Journal of Organometallic Chemistry 177 (1979) 245—253

TOTAL SYNTHESIS OF STEROID ANALOGUES BY ORGANOMETALLIC PROCEDURES *

G P CHIUSOLI, G SALERNO, E BERGAMASCHI,

Istituto di Chimica Organica, Universita, Via D Azeglio 85, 43100 Parma (Italy)

G D ANDREETTI, G BOCELLI and P SGARABOTTO

Istituto di Strutturistica Chimica, Università, and Centro di Studio per la Strutturistica Diffrattometrica, CNR, Via D Azeglio 85 43100 Parma (Italy)

(Received March 19th, 1979)

Summary

The synthesis of steroid-type structures has been achieved by means of a series of coupling, alkylation, carbonylation and cyclization steps, all of which involve organometallic reagents or catalysts The ring closures are effected with carbonyl complexes of nickel and with tin tetrachloride. The X-ray structure of the main product resulting from two successive cyclizations is described

Introduction

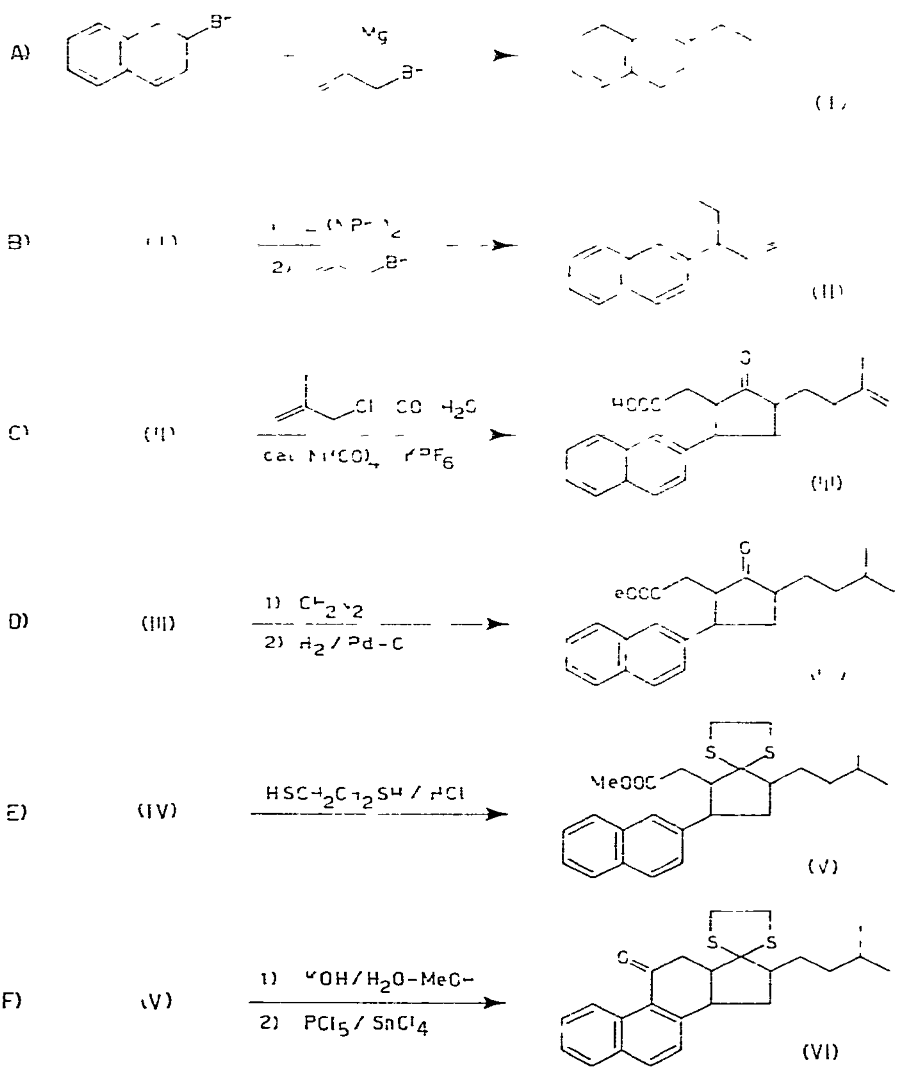
During the last two decades organometallic chemistry has developed to the point that applications to syntheses of rather complex molecules are possible Steroids and their analogues have recently attracted the interest of workers in organometallic chemistry [1,2]. We report here a total synthesis of a molecule containing the steroid skeleton as a model of a general procedure based on C—C coupling and annulation reactions. The key-step is based on a ring-forming carbonylation, which was shown by us to be particularly effective with 1,5-hexadiene systems [3]

