was slowly pipetted in. The temperature rose to 10 °C during the 15-min addition and then cooled back down to 6 °C. Then a 0.02-mol sample of the allylic chloride dissolved in 10 mL of THF was added dropwise to the clear solution at a moderate rate from the dropping funnel. A white precipitate (AgCl) formed almost immediately but the reaction was allowed to continue at room temperature in the dark under argon for 24 h. The reaction mixture was gravity filtered into a separatory funnel containing several chips of ice. The THF solution was diluted with ether, extracted several times with iced saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Most of the ether and the THF was removed under reduced pressure and the remaining impurities (THF, pyridine, and starting material) were distilled off under high vacuum at room temperature. The remaining viscous liquid is the desired hydroperoxide.

A. 3-Hydroperoxycyclohexene. This allylic hydroperoxide was prepared in an 83% yield from 3-chlorocyclohexene (Aldrich) as described above in the general procedure. The reaction was followed by VPC[27] (oven, 160 °C), the chloride peak (R_f 2 min) gradually disappearing with the concomitant growth of peaks corresponding to 2-cyclohexen-1-one and -1-ol (R_f ~5.5 min). The hydroperoxide could be distilled under high vacuum (0.1 mm) into a receiver cooled with liquid nitrogen by cautiously warming the distillation flask with a 40 °C water bath [lit. bp 47–48 °C (0.2 mm),[30] 39–40 °C (0.1 mm)[31]]: NMR ($CDCl_3$) δ 1.83 (m, 6 H), 4.5 (m, 1 H), 5.88 (m, 2 H, olefinic), 9.13 (broad s, 1 H, hydroperoxide).

B. 3-Hydroperoxy-2-methoxycyclohexene (1). Enol ether allylic hydroperoxide **1** was obtained in 75% yield from chloride **2** using the above general procedure. It can be stored for long periods of time unchanged at −20 °C under argon: NMR ($CDCl_3$) δ 1.60 and 2.03 (overlapping multiplets, 6 H, probably 4 H and 2 H, respectively), 3.53 (s, 3 H, methoxy), 4.43 (t, 1 H), 4.92 (t, 1 H), 9.17 (broad singlet, variable, 1 H, hydroperoxy); IR (neat) 3400 (m), 2941 (s), 1717 (w), 1660 (s), 1600 (w), 1428 (m), 1370 (m), 1329 (w), 1316 (w), 1292 (w), 1254 (w), 1212 (s), 1189 (s), 1165 (s), 1156 (s), 1087 (m), 1064 (m), 1026 (m), 971 (m), 922 (w), 877 (w), 803 (m), 710 cm^{-1} (w). The absorption at 3400 cm^{-1} is due to the hydroperoxy group, while the 1660 cm^{-1} absorption is attributable to the vinyl ether carbon–carbon double bond.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.28; H, 8.25.

C. 2-Methoxy-2-cyclohexen-1-yl Nitrate (3). When a $AgNO_3$/ether/$NaHCO_3$ system replaced the AgO_3SCF_3/THF/pyridine system in the general procedure above, in the case of 3-chlorocyclohexene, the results were essentially unchanged. In the instance of chloride **2**, workup, evaporation of the ether under reduced pressure, and distillation of the residue at 0.005 mm at room temperature into a dry ice cooled receiving flask gave a 50% yield of a compound whose spectral data and combustion analysis were consistent with 2-methoxy-2-cyclohexenyl nitrate. The compound gradually decomposed and turned yellow upon standing in air at room temperature. The compound remaining in the distillation flask proved to be hydroperoxide **1**: NMR ($CDCl_3$) δ 1.90 (m, 6 H), 3.53 (s, 3 H), 5.05 (t, 1 H), 5.45 (m, 1 H); IR (neat) 2968 (m), 1741 (m), 1675 (m), 1634 (s), 1445 (m), 1380 (m), 1334 (w), 1304 (m), 1279 (s), 1217 (s), 1195 (m), 1177 (m), 1164 (m), 1132 (w), 1097 (m), 1056 (m), 1029 (m), 973 (m), 948 (m), 926 (m), 860 (s), 813 (w), 802 (w), 756 (w), 716 (w), 691 cm^{-1} (w). The 1634 and 1279 cm^{-1} absorptions are attributable to the $-ONO_2$ group. MS (70 eV) *m/e* 173 (M^+), 111 ($M^+ - NO_3$).

Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40. Found: C, 48.05; H, 6.40.

Registry No.—Silver triflate, 2923-28-6; 3-hydroperoxycyclohexene, 4845-05-0; 3-chlorocyclohexene, 2441-97-6.

