at six intradermal sites and challenged iv 48–72 h later with 1 mg of dinitrophenylated human serum albumin ($DNP_{35}HSA$) plus 2 mg of Evans blue in 0.2 mL of 0.15 N NaCl. Thirty minutes after challenge the animals were sacrificed and the diameter of the skin reactions was measured on the inverted skin. Percent inhibition was calculated with the formula, $\% = 100(1 - a/b)$, where a is the sum or the reaction diameters in the treated animals and b the sum of the reaction diameters in the control animals.[21] Each variable was tested in groups of five rats.

***trans*-2,3b,4,5,7,8b,9,10-Octahydronaphtho[1,2-*c*:5,6-*c*']dipyrazole (1).** A mixture of 1.11 g (5 mmol) of 4,[11] 1 mL (ca. 0.02 mol) of hydrazine hydrate, and 50 mL of ethanol was refluxed for 6 h. After the total volume was reduced to about one-half, the compound slowly precipitated at room temperature. The solid was collected, dried, and recrystallized twice from ethanol to yield 0.7 g (65%) of 1 as very fine off-white crystals: mp 300 °C dec; IR (Nujol) 3200 (s, br), 1600 (w), 1580 (w), 1340 (m), 1180 (m), 1100 (m), 1080 (m), 980 (s), 880 (m), and 820 cm^{-1} (m); NMR (Me_2SO-d_6) δ 7.40 and 7.30 (s's, 2), and 12.6 (br s, 2); mass spectrum m/e 214 ($M^{+\cdot}$). Anal. ($C_{12}H_{14}N_4$) C, H, N.

***trans*-2,7-Dimethyl-3b,4,5,8b,9,10-hexahydronaphtho[1,2-*c*:5,6-*c*']dipyrazole (5).** This compound was prepared in 31% yield following an identical procedure as for compound 1. Recrystallization from acetone afforded 5 as small white crystals: mp 231–232 °C; IR (Nujol) 1600 (w), 1560 (m), 1300 (m), 1250 (m), 1160 (s), 1020 (w), 1000 (w), 950 (m), 880 (m), 840 (s), and 720 cm^{-1} (m); NMR ($CDCl_3$) δ 2.80 (m, 10), 3.90 (s, 6), and 7.20 (s, 2); mass spectrum m/e 242 ($M^{+\cdot}$). Anal. ($C_{14}H_{18}N_4$) C, H, N.

***trans*-3,8-Diphenyl-3b,4,5,8b,9,10-hexahydronaphtho[1,2-*c*:5,6-*c*']dipyrazole (6).** This compound was prepared in 26% yield by a similar procedure as for 1 and 5. Recrystallization from acetone afforded 6 as yellow needles: mp 275–276 °C dec; IR (Nujol) 1600 (m), 1580 (m), 1500 (s), 1050 (m), 960 (m), 770 (m), and 700 cm^{-1} (m); NMR (CF_3COOH) δ 3.00 (br m, 10), 7170 (s, 10), and 8.00 (s, 2); mass spectrum m/e 366 ($M^{+\cdot}$). Anal. ($C_{24}H_{22}N_4$) C, H, N.

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Neuroleptics Related to Butaclamol. Synthesis and Some Psychopharmacological Effects of a Series of 3-Aryl Analogues

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The synthesis and some pharmacological effects of 16 3-aryl analogues of butaclamol, a new antipsychotic drug, are described. The animal models were predictive of neuroleptic activity as well as side effects commonly associated with neuroleptic therapy. The results indicate that the 3-substituent plays a critical role with regard to the potency of the compounds as well as to their tendencies to induce extrapyramidal side effects and/or hypotension.

The synthesis of 3-substituted benzo[6,7]cyclohepta-[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol derivatives[1] has led to the emergence of a chemically novel class of neuroleptic agents of which butaclamol,[2,3] the 3-*tert*-butyl derivative, is the most interesting member. Clinical studies[4-8] have established that butaclamol is a potent antipsychotic drug which is devoid of side effects arising from interference with the autonomic nervous system but which induces extrapyramidal side effects.

