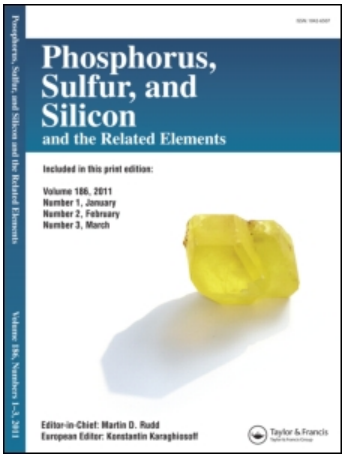

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EVALUATION OF THE N-PHTHALOYL MOIETY AS PROTECTING GROUP IN AMINOACYLPHOSPHONIC DERIVATIVES

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EVALUATION OF THE N-PHTHALOYL MOIETY AS PROTECTING GROUP IN AMINOACYLPHOSPHONIC DERIVATIVES

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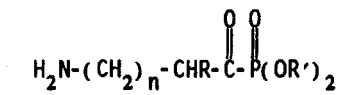
Reaction of dimethyl benzoylphosphonate with hydrazine hydrate gave exclusively benzhydrazide. Reaction of methyl lithium benzoylphosphonate with hydrazine hydrate gave the corresponding hydrazone (3) as a 65:35 mixture of E and Z isomers. Reaction of hydrazine hydrate with diisopropyl 4-phthalimidobutanoylphosphonate gave mainly products resulting from nucleophilic attack of hydrazine on the carbonyl of the acylphosphonate and only a small percentage of phthalhydrazide. From our results it appears that the N-phthaloyl protecting group is not suitable for the transient protection of amino groups during attempts to synthesize aminoacylphosphonates.

Key words: Acylphosphonate, aminoacylphosphonate, hydrazone, phosphonate, phthalimidoacylphosphonates.

INTRODUCTION

In recent years we are involved in the study of the chemistry of acylphosphonic acids[1] and their derivatives.[2] In this context we recently reported the initial results of studies directed towards the synthesis of aminoacylphosphonates (e.g., 1).[3] As the target molecules comprise of several functional groups, the synthetic study had to be focused on the choice of the appropriate protecting groups. One of the strategies tested was the synthesis of dialkyl phthalimidoacylphosphonates (2) as intermediates for the synthesis of aminoacylphosphonates (1). For the conversion of these to the desired aminoacylphosphonates (1), the N-phthaloyl group would have to be removed. Since N-pthaloyl groups are usually removed by hydrazine, and molecules of type 2 also contain a keto group which is reactive towards this reagent, there was need to examine the relative reactivities of the acylphosphonic keto group and the carbonyl groups of the phthalimide moiety.



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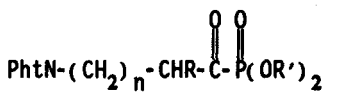

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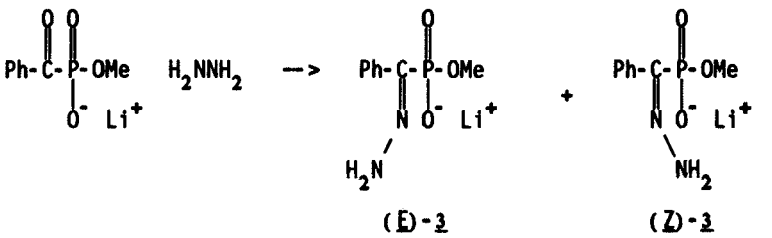
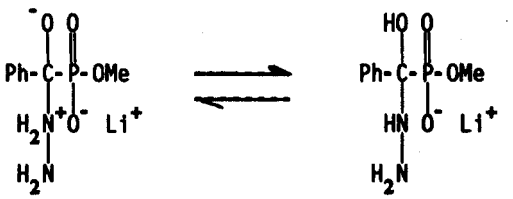
In this paper we wish to describe some experiments that examine the reactions of an acylphosphonate diester and a monoester toward hydrazine, as well as to evaluate the potential of the phthalimido moiety as a transient protecting group in aminoacylphosphonates by attempting selective deblocking in a phthalimidoacylphosphonate.