References and Notes

(1) Address correspondence to Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel.
(2) A. A. Frimer and P. D. Bartlett, in preparation.
(3) For reviews see (a) O. L. Magelli and C. S. Sheppard in "Organic Peroxides", Vol. I. D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1970, pp 1–19; (b) R. Hiatt, *ibid.*, Vol. II, pp 1–39 and 114–115; (c) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, pp 1–41; (d) A. V. Tobelsky and R. B. Mesrobian, "Organic Peroxides," Interscience, New York, N.Y., 1954, pp 1–11.
(4) F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 295 (1969).
(5) Aldrich Chemical Co.
(6) Silver triflate may also be used (vide infra); when, however, silver acetate was utilized, a 50% yield of 3-acetoxycyclohexene was obtained in addition to the desired allylic hydroperoxide.
(7) These precautions were taken to prevent the reduction of the AgCl salt, which precipitates out as Ag^0. The latter in turn can catalyze the decomposition of the hydrogen peroxide or hydroperoxide. In one run, in which the silver reaction was not run in the dark, the hydroperoxide formed from 3-chlorocyclohexene ignited spontaneously after isolation and concentration.
(8) The reaction proved much more rapid in this case when pyridine was used instead of bicarbonate.
(9) A synthesis, in low yield, of 2-cyclohexen-1-yl nitrate from cyclohexene, ferrous sulfate, and cupric nitrate has been reported.[10] The major product in that preparation was 2-cyclohexen-1-one and the reaction presumably proceeds via a free-radical process.
(10) F. Manisci, M. Cecere, and R. Gathi, *Gazz. Chim. Ital.*, **93**, 1288, 1294 (1963).
(11) The corresponding bromide has been synthesized by Garbisch.[12] Since we were interested in a general synthesis of allylic hydroperoxides, beginning from the corresponding ketone or alcohol, we proceeded as described in the text.
(12) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109, 2119 (1965).
(13) (a) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966); (b) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966); (c) J. B. Lee and T. J. Nolan, *Tetrahedron*, **23**, 2789 (1967); (d) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971); (e) E. I. Snyder, *ibid.*, **37**, 1466 (1972); (f) R. Aneja, A. P. Davies, and J. A. Knaggs, *Tetrahedron Lett.*, 67 (1974), and references cited therein.
(14) (a) H. O. House and R. K. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957); (b) R. L. Wasson and H. O. House, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 552.
(15) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).
(16) (a) M. A. Tobias, J. G. Strong, and R. P. Napier, *J. Org. Chem.*, **35**, 1709 (1970). (b) The low yields are attributable to a competing Favorskii rearrangement; see R. W. Mouk, K. M. Patel, and W. Reusch, *Tetrahedron*, **31**, 13 (1975), and references cited therein. (c) Methylated (4,4-dimethyl and 3-methyl) analogues of **8** have been synthesized by a different route; see E. Wenkert, N. F. Golob, S. S. Sathe, and R. A. J. Smith, *Synth. Commun.*, **3**, 205 (1973).
(17) K. E. Wilson, R. T. Seidner, and S. Masumune, *Chem. Commun.*, 212 (1970). This is the hydride of choice, since others tend to reduce the double bond in 2-en-1-ones as well.
(18) Interestingly enough alcohol **4** boils lower and has a shorter retention time on a Carbowax 20M VPC column than the corresponding ketone **6**, due to intramolecular hydrogen bonding.
(19) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970); see also E. W. Collington and A. I. Meyers, *ibid.*, **36**, 3044 (1971).
(20) (a) The ethoxy analogue of **2** has been synthesized[20b] by heating chlorocyclohexanone diethyl acetal with quinoline phosphate at an oil bath temperature of 170–190 °C with a gradually falling pressure of 20–90 mm [bp 92–96 °C (15 mm)]. (b) Winthrop Chemical Co., U.S. Patent 2 119 802 (1934), p 3, lines 19–31.
(21) The NMR spectrum of compound **2** was nearly identical with that of the corresponding bromo analogue, prepared according to the instructions of Garbisch.[12] As would be expected, the only observable difference occurred for the allylic hydrogen α to the halogen (see Table I).
(22) A. D. Walsh, *Trans. Faraday Soc.*, **42**, 99, 269 (1946).
(23) C. E. Frank, *Chem. Rev.*, **46**, 155, 162 (1950).
(24) For similar examples see (a) L. Bateman and H. Hughes, *J. Chem. Soc.*, 4594 (1952); (b) W. F. Brill, "Oxidation of Organic Compounds", *Adv. Chem. Ser.*, **No. 75**, 93 (1968).
(25) The aluminum salts tend at times to form a clear, viscous gel and the Na_2SO_4 paste aids in crystalline precipitate formation.
(26) Literature references for alternate methods of preparation: (a) D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4713, 4720 (1952); (b) H. Adkins, R. M. Elofsen, A. G. Rossow, and C. C. Robinson, *J. Am. Chem. Soc.*, **71**, 3622, 3629 (1949); (c) H. W. Durbeck, C. G. B. Frischkorn, and K. Hilpert, *Tetrahedron*, **27**, 2927, 2936 (1971).
(27) 9 ft × 0.25 in. aluminum column packed with 20% Carbowax 20M on Chromosorb W AW DMCS; helium carrier gas flow rate 85 mL/min; injector 200 °C; thermal detector 250 °C.
(28) Silver acetate may also be used.
(29) THe 3M Corp. technical information circular (April 8, 1969) lists the following properties: bp 162 °C (760 mmHg), 84 °C (43 mm), 54 °C (8 mm), density 1.696 (24.5 °C), formula weight 150.02, colorless liquid which fumes in moist air.
(30) E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121, 132 (1942).
(31) L. Bateman and G. Gee, *Proc. R. Soc. London, Ser. A.*, **195**, 376, 382 (1948).

