Ene Reaction of the Active Imino Group. A Novel Synthesis of α-Amino-Acids [1]

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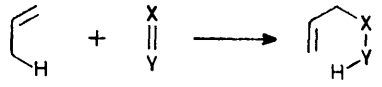
The thermal (120 °C) and catalytic ($SnCl_4$, BF_3, and $AlCl_3$) ene addition reactions of butyl *N*-(*p*-tolylsulphonyl)-iminoacetate with alkenes give adducts which are readily convertible into γδ-unsaturated α-amino-acids.

THE ene reaction involves the addition of an alkene possessing an allylic hydrogen atom to a multiple bond (enophile) (Scheme 1),[2] and is of theoretical and synthetic



SCHEME 1

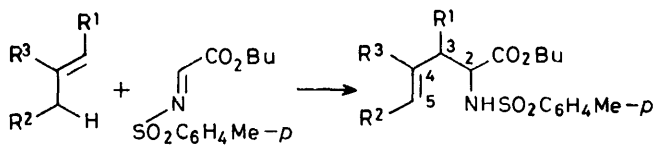
interest.‡ Because enophilic activity is exhibited by different types of electron-deficient multiple bonds (C=C, C≡C, C=O, N=N, *etc.*) the ene reaction is a convenient route to compounds with diverse structures and functional groups, often in a highly stereoselective fashion.§ We have now examined its utility for the synthesis of α-amino-acids.[1]

The addition of alkenes (1) to butyl *N*-(*p*-tolylsulphonyl)iminoacetate (2) which could be readily prepared by the reaction of butyl glyoxylate with *N*-sulphinyltoluene-*p*-sulphonamide,[4] is the first example of an ene reaction involving an active C=N group. It gives the adducts (3), which can be easily converted into α-amino- or γδ-unsaturated α-amino-acids. Therefore the reaction offers a new approach to the synthesis of this class of compounds.

TABLE 1

Adduct	Reaction time/h	Temperature (*t*/°C)	Molar ratio of (2) to (1)	Yield (%)	M.p. (b.p.[a]) (*t*/°C)	$\nu_{max.}$/cm^{-1} SO_2	$C{=}CH_2$	C=O	NH
(3a)	24	120	1 : 7	70	47—48	1 160, 1 345	1 640	1 740	3 300
(3b)	16	120	1 : 5	78	39—40	1 160, 1 350		1 730	3 340
(3c)	16	120	1 : 5	75	(170 at 10^{-4} Torr)	1 160, 1 340	1 640	1 740	3 340
(3d)	10	120	1 : 3	79	(170 at 10^{-4} Torr)	1 160, 1 340	1 650	1 740	3 300
(3e)	8	120	1 : 3	90	(170 at 10^{-4} Torr)	1 170, 1 350		1 740	3 300
(3f)	8	120	1 : 3	91	(170 at 10^{-4} Torr)	1 160, 1 350		1 740	3 350
(3g)	8	120	1 : 3	88	(170 at 10^{-4} Torr)	1 170, 1 350		1 745	3 350
(3h)	4	120	1 : 1	92	63	1 160, 1 340	1 630	1 740	3 300
(3i)	4	130	1 : 2	82	*b*	1 160, 1 340		1 730	3 300
(4)	20	120	1 : 5	56	72	1 160, 1 340		1 710	3 300
(5)	16	120	1 : 3	81	61	1 160, 1 340		1 740	3 300
(6)	0.5	125	1 : 2	76	(170 at 10^{-4} Torr)	1 160, 1 340		1 735	3 300
(7)	0.5	125	1 : 1	74	79	1 160, 1 340		1 740	3 300

[a] Air-bath temperature. [b] Not distilled.