Results and discussion

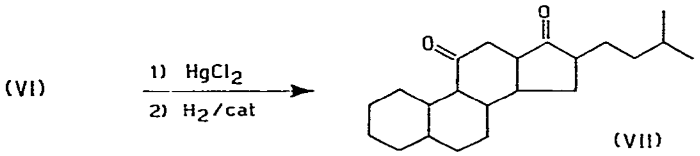
The synthesis consists of steps A—F

---

* Dedicated to Professor H Normant on the occasion of his 72nd Birthday on June 25th 1979



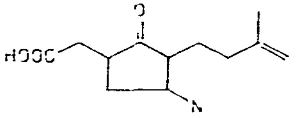
Product VI contains the steroid skeleton Work is in progress to hydrogenate it to the diketone VII.



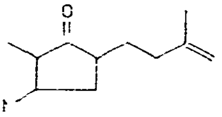
Step A was achieved by conventional Grignard methods [4] An alternative procedure consists of the reaction of allylnickel halides with 2-bromonaphthalene [5].

Step B, consisting of the allylation of 2-allylnaphthalene, was easily and selectively performed by metallation of the methylene group with lithium diisopropylamide, followed by reaction with allyl halide [6].

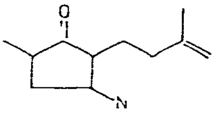
Carbonylation (step C) was carried out on the resulting 3-(2-naphthyl)-1,5-hexadiene (II) under mild conditions (50—60° C) simply by passing carbon monoxide into an acetone/water solution of II containing tetracarbonylnickel and potassium hexafluorophosphate. Most of the product obtained consisted of diastereomeric acids of type III and IIIa (N = naphthyl) which gave rise to two main GLC peaks. Other by-products, resulting from intermediate steps in the carbonylation process, were formed in minor amounts (IIIb—IIIg), their structures were indicated by familiar mass fragmentation patterns [3] but they have not been investigated further.



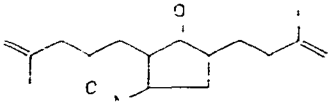
(IIIa)



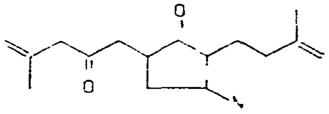
(IIIb)



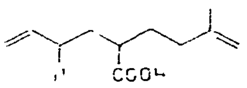
(IIIc)



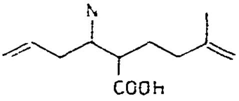
(IIId)



(IIIe)



(IIIf)



(IIIg)

After methylation, the NMR spectrum of a III + IIIa mixture shows various signals from the methoxyl group. The main absorptions are at τ 6.6 and 6.4 ppm. Structure IIIa must correspond to the compounds absorbing at lower field. It results from attack of the methallyl group at the wrong side (C(1)) of the hexadiene system. III and IIIa were obtained in a combined yield of ca 27%. However, almost 60% of the 2-naphthylhexadiene used was recovered, and optimization should lead to far better results. Since one diastereoisomer of type III is the precursor of the cyclized compound VI, and IIIa cannot give rise to a ring with the naphthyl group, we decided to proceed to the final cyclization step before separating the desired compound. Compound III, however, could not be subjected as such to a Friedel—Crafts-type cyclization, because of the tendency of its acid chloride to give a lactone and the ease of addition of hydrogen chloride to the double bond of the methallyl group. Thus the mixture of acids III and IIIa was esterified with diazomethane, hydrogenated with H_2/Pd to saturate the double bond (step D), and protected by reaction of the carbonyl group with ethanedithiol [7] (step E). The carboxyl group was freed again by alkali treatment, transformed into the acid chloride by means of phosphorus pentachloride and subjected in situ to Friedel—Crafts-type cyclization with tin tetrachloride [8] (step F). This cyclization is regiospecific, the ring