There exist several reports on the reactions of hydrazine derivatives with acylphosphonates. Phenylhydrazine,[4] 2,4-dinitrophenylhydrazine[5] and p-toluenesulfonylhydrazine[6] were reported to give mainly the corresponding hydrazones (in case of the phenylhydrazones mixtures of geometrical isomers were observed and structures were assigned based on infrared data).[4] In contrast, N,N-dimethylhydrazine was reported to give mixtures of N,N-dimethylhydrazones along with products of C—P bond cleavage, namely N,N-dimethylacylhydrazides.[7]

RESULTS AND DISCUSSION

In our hands the reaction of dimethyl benzoylphosphonate with phenylhydrazine, gave only N-phenyl-N′-benzoylhydrazide. Similar result was obtained in the reaction of dimethyl benzoylphosphonate with hydrazine. However no fission of the C—P bond could take place when hydrazine was reacted with methyl lithium benzoylphosphonate, since the ionized phosphoryl group cannot function as a leaving group. Monitoring this reaction by ^{31}P nmr spectroscopy showed the appearance of a transient peak at 16 ppm. This is interpreted as resulting from the tetrahedral intermediate 4 which is formed when hydrazine is added to the carbonyl group. The reaction led to the formation of a mixture of geometrical isomers of hydrazone 3 [(E)-3: (Z)-3 = 65:35]. Isomers 3 showed resonances in the ^{31}P nmr spectrum at 9.40 and 6.30 ppm. The assignment of the structures of hydrazones **3** is based on their analogy to the corresponding oximes.[2b] In that series also the E isomers appeared in low field relative to the Z isomers in the ^{31}P nmr spectrum. The validity of this assumption is further confirmed by the results obtained from a single crystal X-ray diffraction analysis of diisopropyl 4-phthalimidobutyrylphosphonate hydrazone (6) (vide infra). The formation of hydrazones 3 confirms previous observation regarding the reactivity of the carbonyl group towards nucleophiles in ionized acylphosphonates.[1d]



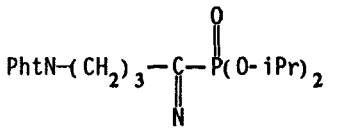


4

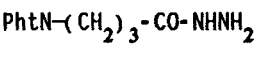
In order to evaluate the applicability of the phthaloyl moiety as an amino protecting group during the synthetic manipulations towards aminoacylphosphonates, we chose diisopropyl 4-phthalimidobutanoylphosphonate[3] (5) as the model compound. Compound 5 was allowed to react with hydrazine either in ethanol or in 2-propanol under the conditions previously found suitable for the removal of the N-phthaloyl group from phthalimidohydroxyiminophosphonates.[1] The results of these experiments are summarized in Table I. Examination of this table reveals that the reaction in both solvents gave predominantly products resulting from attack at the keto group. However, while the reaction in ethanol gave 34% of the product of alcoholysis, that in the more sterically hindered 2-propanol gave mainly the condensation product, namely diisopropyl 4-phthalimidobutanoylphosphonate hydrazone (6) as a mixture of two geometrical isomers [(E)-6: (Z)-6 = 80: 20]. The major isomer crystallized in the space group P1 having unit cell dimensions of a = 7.992(1)A, b = 17.653(2)A, c = 7.727(1)A, α = 102.08°, β = 103.97°, τ = 86.35° and Z = 2. (Other pertinent data can be found in Tables II–IV and in the supplementary material). The structure, as determined by single crystal X-ray analysis possesses the (E) geometry (see Figure 1). In this case too, the (E) isomer resonates at lower field in the ^{31}P nmr spectrum thus confirming the correlation previously mentioned.[2b]

4-Phthalimidobutanoylhydrazide (7) was isolated from the reaction mixture and its structure was determined by infrared and ^1H nmr spectroscopy and mass spectrometry. Ethyl 4-phthalimidobutanoate (8a) and the corresponding 2-propyl ester (8b) were identified in the reaction mixtures by chromatographic comparison with authentic samples which were synthesized by reacting 4-phthalimidobutanoyl chloride with ethanol and 2-propanol, respectively. Phthalhydrazide (9) was isolated from the reaction mixtures and identified by comparison with an authentic sample.

Products were determined by high performance liquid chromatography. Examination of the reaction mixtures by ^{31}P nmr showed the presence of $(i\text{-PrO})_2$ PHO in amounts corresponding to those of the P—C bond cleavage products.



