was obtained from Sigma Chemical Co. Propranolol hydrochloride (Inderal HCl) was supplied by Ayerst Laboratories, Inc. (*R*)-Norepinephrine was obtained from Sigma Chemical Co. Phentolamine hydrochloride (Regitine HCl) was supplied by CIBA Pharmaceuticals. Methacholine chloride (Mecholyl) was obtained from Merck and Co.

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Antidepressant Agents. 9.[1] 3,3-Diphenylcyclobutylamines, a New Class of Central Stimulants

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3,3-Diphenylcyclobutylamine (**4**), *N*-methyl-3,3-diphenylcyclobutylamine (**6**), and *N*,*N*-dimethyl-3,3-diphenylcyclobutylamine (**7**) have been prepared and tested as potential antidepressant agents. The secondary (**6**) and tertiary (**7**) amines strongly decrease the accumulation of NA and 5-HT in brain slices in vitro and in vivo. The cyclobutylamines also cause motor stimulation. The most potent compound in this respect is the tertiary amine **7**. The increase in locomotion is not blocked by pretreatment with phenoxybenzamine, methergoline, or α-methyltyrosine. Pretreatment with pimozide or reserpine reduces the hyperactivity induced by **7**. This hyperstimulation seems to be caused by a mechanism of action which differs from that of amphetamine. **7** may cause increase in locomotion by release of dopamine from granular stores.

In a research program aiming at new antidepressant agents, we have investigated compounds showing an inhibitory activity on the neuronal accumulation of noradrenaline (NA) and of 5-hydroxytryptamine (5-HT). The preparation and pharmacological effects of a series of diphenylcycloalkylamines, e.g., 3,3-diphenylcyclopentylamines, 3,3- and 4,4-diphenylcyclohexylamines,[2] and 4,4-diphenyl-1-methylcyclohexylamines,[3] were recently reported. We have now included the four-membered ring analogues in our investigation and wish to report the synthesis and some pharmacological properties of 3,3-diphenylcyclobutylamines of general structure **1**.

The new compounds have been examined for reduction of the accumulation of NA, dopamine (DA), and 5-HT in mouse brain slices. The behavioral and toxicological effects of these compounds, including the interaction with 5-hydroxytryptophan (5-HTP), have also been studied in mice. Furthermore, an experimental comparison of the

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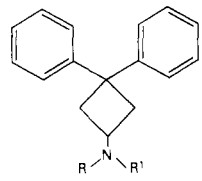

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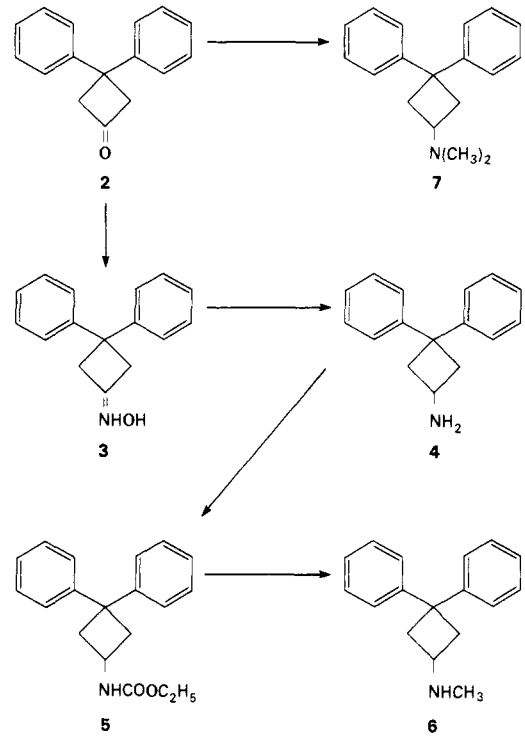
new compounds with amphetamine has been performed.