In the present study, the synthesis of a series of 15 3-aryl analogues of butaclamol is described. These derivatives as well as the previously described 3-phenyl analogue[1] were evaluated in animal models which are either indicative of the relative potencies of these compounds as neuroleptic agents or are predictive of their tendency to induce extrapyramidal side effects and hypotension. The compounds were compared to butaclamol.

Chemistry. The 3-aryl analogues studied comprised

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phenyl and substituted phenyl, benzyl, thienyl, furyl, and pyridyl derivatives. Their structures and relevant chemical data are shown in Table I. Compounds **2–14** and **16** were synthesized by the reaction of (±)-(4a,13b-*trans*)-1,2,-4,4a,8,9,13b,14-octahydro-3*H*-benzo[6,7]cyclohepta[1,-2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-one[9] with the appropriate aryl magnesium bromide derivative, while **15** was obtained from the reaction with 2-furyllithium, followed by conversion to the hydrochloride salts.

The relative configuration at position 3 in butaclamol hydrobromide has been shown to be trans 3-hydroxyl, 13b-hydrogen by a crystallographic study,[10] and the same stereochemistry is assigned for the novel analogues described herein, on the basis of considerations which had allowed the prediction[1] of the configuration at position 3 of butaclamol.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are corrected. All new compounds gave IR and NMR spectra in accord with their respective structures and were homogenous by TLC. The NMR spectra were recorded on a Varian A-60A instrument.

(±)-(4a,13b-*trans*)[3(OH),13b(H)-*trans*]-2,3,4,4a,8,-9,13b,14-Octahydro-3-(2-methylphenyl)-1*H*-benzo[6,7]-cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol Hydrochloride (2). A solution of (±)-(4a,13b-*trans*)-1,2,4,4a,8,-9,13b,14-octahydro-3*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido-[2,1-*a*]isoquinolin-3-one[9] (3 g, 0.01 mol) in benzene (80 mL) was added dropwise to a 2-toluylmagnesium bromide solution prepared from 2-bromotoluene (6.8 g, 0.04 mol) and Mg (0.95 g, 0.04 g-atom) in ether (25 mL). The mixture was stirred at 20–25 °C for 2 h and then a 10% aqueous NH_4Cl solution was added to destroy the excess of the Grignard reagent. The organic layer afforded an oil which was dissolved in ether and treated with anhydrous HCl. The crude HCl salt was crystallized from methanol–ether to afford the product, **2** (2.7 g, 62.6%), mp 272–275 °C.

A similar reaction of the above ketone with the Grignard reagent prepared from the appropriate hydrocarbon bromide afforded compounds 4–14 and 16, described in Table I. For the preparation of **3**, benzylmagnesium chloride was used, while 2-furyllithium, prepared from furan and *n*-butyllithium, was used as the nucleophilic addition reagent in the synthesis of **15**.

Pharmacology Methods. Animals. Experiments were performed on male Sprague–Dawley rats. The animals were housed in air-conditioned quarters and had free access to food and water until the start of the experiment.

Materials. The doses used were calculated as the free base. The compounds were dissolved in distilled water or suspended in distilled water with a few drops of Tween 80 (2–3 drops/10 mL). Fresh solutions were prepared on the day of the experiment. In addition to the test compounds, the following drugs were used: *d*-amphetamine sulfate (K & K Laboratories) and epinephrine bitartrate (Sigma Chemical Co.).

Statistics. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[11]

***d*-Amphetamine-Induced Stereotyped Behavior in Rats.** Details of the methodology and scoring system were recently described.[3] Groups of four or more rats (160–180 g) were injected ip with *d*-amphetamine, 10 mg/kg, followed 15 min later by an ip injection of graded doses of the test compounds or the vehicle. The highest dose evaluated was 20 mg/kg. Observations were made at 15-min intervals after the injection of amphetamine and the behavior of the rats was scored from 0 to 2, "0" referring to normal, "1" to excited, and "2" to stereotyped behavior.