(6)



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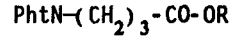

8a, R = Et
8b, R = iPr

Although ^{31}P nmr examination of the reaction mixtures indicated the presence of minor phosphorus containing compounds, we were not able to isolate any complementary products corresponding to the 20% phthalhydrazide obtained. However, from the results presented above it is apparent that the carbonyl group of the acylphosphonic function is the main focus of electrophilicity in the molecule of phthalimidoacylphosphonate, leading to preferential alcoholysis, condensation and hydrazinolysis. From these results it appears that the N-phthaloyl protecting group is not suitable for the transient protection of amino groups during attempts

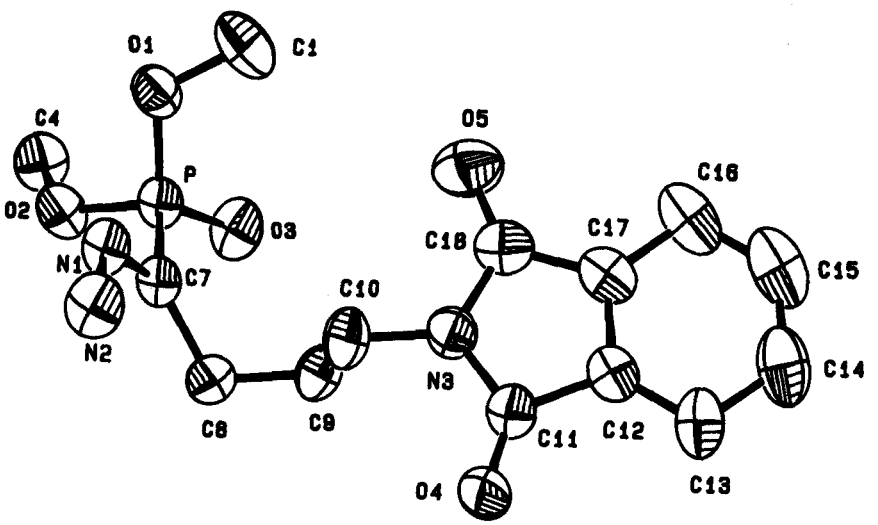

FIGURE 1 An ORTEP view and labeling scheme of compound (E)-6 using 50% probability ellipsoids. For clarity, the methyl groups of the isopropyl moieties (C1, C2, C5, C6) were not drawn.

TABLE I

Results from the reactions of diisopropyl 4-phthalimidobutanoylphosphonate (5) with hydrazine

Solvent	Hydrazone 6	Hydrazide 7	Ester 8	Phthalhydrazide 9
Ethanol	36.0 %	2.7%	34.0 %	20.0 %
2-Propanol	62.0 %	4.0 %	9.0 %	23.0 %

to synthesize aminoacylphosphonates. Future efforts will address N-urethane type protecting groups, as potential transient blockers in synthetic schemes, for the preparation of aminoacylphosphonates.

EXPERIMENTAL

General. Melting points were determined by a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of The Hebrew University of Jerusalem. Infrared spectra were determined on an Analect FTIR spectrometer. Nuclear magnetic resonance spectra were obtained on a Bruker WH-300 or on a Varian VXR-300s instrument. Chemical shifts are reported in p.p.m. downfield from TMS or TSP as internal standards in ^{1}H-nmr spectra and from 85% H_3PO_4 as external standard in ^{31}P-nmr spectra. Positive chemical shifts are at low field with respect to the standard. Mass spectra were obtained on LKB 2091 gas chromatograph-mass spectrometer. High performance liquid chromatography (HPLC) was carried out on a Merck Hitachi Model L-6200 intelligent pump.

Reaction of Hydrazine with Dimethyl Benzoylphosphonate. Hydrazine hydrate solution (100 mL, 1 M in ethanol) was added dropwise, during 20 min. to a chilled sol. of dimethyl benzoylphosphonate (21.4 g, 0.1 mol) in absolute ethanol (100 ml). The reaction mixture was stirred for 30 min. at 0°C, then the precipitated benzoic hydrazide was collected by filtration, m.p. 114–6°C (lit. m.p. 113–7°C[8]). Yield: 10.9 g, 80%. ^{1}H-NMR ($CDCl_3$): 7.17–7.70 (d, J = 5.2 Hz), 7.49–7.39 (m, 3H). Anal. Calcd. for: $C_7H_9N_{20}$: C, 61.76; H, 5.88; N, 20.58. Found: C, 61.06; H, 5.92; N, 20.13. Examination of the reaction mixture by ^{31}P-NMR showed the formation of dimethyl phosphite ($\delta^{31}P$ = 13.3 ppm, J_{HP} = 700 Hz, d sept).