Chemistry. A number of methods were tried in order to construct the strained four-carbon ring (cf. ref 4). An attempt to react the ditosylate or the dimesylate of 2,2-diphenylpropane-1,3-diol with the sodium salt of diethyl malonate in analogy with a method described by Buchta and Geibel[5] failed. This reaction was expected to give a suitable intermediate, diethyl 3,3-diphenylcyclobutanedicarboxylate. However, complex mixtures were formed and the desired product could not be detected. Attempts were also made to cyclize the 1-bromo- or 1-tosyloxy-4,4-diphenylbutan-2-one ethylene acetal under alkaline conditions. This reaction was expected to give 3,3-diphenylcyclobutanone in analogy with a method discussed by Seebach.[6] However, no reaction took place.

Another possible route to the cyclobutanone seemed to be the oxidation of 3,3-diphenyl-1-methylenecyclobutane, which has been stated to be formed by a thermal cycloaddition reaction of 1,1-diphenylethylene and allene.[7] A crude product from such a cycloaddition reaction was thus oxidized with a potassium permanganate sodium periodate reagent and the desired cyclobutanone was isolated. However, the procedure was cumbersome and the yield was low.

During the course of our work a synthesis of 3,3-diphenylcyclobutanone appeared in the literature.[8] The ketone was prepared in low yield by the reaction of diphenylketene with 2 equiv of diazomethane.[9] The latter synthesis, although low yielding, was used and the desired amines were prepared from 3,3-diphenylcyclobutanone as shown in Scheme I.

Scheme I



Pharmacological Results

The quantitative data are given in Table I and in Figures 1 and 2.

Inhibition of the NA Accumulation in Vitro and in Vivo. The 3,3-diphenylcyclobutylamines decreased the accumulation of [^{3}H]-NA within the same concentration range as the tricyclic antidepressants desipramine and chlorimipramine. The secondary amine **6** and the tertiary amine **7** were more active in vitro than the corresponding primary amine **4**. This order of activity is similar to that found in the imipramine series[10,11] but is in contrast with our findings in the cyclopentyl- and cyclohexylamine series.[2] The new compounds also reduced NA accumulation in brain slices after ip administration in the same order of potency as in the in vitro studies. The amines **6** and **7** were equipotent with desipramine and amphetamine.

Inhibition of the 5-HT Accumulation in Vitro and in Vivo. The cyclobutylamines interfere with the accumulation of 5-HT in the order of potency: tertiary > secondary = primary. This order is similar to that observed in the imipramine series[11] but differs from the order observed in the cyclopentyl- and cyclohexylamine series.[2]

Inhibition of DA Accumulation in Vivo. The secondary amine **6** and the tertiary amine **7** reduced DA accumulation in striatal slices after ip administration, whereas the primary amine **4** and only a weak effect. However, the new compounds were weaker inhibitors of the accumulation of DA than of that of NA and 5-HT.

Potentiation of 5-HTP in Mice. Pretreatment with inhibitors of the accumulation of 5-HT potentiates the behavioral effects of 5-HTP, e.g., head twitches.[12] The two compounds **6** and **7**, which decreased 5-HT accumulation in vivo, also potentiated the behavioral effects of 5-HTP. Both **6** and **7** were as potent as chlorimipramine.

Mydriatic Effects and Acute Toxicity. The new compounds had weaker mydriatic effects than chlorimipramine. The order of potency of the mydriatic effects was secondary amine **6** > primary **4** > tertiary **7**. The iv toxicities of the new compounds were in the same range as those of the reference compounds.

Motor Activity. Animals receiving the three cyclobutylamines showed significantly increased locomotion compared with the control animals especially during the later phase of the observation period (Figure 1).

The hyperactivity and the behavioral effects were rather similar to those of amphetamine, characterized by motor excitation, irritability, sniffing, tremor, rearing, and stereotype-like behavior such as circling and repetitive movements of the head. The tertiary amine **7** was the most potent and its effect on locomotion was therefore further studied in an attempt to classify the mechanism of the central stimulation (Figure 2).

