indoles, this is not the situation, as may be seen in Figs. 1–3. These substances have K'_{11} values; other pertinent information is listed in Table II.

CONCLUSION

The stoichiometry of the complex has not been delineated, but slopes of less than one as encountered in Figs. 1–3 imply a 1:1 complex. This does not prove the absence of other complex species (16).

Table II illustrates that all K'_{11} values, including that of methysergide, are of approximately the same magnitude. This indicates that a good portion of the capacity for complexation of the high molecular weight ergot alkaloids lies within the indole moiety of the molecule. The role the cyclic tripeptide portion plays in the mutual attraction of caffeine and related xanthines for these proteinaceous alkaloids has yet to be spelled out; however, it is likely that these protein substituents may alter binding in some way.

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Absolute Configuration of (+)-*trans*-2-*o*-Tolylcyclohexanol by X-Ray Crystallography

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Abstract □ The determination of the absolute configuration of the 3-nitro-4-bromobenzoate ester of (+)-*trans*-2-*o*-tolylcyclohexanol by X-ray crystallographic analysis is reported. The results give unequivocal proof that the original assignments of (1S,2R)-(+)-*trans*-2-*o*-tolylcyclohexanol, (1R,2R)-(−)-*cis*-2-*o*-tolylcyclohexanol, and (2R)-(+)-2-*o*-tolylcyclohexanone are correct.

Keyphrases □ X-ray crystallography—configuration, (+)-*trans*-2-*o*-tolylcyclohexanol □ (+)-*trans*-2-*o*-Tolylcyclohexanol—configuration confirmation, X-ray crystallography

The absolute configurations of (+)-*trans*-2-*o*-tolylcyclohexanol (I) and (−)-*cis*-2-*o*-tolylcyclohexanol (II) were reported in an earlier communication (1) on the basis of the positive Cotton effect of the carbonyl chromophore of the (+)-2-*o*-tolylcyclohexanone (III) obtained from the oxidation of I and II. Compounds I and II are two of several key reference compounds currently used in this laboratory in a study associated with Cotton effects of aromatic chromophores. Although the original assignment of absolute configurations of I and II was considered reliable, an unquestionable proof was desired. Unequivocal proof is now given from X-ray crystallographic analysis of the 3-nitro-4-bromobenzoate ester of I that the initial assignments of (1S,2R)-(+)-*trans*-2-*o*-tolylcyclohexanol for I, (1R,2R)-(−)-*cis*-3-*o*-tolylcyclohexanol for II, and (2R)-(+)-2-*o*-tolylcyclohexanone for III are correct.

Figure 1 shows perspective drawings of the three-dimensional structure and correct absolute configuration of the 3-nitro-4-bromobenzoate ester of (+)-*trans*-2-*o*-tolylcyclohexanol.

EXPERIMENTAL

(1S,2R)-(+)-*trans*-2-*o*-Tolylcyclohexyl 3-nitro-4-bromobenzoate was prepared by reaction of the known (+)-*trans*-2-*o*-tolylcyclohexanol (I) with 3-nitro-4-bromobenzoyl chloride in pyridine. The ester was purified by chromatography on silica gel, using a 50:50 benzene–hexane mixture, and recrystallized from hexane, m.p. 64.5–65.5°, IR (KBr) 1720 cm.$^{-1}$ (C=O), 1536, 1352 (NO_2), $[\alpha]_D^{27}$ + 100° (c 1.0, methanol).

The compound crystallizes in space group $P2_12_12$ with the following crystal data:

a = 7.922 ± 0.002 $\alpha = \beta = \gamma = 90°$
b = 26.342 ± 0.008 Dm = 1.4 (flotation in CsCl solution)
c = 18.694 ± 0.006 $D_{calc.}$ 1.426 Z = 8 molecules/unit cell

X-ray intensities were measured on a crystal approximately 0.13 × 0.38 × 0.53 mm. to $2\theta = 45°$, corresponding to an interplanar spacing of 0.93 Å, on a computer-controlled, four-circle diffractometer. The $\omega/2\theta$ scan technique using Nb-filtered Mo radiation was employed. A total of 2928 independent reflections were measured, of which 1852 had intensities greater than twice the standard deviation of their measurement. Absorption corrections were applied using the method of De Meulenaer and Tompa (2), and struc-