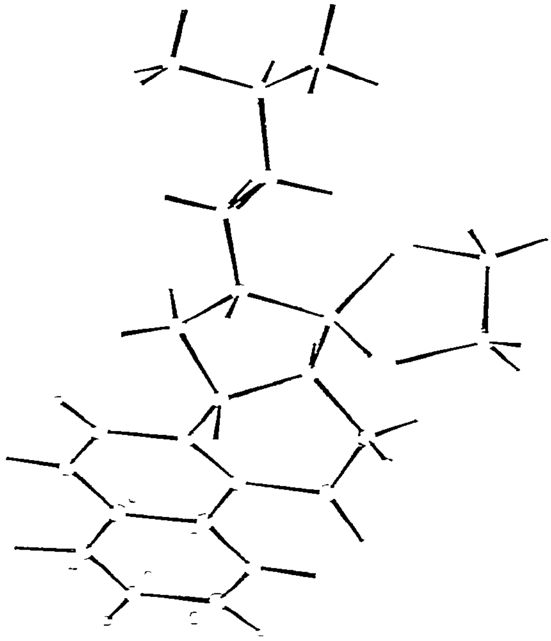


TABLE 1

ATOMIC COORDINATES (X10^4) FOR HEAVY ATOMS AND ATOMIC COORDINATES (X10^3) FOR HYDROGEN ATOMS

	x/a	*y/b*	*z/c*		*x/a*	*y/b*	*z/c*
S(1)	8 895(1)	2410(1)	10 680(2)	H(1)	803(3)	—28(4)	18(7)
S(2)	9 133(1)	4040(1)	7 823(2)	H(2)	755(3)	—75(5)	—373(8)
O(1)	8 760(2)	—226(3)	3 654(6)	H(3)	580(4)	47(5)	—590(9)
C(1)	7 454(4)	279(5)	—898(9)	H(4)	471(4)	221(5)	—432(8)
C(2)	7 055(5)	5(6)	—2 997(10)	H(5)	524(3)	408(5)	241(8)
C(3)	6 096(5)	699(7)	—4 256(11)	H(6)	461(3)	359(4)	—133(7)
C(4)	5 538(5)	1670(7)	—3 378(10)	H(7)	868(3)	91(4)	737(7)
C(5)	5 916(4)	1995(5)	—1 183(9)	H(8)	932(3)	137(3)	566(6)
C(6)	6 906(3)	1277(4)	124(7)	H(9)	815(3)	322(3)	445(6)
C(7)	7 278(3)	1632(4)	2 308(7)	H(10)	701(3)	239(4)	659(7)
C(8)	6 688(3)	2656(4)	3 083(8)	H(11)	650(3)	500(4)	441(8)
C(9)	5 710(3)	3356(5)	1 707(10)	H(12)	590(4)	464(5)	585(9)
C(10)	5 348(3)	3013(5)	—336(10)	H(13)	713(4)	410(5)	940(1)
C(11)	8 293(3)	862(4)	3 856(8)	H(14)	1048(5)	137(6)	997(1)
C(12)	8 740(3)	1443(4)	5 793(7)	H(15)	1051(4)	174(5)	1282(9)
C(13)	8 082(3)	2796(4)	5 844(8)	H(16)	987(5)	385(6)	1160(9)
C(14)	7 076(3)	3001(4)	5 405(8)	H(17)	1081(4)	313(5)	1055(9)
C(15)	6 580(4)	4367(5)	5 830(10)	H(18)	640(4)	636(5)	806(8)
C(16)	7 288(4)	4432(5)	8 027(10)	H(19)	743(4)	599(5)	741(8)
C(17)	8 324(4)	3437(4)	8 021(8)	H(20)	720(4)	566(5)	1183(8)
C(18)	10 067(5)	2069(8)	10 998(13)	H(21)	838(4)	520(5)	1125(8)
C(19)	10 100(5)	3248(8)	10 468(15)	H(22)	769(3)	757(4)	984(8)
C(20)	7 115(5)	5729(6)	8 489(13)	H(23)	835(4)	801(5)	1413(9)
C(21)	7 619(5)	5881(7)	10 839(12)	H(24)	890(4)	644(6)	1346(1)
C(22)	7 525(6)	7210(7)	11 164(14)	H(25)	807(4)	676(5)	1463(1)
C(23)	8 195(8)	7197(9)	13 455(16)	H(26)	607(4)	831(5)	917(1)
C(24)	6 519(8)	8169(9)	10 834(20)	H(27)	669(4)	894(5)	1125(9)
				H(28)	613(4)	807(5)	1193(9)