Asymmetric Induction in the Synthesis of Thiophene-Containing Steroidlike Molecules via Olefinic Cyclization. Precoiling as Model Description for the Stereochemical Course of the Reaction

Anton A. Macco,* Rud J. de Brouwer, and Henk M. Buck

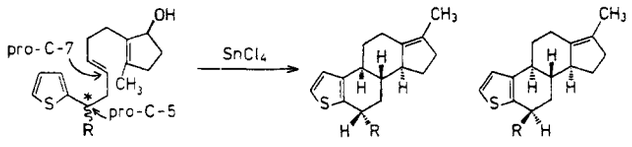
Department of Organic Chemistry, Eindhoven University of Technology, The Netherlands

Received February 18, 1977

Recently, Corvers et al.[1a] published the preparation of heterocyclic steroids with thiophene as A ring via a cationic

olefinic cyclization. These compounds could be converted into the corresponding "estrogens" with a trans-anti-trans structure.[1b] In order to obtain more insight into the stereochemical pathway of the cyclization process for these compounds and also for similar precursors as were developed by Johnson,[2,3] we introduced a chiral center at position pro-C-5 of compound 1 (R = CH_3, *tert*-butyl; Scheme I). In contrast

Scheme I[a]



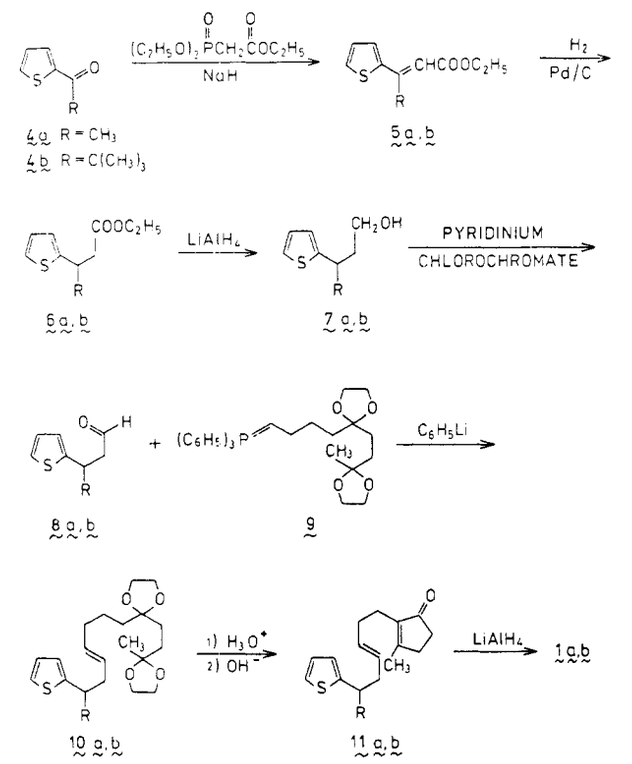
1a R=CH3 2a R=CH3 3a R=CH3
1b R=C(CH3)3 2b R=C(CH3)3 3b R=C(CH3)3

[a] The enantiomers are not drawn.

to the work of Johnson, who prepared diastereomeric-free 11α-methylprogesterone via olefinic cyclizations, the asymmetric center in our cases is one C–C distance further from the cyclization initiator, the allylic cation. Johnson ascribed the highly stereochemical outcome of the cyclization reaction in part to the nonbonded interaction in the transition state for the formation of the 11β isomer between the methyl groups attached to pro-C-11, pro-C-10, and possibly pro-C-13. Although in our substrates no alkyl substituent interaction is possible, there is still found *one* enantiomeric pair after cyclization of **1b** and 97% diastereomeric purity after cyclization of **1a.**