The results are expressed as the minimal effective dose (MED), arbitrarily defined as the lowest dose which antagonized all the behavioral effects of amphetamine.

Conditioned Avoidance Behavior in Rats. The method of Morpurgo[12] was followed. Rats were trained to leave the starting chamber and move into one of two exit compartments, which was lighted. Failure to leave the starting chamber within 10 s was punished with shock. Details of our three-chambered discrimination box and training procedure are described in a previous paper.[13] On the day of the experiment groups of six or more rats (250–400 g) were tested in a control session of two trials prior to drug administration to ensure an accurate response. Graded doses of the test compounds were administered ip to groups of six or more rats, and the drug effect was evaluated in ten trials 30 min after injection. The "active avoidance failure", i.e., failure to leave the starting chamber prior to the onset of the shock, was recorded, and the mean number of failures per group was calculated as a percent of the total number of trials. The results are expressed as the ED_{50} values, defined as the dose of a compound that caused a 50% failure in the active avoidance response.

Epinephrine-Induced Mortality in Rats. The method of Janssen et al.[14] was followed. Groups of six or more rats (220–250 g) were injected ip with graded doses of the compounds, followed 1 h later by an iv injection of epinephrine bitartrate, 0.25 mg/kg. This dose of epinephrine is lethal to nontreated rats. Mortality was determined over a 24-h period. The results are expressed as protective ED_{50} values.

Catalepsy in Rats. The assessment of catalepsy in rats (160–180 g) was based upon the method of Morpurgo.[15] The compounds were injected ip, to groups of six rats, at a dose which was tenfold the dose that antagonized amphetamine-induced stereotyped behavior. Catalepsy was evaluated after 1, 2, 4, 6, and 24 h according to stages III and IV of Wirth et al.[16] The rats were placed on a table with one front paw set on a cork (a) 3 cm high, the other remaining on the table (stage III), (b) 9 cm high, the other permitted to hand freely (stage IV). The reaction was considered to be positive when the rat failed to correct the imposed posture within 10 s. Both stages were tested on the right and left forepaws, and 0.5 point was given for each paw with a positive stage III reaction and 1 point for each paw with a positive stage IV reaction. Thus, 3 was the maximum score attainable. The mean cataleptic scores were calculated and the highest one was expressed as a percent of the maximum attainable score.

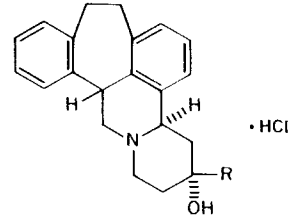
Results

***d*-Amphetamine-Induced Stereotyped Behavior in Rats.** Sixteen 3-aryl analogues of butaclamol were evaluated with regard to their effect on amphetamine-induced stereotyped behavior. All compounds antagonized the behavioral effects of amphetamine in a dose-dependent fashion although their activity varied greatly. In Table I, column 7, the MED values are shown. The most potent compound in the series was the 2-methoxyphenyl derivative **4** which was equipotent to butaclamol. The least effective compound in the series was the benzyl derivative **3** which afforded only partial protection at the highest dose (20 mg/kg). While the antiamphetamine activity of the various substituted phenyl derivatives differed greatly from each other, the activity of the heteroaryl analogues **13–16** was remarkably similar.

Conditioned Avoidance Behavior in Rats. Most of the compounds, like butaclamol, disrupted the conditioned avoidance response (CAR) at doses similar to those which antagonized amphetamine-induced stereotyped behavior (Table I, column 8). The exceptions fell into two categories. The 3-pyridyl derivative **16** antagonized amphetamine at 5 mg/kg, while the ED_{50} for depressing CAR was 1 mg/kg; i.e., avoidance behavior was depressed at much lower doses than the amphetamine-induced abnormal behavior. In contrast, the 2-toluyl (**2**), the 4-methoxyphenyl (**6**), the 2-trifluoromethylphenyl (**12**), and the 2-thienyl (**13**) derivatives depressed amphetamine stereotypy at considerably lower doses than avoidance behavior; thus, the "MED vs. amphetamine"/"CAR ED_{50}" dose ratios were <0.5 for these agents. The possible significance of this finding is elaborated upon in the Discussion.