The DA receptor blocker pimozide[13] antagonized the hyperactivity, while the NA receptor blocker phenoxybenzamine[14] as well as the 5-HT receptor blocker methergoline[15] had no influence. Reserpine treatment, which results in a lowering of both NA and DA as well as 5-HT levels in the brain by impairment of the granular binding of monoamines,[16] reduced the effect of **7** strongly. The tyrosine hydroxylase inhibitor, α-methyltyrosine, which reduces both NA and DA levels in the brain,[17] did not counteract the hyperactivity.

For comparison, some corresponding experiments were performed with amphetamine instead of compound **7**. Pimozide suppressed the amphetamine-induced hyperactivity even below the level of the control. α-Methyltyrosine antagonized the effect of amphetamine resulting in normal activity (Figure 2).

Table I. Some Pharmacological Effects of 3,3-Diphenylcyclobutylamines

Compd	R	R¹	Inhibition of accumulation[a] In vitro, IC_{50}, μM NA	In vitro, IC_{50}, μM 5-HT	In vivo ED_{50}, μmol/kg ip NA	In vivo ED_{50}, μmol/kg ip 5-HT	In vivo ED_{50}, μmol/kg ip DA	Potentiation of 5-HTP,[b] ED_{50}, μmol/kg ip	Mydriatic effect,[c] PD_{200}, μmol/kg iv	Acute toxicity,[d] LD_{50}, μmol/kg iv
4	H	H	2.2 (1.0-3.9)	2.8 (1.4-5.1)	103 (78-151)	162 (116-309)	>154[e] (7%)	>38	15	192
6	H	CH_3	0.8 (0.4-1.6)	3.0 (1.3-6.4)	31 (15-55)	95 (61-194)	91	9 (5-14)	9	128
7	CH_3	CH_3	0.8 (0.4-1.4)	0.9 (0.6-1.4)	32 (22-44)	48 (34-72)	104	17 (9-30)	24	104
Desipramine			1.6 (0.7-5.1)	9.3 (4.9-16)	34 (25-51)	>66[e] (23%)	>100[e] (0%)	>170	63	116
Chlorimipramine			0.9 (0.6-1.8)	0.07 (0.04-0.10)	109 (75-439)	20 (16-25)	>113[e] (9%)	8 (5-11)	6	142
DL-Amphetamine			1.0 (0.7-1.3)	45 (33-72)	44 (20-56)	>100[e] (0%)	60	>27		

[a] Inhibition of 5-min accumulation of the labeled transmitter amines in slices of mouse hypothalamus (NA and 5-HT) or striatum (DA) expressed as the dose producing 50% inhibition, 95% confidence limits in parentheses. In vitro: the test compound was added to the incubation medium. In vivo: the mice were killed 0.5 h after the ip injections and the amine accumulation in brain slices was determined in vitro. [b] The dose of the test compound producing head twitches in 50% of the animals when given 1 h prior to 5-hydroxytryptophan (5-HTP), 90 mg/kg iv, 95% confidence limits in parentheses. [c] PD_{200} is the dose which increases the pupil diameter by 200%. [d] Lethality within 24 h after administration. [e] Percent inhibition at the highest dose tested is given in parentheses.