TABLE 2

BOND DISTANCES AND ANGLES IN COMPOUND VI

a Bond distances (Å)

S(1)—C(17)	1 913(7)	C(8)—C(14)	1 577(7)
S(1)—C(18)	1 767(9)	C(9)—C(10)	1 417(9)
S(2)—C(17)	1 799(8)	C(11)—C(12)	1 579(7)
S(2)—C(19)	1 972(9)	C(12)—C(13)	1 502(6)
O—C(11)	1 203(5)	C(13)—C(14)	1 538(7)
C(1)—C(2)	1 434(9)	C(13)—C(17)	1 598(8)
C(1)—C(6)	1 374(7)	C(14)—C(15)	1 510(7)
C(2)—C(3)	1 483(10)	C(15)—C(16)	1 631(9)
C(3)—C(4)	1 311(10)	C(16)—C(17)	1 602(8)
C(4)—C(5)	1 495(9)	C(16)—C(20)	1 471(10)
C(5)—C(6)	1 532(7)	C(18)—C(19)	1 481(11)
C(5)—C(10)	1 341(8)	C(20)—C(21)	1 578(11)
C(6)—C(7)	1 501(7)	C(21)—C(22)	1 530(12)
C(7)—C(8)	1 336(6)	C(22)—C(23)	1 613(13)
C(7)—C(11)	1 624(7)	C(22)—C(24)	1 527(13)
C(8)—C(9)	1 532(7)		

b Bond angles (deg)

C(17)—S(1)—C(18)	103 2(5)	C(12)—C(13)—C(17)	114 0(7)
C(17)—S(2)—C(19)	101 8(5)	C(12)—C(13)—C(14)	112 2(10)
C(2)—C(1)—C(6)	118 3(8)	C(14)—C(13)—C(17)	110 6(8)
C(1)—C(2)—C(3)	127 2(9)	C(8)—C(14)—C(13)	115 9(6)
C(2)—C(3)—C(4)	117 5(7)	C(13)—C(14)—C(15)	102 0(9)
C(3)—C(4)—C(5)	117 6(11)	C(8)—C(14)—C(15)	113 6(7)
C(4)—C(5)—C(10)	116 9(8)	C(14)—C(15)—C(16)	99 7(9)
C(4)—C(5)—C(6)	125 0(8)	C(15)—C(16)—C(20)	111 6(8)
C(6)—C(5)—C(10)	118 0(6)	C(15)—C(16)—C(17)	111 0(6)
C(1)—C(6)—C(5)	114 4(6)	C(17)—C(16)—C(20)	118 0(11)
C(5)—C(6)—C(7)	124 3(10)	C(13)—C(17)—C(16)	96 4(6)
C(1)—C(6)—C(7)	121 3(10)	S(2)—C(17)—C(16)	117 4(10)
C(6)—C(7)—C(11)	126 8(8)	S(2)—C(17)—C(13)	111 8(6)
C(6)—C(7)—C(8)	115 6(7)	S(1)—C(17)—C(16)	111 8(5)
C(8)—C(7)—C(11)	117 5(6)	S(1)—C(17)—C(13)	117 7(7)
C(7)—C(8)—C(14)	115 3(9)	S(1)—C(17)—S(2)	102 5(4)
C(7)—C(8)—C(9)	118 5(6)	S(1)—C(18)—C(19)	107 0(10)
C(9)—C(8)—C(14)	126 3(10)	S(2)—C(19)—C(18)	106 9(8)
C(8)—C(9)—C(10)	126 3(10)	C(16)—C(20)—C(21)	114 1(10)
C(5)—C(10)—C(9)	117 4(10)	C(20)—C(21)—C(22)	112 8(8)
O—C(11)—C(7)	122 1(7)	C(21)—C(22)—C(24)	111 7(12)
C(7)—C(11)—C(12)	123 9(9)	C(21)—C(22)—C(23)	108 1(10)
O—C(11)—C(12)	114 0(9)	C(23)—C(22)—C(24)	116 8(10)
C(11)—C(12)—C(13)	108 0(6)		

c Selected torsional angles (deg)