Epinephrine-Induced Mortality in Rats. Table I, column 9, summarizes the protective ED_{50} values against epinephrine-induced mortality. As the antiepinephrine effect is a measure of peripheral antiadrenergic activity

Table I. Chemical and Pharmacological Data on 3-Substituted Analogues of Butaclamol



Compd	R	Mp, °C	Crystn solvent[a]	Yield, %	Formula[b] (analyses)	Amphetamine-induced stereotyped behavior, MED,[c] mg/kg ip	Conditioned avoidance response, ED_{50},[d] mg/kg ip	Epinephrine-induced mortality, ED_{50},[e] mg/kg ip	Catalepsy, % of max[f]	Rel adrenolytic act., (epinephrine ED_{50})/(amphetamine MED)
Butaclamol[g]	$C(CH_3)_3$					0.63	0.64 ± 0.13	15.0 ± 3.0	67 (6)	24
1	C_6H_5[g]					2.5	3.0 ± 1.5	5.5 ± 1.8	32 (6)	2.2
2	2-CH_3-C_6H_4	272–275	A, B	62	$C_{28}H_{29}NO$·HCl (C, H, Cl, N)	1.25	3.3 ± 1.3	6.4 ± 3.3	61 (4, 6)	5.1
3	$C_6H_5CH_2$	255	A	28	$C_{28}H_{29}NO$·HCl (Cl, N)	>20		>40		
4	2-OCH_3-C_6H_4	240	A, B	14	$C_{28}H_{29}NO_2$·HCl (Cl, N)	0.63	0.92 ± 0.05	4.0 ± 0.5	89 (4, 6)	6.3
5	3-OCH_3-C_6H_4	272–274	A, B	36	$C_{28}H_{29}NO_2$·HCl (Cl, N)	1.25	1.4 ± 0.4	2.7 ± 0.8	83 (6)	2.2
6	4-OCH_3-C_6H_4	250–252	A, B	51	$C_{28}H_{29}NO_2$·HCl (Cl, N)	2.5	5.8 ± 1.9	13.2 ± 2.0	83 (6)	5.3
7	3,4-$(OCH_3)_2$-C_6H_3	227–230	C	18	$C_{29}H_{31}NO_3$·HCl·H_2O (N, Cl)	5.0	6.0 ± 1.8	1.1 ± 0.05	100 (4)	0.22
8	2,4-$(OCH_3)_2$-C_6H_3	170–173	D	66	$C_{29}H_{31}NO_3$ (C, H, N)[h]	10.0	16.0 ± 6.8	18.0 ± 3.4	44 (6)	1.8
9	2-Cl-C_6H_4	272–274	E	54	$C_{27}H_{26}ClNO$·HCl (Cl, N)	2.5	3.3 ± 0.8	11.0 ± 4.2	100 (4, 6)	4.4
10	3-F-C_6H_4	292–294	A	23	$C_{27}H_{26}FNO$·HCl (C, H, Cl, N)	5.0	7.0 ± 4.0	14.3 ± 2.3	100 (4, 6)	2.9
11	4-Br-C_6H_4	275–278	A, B	51	$C_{27}H_{26}BrNO$·HCl (Cl, N)	20.0	14.0 ± 1.8	6.9 ± 0.44	72 (4)	0.35
12	2-CF_3-C_6H_4	224–230	A	37	$C_{28}H_{26}F_3NO$·HCl (Cl, F, N)	10.0	22.2 ± 3.6	>20	100 (6)	>2
13	2-Thienyl	249–251	A, B	54	$C_{25}H_{25}NOS$·HCl (Cl, N)	2.5	5.6 ± 1.8	22.0 ± 6.1	100 (6)	8.8
14	3-Thienyl	265	A, B	28	$C_{25}H_{25}NOS$·HCl (H, Cl, N)[i]	5.0	8.0 ± 1.7	90.0 ± 8.0	93 (6)	18.0
15	2-Furyl	244–246	A, B	41	$C_{25}H_{25}NO_2$·HCl (Cl, N)	5.0	6.7 ± 1.6	82.0 ± 9.0	83 (4, 6)	16.4
16	3-Pyridyl	283–285	F	45	$C_{26}H_{26}N_2O$·2HCl·H_2O (C, H, N)	5.0	1.0 ± 0.45	4.7 ± 2.0	94 (4, 6)	0.94

