reflux for 1 h, which also gave rise to removal of the formyl group, probably via oxidation to carboxylic group followed by decarboxylation[9].

Treatment of the reaction mixture with sodium borohydride gave the isomeric methoxylated derivatives formulated as **4** (the NMR showed absence of the aldehyde proton, which was replaced by a pyrrol-α-H signal at δ 6.55, and the UV-absorption at 216 nm conformed with the literature data for an alkyl-substituted pyrrole), which were analyzed by GLC-m.s.[1].

The fragmentation patterns, characterized by peaks arising from cleavages adjacent to methoxyl groups (**4**) allowed the position of the original double bonds to be established as shown in **2** and **3**; peaks arizing by loss of methanol from the primary fragments also occurred and both the methoxylated derivatives gave the base peak at *m/e* 80. No evidence has been obtained to establish unambiguously the stereochemistry of the double bonds, but on the basis of the chemical shift of the allylic methylene protons (1.94 ppm), we tentatively assumed it to be *trans*[10].

The most polar component of the aldehyde fraction gave a single peak in GLC and a m.s. with substantially a single molecular ion at M^+/e 413, corresponding to a di-unsaturated C_{23} alkyl-3-substituted pyrrole-2-aldehyde (**5**). The UV- (λ_{max} 248, 302 nm; ε 6000 and 17,000), IR- (3445, 3250, 1660 and 1645 cm^{-1}) and NMR- [9.22 (1 H, s), 6.76 and 5.94 (each 1 H, d, J 2.4 Hz), 5.24 (4 H, t, J 6 Hz), 2.70 (2 H, t, J 6 Hz), 1.94 (8 H, q, J 6 Hz), 1.26 (bs) and 0.90 (3 H, distorted t) ppm spectra accord with this formulation. The methoxymercuration-demercuration procedure was also applied to this material. Direct GLC-m.s.[1] of the reaction mixture (organic layer) showed the presence of a monomethoxy derivative (M^+/e 417) and a dimethoxy derivative (M^+/e 449). The fragmentation patterns of the methoxylated materials were interpreted as shown in **6** and **7** and allowed the position of the original double bonds to be established as shown in **5**.

Ester fraction. Chromatography on 12% $AgNO_3$-impregnated silica gel in benzene of this fraction also gave 3 principal portions. The less polar portion (7 mg), examined by GLC-m.s.[1], contained 4 homologue components giving M^+/e at 447, 419, 405 and 391 (relative proportions 7, 40, 24 and 29%, respectively, determined from GLC peak areas). The mass spectra from all GLC peaks were marked by intense fragments at M^+-59 (loss of carbomethoxyl group) and *m/e* 138, which we supposed to be due to the ion c. From this we suggest that these correspond to alkyl-3-substituted pyrrole-2-carboxylic acid methyl esters **8**; the most relevant criteria confirming these assignements are the NMR- and UV-spectra. In the NMR this material showed 1 H doublets (J 2.4 Hz) at 6.64 and 5.84, a 3H s at 3.78, a 2H t (J 6 Hz) at 2.7 and also signals at 1.26 (bs) and 0.90 (distorted t) ppm. The UV-absorptions at 240 and 273 nm (ε, 5000 and 12,500 assuming a m.w. of 405) confirmed the relative position of the substituents (i.e. 2-carbomethoxy and 3-alkyl chain)[11]. The IR showed peaks corresponding to NH (3460 cm^{-1}) and C = O ester (1685 cm^{-1}).

The middle polar portion (15 mg) was a mixture of 2 compounds in the relative proportion of 7:3 giving in the GLC-m.s.[1] M^+/e at 445 and 417, respectively, and very similar fragmentations with major peaks at M^+-59 and *m/e* 138 (c). This together with UV, IR and NMR. [5.24 (2H, t, J 6 Hz), 1.96 (4H, q, J 6 Hz); disubstituted double bond] data of the mixture almost identical to those of **8** allowed us to suggest that these correspond to a C_{23} and C_{21} mono-unsaturated alkyl-3-substituted pyrrole-2-carboxylic acid methyl esters **9** and **10**, respectively. No attempts were made to locate double bonds.