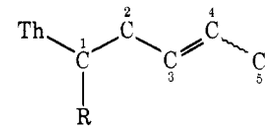
The preparation of the latter compounds is outlined in Scheme II. The crucial step in these syntheses was the Wittig

Scheme II



condensation of aldehydes **8a** and **8b** with ylide **9**[4] to yield *E* alkenes **10a** and **10b**, respectively. The *E* configuration of the alkenes is a prerequisite, since *Z* isomers fail to give tetracyclic material.[1] The reaction of **8** (R = H) carried out under Schlosser conditions[5] with butyllithium as base afforded *Z*

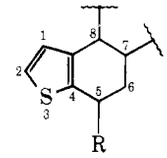
Table I[a,b]



Compd	C_2 (*E*)	C_2 (*Z*)	$\Delta\delta$	C_5 (*E*)	C_5 (*Z*)	$\Delta\delta$
10, R = H[c]	35.71	30.54	5.17	33.80	28.50	5.30
10a	43.41			33.75		
10b	34.85	30.88	3.97	33.61	28.54	5.07
11, R = H[c]	35.55			32.15		
11a	43.38			32.15		
11b	35.25	30.64	4.61	32.09	26.94	5.15

[a] Values given in parts per million downfield from Me_4Si. [b] Th = 2-substituted thiophene. [c] The values for these compounds are obtained from ref 1.

Table II[a]



Compd	C-5	C-6	C-7	C-8
2, R = H[b]	26.29	29.29	42.48	49.76
2a	33.22	39.22	42.70	50.33
2b	48.72	33.45	42.35	50.05

[a] Values in parts per million downfield from Me_4Si. [b] The values of this compound are obtained from ref 1.

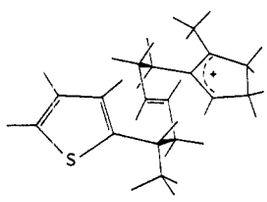
alkenes predominantly, whereas the use of phenyllithium resulted in the formation of *E* alkenes quantitatively.[6] Aldehydes **8a** and **8b** yielded *E* alkenes only if the reactions were carried out at temperatures between −30 and −50 °C. The configuration of the alkenes could be confirmed unequivocally with ^{13}C NMR spectroscopy.[7] The differences in chemical shift ($\Delta\delta$) between the allylic carbon atoms are characteristic for *E* and *Z* isomers. In Table I the data are given for the compounds under discussion.

Cyclization of alkenes **1a** and **1b** with 1.2 equiv of $SnCl_4$ afforded tetracyclic material in 50% yield, which is in good agreement with the experiments performed on the unsubstituted alkenes **1** (R = H).[1] This correspondence in yields is important, otherwise other factors than asymmetric induction might play a role. Variation of the $SnCl_4$ equivalency lowered the yield of tetracyclic product. The by-products consisted of polymers[8] (caused by the action of the Lewis acid on thiophene) and Diels–Alder products, generated from the unstable cyclopentenole ring. Upon cyclization of racemic **1a** and **1b**, **2a** and **2b** were formed, respectively. The corresponding diastereomer **3b** could not be detected. *Thus this cyclization occurred with complete asymmetric induction.* If this experiment was carried out with material in a pure enantiomeric form, the tetracyclic product would also be enantiomerically pure.[2] Upon cyclization of **1a**, 97% of the tetracyclic products consisted of **2a**, as shown by HPLC. Presumably, the remaining 3% is diastereomer **3a** (M^+ *m/e* 258; see Experimental Section). No further experiments have yet been carried out to increase the amount of **3a** for further ^{13}C NMR structure identification. Based on the ^{13}C NMR data (Table II) the configuration of the products **2a** and **2b** could be determined. If substituent R occupies the β position, a γ-gauche interaction would cause an upfield shift of C-7 in the order of 1–3 ppm as compared with **1** (R = H). A similar effect amounts to 6.3 ppm in methyl-substituted cyclohexanes, where the axial position of a methyl substituent has been firmly established.[9,14] This

effect is not observed. Therefore, we concluded that compounds were formed with R in the α position. The small downfield shift of C-8 is also in accordance with the α position of R.