[a] A = methanol; B = ether; C = acetone; D = cyclohexane; E = acetonitrile; F = 2-propanol. [b] Compounds were analyzed for the elements shown in parentheses. All results were within ±0.4% of the calculated values. [c] MED = minimal effective dose, defined as the dose which antagonized all the behavioral effects of amphetamine (10 mg/kg ip) during the entire 4-h experimental period. [d] ED_{50}, defined as the dose which caused a 50% failure in the active avoidance response. [e] ED_{50}, defined as the dose which protected 50% of the rats against the lethal effect of epinephrine. [f] Catalepsy was evaluated at a dose which was tenfold the dose that antagonized amphetamine-induced stereotyped behavior. The highest mean catalepsy score is expressed as a percent of the maximum attainable score. The number(s) in parentheses indicates the hour at which the peak effect was observed. [g] See ref 1. [h] This compound was characterized and tested as the free base. [i] C: calcd, 70.81; found, 70.28.

and the antiamphetamine effect is a measure of antipsychotic activity, the ratio of the doses that antagonize epinephrine and amphetamine is a measure of the relative potency of a neuroleptic drug as an adrenergic blocking agent. These ratios are listed in the last column of Table I.

The results showed that the antiepinephrine/antiamphetamine dose ratios were not as favorable for any of the 3-aryl analogues as that of butaclamol. However, the compounds could be divided into three categories. The 2-thienyl (**13**), the 3-thienyl (**14**), and the 2-furyl (**15**) analogues were very weak epinephrine antagonists, the aforementioned ratios being 8.8, 18, and 16.4, respectively. With these agents, side effects arising from α-adrenergic blockade would be minimal. In contrast, compounds **7**, **11**, and **16** were potent epinephrine antagonists and the ratios of their antiepinephrine and antiamphetamine efficacies were <1. The aforementioned side effects would be pronounced with these compounds. The remaining agents occupied an intermediary position. However, since they were more potent in antagonizing amphetamine, the antiepinephrine/antiamphetamine dose ratios were >1, ranging from 1.8 for compound **8** to 6.3 for compound **4**.

Catalepsy in Rats. The results are shown in Table I, column 10. In order to compare the catalepsy-inducing potency of the compounds they were evaluated at a dose which was tenfold the dose that antagonized amphetamine-induced stereotyped behavior. The least cataleptic compound in the series was the phenyl analogue **1**. The mean cataleptic scores were slightly <1, i.e., 32% of maximum which was due to the fact that although the rats were ataxic and strongly depressed they lacked rigidity and thus the criterion of leaving the front paw on a 9-cm high cork was not fulfilled. Compound **8** was also less cataleptic than butaclamol but this was a relatively weak analogue. All other aryl derivatives were as cataleptic as butaclamol or more so. Most of the compounds exerted peak activity 6 h after administration; exceptions were compounds **7** and **11** which showed peak activity after 4 h.

Discussion

The present experiments describe the pharmacological effects of 16 3-aryl-substituted benzocycloheptapyridoisoquinolinols in four animal models which either indicate whether a compound is a potential neuroleptic drug or predict the liability to cause side effects most frequently associated with antipsychotic therapy.