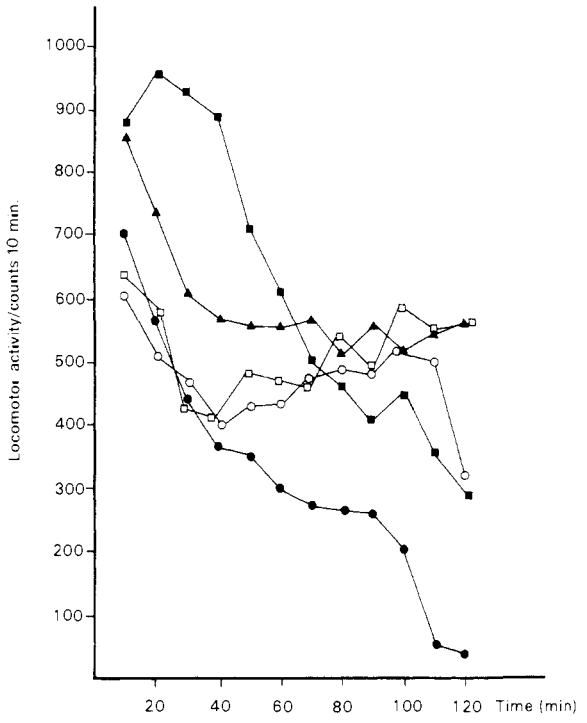


Figure 1. Locomotor activity in mice after giving compounds 4, 6, or 7 (20 mg/kg ip). Each value represents the mean activity for groups of six to eight mice. One-way analysis of variance was used over the total observation period (2 h), followed by Student's t test (two-tailed). Control (●—●), compound 4 (○—○), compound 6 (□—□), compound 7 (▲—▲), D-amphetamine (■—■).

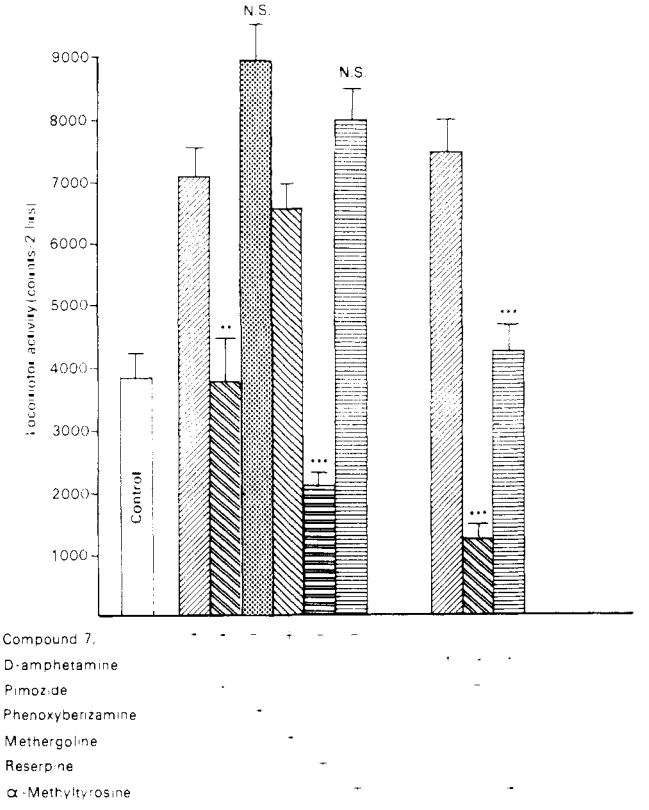


Figure 2. Hyperactivity induced by compound 7 and by D-amphetamine. Pretreatment with the following compounds [compound, dose (mg/kg ip), and time before giving 7 (20 mg/kg ip) or D-amphetamine (2.5 mg/kg ip)]: pimozide, 1, 2 h; phenoxybenzamine, 5, 15 min; methergoline, 2.5, 30 min; reserpine, 2.5, 24 h; α-methyltyrosine, 200, 2 h. Each column represents the mean total locomotion (counts/2 h) for groups of six to eight mice. The extensions stand for SEM. Statistical analysis as described in Figure 1. **, $p < 0.01$; ***, $p < 0.001$, compared with compound 7 or D-amphetamine alone (Student's t test).

Discussion

Previous studies with rigid spiro amines have demonstrated some of the structural requirements for a selective and potent inhibitor of NA accumulation. It was shown that the amino group of the tricyclic antidepressant agents should be located in a strictly defined region, the "amine space", in order to obtain optimal activity.[18] It is interesting to note that the region in space available for the terminal amino group of the cyclobutylamines overlaps with the "amine space" of the rigid spiro amines. However, the amines in this study are more flexible in the aromatic part of the molecule. This could possibly be the explanation to their activity also as inhibitors of the accumulation of 5-HT and DA.