TABLE II

Crystallographic data for (E)-6

(A) Crystal Parameters[a]	
Formula	$C_{18}H_{26}N_3O_5P$
a, Å	7.992(1)
b, Å	17.653(2)
c, Å	7.727(1)
α, deg	102.08(1)
β, deg	103.97(1)
γ, deg	86.35(1)
V, Å^3	1034(1)
space group	P1
Z	2
d(calcd), g cm^{-3}	1.26
d(obsd)[b], g cm^{-3}	1.27
mol. wt.	395
(B) Measurement of Intensity Data	
Instrument:	Philips PW 1100
Radiation:	Mo (Kα)
Temperature:	23°C
(C) Treatment of Intensity Data[c]	
μ, cm^{-1} d	1.25
No. Unique Data:	3605
Obs. Unique Data [$F_o > 6\sigma F^o$]	2823
No. of param. refined	260
Max. param. shift in final refinement cycle	0.1
Max. electron density on final refinement cycle	
R1[e]	.0463
R2[f]	.0479

[a] From a least square fit to the setting angles of 20 reflect with 2θ>25 deg.

[b] By floatation.

[c] F_o and $\sigma(F_o)$ were corrected for background, attenuation and Lorentz-polarization effects of X radiation.

[d] No absorption corrections were performed.

[e] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$

[f] $R2 = [\Sigma w(|Fo| - |Fc|)^2/\Sigma w|Fo|^2]^{1/2}$

Reaction of Hydrazine with Lithium Methyl Benzoylphosphonate. Lithium methyl benzoylphosphonate hydrazone (3). To a solution of lithium methyl benzoylphosphonate (5 g, 0.024 mol) in methanol (100 mL) is added 24 ml 1 M solution of hydrazine in methanol. After stirring the solution overnight the product 3 is isolated in 94% yield by concentrating the solution. IR (KBr) 3413, 3405, 3279, 1573, 1235,

TABLE III

Bond distances (Å) for (E)-6

P	-- O(1)	1.575(2)
P	-- O(2)	1.574(2)
P	-- O(3)	1.471(2)
P	-- C(7)	1.798(3)
N(1)	-- N(2)	1.364(4)
N(1)	-- C(7)	1.291(3)
N(3)	-- C(10)	1.459(4)
N(3)	-- C(11)	1.390(4)
N(3)	-- C(18)	1.406(5)
O(1)	-- C(1)	1.457(4)
O(2)	-- C(4)	1.471(5)
O(4)	-- C(11)	1.211(4)
O(5)	-- C(18)	1.208(5)
C(1)	-- C(2)	1.45(1)
C(1)	-- C(3)	1.465(7)
C(4)	-- C(5)	1.486(5)
C(4)	-- C(6)	1.500(5)
C(7)	-- C(8)	1.513(4)
C(8)	-- C(9)	1.535(4)
C(9)	-- C(10)	1.517(4)
C(11)	-- C(12)	1.494(5)
C(12)	-- C(13)	1.378(5)
C(12)	-- C(17)	1.388(5)
C(13)	-- C(14)	1.400(6)
C(14)	-- C(15)	1.379(7)
C(15)	-- C(16)	1.382(7)
C(16)	-- C(17)	1.389(5)
C(17)	-- C(18)	1.483(5)

Estimated standard deviations in the last significant figure are given in parenthesis.

1244, 1077 cm^{-1}. NMR, (D_2O): ^1H: 7.58–7.49 (3H, m) 7.33–7.31 (2H, d, J = 7 Hz) 3.57 (3H, d, J = 10.8 Hz); ^{31}P: 9.43 (q, E isomer, 65%), 6.27 (q, Z isomer, 35%). Anal. Calcd. for $C_8H_{10}N_2OPLi_3$: C, 43.63; H, 4.54; N, 12.72. Found: C, 43.26; H, 4.56; N, 12.29.

