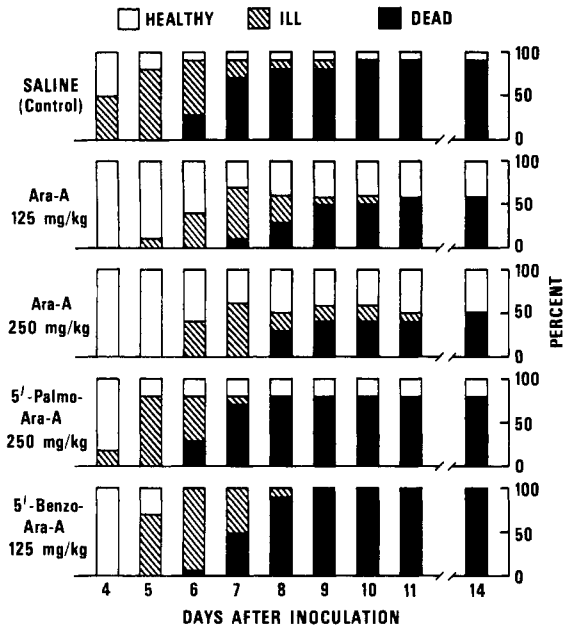

Figure 4. Comparison of ara-A and the 5'-esters in mice inoculated with herpesvirus. Virus inoculation was as described in Figure 2. The drugs were prepared in saline and given twice daily at the indicated total daily dose by ip injection. Drug treatments were initiated on the day after virus inoculation and continued for 5 days; *i.e.*, each animal received a total of ten treatments.

Discussion

The results of the studies reported herein confirm the previous reports regarding the antiviral activity of ara-A. Ara-A has been shown to be active against herpesvirus *in vitro* but not against several RNA viruses. Comparisons of virus yields from herpesvirus infected primary rabbit kidney cultures showed that ara-A did reduce the virus yield when incorporated into the growth medium. Our previous data with ara-C[10] would indicate that ara-A is less active in this *in vitro* test system than is ara-C. The 5'-benzoyl ester of ara-A shared *in vitro* properties with ara-A; *i.e.*, it was nearly as active as ara-A in the *in vitro* tests. However, the 5'-palmitoyl ester of ara-A was considerably less active than ara-A; perhaps this decreased *in vitro* activity is associated with the extreme insolubility of this compound.

Ara-A was shown to be effective in treating mice infected with herpesvirus. It was shown that the activity of ara-A could be maximized by initiating therapy early after virus inoculation and continuing drug treatment twice per day for 5 days with total daily doses of 250 mg/kg. Under these conditions where ara-A was shown to be effective, the 5'-esters of ara-A were devoid of *in vivo* antiviral activity. These observations are in contrast to the early studies with the 5'-esters of ara-C which were shown to have enhanced activity over ara-C itself.[9]

The reasons underlying the loss of *in vivo* antiviral activity of ara-A following esterification at the 5' position of this purine antagonist are unknown. It has been suggested[9] that the enhanced *in vivo* biological activities which have been observed with the 5'-esters of ara-C result from the fact that the ester is slowly hydrolyzed, thereby maintaining low levels of ara-C for long time periods. It is known that the triphosphate of ara-A is an effective inhibitor of DNA polymerase.[12] If indeed the mechanism of antiviral activity of ara-A is dependent upon the conversion (phosphorylation) of the nucleoside to the nucleotide with subsequent inhibition of viral DNA synthesis, then it is tempting to speculate that the esterases of the host are less effective in releasing ara-A from its 5'-acylates than they are in performing the comparable conversion of ara-C esters to the nucleoside.

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Synthesis and Antiinflammatory Evaluation of Certain 5-Alkoxy-2,7-dialkyltryptamines