(1) (2) (3)

	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	Me	H	H
d	H	H	Me
e	H	Et	H
f	Me	Me	H
g	H	Pr	H
h	H	H	Ph
i	H	Ph	H

RESULTS AND DISCUSSION

The thermal (120 °C) reaction of the iminoacetate (2) [4] with a series of alkenes with terminal or di- and tri-substituted double bonds gave in each case the ene adducts (3)—(7) in good to excellent yields (Table 1) essentially as a single product as indicated by t.l.c.

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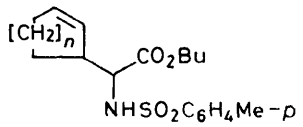
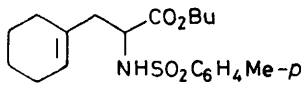
‡ The ene reaction, though lacking appropriate elements of symmetry, could be considered as a $\pi 2_s + \pi 2_s + \sigma 2_s$ pericyclic process. Establishing experimentally its concerted or non-concerted character for particular cases is therefore of theoretical significance.

§ Notably for the intramolecular variant of an ene reaction.[3]

Their structures were confirmed by elemental analyses and spectral data. The i.r. spectra contained bands corresponding to the appropriate C=O, SO_2, C=C, and NH



(4) n = 2
(5) n = 3



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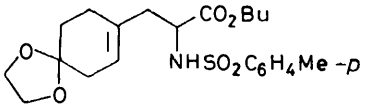


(7)

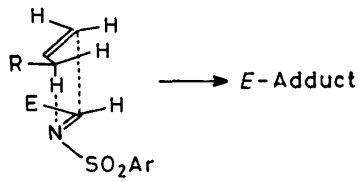
functional groups and the ^1H n.m.r. spectra contained signals for all the expected protons (Table 2). For compounds (3e), (3f), (3g), and (3i) where geometric isomers are possible values of the coupling constants for the olefinic protons of *ca.* 15 Hz proved their *E* configuration. The marked preponderance of the *E*- over the *Z*-isomer indicates that in both modes of addition with an *endo*- or *exo*-butoxycarbonyl group (Scheme 2 depicts only *endo*-addition) the transition state (A) is favoured. In (A) the alkene adopts a conformation in which the steric interaction of the alkyl group R and the hydrogen atom at C-1, *cis* to the $-CH_2R$ substituent, is avoided. This result could be construed as evidence in favour of a concerted process and militating against a biradical intermediate which should lead to an equilibrium ratio of *E*- and *Z*-isomers and the formation of side-products. Analogous stereoselectivity was observed previously in the ene reaction of diethyl mesoxalate and butyl glyoxylate with alkenes for which independent evidence for a concerted mechanism was

TABLE 2

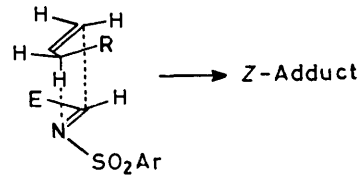
100 MHz ^1H n.m.r. data for the adducts (3)—(7)

