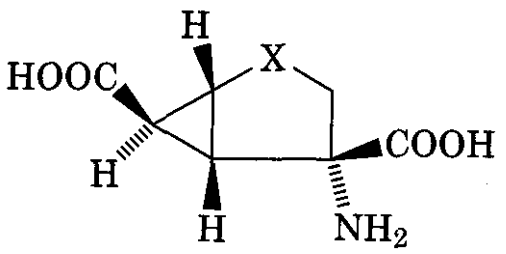
lustrates that the achievement of conformational integrity by incorporation of a flexible pharmacophore into a bulky, complex molecule may be at the expense of biological activity.

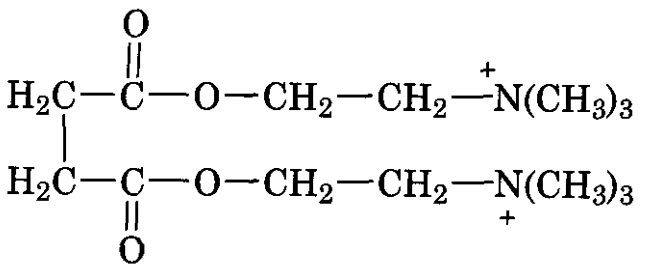
Rigidity was introduced into the glutamic acid moiety in a series of bioisosteric congeners (**46–48**) (34). These systems showed po-



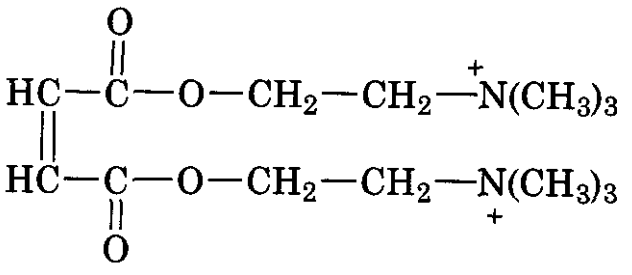
(46) X = CH_2
(47) X = O
(48) X = S

tent agonist activity at subpopulations of metabotropic glutamate receptors. The geometry of these congeners led to the conclusion that glutamic acid itself interacts with the metabotropic glutamate receptors in a fully extended conformation.

The rotational orientation of the ester moieties of the myoneural blocking agent succinyldicholine (**49**) was restricted by introduction of a double bond into the succinic acid portion (**50**), (**51**) (35). The E-fumarate ester



(49)



(50)

(**51**) was approximately one-half as potent as the flexible succinate ester (**49**), whereas the *Z*-maleate ester (50) was 1/40 as potent as the succinate. These results led to the conclusion that the molecular shape of the E-ester (51) more closely approximates that assumed by succinylcholine when it interacts with myoneural nicotinic receptors.

Restricted rotation was also introduced into the succinic acid moiety of succinyldicholine by preparation of the choline esters of *cis*- and *trans*-cyclopropane-1,2-dicarboxylic acids (52) and (53)(**36, 37**). Myoneural blocking activity was assessed in dogs (**37**) and cats (36) and, as indicated above for the E- and *Z*-olefinic esters (51) and (**50**), the extended *trans*-isomer (**53**) demonstrated much greater potency and a longer duration of action than those of the cis-isomer (**52**). The cyclobutane congeners (**54**) and (**55**) presented unexpected results that are difficult to rationalize: the *cis*-isomer (54) was much less potent than the trans-isomer (55)in a cat assay for myoneural blockade, but it presented a decidedly longer duration of action than that of the *trans*-isomer (36).

4 HOMOLOGATION OF ALKYL CHAIN OR ALTERATION OF CHAIN BRANCHING; CHANGES IN RING SIZE; RING-POSITION ISOMERS; AND SUBSTITUTION OF AN AROMATIC RING FOR A SATURATED ONE, OR THE CONVERSE

Change in size or branching of an alkyl chain on a bioactive molecule may have profound (and sometimes unpredictable) effects on physical and pharmacological properties. Alteration of the size and/or shape of an alkyl substituent can affect the conformational preference of a flexible molecule and may alter the spatial relationships of the components of the pharmacophore, which may be reflected in the ability of the molecule to achieve complementarity with its receptor or with the catalytic surface of a metabolizing enzyme. The alkyl group itself may represent a binding site with the receptor (through hydrophobic interactions), and alteration of the chain may alter its binding capacity. Position isomers of substituents (even alkyl groups) on an aromatic ring may possess different pharmacological properties. In addition to their ability to affect electron distribution over an aromatic ring sys-