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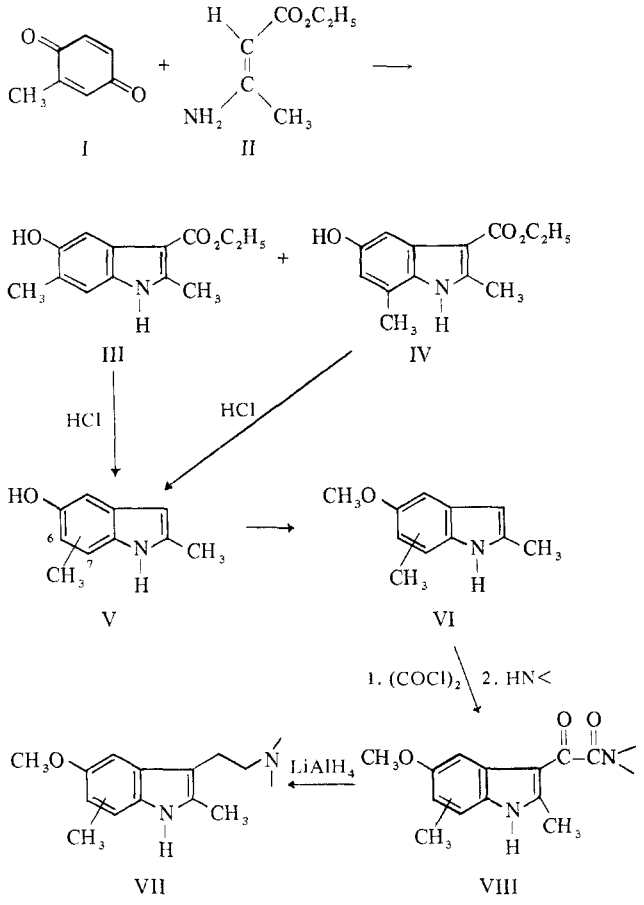
A variety of 5-methoxy-2,7-dialkyltryptamines was prepared and evaluated for central nervous system and antiinflammatory activites. Of these, the azabicyclononane derivative IX proved most interesting as a potential antiinflammatory agent. Various congeners of IX were synthesized but none was as active as IX. The Nenitzescu condensation between 2,5-dichlorobenzoquinone and alkyl 3-aminocrotonates to give 4,7-dichloro-5-hydroxy-2-methylindole-3-carboxylates is discussed.

The important place held by the indole nucleus in pharmaceutical chemistry and in animal as well as plant biochemistry is too well recognized to require documentation here (for reviews see *inter alia* ref 1). Suffice to note that a strong rationale is provided for the exploratory efforts of medicinal chemists seeking to develop novel pharmaceutical agents. Thus, when in the course of our synthesis of indoloquinone congeners of the mitomycin antibiotics, entry to the hitherto unrecorded 7-methyl-5-hydroxyindole series became available to us,[2] we undertook the preparation of a number of representative derivatives of this class for biological screening, and the results of this effort constitute the subject of this

paper. Our original indoloquinone studies[2] involved an investigation of the Nenitzescu reaction between toluquinone and ethyl 3-aminocrotonate and resulted in the discovery that, in addition to the anticipated 6-methyl-5-hydroxy derivative III, there also was formed an equivalent amount of the hitherto unnoted 7-methyl isomer IV. Since we were able to effect an efficient separation of the two isomers on a useful laboratory scale (see Experimental Section), we were enabled to undertake the investigation reported here.

Testing of the decarbethoxylated 2,7-dimethyl-5-hydroxyindole (Va) indicated this compound to be a weak motor depressant. This observation suggested the preparation of the corresponding tryptamine derivatives in this as well as the 6-methyl series. The synthesis of these substances was accomplished in the standard manner[3] as indicated in the sequence V–VII (Scheme I).

Scheme I

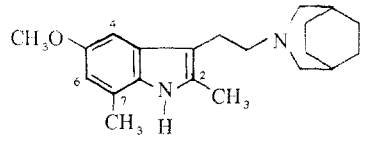


a series, 7-CH_3
b series, 6-CH_3

Of the various tryptamines (see Table IV) prepared at the time, as well as those prepared later, none induced a sufficient degree of diminished motor activity in mice (50% inhibition at 50 mg/kg ip)[4] to be of substantial interest. On the other hand, many of these compounds did produce significant ataxia at 14–130 mg/kg ip, as measured by reduced rod-walking ability in mice,[4] but more interesting CNS activity was observed for a series of related 2,4-dimethyl-5-methoxytryptamines.†

Biological testing of these tryptamines did reveal indications of potential antiinflammatory action. Among the several compounds of interest, the azabicyclononane-tryptamine derivative IX was clearly the most compelling. Furthermore, IX did not appear to be CNS active, at least in terms of motor depressant,[4] rod-walking,[4] and antidepressant assays[5] in mice. Further biological study of this compound was undertaken and a synthetic program to elucidate the structure-activity relationships was initiated.