Adduct	Chemical shift [a] (δ relative to Me_4Si = 0) and coupling constants (J/Hz)
(3a)	5.62 (1 H, m, 4-H), 5.04 (2 H, m, 5-H_2), 3.99 (1 H, dt, $J_{NH,2}$ 7.1, $J_{2,3}$ 6.5, 2-H), and 2.50 (2 H, m, 3-H_2)
(3b)	5.28 (3 H, m, 4-H, 5-H, NH), 2.42 (2 H, m, 3-H_2), and 1.61 (3 H, d, $J_{5,6}$ 5.75, 6-H_3)
(3c)	5.61 (1 H, m, $J_{4,5}$ 17.5, $J_{4,5'}$ 9.75, $J_{3,4}$ 8.25 4-H), 5.00 (2 H, m, 5-H_2), 3.79 (1 H, dd, $J_{NH,2}$ 10.0, $J_{2,3}$ 6.0, 2-H), 2.50 (1 H, m, 3-H), and 1.04 (3 H, d, $J_{3,Me}$ 6.0, 3-Me)
(3d)	4.74 (2 H, m, 5-H_2), 4.04 (1 H, dt, $J_{NH,2}$ 9.5 $J_{2,3}$ 7.0, 2-H), 2.41 (2 H, m, 3-H_2), and 1.65 (3 H, s, 4-Me)
(3e)	5.50 (1 H, dt, $J_{4,5}$ 15, $J_{5,6}$ 6.0, 5-H), 5.16 (1 H, dt, $J_{3,4}$ 7.75, 4-H), 3.95 (1 H, dt, $J_{NH,2}$ 9.5, $J_{2,3}$ 5.5, 2-H), 2.41 (2 H, m, 3-H_2), 1.94 (2 H, dq, $J_{6,7}$ 7.58, 6-H_2), and 0.94 (3 H, t, 7-H_3).
(3f)	5.29 (3 H, m, 4-H, 5-H, NH), 2.43 (1 H, m, 3-H), 1.59 (3 H, d, J 6.0, 6-H_3), and 1.01 (3 H, d, J 6.0, 3-Me)
(3g)	5.46 (1 H, dt, $J_{4,5}$ 15.5 $J_{3,4}$ 6.25, 4-H), 5.16 (1 H, dt, $J_{5,6}$ 6.25, 5-H), 3.96 (1 H, dt, $J_{NH,2}$ 9.0 $J_{2,3}$ 5.5, 2-H), 2.65 (2 H, m, 3-H_2), 1.93 (2 H, dt, $J_{6,7}$ 7.5, 6-H_2), and 0.90 (3 H, t, $J_{7,8}$ 6.5, 8-H_3)
(3h)	5.29 (1 H, s, 5-H), 5.09 (1 H, s, 5'-H), 3.93 (1 H, dt, $J_{NH,2}$ 9.5 $J_{2,3}$ 7.0, 2-H), and 2.85 (2 H, d, 3-H_2)
(3i)	6.39 (1 H, d, $J_{4,5}$ 15.5, 5-H), 5.96 (1 H, dt, $J_{3,4}$ 6.75, 4-H), 4.09 (1 H, dt, $J_{NH,2}$ 8.75, $J_{2,3}$ 5.75, 2-H), and 2.63 (2 H, dd, J 5.75, 3-H_2)
(4)	5.89 (1 H, dd), 5.38 (1 H, dd), 3.10 (3 H, m), and 1.66 (2 H, m) (ring protons); 3.86 (1 H, dd, $J_{NH,2}$ 10.75 $J_{2,3}$ 4.75, 2-H)
(5) [b]	5.80 (1 H, m), 5.34 (1 H, d), and 2.49 (1 H, m) (ring protons); 3.80 (dd, $J_{NH,2}$ 10.0 $J_{2,3}$ 6.5, 2-H)
(6) [b]	5.41br (1 H, s) and 1.85 (4 H, m) (ring protons); 3.98 (1 H, dt, $J_{NH,2}$ 9.0, $J_{2,3}$ 7.0, 2-H), and 2.39 (2 H, m, 3-H_2)
(7) [b]	5.34 (2 H, m, C=CH and NH), 2.17 (6 H, m, 3-H_2 and 4 ring protons), and 1.56 (1 H, t, J 6.25, 2-H)

[a] Signals corresponding to the C_6H_4Me, NH, and OC_4H_9 groups appeared at typical chemical shifts which were approximately the same for all the adducts (3—7); *e.g.* (3e): 7.73 and 7.25 (2 × 2 H, 2 × d, ArH), 5.28 (1 H, d, $J_{NH,2}$ 9.5, NH), 3.88 (2 H, t, J 6.0, $-OCH_2-$), 2.38 (3 H, s, ArMe), 1.39 (4 H, m, CH_2CH_2), and 0.90 (3 H, t, J 6.0, Me). [b] Remaining ring proton signals overlap with those of the butoxy-group protons.