The fact that the *tert*-butyl group renders a total asymmetric induction is not very surprising because of its bulkiness. However, such a high specificity induced by a relatively small methyl substituent at a large distance from the cyclization initiator is quite unexpected. This implies that we are dealing with a concerted cyclization[10] starting from the allylic cation via a distinct productlike transition state in which the nonbonded interaction between the alkyl group at pro-C-5 and the hydrogen atoms at pro-C-7 and at pro-C-9 is in favor of the α isomer. Apparently (at low temperatures) the initially formed ion pair of the allylic cation, resulting from heterolysis of the allylic–O bond, manifests itself via a conformational equilibrium in which the precoiled conformer given in Chart I (illustrated for methyl at pro-C-5 in α position) is the most

Chart I



favorable one. This conformer leads to the thermodynamically most stable tetracyclic product. Molecular orbital calculations are in progress to support this model description.

Experimental Section

The ^{1}H NMR data were obtained on a Varian EM-360A spectrometer using Me_4Si as internal standard (δ 0.00). The ^{13}C NMR data were recorded on a Varian HA-100 equipped with a Digilab FTS-NMR-3. Microanalyses were carried out in our laboratories by Messrs. P. van den Bosch and H. Eding. HPLC analyses were carried out by Mr. G. J. Bezemer. 2-Acetylthiophene (**4a**)[11] and pivaloylthiophene (**4b**)[12] were prepared according to the literature.

3-(2-Thienyl)but-2-enoic Acid Ethyl Ester (5a). To a suspension of 0.2 mol (6 g) of sodium hydride (80% in paraffin) in 100 mL of dimethoxyethane (under a nitrogen atmosphere) was added 0.2 mol (42.4 g) of triethyl phosphonoacetate at a temperature below 20 °C. After the solution was stirred for 1 h 0.2 mol (25.2 g) of acetylthiophene was added and refluxed for 16 h. The mixture was poured into water and the product extracted into ether. After the combined ether layers were dried with $MgSO_4$, the solvent was stripped off. Distillation gave 24 g of **5a** (61%), bp 147–154 °C (14 mm). This product was obtained as a mixture of *Z* and *E* isomers (*Z*/*E* ~3/10): NMR (CCl_4) δ 1.06–1.50 (2 t, 3, CH_2CH_3), 2.25–2.54 (m, 1, C=CCH_3), 3.84–4.39 (2 q, 2, CH_2CH_3), 5.73, 6.12 (m, 1, C=CH), 6.76–7.66 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpent-2-enoic acid ethyl ester (5b) was prepared as for **5a.** Only the *E* isomer was obtained: bp 99–103 °C (0.25 mm); yield 60%; NMR (CCl_4) δ 0.99 (t, 3, CH_2CH_3), 1.12 [s, 9, $C(CH_3)_3$], 3.86 (q, 2, CH_2CH_3), 5.99 (s, 1, C=CH), 6.54–7.20 (m, 3, ThH).

3-(2-Thienyl)butanoic Acid Ethyl Ester (6a). A mixture of 0.12 mol (23.8 g) of **5a** was hydrogenated in 150 mL of ethanol with 3 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 21.4 g (89%) of **6a:** bp 123 °C (12 mm); NMR (CCl_4) δ 1.13 (t, 3, CH_2CH_3), 1.31 (d, 2, CH_3), 2.15–2.85 (AA'B, 2, CH_2CHCH_3), 3.15–3.70 (m, 1, CH), 3.96 (q, 2, CH_2CH_3), 6.55–7.05 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpentanoic acid ethyl ester (6b) was prepared analogous to **6a:** yield 75%; bp 79–80 °C (0.25 mm); NMR (CCl_4) δ 1.00 (t, 3, CH_2CH_3), 0.95 [s, 9, $C(CH_3)_3$], 2.48–2.65 (AA'B, 2, CH_2CO_2), 3.12–3.38 (m, 1, $CHCH_2$), 3.88 (q, 2, CH_2CH_3), 6.63–7.04 (m, 3, ThH).

3-(2-Thienyl)butanol (7a). A solution of 0.02 mol (3.96 g) of **6a** in 10 mL of ether was added dropwise to a suspension of 0.02 mol (0.76 g) of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing, 1 N sodium hydroxide was added. Filtering, drying, and distillation yielded 2.81 g (90%) of **7a:** bp 121 °C (12 mm); NMR (CCl_4) δ 1.23 (d, 3, $CHCH_3$), 1.72 (m, 2, CH_2CH_2OH), 2.80–3.50 (m, 1, $CHCH_3$), 3.43 (t, 3, CH_2OH), 3.96 (s, 1, OH), 6.70–7.10 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpentanol (7b) was prepared as for **7a:** yield 99%; bp 82–85 °C (0.01 mm); NMR (CCl_4) δ 0.88 [s, 9, $C(CH_3)_3$], 1.50–2.08 (m, 2, CH_2CH_2OH), 2.61–2.87 (m, 1, CH), 3.28 (s, 1, OH), 3.18–3.42 (m, 2, CH_2OH), 6.60–7.03 (m, 3, ThH).