Amphetamine-induced stereotyped behavior, regarded as an animal model of psychosis,[17] is antagonized by neuroleptic drugs with high specificity.[14,17] Neuroleptic drugs have also been shown to suppress the conditioned avoidance response (CAR).[14,18] Brain dopamine (DA) seems to be involved in both animal models since amphetamine stereotypy[19,20] as well as CAR[21] depends on an intact nigro-neostriatal dopaminergic system, and bilateral destruction of this pathway abolishes both behaviors. Neuroleptic drugs are believed to antagonize amphetamine-induced stereotyped behavior and depress CAR through blockade of the postsynaptic DA receptors. The antipsychotic activity in schizophrenic patients is probably also mediated by this mechanism, since a positive correlation exists between neuroleptic-induced increased DA turnover and therapeutic effect.[22]

The present experiments have shown that the 3-aryl-substituted analogues of butaclamol antagonized amphetamine stereotypy and depressed conditioned avoidance behavior, indicating that they would ameliorate psychosis in humans. However, the potency of the compounds varied greatly, the 2-methoxyphenyl derivative **4** being as active as butaclamol and the benzyl derivative **3** showing slight activity at a more than 30 times larger dose.

The experiments have further shown that most of the compounds affected amphetamine-induced stereotyped behavior and CAR at similar doses. Exceptions were compounds **2**, **6**, **12**, and **13** which antagonized amphetamine at considerably lower doses than CAR; thus, the ratios of these doses were 0.38, 0.43, 0.45, and 0.45, respectively. In contrast, the ratios of the "MED vs. amphetamine stereotypy"/"CAR ED_{50}" ranged from about 1 to 3.6 for butaclamol, haloperidol, fluphenazine, chlorpromazine, and thioridazine[23] (compounds are randomly listed). This observation was of interest because it was suggested recently by Randrup et al.[24] that an "ideal antipsychotic drug" should not only eliminate psychotic behavior but also replace it by normal behavior. Currently used neuroleptic drugs do not restore normal behavior in schizophrenic patients, which is a "major problem in the therapy of schizophrenia". They suggest that novel drugs should alter amphetamine-induced abnormal behavior but should have relatively little effect on various manifestations of "normal" behavior, thus, for example, on CAR.

Catalepsy is regarded as a measure of extrapyramidal side effects;[25] it is induced by neuroleptic drugs through blockade of the DA receptors and the ensuing functional deficiency of DA.[26] Among the presently evaluated compounds only the phenyl derivative **1** was of interest. Rats treated with this compound resembled chlorpromazine-treated animals;[3] i.e., they were strongly depressed but were not rigid and, thus, the criterion to obtain higher cataleptic scores could not be fulfilled. It is anticipated that relatively few extrapyramidal side effects would occur during treatment with **1**. In contrast to the phenyl derivative, all other aryl-substituted analogues were as cataleptic as butaclamol or more so.

Hypotension is a frequent side effect of some, but not all, antipsychotic drugs and is due to their adrenergic blocking properties. The antagonism of epinephrine-induced mortality in rats is a measure of the adrenolytic potency,[14] but this effect is unrelated to any of the behavioral effects. The present study has shown that the relative adrenolytic activity of all 3-aryl-substituted analogues was greater than that of butaclamol; i.e., hypotension with these agents would occur more likely than with butaclamol which is devoid of this side effect.[4-8] However, the 3-substituent seems to play an important role with regard to this effect as well since the antiepinephrine/antiamphetamine dose ratios ranged from 0.22 for **5** to 18 for **14**.