Reaction of Hydrazine with Diisopropyl 4-Phthalimidobutanoylphosphonate. a: Preparative Scale Experiment: 10 ml of 1 M solution of hydrazine hydrate in ethanol was added to diisopropyl 4-phthalimidobutanoyl phosphonate (3.81 g, 0.01 mole) in 50 ml ethanol. After 10 minutes a precipitate appeared. Stirring was continued overnight at room temperature and the precipitate, 4-phthalimidobutanoylhydrazide (7), was collected by filtration, washed with ethanol and recrystallized from ethyl acetate, yield 67 mg, m.p. 182–3°C. ^1H-NMR ($CDCl_3$): 2.06 (t, 2H); 2.2 (t, 2H); 3.75 (t, 2H); 7.74 (m, 2H); 7.86 (m, 2H); MS: m/e = 246, (M-1). IR (Nujol): 3333, 1702, 1630, 1522, 1100, 1028, 884 cm^{-1}. Anal. Calcd. for: $C_{12}H_{13}N_3O_3$: C, 58.30; H, 5.26; N, 17.0. Found: C, 58.02; H, 5.42; N, 16.74.

The filtrate was evaporated, water was added to the residue then extracted by (3 × 50 ml) chloroform. The chloroform extracts were dried over magnesium sulfate, evaporated to yield diisopropyl 4-phthalimidobutanoylphosphonate hydrazone (6). Recrystallization from ethyl acetate gave 480 mg (12%) mixture of E and Z isomers, m.p. 125°C. IR (nujol): 3235, 3400, 3328, 1717, 1707, 1558, 1443, 982 cm^{-1}. NMR: ($CDCl_3$) ^1H: 1.35–1.29 (m, 12H); 1.97 (m, 2H); 2.4 (m, 2H); 3.76 (m, 2H); 4.70 (m, 2H); 6.18 (m, 1H): 7.74 (m, 2H); 7.84 (m, 2H); 8.43 (m, 1H); ^{31}P: 10.10 (m, E isomer, 80%), 5.66

TABLE IV

Bond angles (deg) for (E)-6

O(1)	-P	-O(2)	101.7(1)
O(1)	-P	-O(3)	114.2(1)
O(1)	-P	-C(7)	109.4(1)
O(2)	-P	-O(3)	115.2(1)
O(2)	-P	-C(7)	103.4(1)
O(3)	-P	-C(7)	112.1(1)
N(2)	-N(1)	-C(7)	119.6(3)
C(10)	-N(3)	-C(11)	123.4(2)
C(10)	-N(3)	-C(18)	124.5(3)
C(11)	-N(3)	-C(18)	112.1(3)
P	-O(1)	-C(1)	120.1(3)
P	-O(2)	-C(4)	120.1(2)
O(1)	-C(1)	-C(2)	108.2(4)
O(1)	-C(1)	-C(3)	108.7(4)
C(2)	-C(1)	-C(3)	116.6(5)
O(2)	-C(4)	-C(5)	107.5(3)
O(2)	-C(4)	-C(6)	108.0(3)
C(5)	-C(4)	-C(6)	113.6(4)
P	-C(7)	-N(1)	114.5(2)
P	-C(7)	-C(8)	118.2(2)
N(1)	-C(7)	-C(8)	127.3(2)
C(7)	-C(8)	-C(9)	113.3(3)
C(8)	-C(9)	-C(10)	112.8(3)
N(3)	-C(10)	-C(9)	112.6(3)
N(3)	-C(11)	-O(4)	125.0(3)
N(3)	-C(11)	-C(12)	105.8(3)
O(4)	-C(11)	-C(12)	129.1(3)
C(11)	-C(12)	-C(13)	129.9(3)
C(11)	-C(12)	-C(17)	107.9(3)
C(13)	-C(12)	-C(17)	122.2(3)
C(12)	-C(13)	-C(14)	116.5(3)
C(13)	-C(14)	-C(15)	121.5(4)
C(14)	-C(15)	-C(16)	121.6(4)
C(15)	-C(16)	-C(17)	117.4(4)
C(12)	-C(17)	-C(16)	120.8(4)
C(12)	-C(17)	-C(18)	108.6(3)
C(16)	-C(17)	-C(18)	130.6(3)
N(3)	-C(18)	-O(5)	124.5(3)
N(3)	-C(18)	-C(17)	105.5(3)
O(5)	-C(18)	-C(17)	130.0(3)

Estimated standard deviations in the last significant figure are given in parenthesis.