3-(2-Thienyl)butanal (8a). A solution of 6.4 mmol (1 g) of **7a** in 6 mL of dichloromethane was rapidly added to a suspension of 9.6 mmol (2.1 g) of pyridinium chlorochromate[13] in 12 mL of dichloromethane at room temperature. After 3 h of stirring no alcohol could be monitored. A fivefold excess of ether was added and the solution filtered over Florisil. Distillation afforded 0.9 g of aldehyde **8a** (91%): bp 104 °C (13 mm); NMR (CCl_4) δ 1.33 (d, 3, $CHCH_3$), 2.20–3.05 (m, 2, CH_2CHO), 3.20–3.87 (m, 1, $CHCH_3$), 6.43–7.06 (m, 3, ThH), 9.49 (t, 1, CHO).

3-(2-Thienyl)-4,4-dimethylpentanal (8b). This compound was prepared analogous to **8a:** yield 67%; bp 84 °C (0.03 mm); NMR (CCl_4) δ 0.88 [s, 9, $C(CH_3)_3$], 2.58–2.70 (m, 2, CH_2CHO), 3.17–3.40 (m, 1, $CHCH_2CHO$), 6.69–7.05 (m, 3, ThH), 9.39 (t, 1, CHO).

2,5-Bis(ethylenedioxy)-12-(2-thienyl)-(*E*)-tridec-9-ene (10a). Phenyllithium (16 mL, 2 N solution) was added to 0.032 mol (20.23 g) of phosphonium salt **9** in 75 mL of tetrahydrofuran (THF) at 0 °C under a nitrogen atmosphere. At −70 °C 0.032 mol of **8a** in 5 mL of THF was added, followed by a second equivalent of C_6H_5Li. The mixture was maintained between −30 and −50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 6.0 g (50%) of **10a:** NMR (CCl_4) δ 1.23 (s, 3, diox CH_3), 1.27 (d, 3, $CHCH_3$), 1.62 (s, 4, $O_2CCH_2CH_2CO_2$), 2.67–3.27 (m, 1, $CHCH_3$), 3.88 (s, 8, 4 $-OCH_2$), 5.10–5.47 (m, 2, CH=CH), 6.54–7.45 (m, 3, ThH).

2,5-Bis(ethylenedioxy)-13,13-dimethyl-12-(2-thienyl)-(*E*)-tetradec-9-ene (10b) was prepared as for **10a:** yield 41%; NMR (CCl_4) δ 0.92 [s, 9, $C(CH_3)_3$], 1.23 (s, 3, diox CH_3), 1.61 (s, 4, $O_2CCH_2CH_2CO_2$), 1.61–2.75 (m, 9, aliphatic H), 3.79 (s, 8, 4 OCH_2), 5.00–5.37 (m, 2, CH=CH), 6.60–7.18 (m, 3, ThH).

2-[6-(2-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enone (11a). A mixture of 6.8 mmol (2.6 g) of diketal **10a,** 30 mL of 0.5 N HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere during 1.5 h, whereupon the solution was rendered alkaline with 1 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane, chromatography yielded 1.6 g (86%) of pure product **11a;** bp 142–143 °C (0.01 mm).

Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.09. Found: C, 74.51; H, 8.15.

NMR (CCl_4) δ 1.25 (d, 3, $CHCH_3$), 1.50–2.57 (m, 13, aliphatic H), 2.57–3.26 (m, 1, $CHCH_3$), 4.97–5.40 (m, 2, CH=CH), 6.45–7.20 (m, 3, ThH).

2-[7,7-Dimethyl-6-(2-thienyl)-(*E*)-oct-3-enyl]-3-methylcyclopent-2-enone (11b) was prepared as for **11a:** yield 70%; bp 156–157 °C (0.01 mm).

Anal. Calcd for $C_{20}H_{28}OS$: C, 75.90; H, 8.92. Found: C. 75.70; H, 8.75.

NMR (CCl_4) δ 0.90 [s, 9, $C(CH_3)_3$], 1.89 (s, 3, cyclopent-CH_3), 1.98–2.67 (m, 11, aliphatic H), 5.00–5.11 (m, 2, CH=CH), 6.58–7.05 (m, 3, ThH).