The most pronounced behavioral effect of the cyclobutylamines observed in this study was the central

stimulation. This effect differs both in course and in type from that of amphetamine. Thus the hyperactivity produced by **7** was antagonized by reserpine but not by α-methyltyrosine, whereas that caused by amphetamine was antagonized by α-methyltyrosine but is not influenced by reserpine.[19] In this respect compound **7** resembles methylphenidate.[19] The results with the receptor antagonists show that the hyperactivity is produced by stimulation of DA receptors, but obviously not by a direct receptor stimulation. The findings agree with the view that the central stimulation caused by amphetamine is dependent upon intact DA synthesis but not upon intact DA granular stores.[19,20] Amphetamine probably acts by releasing newly synthesized DA from reserpine-resistant extragranular stores.

The effect of compound **7** like that of methylphenidate is, on the other hand, dependent on intact granular stores. Both compounds seem to act, at least partly, by enhancement of the effect of impulse transmitting DA, probably by inhibiting the membrane re-uptake.[21]

Experimental Section

Pharmacology. The compounds were administered as salts intraperitoneally (ip) or intravenously (iv) to male albino mice (the NMRI strain) weighing 18–22 g.

Inhibition of the accumulation of NA, DA, and 5-HT was measured in brain slices in vitro, after addition of the test compound either to the incubation medium or by injection in vivo, by simultaneously recording the accumulation of [^{3}H]-NA or [^{3}H]-DA and of [^{14}C]-5-HT as described previously.[12,22] In the in vivo measurements the test compounds were injected 0.5 h before the sacrifice of the animals. The EC_{50} and ED_{50} values were calculated from log dose–response curves by linear regression analysis and based on four concentrations or dose levels including four determinations per dose level.

The assessment of 5-HTP potentiation was performed as described previously.[12] The ED_{50} values were estimated by probit analysis[23] and are based on at least four doses with five animals per dose level.

The motor activity was measured in electronic activity cages (Activity Meter type DO, Farad Electronics, Sweden). The animals were tested individually and controls with saline were run simultaneously. The activity was recorded 20 min after administration of the test compounds or saline. The animals were pretreated with the following compounds [compound, dose (mg/kg ip), and time before test compound is given]: reserpine, 2.5, 24 h; phenoxybenzamine, 5, 15 min; pimozide, 1, 2 h; DL-α-methyltyrosine methyl ester hydrochloride 200, 2 h; methergoline, 2.5, 30 min. The mydriatic effect was estimated by observing the pupil diameter after iv injection.[18] Acute toxicity (24 h) was determined as described previously.[18]

Chemistry. The melting points are uncorrected and were determined in open capillary tubes. Elemental analyses were performed at the laboratories of Dr. A. Bernhardt, Elbach über Engelskirchen, West Germany, and are indicated by symbols of the elements. The analytical results obtained were within ±0.4% of the theoretical values if not otherwise stated. IR, NMR, and MS data were consistent with the assigned structures.

3,3-Diphenylcyclobutanone (2). Method A. A thermal cycloaddition reaction was performed essentially according to Cripps' general method[24] by heating a mixture of 1,1-diphenylethylene (160 g, 0.89 mol), allene (20 g, 0.5 mol), 1 g of hydroquinone, and 50 mL of toluene[25] at 200 °C for 16 h. The complex mixture of products was distilled in vacuo. A fraction, 13 g, boiling at 113–120 °C (2.5 Pa) [lit.[7] bp 99.5–106.0 °C (0.22–0.44 mm) (30–60 Pa), the substance was not further characterized] was highly enriched in 1-methylene-3,3-diphenylcyclobutane as shown by NMR. A solution of this crude product (13 g) in 50 mL of Me_2CO was added to a stirred solution of $NaIO_4$ (107 g, 0.5 mol) in 600 mL of H_2O and 300 mL of Me_2CO and then a solution of $KMnO_4$ (1.3 g, 8 mmol) in 50 mL of H_2O was added dropwise at 25 °C. After continued stirring for 16 h the solvent was removed in vacuo and the residue extracted with Et_2O. Drying ($MgSO_4$) and evaporation of the solvent gave 12.5 g of a viscous oil which was chromatographed on silica (Merck Kieselgel, 30–70 mesh, 1.2 kg) with toluene as eluent. The crude ketone **2** (4.7 g) was obtained and recrystallized from MeOH: yield 4.3 g (3.8% from allene); mp 82–83 °C (lit.[9] 84–85 °C).