(A)



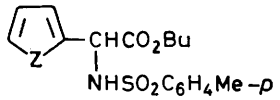
(B)

R = alkyl or aryl
Ar = *p*-MeC_6H_4
E = CO_2Bu

SCHEME 2

obtained.[5] A comparison of reaction time, temperature, and yields of the thermal ene reaction of butyl glyoxylate,[6] diethyl mesoxalate,[7] and the iminoacetate (2) indicates that the sulphonate-activated imino-group is more reactive than the carbonyl group even when the carbonyl group is activated by two alkoxycarbonyl substituents.

The iminoacetate (2) also exhibited a higher reactivity than carbonyl enophiles in electrophilic substitution. It



(8) Z = O
(9) Z = S

reacted readily with furan and thiophen to give the amino-acid derivatives (8) and (9) whereas the analogous reaction of butyl glyoxylate [8,9] and diethyl mesoxalate [8] with furan required the presence of an acid catalyst and that with thiophen proceeded only in poor yield.[10]

Numerous ene reactions that require an elevated temperature have been carried out successfully at room temperature in the presence of Lewis acid catalysts.[11-13] These catalysts were particularly effective for enophiles with an active carbonyl group.[12,13] The reactions proceeded in much higher yield and with greater stereospecificity.[13]

The reaction of the iminoacetate (2) with alkenes (pent-1-ene, hex-1-ene, and isobutene) in the presence of $SnCl_4$, $AlCl_3$, and BF_3 was examined. The reactions were accelerated and similar yields of the adducts to those in the absence of catalyst were obtained in only 10 min at room temperature. The catalysed reaction could also be carried out at temperatures as low as −78 °C which is convenient for handling the volatile alkenes propene and butene. The application of the imine ene reaction to the synthesis of α-amino-acids or γσ-unsaturated α-amino-acids was demonstrated by the conversion of the adduct (3e) into the saturated tosylated amino-acid butyl ester (12) and the (*E*)-2-aminohept-4-enoic acid (11). Basic hydrolysis of the adduct (3e) and subsequent detosylation with sodium in liquid ammonia gave (11) in 85% overall yield. Catalytic hydrogenation of the adduct (3e) afforded the tosyl derivative (12) in 90% yield. Of particular interest is the easy access to the unsaturated compounds since several α-amino-acids of non-protein origin have a double bond at the γδ-position [14] or a functional group which could be derived from the latter;[15] *e.g.* the adduct (7) has the carbon skeleton of the antibiotic α-amino-acid anticapsine. The foregoing ene reaction opens a new approach to the synthesis of these natural α-amino-acids.

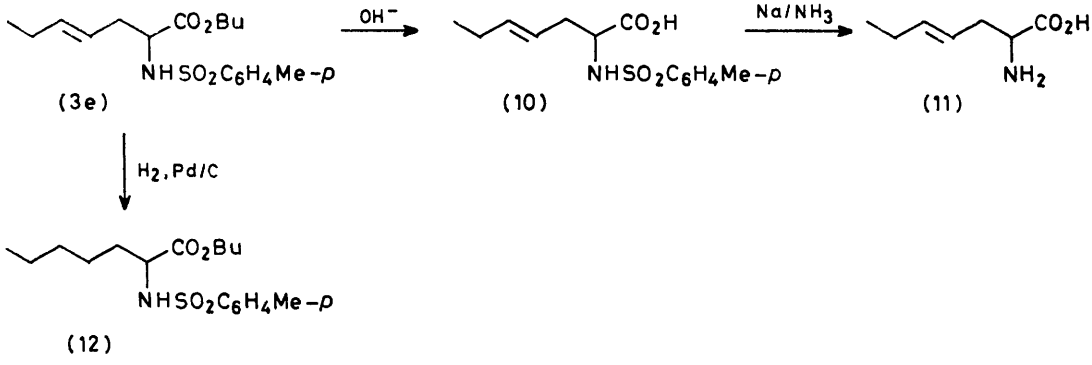
TABLE 3

Elemental analyses [a]