2-[6-(2-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enol (1a). 2-[7,7-Dimethyl-6-(2-thienyl)-(*E*)-oct-3-enyl]-3-methylcyclopent-2-enol (1b). At −30 °C 1.8 mmol (78 mg) of $LiAlH_4$ was added in small portions to a solution of 1.8 mmol of ketone **1a** or **1b.** After 0.5 h 1 N sodium hydroxide was added. The mixture was filtered, dried, and concentrated at low temperature. Due to their susceptibility to dehydration, the cyclopentenols were used immediately for cyclization experiments. The products obtained from the cyclization experiments were first purified by column chromatography. On TLC pure tetracyclic material HPLC (Lichrosorb RP 18) was carried out to determine the diastereomeric ratio.

5,11α-Dimethyl-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]tridec-4-ene (2a). To a solution of 500 mg of unsaturated alcohol **1a** in 10 mL of dichloromethane at −95 °C, 1.2 equiv of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product extracted with dichloromethane. Chromatography yielded 250 mg of product (50%). HPLC analysis revealed that the product consisted of 97% **2a** and 3% **3a** (M^+ *m/e* 258).

Anal. Calcd for $C_{17}H_{22}S$: C, 79.01; H, 8.48. Found: C, 78.86; H, 8.48.

NMR (CCl_4) δ 1.27 (d, 3, $CHCH_3$), 1.60 (s, 3, C=CCH_3), 1.00–3.30 (m, 14, aliphatic H), 6.66–6.95 (AB, 2, ThH).

5-Methyl-11α-*tert*-butyl-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]-

tridec-4-ene (2b) was prepared as for **2a**, yield 50%.

Anal. Calcd for $C_{20}H_{28}S$: C, 79.94; H, 9.39. Found: C, 80.07; H, 9.60. This product turned out to be diastereomeric free.

NMR (CCl_4) δ 1.00 [s, 9, $C(CH_3)_3$], 1.58 (s, 3, $C{=}CCH_3$), 1.80–2.90 (m, 14, aliphatic H), 6.70–6.95 (AB, 2, ThH).

Acknowledgment. The authors are indebted to Dr. Jan W. de Haan and Miss Marianne E. van Dommelen for recording and interpretation of spectral data and for helpful discussions during the course of this work. This investigation has been supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

Registry No.—**1a**, 62815-66-1; **1b**, 62815-67-2; **2a**, 62815-68-3; **2b**, 62815-69-4; **3a**, 62928-71-6; (*E*)-**5a**, 62815-70-7; (*Z*)-**5a**, 62815-71-8; **5b**, 62815-72-9; **6a**, 62815-73-0; **6b**, 62815-74-1; **7a**, 62815-75-2; **7b**, 62815-76-3; **8a**, 62815-77-4; **8b**, 62815-78-5; **9**, 62815-79-6; **10a**, 62815-80-9; **10b**, 62815-81-0; **11a**, 62815-82-1; **11b**, 62815-83-2; triethyl phosphonoacetate, 867-13-0; 2-acetylthiophene, 88-15-3; 2-pivaloylthiophene, 20409-48-7.

References and Notes

(1) (a) A. Corvers, J. H. van Mil, M. M. E. Sap, and H. M. Buck, *Recl. Trav. Chim. Pays-Bas*, **96**, 18 (1977); (b) A. Corvers, J. W. de Haan, and H. M. Buck, to be published; A. Corvers, Thesis, Eindhoven University of Technology, March 1977.
(2) W. S. Johnson and G. E. Dubois, *J. Am. Chem. Soc.*, **98**, 1038 (1976).
(3) W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Am. Chem. Soc.*, **98**, 1039 (1976).
(4) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).
(5) M. Schlosser and K. F. Christman, *Angew. Chem., Int. Ed. Engl.*, **5**, 126 (1966).
(6) A. Corvers, P. Scheers, and H. M. Buck, unpublished results.
(7) J. W. de Haan and L. J. M. van de Ven, *Org. Magn. Reson.*, **5**, 147 (1973).
(8) Bruce, Challenger, Gibson, and Allenby, *J. Inst. Pet. Technol.*, **34**, 226 (1948).
(9) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1827 (1974).
(10) This is also confirmed for phenyl analogues. See P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkman, *J. Am. Chem. Soc.*, **95**, 7502 (1973).
(11) "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 14.
(12) "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 8.
(13) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.* 2647 (1975).
(14) F. W. Vierhapper and R. L. Willer, *Org. Magn. Reson.*, **9**, 13 (1977).