The most polar fraction (10 mg) contained a single component giving in GLC-m.s.[1] M^+/e 443 corresponding to **11**; the UV, IR and NMR data, which inter alia excluded the presence of a conjugated diene, were consistent with this formulation.

Acid fraction. The minor, most polar fraction (6 mg), examined by m.s. contained 2 components giving M^+/e at 431 and 403 and a major peak at *m/e* 124 (ion d). Treatment with diazomethane gave a material identical in SiO_2-$AgNO_3$ TLC with the mixture of **9** and **10**.

Summary. A novel group of compounds characterized by saturated, mono- and di-unsaturated long alkyl chain (C_{18} to C_{23}) linked at position 3 of a pyrrol-2-aldehyde residue has been isolated from the marine sponge *Oscarella lobularis*, which also yielded a series of corresponding pyrrol-2-carboxylic acids and methyl esters.

G. Cimino, S. de Stefano and L. Minale[12]

Laboratorio per la Chimica di Molecole di Interesse Biologico del C.N.R., Via Toiano 2, Arco Felice (Napoli, Italy), 2 July 1975.

[9] The easy decarboxylation of pyrrole-2-carboxylic acid is well documented: R. Livingstone in *Rood's Chemistry of Carbon Compounds*, 2nd ed. (Ed. S. Coffey; Elsevier Scientific Publishing Company, Amsterdam 1973), vol. 4, p. 362.

[10] F. C. Stehling and K. W. Bocta, Analyt. Chem. *39*, 1467 and 1479 (1966).

[11] Reference[6], p. 76.

[12] Acknowledgments. We thank Mr. A. Milone for GLC-m.s. measurements and Mr. G. Scognamiglio for the technical assistance.

Chirality of (+)-Octoclothepin, a Stereospecific Neuroleptic Agent[1]

Two chiral neuroleptic agents exhibiting stereospecificity of biological action have been reported in the literature. These are methotrimeprazine, of which the (−)-enantiomer is the more potent[2] and butaclamol, of which the (+)-enantiomer is about as potent[3,4] as fluphenazine. The absolute configuration of (−)-methotrimeprazine is unknown, but that of (+)-butaclamol has been determined by X-ray crystal structure analysis[3].

We now find that the neuroleptic activity of octoclothepin[5,12] is confined to its (+)-enantiomer (see Table). This finding, though at variance with the earlier results

[1] 17th Communication on seven-membered heterocycles; 16th Communication: D. Berney, T. J. Petcher, J. Schmutz, H. P. Weber and T. G. White, Experientia *31*, 1327 (1975).

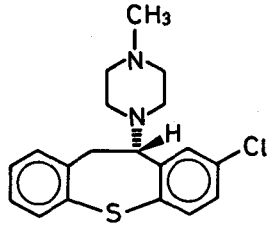
[2] S. Courvoisier, R. Ducret, J. Fournel and L. Julou, C. r. Soc. Biol., Paris *151*, 1378 (1957).

[3] F. T. Bruderlein, L. G. Humber and K. Voith, J. med. Chem. *18*, 185 (1975).

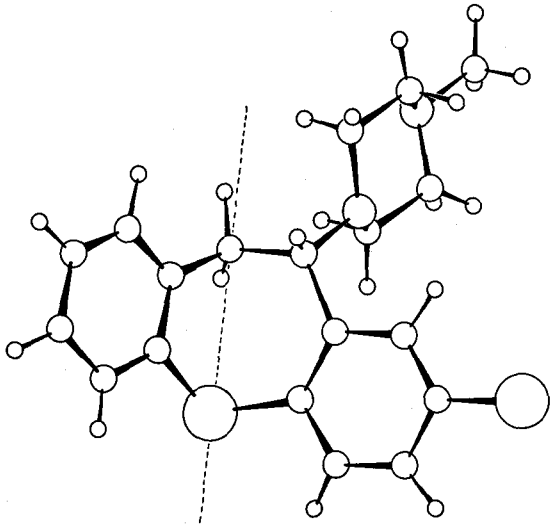
[4] W. Lippmann, T. Pugsley and J. Merker, Life Sci. *16*, 213 (1975).

