residue and it was again taken to dryness. The residue was extracted several times with a total of 200 mL of hot absolute ethyl alcohol. The alcoholic solution was concentrated to approximately 50 mL, filtered, and treated with 15 mL of pyridine. After standing in the refrigerator overnight the crystals were collected, washed with alcohol, and air dried. The yield for several runs was from 8 to 9 g of very pure, almost colorless valine. Paper chromatography showed the sample to be homogeneous, having the same R_f value as a standard sample of valine (1-butanol/acetic acid/water/pyridine; 10:2:2:1).

Anal. Calcd for $C_5H_{11}O_2N$: C, 51.28; H, 9.4; N, 11.96. Found: C, 50.90: H, 8.96; N, 11.99.

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Registry No.—1, 78-84-2; **2**, 67226-50-0; **3**, 67226-51-1; **4**, 67226-52-2; **5**, 67226-53-3; **6**, 67226-54-4; **7**, 516-06-3.

References and Notes

(1) See J. R. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol. 1, Wiley, New York, N.Y., 1961, p 698; *ibid.*, Vol. 3, pp 2371–2375.
(2) This amino nitrile has been prepared directly from **2** by the action of ammonia at high temperature and pressure. We carried out the reaction using liquid ammonia at atmospheric pressure, but no amino nitrile could be isolated. However, on a micro scale after hydrolysis some valine could be detected by paper chromatography: see W. T. Gresham and C. E. Schwertzer, U.S. Patent 2 520 312 (1950); *Chem. Abstr.*, **44**, 10732g (1950).
(3) The hydrolysis rate may be increased by increasing the temperature and pressure with no change in the purity of the final product: see ref 1, p 2372.

α-Diazo-β-oxycarboxylates

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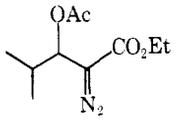
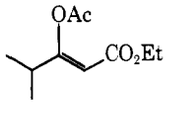
The aldol condensation of α-diazoacetic esters or α-diazomethyl ketones with aldehydes or ketones has been shown to be a facile method of synthesis of α-diazo-β-hydroxycarbonyl compounds,[1] whose pyrolysis has led to β-dicarbonyl substances. In order to study the effect of modification of the hydroxy group and introduction of a neighboring double bond, the following four α-diazo-β-oxy esters were prepared and their pyrolyses were investigated.



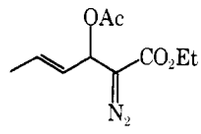
1



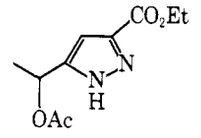
2

Treatment of a tetrahydrofuran solution of isobutyraldehyde and ethyl diazoacetate with *n*-butyllithium at −78 °C and interaction of the resultant lithio salt of the α-diazo-β-hydroxy ester with acetic anhydride yielded ester **1**, whose thermal decomposition gave the enol acetate of ethyl β-oxoisocaproate (**2**). This experience lays the groundwork for a simple, three-step method of preparation of unique enol esters of unsymmetrical β-diketones.

The presence of a double bond vicinal to the acyloxylated carbon causes the pyrolysis to take a different path. Thus, whereas the condensation of crotonaldehyde with diazoacetic ester and subsequent acetylation led to the expected diester **3**, its thermolysis afforded pyrazole **4**. Presumably, ester **3** had



3



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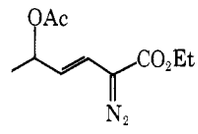
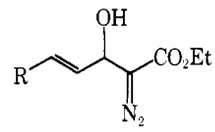


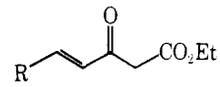
5

experienced an allyl acetate rearrangement and the resultant isomer (**5**) had undergone the known transformation of vinyl diazo compounds into pyrazoles.[2]

Interaction of ethyl lithiodiazoacetate with acrolein and with crotonaldehyde yielded esters **6a** and **6b**, respectively, whose pyrolysis resulted in the formation of β-keto esters **7a**[3] and **7b**,[3c] respectively. This two-step reaction scheme con-



6



7

a, R = H
b, R = Me

stitutes the shortest, presently known method of preparation of vinyl keto ester annelating agents, such as the Nazarov reagent **7a**. Their use in natural products synthesis is already on record.[3e,4,5]

Experimental Section

Infrared spectra of neat liquids were measured on a Perkin-Elmer 137 spectrophotometer and ^1H NMR spectra of deuteriochloroform solutions on a Varian EM-390 spectrometer.

General Procedure for the Preparation of Diazoesters 1, 3, and 6. The aldehyde and ethyl diazoacetate (in 87% methylene chloride solution), 20 mmol each, were added separately to 50 mL of anhydrous tetrahydrofuran, kept constantly at −78 °C. A 2.4 M hexane solution of *n*-butyllithium, 20 mmol, was added dropwise over a period of 45 min to the stirring, yellow solution under nitrogen at −78 °C and the mixture was stirred for 30 min more at the same temperature. Thereafter 2 mL of acetic anhydride in 50 mL of dry ether (for the preparation of **1** or **3**) or 2 mL of glacial acetic acid in 50 mL of anhydrous ether (for the preparation of **6**) was added at one time to the stirring solution and the resultant yellow suspension was stirred at room temperature for 1 h. The mixture was washed four times with 20 mL each of saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated under vacuum at room temperature. (Increase of the temperature of the reaction and workup decreased the product yields and led to oils with colors deeper than the yellow color characteristic of α-diazocarbonyl compounds!)

The above procedure used on isobutyraldehyde and ethyl diazoacetate, followed by acetylation, gave 3.9 g of crude diester **1**, which was used in the next reaction without purification. Chromatography of the substance on 200 g of neutral alumina (activity III) and elution with hexane yielded 1.3 g of **1**: IR 4.76 (s, N_2), 5.76, 5.89 (s, C=O) μm; ^1H NMR δ 0.96 (d, 3, J = 6 Hz, Me), 0.99 (d, 3, J = 6 Hz, Me), 1.23 (t, 3, J = 7 Hz, Me of Et), 1.7–2.5 (m, 1, CH), 2.03 (s, 3, Me of Ac), 4.20 (q, 2, J = 7 Hz, CH_2), 5.23 (d, 1, J = 9 Hz, OCH). Anal. Calcd for

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