The various congeners of IX, all containing the azabicyclo-



IX

nonane system, are listed in Table VI. They include the 7-demethyl, 2,7-bisdemethyl, 5-demethoxy, and 5-hydroxy derivatives as well as the corresponding gramine-type compound. Other analogs included compounds in which the methyl groups at C_7, at C_2, or on the 5-oxygen atom were homologated to ethyl groups and in which the C_7 methyl was replaced by the same group at C_6. Compounds were also prepared which retained all the features found in IX and to which had been added a methyl group at C_6 or N_1, or a chlorine atom at C_4. Note also that among the amine functions investigated (see Table IV) are homopiperidine (entry **71**), various other five- and six-membered alicyclic amines, and two additional bicyclo derivatives (entries **73** and **74**). With the following exceptions, these substances were prepared by conventional procedures which do not require comment.

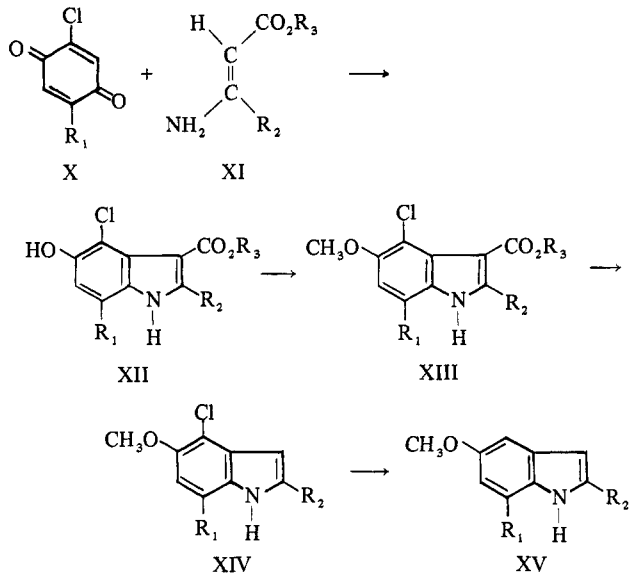
The 7-demethyl analog was obtained by an alternative procedure[6] to that of Speeeter and Anthony[3] described above. This synthesis involved the preparation of the 3-chloroacetylindole from the halomagnesium derivative of 2-methyl-5-methoxyindole and chloroacetyl chloride, reaction with 3-azabicyclo[3.2.2]nonane, and finally reduction with lithium aluminum hydride. The 1-methyl derivative was obtained conveniently and in high yield by methylation of the sodium salt of IX, prepared by treatment of IX with dimsyl sodium. The free 5-hydroxytryptamine derivatives were prepared *via* 5-acetoxy intermediates.

Despite the availability of the 5-hydroxy-2,7-dimethylindole ester IV from a Nenitzescu reaction, this procedure when used directly with an alkylbenzoquinone is not by any means a practical method for the general preparation of 2,7-dialkyl-5-hydroxyindoles, the yields of which in most recorded instances do not exceed 2%.[2] However, the Nenitzescu method can be adapted to a useful synthesis of the 7-alkyl derivatives by utilization of a 2-chloro-5-alkyl-1,4-benzoquinone (X), which appears to provide exclusively the 4-chloro-7-alkyl isomer XII. The chlorine atom, which so effectively controls the direction of isomer formation, then is removed by catalytic hydrogenolysis. We have previously reported[7] an alternate synthesis of 2,7-dimethyl-5-methoxyindole (VIa) by this method and in this paper we note the preparation of 2-ethyl-7-methyl-5-methoxyindole (XVa) and 7-ethyl-2-methyl-5-methoxyindole (XVb) in acceptable overall yields of 20 and 32%, respectively, for the four steps shown in sequence X + Xi → XV (Scheme II).

Although we were not fully successful in obtaining the desired 7-chloro analog, our experience in attempting to synthesize 7-chloro-5-methoxy-2-methylindole merits recording. Our approach to this compound reflected our bias toward the Nenitzescu synthesis and initially was based on an observation made several years ago in our laboratory

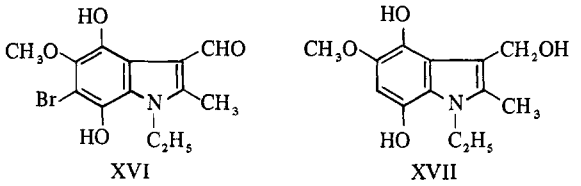
†G. R. Allen, Jr., V. G. DeVries, E. N. Greenblatt, R. Littell, F. J. McEvoy, and D. B. Moran, unpublished work, Lederle Laboratories.