C(7)—C(8)—C(14)—C(13)	38 5(12)	C(14)—C(15)—C(16)—C(20)	164 3(9)
C(7)—C(8)—C(14)—C(15)	156 1(9)	C(14)—C(13)—C(17)—S(1)	95 8(9)
C(12)—C(13)—C(14)—C(8)	—63 2(11)	C(14)—C(13)—C(17)—S(2)	—146 0(8)
C(17)—C(13)—C(14)—C(8)	168 3(8)	C(15)—C(16)—C(17)—C(13)	—5 0(10)
C(8)—C(14)—C(15)—C(16)	—167 8(8)	C(20)—C(16)—C(17)—C(13)	—135 5(9)
C(8)—C(7)—C(11)—C(12)	—21 0(14)	C(15)—C(16)—C(20)—C(21)	167 3(9)
C(7)—C(11)—C(12)—C(13)	—2 1(12)	C(17)—C(16)—C(20)—C(21)	—62 5(13)
C(11)—C(12)—C(13)—C(17)	166 8(8)	C(16)—C(20)—C(21)—C(22)	172 8(10)
C(11)—C(12)—C(13)—C(14)	40 1(11)	C(20)—C(21)—C(22)—C(23)	—171 2(10)
C(14)—C(13)—C(17)—C(16)	—23 0(10)	C(20)—C(21)—C(22)—C(24)	59 0(14)
C(14)—C(15)—C(16)—C(17)	30 5(10)		

closure occurring at the α-carbon atom of the naphthalene ring. By means of this reaction ca. 35% of the acid mixture used after protection was transformed into a solid product, which was purified by TLC and repeatedly crystallized from ethanol. Its crystal structure was determined by X-ray diffraction as reported below. Work is in progress to clarify the stereochemistry of the intermediate steps.

Molecular geometry of VI. A view of VI is represented in Fig. 1. The atomic coordinates are listed in Table 1. Bond distances, bond angles, and some torsional angles are reported in Table 2. The C—H bond distances range from 0.96(5) to 1.25(5) Å. Bond lengths and bond angles are mainly as expected. The configurational features shown by X-ray analysis are the *trans* C/D junction and the position of hydrogens at C(16) and at C(14), which are both on the same side of ring D. The 3-methylbutyl group is equatorial. Ring C adopts a conformation intermediate between twist-boat and half-chair (with the puckering coordinates suggested by Cremer and Pople [9] $Q = 0.53$ Å, $\theta_2 = 52.0°$, and $\phi_2 = 284.1°$).

The conformation of ring D is a distorted envelope with apex at C(17) ($Q = 0.44$ Å, $\phi_2 = 222.1°$) and that of the 1,3-dithiolane ring is midway between envelope and twist ($Q = 0.45$ Å, $\phi_2 = 72.0°$).

Intramolecular contacts cause some distortions within the naphthalene system with rings A and B individually planar but significantly non-coplanar (2.2°) and with C(11) and C(14) out by 0.102(10) and 0.055(10) Å from plane B.

Packing is mainly determined by Van der Waals interactions.

Experimental

The starting materials, 2-bromonaphthalene, allyl chloride, and methallyl chloride were pure Carlo Erba products.

Analyses were carried out by GLC (Varian Aerograph series 1400 and 2700) with Carbowax 20M (5% polyethyleneglycol) and SE 30 (5% silicone) columns, by IR spectroscopy (Perkin—Elmer Infracord 137 instrument), by ^{1}H NMR (Varian EM 360 and XL 100 instruments), and mass spectroscopy (MAT CH5 Varian instrument at 70 eV).

Separations were carried out on Merck silica gel by column chromatography or by TLC (Merck silica gel PF 254).

Melting points are uncorrected.