Compound	Molecular formula	Elemental analyses Found (%) C	H	N	Required (%) C	H	N
(3a)	$C_{16}H_{23}NO_4S$	59.2	7.3	4.1	59.1	7.1	4.3
(3b)	$C_{17}H_{25}NO_4S$	60.5	7.5	3.8	60.1	7.4	4.1
(3c)	$C_{17}H_{25}NO_4S$	60.0	7.5	4.1	60.1	7.4	4.1
(3d)	$C_{17}H_{25}NO_4S$	60.3	7.5	4.1	60.1	7.4	4.1
(3e)	$C_{18}H_{27}NO_4S$	61.1	7.9	4.2	61.2	7.7	4.0
(3f)	$C_{18}H_{27}NO_4S$	61.1	7.6	3.6	61.2	7.7	4.0
(3i)	$C_{22}H_{27}NO_4S$	61.5	7.2	3.8	61.5	7.2	4.0
(4)	$C_{18}H_{25}NO_4S$	62.4	7.4	3.6	62.4	7.5	3.8
(5)	$C_{19}H_{27}NO_4S$	66.0	6.8	3.3	65.8	6.8	3.5
(6)	$C_{20}H_{29}NO_4S$	63.1	7.7	3.6	62.8	7.6	4.0
(7)	$C_{22}H_{31}NO_6S$	60.3	7.1	3.3	60.4	7.1	3.2

[a] Compounds (3g), (3h), and (11) were characterized only spectroscopically.

a sealed tube for 0.5—24 h. The solvent and excess of alkene were evaporated under reduced pressure and a benzene–hexane solution of the residue was filtered through a short silica gel (Merck 60, 230—400 mesh) column. Reaction conditions, yields, m.p.s, b.p.s, and spectral data are in Tables 1 and 2.



EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP-200, Beckman Acculab TM1 or Beckman IR 4240 spectrophotometer. ^1H N.m.r. spectra were measured with a Jeol JNM-4H-100 spectrometer in [^2H]chloroform with Me_4Si as internal standard, unless otherwise specified. Elemental analyses are in Table 3.

Thermal Reaction of Butyl N-(p-*Tolylsulphonyl*)*iminoacetate* [4] (2) *with Alkenes. General Procedure.*—A solution of (2) (1 mmol) and the alkene (1) (1—7 mmol, freshly distilled from lithium aluminium hydride) in dry benzene (0.5 ml) was flushed with nitrogen and heated at 120 °C in a sealed tube for 0.5—24 h. The solvent and excess of alkene were evaporated under reduced pressure and a benzene–hexane solution of the residue was filtered through a short silica gel (Merck 60, 230—400 mesh) column. Reaction conditions, yields, m.p.s, b.p.s, and spectral data are in Tables 1 and 2.

Catalysed Reaction of the Iminoacetate (2) *with Pent-1-ene.*—To a solution of (2) (283 mg, 1 mmol) and pent-1-ene (350 mg, 5 mmol) in dichloromethane (1 ml) chilled to 0 °C tin(IV) chloride (0.1 ml, 1 mmol) was added. After 30 min the mixture was diluted with dichloromethane (10 ml), washed with water (10 ml), dried ($MgSO_4$), and evaporated. A solution of the residue in benzene–ether (4 : 1) was filtered through a short silica gel (Merck 60, 230—400 mesh) column and evaporated again. Distillation furnished (3e) (307 mg, 87%) identical (t.l.c., i.r., ^1H n.m.r.) with the sample obtained in the thermal reaction.