[5] J. O. Jílek, K. Šindelář, J. Pomykáček, O. Horešovský, K. Pelz, E. Svátek, B. Kakáč, J. Holubek, J. Metyšová and M. Protiva, Coll. Czech. chem. Commun. *38*, 115 (1972).

of JÍLEK et al.[5], has been confirmed by subsequent work of that group[6]. X-ray crystal structure analysis has shown that the absolute configuration of (+)-octoclothepin is *S*, following the convention of CAHN, INGOLD and PRELOG[7]. These results may have implications for the geometry of the neuroleptic receptor site. The conformation and configuration of the molecule, as oberved in crystals of the base, are shown in the Figure. The structure was solved by direct methods from diffractometer data, refined by block-diagonal least-squares to $R = 0.039$, and the absolute configuration was determined by a HAMILTON R-factor ratio test[8], significant at better than the 0.005 level of probability, and by measurement of Friedel pairs.



(+), S-Octoclothepin



(+)-*S*-Octoclothepin: perspective drawing of the structure as observed in crystals of the base. The dotted line indicates the fold axis of the central seven-membered ring.

Neuroleptic activities of octoclothepin and its enantiomers (∅ = inactive with 20 mg/kg)

	Octoclothepin (±)	(+)	(−)
Apomorphine antagonism[a] rat (ED_{50} mg/kg s.c.)			
Δt: 30′	0.12	0.06	13.5
240′	0.06	0.03	∅
480′	0.43	0.13	
Amphetamine antagonism[b] rat (ED_{50} mg/kg s.c.)	0.12	0.07	2.55
Induction of catalepsy[c] rat (ED_{30}'' mg/kg s.c.)	1.98	1.47	∅

[a] Determined by a method based on JANSSEN et al.[9]. Following the s.c. administration of the test compound, the rats were treated after specified time intervals (Δt) with 2 mg/kg apomorphine-HCl i.v. The presence or absence of gnawing after this normally supra-maximal dose of apomorphine was noted 10, 20 and 30 min after its injection. The dose which reduces the frequency of gnawing to 50% was calculated[10].

[b] Determined after concurrent s.c. administration of a supra-maximal dose of 10 mg/kg D-amphetamine sulphate and the test substance. Beginning 30 min after the injections, 4 observations were made at 10-min intervals for the presence or absence of typical amphetamine-induced stereotypies. The average frequency of stereotypies at each dose level was determined and the dose which reduces the frequency of stereotypies to 50% was calculated[10].

[c] Measured by the method of STILLE et al.[11]. The average duration of catalepsy at various times after s.c. injection of the test substance was determined and, for the time interval at which the maximal cataleptic effect occurred, the drug dose which produces catalepsy lasting on average for 30 sec was derived from the duration/log-dose regression line. In each of these tests, 3 dose levels of test substance and 8 to 10 rats per dose level were employed.

Summary. The biological activity of the neuroleptic agent octoclothepin has been shown to be confined to its (+)-enantiomer which has the *S*-configuration.

T. J. PETCHER[13], J. SCHMUTZ[14], H. P. WEBER[13] and T. G. WHITE[14]

Sandoz Ltd., Pharmaceutical Division, Chemical Research, CH-4002 Basel (Switzerland), and Research Institute Wander Ltd., P. O. Box, 2747, CH-3001 Bern (Switzerland), 28 July 1975

[6] M. PROTIVA, personal communication.
[7] R. S. CAHN, C. K. INGOLD and V. PRELOG, Experientia *12*, 81 (1956).
[8] W. C. HAMILTON, Acta cryst. *18*, 502 (1965).
[9] P. A. JANSSEN, C. J. NIEMEGEERS and A. H. JAGENEAU, Arzneimittel-Forsch. (Drug Res.) *10*, 1003 (1960).
[10] J. T. LITCHFIELD and F. WILCOXON, J. Pharmac. *96*, 99 (1949).
[11] G. STILLE, H. LAUENER, E. EICHENBERGER, F. HUNZIKER and J. SCHMUTZ, Arzneimittel-Forsch. (Drug Res.) *15*, 841 (1965).
[12] We thank Dr. M. PROTIVA, Research Institute of Pharmacy and Biochemistry, Prague, for a gift of the enantiomers of octoclothepin.
[13] Sandoz Ltd., Pharmaceutical Division, Chemical Research, Basle, Switzerland.
[14] Research Institute Wander Ltd. (a Sandoz research unit), Berne, Switzerland.