Preparations

2-Allylnaphthalene was prepared by a published method [4]. 3-(2-Naphthyl)-1,5-hexadiene was prepared according to the procedure described for monoallylation of active methylene groups (lithium diisopropylamide in tetrahydrofuran at —70°C and allyl bromide) [6]. An 85% yield of isolated product was obtained by column chromatography (n-hexane/ethyl acetate 98/2 on silica gel) M^+ 208, m/e 167, 152, 139, 128, 115, 89, NMR ($CDCl_3$) τ 2.2—3 (7 H, aromatic protons), 3.5—4.7 (2 H, CH=), 4.8—5.3 (4 H, CH_2=), 6.6 (quartet, J 7 cps, 1 H, allylic CH), 7.5 ppm (triplet, J 7 cps, 2 H, allylic CH_2).

Carbonylation of 3-(2-naphthyl)-1,5-hexadiene. 3-(2-Naphthyl)-1,5-hexadiene, 16.8 g, was placed into a 500 ml three-necked flask equipped with reflux condenser at —40° C, stirrer, dropping funnel and gas inlet tube. Acetone, 230 ml, KPF_6, 27 g, and H_2O, 70 ml, were added under nitrogen. A slow stream of carbon monoxide, ca. 4 l/h, was passed at room temperature into a 250 ml flask, connected with the reaction flask and containing 110 g of the complex bis(diethyl fumarate)nickel dibromomanganese [10] dissolved in 100 ml of methylcellosolve under nitrogen. The carbon monoxide stream reacted with the complex to form tetracarbonylnickel and carried the latter into the reaction flask, which was kept at —70° C. After 1 h the mixture was warmed at ca. 50° C and 14.3 ml of methallyl chloride, dissolved in 30 ml of acetone, were dropped into the solution during 20 min. A deep red colour developed, and this turned to green at the end of the reaction (5 h). The residual tetracarbonylnickel, together with little solvent and volatile materials was carried by nitrogen through a low temperature trap, then through a series of traps containing solutions of iodine in alcohol, which destroyed the toxic tetracarbonylnickel. (The procedure described is safe because handling of the latter compound is avoided.)

After distillation of the solvent and the usual treatment the residue was extracted with diethyl ether, acidic components were removed to leave an ethereal solution containing unreacted naphthylhexadiene, and probably ketones IIIb, c (M^+ 292) and IIId, f (M^+ 374), this portion was not investigated further. The acid components dissolved in $CHCl_3$, giving 8.1 g of a mixture containing 90% of acids III and IIIa. GLC of the methyl esters (SE 30 column at 270° C) showed two peaks at a 70/30 area ratio corresponding to stereoisomers (combined yield ca. 27%). Minor amounts of 3-methyl-3-butenoic acid and probably of IIIf + IIIg (M^+ 322) were also present, but were not investigated further.

A small amount of the methyl esters of III + IIIa was hydrogenated at the double bonds and separated by TLC on SiO_2 (ethyl/n-hexane 1/10). NMR ($CDCl_3$) of a single compound, coincident with the second and major GLC peak: τ 2.1—2.7 (7 H, aromatic protons), 6.5 (s, 3 H, OCH_3), 6.25—9.35 (12 H, aliphatic protons), 9.1 ppm (d, 6 H, J 6 cps, 2 CH_3). The NMR spectrum of a mixture corresponding to the first GLC peak differed in the OCH_3 absorptions, which were found at τ 6.30, 6.37, 6.52, and 6.64 ppm. Mass spectroscopy of both GLC peaks gave M^+ 352, m/e 279, 212, 208, 167, 154, 141, 128.

Hydrogenation of III + IIIa. The mixture of III + IIIa was esterified with CH_2N_2 and purified by column chromatography (SiO_2). The hydrogenation was carried out quantitatively in methanol with hydrogen and Pd—C 10%.

Protection of the carbonyl group. Ethanedithiol (9 ml) was mixed with 9.6 g of the hydrogenated mixture IV + IVa and dry HCl was passed into the solution for 2 h. A quantitative yield of protected products was obtained. Two main peaks in the 70/30 area ratio were observed by GLC. A small amount of the component corresponding to the major peak was separated by TLC on SiO_2 (ethyl acetate/n-hexane 1/10), saponified with KOH and converted to free acid V, m.p. 132—134° C ($EtOH/H_2O$). Methyl ester: M^+ 428, m/e 400, 367, 355, 335, 326, 167, 141, 131. NMR ($CDCl_3$) τ 2.1—2.8 (7 H, aromatic protons), 6.8 (s, 3 H, OCH_3), 6.6—9.4 (16 H, aliphatic protons), 8.9 ppm (d, 6 H, J 6 cps, 2 CH_3).