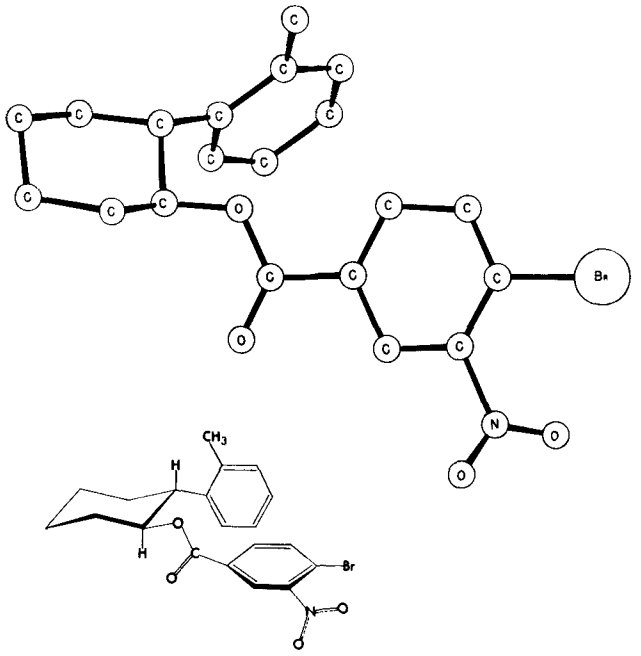

Figure 1—*(1S,2R)*−(+)-trans-*2*-o-*Tolylcyclohexyl 3-nitro-4-bromobenzoate.*

ture amplitudes were obtained from the intensities in the usual fashion. A sharpened, origin-removed, three-dimensional Patterson synthesis enabled the positions of the two unique bromine atoms to be found; the coordinates of the 50 other nonhydrogen atoms comprising the two molecules in the asymmetric unit were determined in subsequent electron-density maps based on phases calculated from the bromine positions. The positional and thermal parameters of all the atoms were refined using full matrix least squares until a discrepancy factor, R, of 0.089 was achieved.

Up to this point the normal bromine scattering curve, f_{Br}^0, was used with no correction for anomolous scattering of the X-rays by the bromine atoms. At this stage, the absolute configuration of the molecule was determined by the following method. The true bromine scattering curve, including anomolous scattering effects, $f_{Br} = f_{Br}^0 + \Delta f_{Br}' + i\Delta f_{Br}''$, was then applied; structure factors were calculated for molecules with atom coordinates x, y, and z and for molecules with atom coordinates $-x$, $-y$, and $-z$. That is, structure factors were calculated for both possible optical isomers. The discrepancy factor, $R = (\Sigma||Fo| - |Fc||)/\Sigma|Fo|$, was 0.098 for one structure and 0.086 for the other enantiomer. The difference is highly significant (3), and the absolute configuration for this structure is thus unambiguously established as the one giving the lower R. One last cycle of least-squares refinement, using the atom coordinates corresponding to the correct optical isomer but neglecting anomalous corrections to the scattering curve, brought R down to 0.079. Although hydrogen atoms could be located from a difference Fourier map, they were not included in the calculations since the additional significance does not compensate for the added cost of refinement for a structure of this size.

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Muscarinic Receptors: 4-Substituted-3-trimethylammoniumtetrahydrofuran Halides

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Abstract □ Preparation of the *cis*- and *trans*-4-hydroxy-3-trimethylammoniumtetrahydrofuran and 4-acetoxy-3-trimethylammoniumtetrahydrofuran halides and 3-trimethylammoniumtetrahydrofuran iodide is described. Weak muscarinic activity was noted for the unsubstituted 3-trimethylammoniumtetrahydrofuran salt, being about 1000-fold less potent than acetylcholine. The *trans*-hydroxy and *trans*-acetoxy compounds showed even less activity, and the *cis*-compounds were inactive.

Keyphrases □ 3-Trimethylammoniumtetrahydrofuran halides, 4-substituted—muscarinic receptors, synthesis, pharmacologic testing □ Muscarinic receptors—3-trimethylammoniumtetrahydrofuran halides, 4-substituted, synthesis, pharmacologic testing

The fundamental problem of relating molecular structure to biological activity at various drug receptors becomes extremely difficult when considering small conformationally mobile molecules such as acetylcholine. Regardless of the existence of preferred conformations in the solid state and in solution (1–5), it should not be assumed that these conformations are those in the drug–receptor surface complex (6).

Various conformationally rigid or semirigid cholinergic agents have been prepared to aid in determination of the architectural features of the drug–receptor complex on various cholinergic sites, *e.g.*, muscarinic, nicotinic, and acetylcholinesterase (7–12). Attempts which incorporate the least number of additional atoms have generally been most successful, although comparisons of closely related compounds in higher series also seem valid (12).

In this study, various analogs of 3-trimethylammoniumtetrahydrofuran iodide were prepared. This system