Determination of the Absolute Configuration of (+)-*cis*-9-(3-Dimethylaminopropyl)-10-methyl-2-trifluoromethyl-9,10-dihydroanthracene (SKF-d-28175)† by *X*-Ray Crystallography

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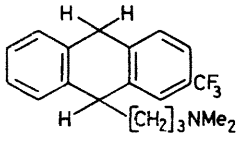
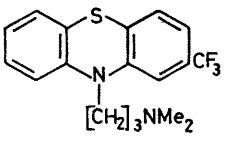
Summary The absolute configuration of the (+)-isomer of *cis*-9-(3-dimethylaminopropyl)-10-methyl-2-trifluoromethyl-9,10-dihydroanthracene has been determined from the *X*-ray crystal structure of its methyl iodide derivative.

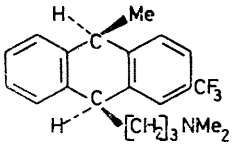
9-(3-DIMETHYLAMINOPROPYL)-2-TRIFLUOROMETHYL-9,10-DIHYDROANTHRACENE (**1**) is a dihydroanthracene analogue of triflupromazine (**2**), a phenothiazine derivative. Triflupromazine is a potent antipsychotic agent,[1,2] and replacement of the sulphur and nitrogen atoms with various other atoms does not result in appreciable loss in its antipsychotic activity.[2] Substitution of a methyl group at the 10-position of (**1**) produces (**3**) which may exist as *cis*-(**3a**) and *trans*-(**3b**) isomers. The *trans* isomer (**3b**) has very little antipsychotic activity.[3] However, the *cis* isomer (**3a**) shows neuroleptic properties in animals, although it is generally less potent than (**1**).[4] Furthermore, both *cis* and *trans* isomers can exist as two optical enantiomers, *e.g.* (**4a**) and (**4b**) for the *cis* isomer. It has also been shown that there is a considerable difference in the potency of the neuroleptic activity in different optical enantiomers.[3]



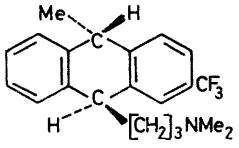
(1)



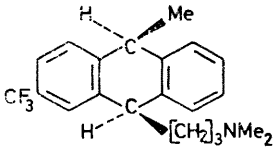
(2)



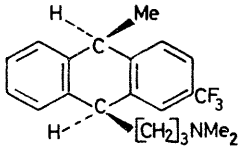
(3a) *cis*



(3b) *trans*



(4a)



(4b)

The crystal structure of the hydrochloride of SKF-d-28175 was determined by the *X*-ray diffraction.[5] However, the determination of absolute configuration was not successful owing to the presence of a pseudocentre of symmetry between the two crystallographically independent molecules in that structure.[5] We now report the absolute configuration of SKF-d-28175, established by *X*-ray crystal structure determination of its methyl iodide derivative which crystallizes in the form of its benzene solvate. The crystals are orthorhombic, $a = 8{\cdot}218(1)$, $b = 11{\cdot}664(1)$, $c = 29{\cdot}404(2)$ Å, space group $P2_12_12_1$, $Z = 4$. The intensity data of 2360 reflections were collected on a Syntex $P2_1$ diffractometer with Cu-K_α radiation. The structure was determined by the application of direct methods with the weighted multisolution tangent-refinement technique.[6] The refinements were carried out by the least-squares method with anisotropic temperature factors for non-hydrgen atoms and isotropic temperature factors for hydrogens. The absolute configuration of the molecule was determined by refining the parameters with the application of anomalous scattering factor of iodine atoms The refinement converged at $R = 0{\cdot}113$ for the (**4a**)-type structures and at $R = 0{\cdot}086$ for the (**4b**)-type structure. The (**4b**) configuration was further confirmed by using the $hk\bar{l}$ intensities of four strong reflections, 111, 113, 151, and 221. For these reflections, the calculated values of $(I_{hkl} - I_{hk\bar{l}})/I_{hkl}$ based on the (**4b**) configuration are +0·59,

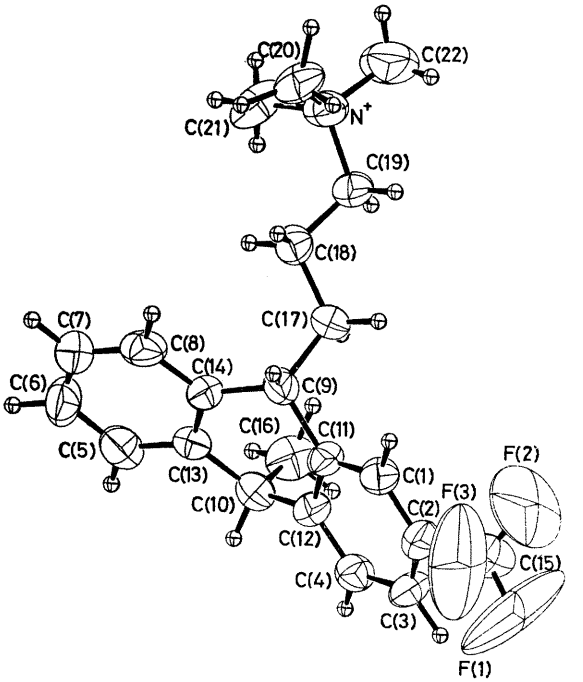


FIGURE. The configuration of the (+)-isomer of the methyl iodide derivative of SKF-d-28175 in ORTEP drawing.

† The title compound was assigned as SKF-d-28175 by the Smith, Kline and French Laboratories.

−0·66, −0·28, and +0·16, respectively, and the corresponding observed values are +0·58, −0·46, −0·23, and +0·12, respectively. The configuration of the molecule is shown in the Figure.‡

The two crystallographically independent molecules in the structure of the hydrochloride of SKF-d-28175 have slightly different conformations.[5] The structure which we report here has the same conformation as one of the molecules (molecule A) in the previous determination.[5]

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‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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[3] C. L. Zirkle and C. Kaiser, personal communication.
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