Cyclization of the protected ketone A solution of the acid mixture V + Va, 0 935 g, in dry benzene was stirred with PCl_5, 0 52 g, at 0° C After a few minutes the mixture was allowed to reach room temperature and after 1 h it was heated under reflux for 10 min. After cooling again at 0° C, 0 6 ml of $SnCl_4$ in 3 ml of dry benzene were added. The solution was stirred for 1 h, then a mixture of concentrated hydrogen chloride and ice was added until the red solution turned white Extraction with chloroform, washing with 10% NaOH, drying over sodium sulphate, and distillation of the solvent, left a thick oil, which was eluted with n-hexane/ethyl acetate 9/1 by TLC on SiO_2 A fraction (0 35 g), corresponding to compound VI, was obtained. Recrystallization from ethanol gave pure crystals. m p. 113°C About 0.4 g remained at the base of the TLC plate.

Crystal structure analysis of VI

Crystal data. $C_{24}H_{28}OS_2$, M = 396 6, triclinic, a = 16 535(3), b = 11 904(3), c = 6 267(2) Å; α 92 4(2), β 109 2(2), γ 64 1(1)°, U 1040 4 Å^3, Z = 2. space group $P\bar{1}$, Cu-K_α radiation, λ 1 5418 Å, μ(Cu-K_α) 45.4 cm^{-1} The sample used for data collection was recrystallized from ethanol as colourless prisms A crystal of 0.2 × 0.3 × 0 7 mm was used for intensities measurement Cell parameters were derived from rotation and Weissenberg photographs and then refined by least-squares of (θ, χ, φ) values of 18 reflections measured on the diffractometer. The intensities were measured at room temperature using Ni-filtered Cu-K_α radiation on a Siemens AED single crystal diffractometer. Data were scaled with respect to one reference reflection which was measured every 20 reflections. The number of independent reflections collected was 4321, 938 of which had $I \leqslant 2\sigma(I)$ and were considered unobserved

The structure was solved by direct methods using the program SHELX [11] and refined by anisotropic full-matrix least-squares down to R 0 10 A difference Fourier map computed at this stage of refinement revealed the position of the hydrogen atoms that were refined isotropically to a final R 0 084, R_w = 0.10 ($w = 1/\sigma^2(F_0)$, where $\sigma^2(F_0)$ were derived from counting statistics)

All the calculations were performed on a CYBER 76 computer of the Consorzio Interuniversitario dell'Italia Nord-Orientale. Casalecchio (Bologna) with financial support from the University of Parma

Observed and calculated structure factor amplitudes together with thermal parameters can be obtained from the authors on request

Acknowledgements

We thank Dr. E. Dradi of the Institute of Organic Chemistry for discussion of NMR spectra.

This work has received financial support by the Italian National Research Council

References

1 R L Funk and K P C. Vollhardt J Amer Chem Soc 99 (1977) 5483
2 G.H. Posner Amer Chem. Soc Div Org Chem Prepr 208 Honolulu 2—6 April 1979

3 G P Chiusoli Accounts Chem Res 6 (1973) 422 and ref cited therein G P Chiusoli G Cometti and V Bellotti Gazz Chim Ital 104 (1974) 259 G P Chiusoli G Sacchelli B Giudici G Cometti and V Bellotti ibid 107 (1977) 241
4 H Gilman N B St John and F Schulze Organic Syntheses Coll Vol II 1943 Wiley New York 425
5 M F Semmelhack and P M Helquist Organic Syntheses 52 (1972) 115
6 P E Pfeffer L S Silbert and J M Chirinko Jr J Org Chem 37 (1972) 451
7 H Hauptmann J Amer Chem Soc 69 (1947) 562
8 W S Johnson Organic Reactions 2 (1944) 126
9 D Cremer and J A Pople J Amer Chem Soc 97 (1975) 1354
10 F Guerrieri and G Salerno J Organometal Chem 114 (1974) 389
11 G Sheldrick SHELX Program for Crystal Structure Determination Cambridge (1976)