Reaction of the Iminoacetate (2) *with Thiophen.*—A mixture of (2) (0.5 g, 1.7 mmol) and thiophen (440 mg, 5.1 mmol) was heated in a sealed tube at 110 °C for 4 h. The excess of thiophen was evaporated off and a solution of the residue in benzene–ether (7 : 3) chromatographed on a silica gel (Serva, 200—300 mesh) column to yield *butyl 2-thienyl-(toluene-*p*-sulphonamido)acetate* (9) (518 mg, 80%), m.p. 68 °C (from benzene–hexane, 1 : 10), $\nu_{max.}$(KBr) 3 300 (NH), 1 720 (C=O), 1 340, and 1 160 (SO_2) cm^{-1}; δ 6.73 (1 H, dd, $J_{3,4}$ 3.5, $J_{3.5}$ 1.25 Hz, 3-H), 6.71 (1 H, dd, $J_{4.5}$ 5.25 Hz, 5-H), 6.50 (1 H, dd, 4-H), and 5.45 (1 H, d, $J_{NH.CH}$ 8.5 Hz, $-CH<$) (Found: C, 55.6; H, 5.8; N, 3.6. $C_{17}H_{21}NO_4S_2$ requires C, 55.6; H, 5.8; N, 3.8%).

Reaction of the Iminoacetate (2) *with Furan.*—A mixture of (2) (0.5 g, 1.7 mmol) and furan (350 mg, 5.1 mmol) was heated in a sealed tube at 110 °C for 4 h. Evaporation of furan and recrystallization of the residue from benzene–hexane (1 : 10) afforded the 2-*furylacetate* (8) (502 mg, 81%), m.p. 75 °C, $\nu_{max.}$(KBr) 3 320 (NH), 1 735 (C=O), 1 130, and 1 165 (SO_2) cm^{-1}; δ 6.82 (1 H, dd, $J_{3,5}$ 1, $J_{4,5}$ 2 Hz, 5-H), 6.04 (1 H, dd, $J_{3,4}$ 3.25 Hz, 3-H), 5.85 (1 H, dd, 4-H), and 5.31 (1 H, d, $J_{NH,CH}$ 8.5 Hz, $-CH<$) (Found: C, 58.0; H, 6.1; N, 3.9. $C_{17}H_{21}NO_5S$ requires C, 58.1; H, 6.0; N, 4.0%).

(E)-2-*Aminohept-4-enoic Acid* (11) *Hydrochloride.*—A solution of the adduct (3e) (0.483 g, 1.37 mmol) and potassium hydroxide (0.75 g, 13.4 mmol) in ethanol–water 1 : 1 (15 ml) was heated at 60 °C for 1 h. The ethanol was evaporated off, and the residue brought to pH 3 with concentrated hydrochloric acid and extracted with chloroform (3 × 20 ml). Evaporation gave a thick oil which was dissolved in ether (20 ml) and saturated with gaseous ammonia to afford the ammonium salt of (10) (0.335 g, 78%). The ammonium salt of (10) (0.24 g, 0.76 mmol) was treated with sodium (0.20 g, 8.7 mmol) in liquid ammonia (20 ml) at reflux for 3 h. The mixture was then evaporated to dryness and to the residue 10% hydrochloric acid (5 ml) was added. The water layer was extracted with ether (8 × 15 ml) and evaporated and the residue extracted with warm ethanol (2 × 2 ml). Removal of the solvent and drying *in vacuo* afforded the hydrochloride of (11) (0.220 g, 85%), δ 5.80 (1 H, dt, $J_{4,5}$ 15.3, $J_{3,4}$ 6.2 Hz, 4-H), 5.35 (1 H, dt, $J_{5,6}$ 7.1 Hz, 5-H), 4.11 (1 H, t, $J_{2,3}$ 6.0 Hz, 2-H), 2.66 (2 H, dd, 3-H_2), 2.04 (2 H, dq, $J_{6,7}$ 7.3 Hz, 6-H_2), and 0.99 (3 H, t, Me).