Method B. The title compound was prepared essentially according to Michejda[9] starting with 115 g of diphenylacetyl chloride. The crude solution of diphenylketene was added to the solution of diazomethane without filtration. No gradient elution was found to be necessary in the isolation procedure. The ketone **2** was isolated by chromatography as described in method A: yield 14.4 g (13% from chloride); mp 82–83 °C.

3,3-Diphenylcyclobutanone Oxime (3). A solution of the ketone **2** (5.0 g, 22.5 mmol) and NH_2OH·HCl (5.0 g, 71.9 mmol) in 50 mL of pyridine was heated under reflux for 4 h. The mixture was poured into ice–water and stirred for 1 h. The white precipitate was collected and washed with cold H_2O and dried. Recrystallization from EtOH gave 4.4 g (82%) of the oxime **3**, mp 133–134 °C. Anal. ($C_{16}H_{15}NO$) C, H, N, O.

3,3-Diphenylcyclobutylamine (4). A solution of the oxime **3** (4.0 g, 16.8 mmol) in 100 mL of dry Et_2O was added dropwise to a slurry of $LiAlH_4$ (3.0 g, 79.0 mmol) in 100 mL of dry Et_2O at a rate sufficient to maintain gentle reflux. The mixture was then heated under reflux for 16 h. After cooling the excess hydride was destroyed by adding 3 mL of H_2O, 3 mL of 15% NaOH solution, and 9 mL of H_2O. The precipitate was filtered off and washed with ether, and the filtrate was dried ($MgSO_4$). The solvent was evaporated in vacuo yielding 3.6 g of a colorless oil, which crystallized on standing, mp 43–47 °C. Recrystallization of the hydrochloride from H_2O afforded 3.5 g (80%) of the amine hydrochloride, mp 273–274 °C. Anal. ($C_{16}H_{18}NCl$) C, H, N, Cl.

***N*-Ethoxycarbonyl-3,3-diphenylcyclobutylamine (5).** Ethyl chloroformate (2.2 g, 20 mmol) was added dropwise during 15 min to a stirred mixture of the amine **4** (3.3 g, 12.7 mmol) in 30 mL of $CHCl_3$ and 10 mL of 2 M NaOH solution at 0 °C. Stirring was continued for a further 15 min and then the organic layer was washed with H_2O and dried ($MgSO_4$). The solvent was removed in vacuo giving 4.2 g of a colorless oil, which crystallized on cooling. Recrystallization from MeOH gave 2.8 g (75%) of compound **5**, mp 130–131 °C. Anal. ($C_{19}H_{21}NO_2$) C, H, N, O.

***N*-Methyl-3,3-diphenylcyclobutylamine (6).** A mixture of the carbamate **5** (2.75 g, 7.6 mmol) and $LiAlH_4$ (1.0 g, 26 mmol) in 50 mL of dry Et_2O was heated under reflux for 4 h. Isolation as described for compound **4** gave 1.9 g of a colorless oil. Recrystallization of the hydrochloride from EtOH afforded 1.7 g (82%) of the amine hydrochloride **6**, mp 260–262 °C. Anal. ($C_{17}H_{20}NCl$) C, H, N, Cl.