An Unusual Side Reaction of 1-Succinimidyl Esters during Peptide Synthesis

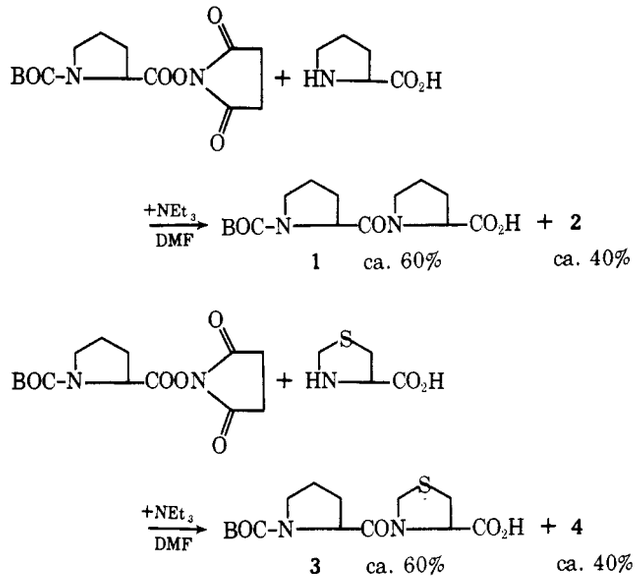
Jaroslav Šavrda

Institut Pasteur, Service de la Tuberculose, 75 Paris (15°), France[1]

Received January 25, 1977

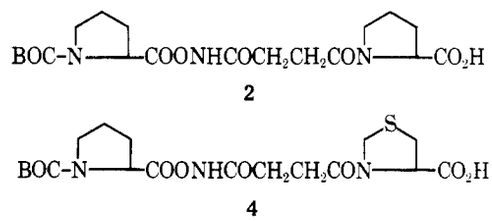
Peptide bond formation mediated through 1-succinimidyl ester couplings in aqueous or nonaqueous solvents is a standard procedure of peptide synthesis.[2] In the present communication we wish to report the observation of a new side reaction of 1-succinimidyl esters.

Coupling of a N-protected amino acid 1-succinimidyl ester with a free amino acid in anhydrous dimethylformamide in the presence of triethylamine results usually in high yields of the dipeptide derivative, as loss through hydrolysis of the activated ester is minimized. As an example, the preparation of *N*-benzyloxycarbonylglycyl-L-proline, containing an 85% ^{13}C-enriched proline residue,[3] is described in the Experimental Section. However, when *N*-tert-butyloxycarbonyl-L-proline 1-succinimidyl ester was coupled under identical conditions with free proline or 4-thiazolidinecarboxylic acid, the expected N-protected dipeptides **1** and **3** were accompanied by secondary products formed in nearly the same amount

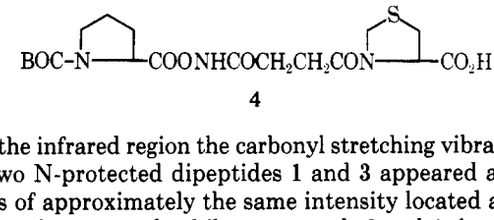


(BOC = *tert*-butyloxycarbonyl)

(contaminants **2** and **4**). Coupling of the activated ester with the sodium salt of proline in an ethanol–water mixture resulted in an important hydrolysis of the ester. The by-products **2** and **4**, which were not chromatographically identical, could not be obtained pure enough for elemental analysis. However, they were obtained free from the corresponding N-protected dipeptides and accompanied only by a trace amount of proline or 4-thiazolidinecarboxylic acid through repeated precipitations. Infrared and NMR spectroscopy as well as mass spectrometry have shown the contaminants to have structures **2** and **4**.



2



4

In the infrared region the carbonyl stretching vibrations of the two N-protected dipeptides **1** and **3** appeared as three bands of approximately the same intensity located at 1605, 1682, and 1755 cm^{-1}, while compounds **2** and **4** showed two strong absorptions centered at 1605 and 1685 cm^{-1} and a band of medium intensity at 1790 cm^{-1}. The appearance of an absorption at higher frequency (1790 cm^{-1}) is consistent with the presence of a carbonyl group implicated in a *O*-acylhydroxylamine linkage.[4]

The general aspect of the proton NMR spectra of contaminants **2** and **4**, in chloroform solution, was essentially the same as that of the corresponding dipeptides[5] **1** and **3**. In particular, the observation of two singlets at δ 1.40 (smaller) and 1.47 ppm (larger) for compound **2** and at δ 1.43 (smaller) and 1.49 ppm (larger) for compound **4** confirmed the presence of the *tert*-butyloxycarbonyl group. On the other hand, contaminants **2** and **4** presented an additional unresolved peak centered at δ 2.75 ppm, corresponding to four protons, which was absent from the spectrum of **1** and **3**, and which is assigned to the methylene protons of the succinic acid group.

Mass spectra of the methylated (diazomethane) contaminants **2** and **4** confirmed the proposed structure and showed that methylation occurred on the carboxylic acid function and on the nitrogen proton of the *O*-acylhydroxylamine derivatives **2** and **4**. The observed fragmentation of the methylated