(m, Z isomer, 20%). MS: m/e = 395 (M^+), 379, 353, 337, 311, 295.
Anal. Calcd. for: $C_{18}H_{23}N_3O_5P$: C, 54.68; H, 6.58; N, 10.63.
Found: C, 54.70; H, 6.69; N, 10.77.

The water layer was acidified by 6N HCl to pH 1, at 0°C. The resulting phthalhydrazide, (9) was filtered washed with water and dried, 85 mg.

b: Analytical Experiments: Separate experiments of the same reaction were carried out in ethanol and in 2-propanol on a 0.2 millimolar scale. The reaction mixtures were analyzed by HPLC using a Li-Chrospher column RP-18 (125 × 4 mm) with water: MeCN = 1:1, flow 0.4 mL/min, analyzed at 230 nm.

X-Ray Crystallography. Data collection was performed on a Philips PW 1100 automated diffractometer using a $\theta-2\theta$ scan mode. The data were corrected for Lorentz polarization but no absorption correction was applied due to the low absorption coefficients. All nonhydrogen atoms were located by the direct methods of SHELX-86 and by subsequent difference maps.The refinement was carried out with SHELX-76.[9] Other pertinent information can be found in Tables S1 through S3 in the supplementary material.[10]

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REFERENCES

1. (a) E. Breuer, R. Karaman, H. Leader, A. Goldblum and R. Moshe, *Phosphorus and Sulfur*, **30,** 113 (1987); (b) E. Breuer, R. Karaman, H. Leader and A. Goldblum, *Phosphorus and Sulfur*, **33,** 61 (1987); (c) E. Breuer, R. Karaman, G. Goldblum and H. Leader, *J. Chem. Soc. Perkin Trans.*, **2,** 2029 (1988); (d) R. Karaman, A. Goldblum, E. Breuer and H. Leader, *J. Chem. Soc. Perkin Trans.*, **1,** 765 (1989).
2. (a) E. Breuer, R. Karaman, D. Gibson, H. Leader and A. Goldblum, *J. Chem. Soc. Chem. Comm.*, 504 (1988); (b) E. Breuer, R. Karaman, A. Goldblum, D. Gibson, H. Leader, B. V. L. Potter and J. H. Cummins, *J. Chem. Soc. Perkin*, **1,** 3047 (1988); 1367 (1989); (c) E. Breuer, R. Karaman, H. Leader and A. Goldblum, *J. Chem. Soc. Chem. Comm.*, 671 (1987); (d) J. Katzhendler, R. Karaman, D. Gibson, H. Leader and E. Breuer, *J. Chem. Soc., Perkin Trans.*, **2,** 589 (1989); (e) E. Breuer, A. Schlossman, M. Safadi, D. Gibson and M. Chorev, *J. Chem. Soc. Perkin Trans.*, **1,** in press.
3. E. Breuer, M. Safadi, M. Chorev and D. Gibson, *J. Org. Chem.*, **55,** 6147 (1990).
4. M. P. Kaushik, B. Lal, C. D. Raghuveeran and R. Vaidyanathaswamy, *J. Org. Chem.*, **47,** 3503 (1982).
5. K. D. Berlin and H. A. Taylor, *J. Am. Chem. Soc.*, **86,** 3862 (1964).
6. M. Regitz, W. Anschutz and A. Liedhegener, *Chem. Ber.*, **101,** 3734 (1968); D. Seyferth and R. S. Marmor, *J. Org. Chem.*, **36,** 128 (1971); D. Seyferth, R. S. Marmor and P. Hilbert, *J. Org. Chem.*, **36,** 1379 (1971).
7. Z. H. Kudzin and A. Kotynski, *Synthesis*, 1028 (1980).
8. Beilsteins Handbuch der Organischen Chemie, **9,** 319.
9. G. M. Sheldrick, SHELX-76: in "Computing in Crystallography," H. Schenck, R. Olthof-Hazekamp, H. van Koningsveld and G. C. Bassi, Eds., (Delft University Press, Delft, The Netherlands, 1978), pp. 34–42.
10. Full crystallographic data are deposited with the Cambridge Crystallographic Data Centre, U.K.