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Antitumor Agents. 31.[1] Helenalin *sym*-Dimethylethylenediamine Reaction Products and Related Derivatives

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Several novel cyclopentenone bearing lactams and related derivatives have been synthesized as potential alkylating antitumor agents. The synthesis of these compounds involved the reaction of helenalin with *sym*-dimethylethylenediamine. These lactams were initially formed by a Michael addition of the amine to the α-methylene grouping of the γ-lactone ring, followed by a nucleophilic ring closure by the attack of the second amine group on the γ-lactone carbonyl. Reaction of helenalin (**1**) with dimethylamine gave, in addition to the single Michael reaction adduct (**2**) of the γ-lactone ring, a new double Michael addition product (**9**). The regeneration of **1** from **2** could be effected in 50% yield by silica gel column chromatography. In vitro assay for the cytotoxicity of these compounds against the growth of tissue culture cells originating from human epidermoid carcinoma of the larynx (H.Ep.-2) showed decreased significant activity due to the loss of the α-methylene-γ-lactone alkylating moiety. Cytotoxicity and in vivo antitumor activity in Walker 256 carcinosarcoma screen were enhanced with the introduction of a cinnamate ester group to the parent molecule. Preliminary in vivo tumor assay also indicated that compounds possessing a cyclopentenone and a C-6 hydroxyl group in either a bicyclic ring system or a tricyclic ring system with a saturated α-methylene grouping of the γ-lactone ring were active against Walker 256 carcinosarcoma growth in rats and marginally active against P-388 lymphocytic leukemia in mice.

Helenalin *sym*-dimethylethylenediamine reaction products were synthesized from helenalin so that the structure–antitumor relationships[2] would be expanded and those results are now reported. The first objective was to determine if the tricyclic ring system of helenalin itself contributes significantly to antitumor or cytotoxic activity. These *sym*-dimethylethylenediamine products were obtained by cleaving the γ-lactone ring of helenalin. The β-unsubstituted cyclopentenone ring was retained since it has been shown that this system contributed significantly to in vitro cytotoxicity (H.Ep.-2)[3,4] and in vivo antitumor activity (Walker 256 carcinosarcoma in rats).[5] The second objective was to generate a C-8 hydroxyl group in addition to the C-6 hydroxyl function for the subsequent introduction of diester moieties, such as cinnamoyl groups, for possible enhancement of the in vivo antitumor activity. The cinnamate ester of helenalin was found to be more cytotoxic than helenalin.[6]

Chemistry. Sesquiterpene lactones containing an α-methylene-γ-lactone grouping are known to form readily the monoadducts with secondary amines via Michael type reaction. For example, the α-methylene moiety of helenalin (**1**) forms an adduct (**2**) with dimethylamine.[3] With this in mind, it was thought that the γ-lactone ring of helenalin might be cleaved and thus generate the desired C-8 free hydroxyl group if an intramolecular nucleophilic attack of the γ-lactone carbonyl could be accomplished by a second amine group which is available in the initial amine adduct. Among the several secondary diamines examined, it was found that reaction of helenalin with *sym*-dimethylethylenediamine gave rise to the expected novel lactam **3** which was stable. Compound **3** was formed by an initial Michael addition of *sym*-dimethylethylenediamine to the α-methylene grouping of **1**, followed by a subsequent nucleophilic ring closure by attack of the second amine group on the γ-lactone carbonyl. The lactam **3**, $C_{19}H_{30}O_4N_2$, mp 209 °C, showed IR bands ($CHCl_3$) at 3540, 3250 (OH), 1700 (cyclopentenone), and 1630 cm^{-1} (amide C=O), and the absence of the lactonic carbonyl absorption. The NMR spectrum ($CDCl_3$) of the lactam was in accord with the assigned structure **3**, i.e., it indicated the presence of two *N*-methyl groups [δ 2.33 (3 H, s, CH_2N-*Me*) and 3.05 (3 H, s, CON-*Me*)], two *C*-methyl groups [δ 1.16 (3 H, d, J = 6 Hz, Me-10) and 1.57 (3 H, s, Me-5)], and a cyclopentenone ring system [δ 6.09 (1 H, dd, J = 3.0 and 6.0 Hz, H-3) and 7.81 (1 H, dd, J = 2.0 and 6.0 Hz, H-2)].

Similar treatment of helenalin acetate (**4**) with *sym*-dimethylethylenediamine led to the lactam acetate **5**. Esterification of **5** with cinnamoyl chloride yielded the

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