Butyl 2-N-(p-*Tolylsulphonyl*)*aminoheptanoate* (12).—A solution of the adduct (3e) (1.0 g, 2.83 mmol) in acetic acid (5 ml) was hydrogenated at atmospheric pressure in the presence of 5% Pd–C catalyst (0.5 g). When the absorption of hydrogen ceased the catalyst was filtered off and the solvent evaporated. Recrystallization of the residue from hexane afforded the saturated *amino-ester* (12) (0.905 g, 90%), m.p. 48 °C, $\nu_{max.}$(KBr), 3 330 (NH), 1 740 (C=O), 1 340, and 1 160 (SO_2) cm^{-1}, δ 7.71 (1 H, d, $J_{NH,2}$ 9.0 Hz, NH), 3.85 (1 H, dt, $J_{2,3}$ 6.0 Hz, 2-H), 3.84 (2 H, t, J 6.2 Hz, OCH_2), 2.40 (3 H, s, ArMe), 1.84—1.04 (12 H, m, 6 × CH_2), and 1.01—0.71 (6 H, m, 2 × Me) (Found: C, 60.7; H, 8.5; N, 3.8. $C_{18}H_{29}NO_4S$ requires C, 60.8; H, 8.2; N, 3.9%).

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REFERENCES

[1] Preliminary communication: O. Achmatowicz, Jr., and M. Pietraszkiewicz, *J. Chem. Soc., Chem. Commun.*, 1976, 484.
[2] H. M. R. Hoffman, *Angew. Chem.*, 1968, **81**, 597.
[3] W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Edn. Engl.*, 1978, **17**, 476.
[4] R. Albrecht and G. Kresze, *Chem. Ber.*, 1965, **98**, 1431.
[5] O. Achmatowicz, Jr., and B. Szechner, *J. Org. Chem.*, 1972, **37**, 964; O. Achmatowicz, Jr., and J. Szymoniak, *ibid.*, 1980, **45**, 1228.
[6] E. J. Klimova and Y. A. Arbuzow, *Dokl. Akad. Nauk SSSR*, 1966, **167**, 1060.
[7] O. Achmatowicz and O. Achmatowicz, Jr., *Rocz. Chem.*, 1961, **36**, 1741.
[8] O. Achmatowicz, Jr., and A. Zamojski, *Rocz. Chem.*, 1968, **42**, 453.
[9] O. Achmatowicz, Jr., and B. Szechner, *Rocz. Chem.*, 1972, **46**, 513.
[10] O. Achmatowicz, Jr., unpublished data.
[11] A. T. Blomquist and I. Himics, *J. Org. Chem.*, 1968, **33**, 1156.
[12] E. J. Klimova and Y. A. Arbuzow, *Dokl. Akad. Nauk SSSR*, 1967, **173**, 1332; E. J. Klimova and Y. A. Arbuzow, *ibid.*, 1968, **180**, 865; B. B. Snider, *Acc. Chem. Res.*, 1980, **13**, 726.
[13] B. B. Snider, *J. Org. Chem.*, 1974, **39**, 255; 1979, **44**, 3567, 4229;
[14] J. F. Thompson, C. J. Morris, and I. K. Smith, *Annu. Rev. Biochem.*, 1969, **38**, 137; P. Wailes and M. C. Whiting, *Nature*, 1954, **174**, 130; L. Fowden, *Biochem. J.*, 1966, **98**, 57; G. Dardene and J. Casimir, *Phytochemistry*, 1968, **7**, 1401; G. Nass, K. Porala, and H. Zaehner, *Naturwiss.*, 1971, **58**, 603; L. Fowden, *Phytochemistry*, 1972, **11**, 1105; W. S. Chilton and G. Tsou, *ibid.*, 1972, **11**, 2853; S. Hatanaka, *Tetrahedron Lett.*, 1974, 3931; R. R. Doyle and B. Levenberg, *Phytochemistry*, 1974, **13**, 2813; S. Hatanaka and H. Katayona, *ibid.*, 1975, **14**, 1434.
[15] N. Neuss, B. B. Moloy, R. Shah, and N. de la Higuera, *Biochem. J.*, 1970, **118**, 571.