***N,N*-Dimethyl-3,3-diphenylcyclobutylamine (7).** A solution of the ketone **2** (1.1 g, 4.9 mmol) in 5 mL of DMF was added to dimethylammonium formate [from HCOOH (0.46 g, 10 mmol) and dimethylamine (1.6 g, 35 mmol) at −10 °C] and the mixture was heated under reflux for 5 h. Et_2O was added to the cooled reaction mixture, and the solution was extracted with 2 M HCl solution. The acidic extracts were made alkaline with a 50% NaOH solution and extracted with Et_2O. The ether extracts were combined and dried over $MgSO_4$. The solvent was evaporated in vacuo and the resulting crude base (1.1 g) had mp 57–58 °C. The amine was converted to its hydrochloride and recrystallized from EtOH–*i*-Pr_2O to give 0.9 g (64%) of the desired amine hydrochloride, mp 222–224 °C. Anal. ($C_{18}H_{22}NCl$) C, H, N, Cl.

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Thiazolinone Analogues of Indolmycin with Antiviral and Antibacterial Activity

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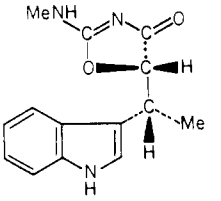
Total synthesis of a series of thiazolinone and thiazolidinone analogues of the antibacterial oxazolinone antibiotic indolmycin is described. The synthetic route involves nucleophilic displacement of mesyloxy and chloro groups from methyl 2-substituted-3-(indol-3-yl)propionates **3** and **4** and butyrate **19** with N-substituted thioureas. The formation of the rearranged chloro esters **29**, **43**, and **44** from β(*RS,RS*)-methyl indolmycenate (**27**), α(*RS,SR*)-methyl 2-hydroxy-3-(2-methylindol-3-yl)butyrate (**39**), and α-methyl 2-hydroxy-3-(indol-3-yl)valerate (**41**) supports a reaction mechanism involving neighboring group participation by the indole C-3 carbon during nucleophilic displacement on the β-carbon of a C-3 substituent. Structure–activity relationships are discussed. Although neither indolmycin nor its diastereoisomer isoindolmycin is antiviral, 2-monoalkylaminothiazolinone analogues have in vitro activity against both RNA viruses and bacteria. The most active compound is the sulfur isostere of indolmycin, and only the levorotatory enantiomer **46**, with the same absolute stereochemistry as natural indolmycin, has antimicrobial activity.

Since replication of viruses occurs only within host cells, and host cell metabolism and viral replication are closely integrated, the development of compounds which selectively interfere with virus-specific processes is one of the more intriguing remaining problems in antimicrobial chemotherapy.

One possible approach involves selective interference with the synthesis or functioning of specific enzymes, either introduced into or induced in the host cell by the virus.[1-5] The absence of detailed information concerning the amino acid sequence and conformation of these enzymes does, however, make it difficult to design rationally compounds that will bind to them selectively. The approach that we have taken involves total synthesis of analogues of a naturally occurring oxazolinone antibiotic, indolmycin. Although there was little a priori reason for believing that indolmycin analogues would bind selectively to a viral enzyme, it seemed that, by modification of a fairly complex structure possessing features consistent with noncovalent bonding to nucleic acids or proteins, and for which a precise stereochemical requirement for biological activity had been demonstrated,[6] the probability of obtaining a compound which bound preferentially to a single macromolecule would be substantially increased.



indolmycin

The present paper describes the synthesis of a series of thiazolinone and thiazolidinone analogues of indolmycin and structural requirements for antiviral and antibacterial activity.

Chemistry. 2-Aminothiazolinones **5**–**11** and **20**–**25** and 2-iminothiazolidinones **12**–**15** and **26** were prepared by nucleophilic displacement of 2-mesyloxy or chloro groups from methyl 3-(indol-3-yl)propionates **3** and **4** and butyrate **19** with N-substituted thioureas.[7]

The 2-alkylaminothiazolinones **6** and **8** and the isomeric 2-imino-3-alkylthiazolidinones **12** and **14**, respectively, were both isolated from reactions in which *N*-monoalkylthioureas were used. Because of the possibilities for tautomerization[8] and both intra- and intermolecular hydrogen bonding,[9] it is not possible to assign thiazolinone

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