Scheme II



a series; $R_1 = CH_3$; $R_2 = C_2H_5$; $R_3 = C_2H_5$
b series, $R_1 = C_2H_5$; $R_2 = CH_3$; $R_3 = t\text{-}C_4H_9$

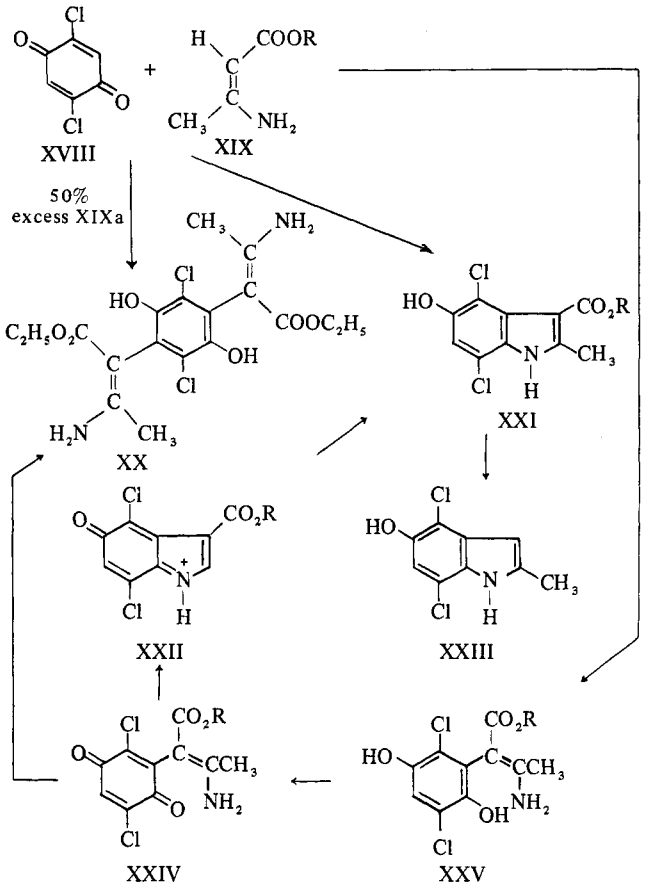
wherein the sodium borohydride reduction of the bromohydroquinone aldehyde XVI to the corresponding 3-hydroxymethyl derivative was accompanied by the formation of substantial amounts of the debrominated product XVII (isolated in the quinone state).[8] This observation and others[9] less pertinent suggested the possibility that metal hydride treatment of 4,7-dichloro-5-hydroxyindole (XXIII) might result in preferential dechlorination at C_4, *via* complex formation between the reagent and the *o*-hydroxyl group, thus providing a convenient route to the desired 7-chloro derivative.‡



The required 4,7-dichloroindole XXIII was presumably available *via* a Nenitzescu reaction and indeed the synthesis of its 3-carbethoxy derivative XXIa already had been reported by a Russian group.[10] Repetition of their procedure, which involved treatment of 2,5-dichloro-1,4-benzoquinone (XVIII) with a 50% excess of ethyl 3-aminocrotonate (XIXa), furnished a product which did not melt below 300°, in rough agreement with the reported decomposition point of 320°. Such melting-point behavior is unusual for a 5-hydroxy-3-carbalkoxyindole, and indeed our product was not the expected 4,7-dichloroindole XXIa but rather the 1:2 hydroquinone adduct XXa resulting from the condensation of dichloroquinone XVIII with two molecules of aminocrotonate XIXa. The formation of 1:1 and 1:2 adducts, such as XX, in the course of a Nenitzescu synthesis has been noted previously.[2,11]

The desired dichloroindole XXIa can be prepared simply by using a molar equivalent of aminocrotonate XIXa rather than a 50% excess. Indole XXIa is then obtained as a complex with 0.5 mol of 2,5-dichlorohydroquinone, from which it can be freed by treatment with silver oxide. However, decarbethoxylation of XXIa proceeded poorly. It has been noted previously that difficult decarbethoxylations in the indole series can be overcome by use of a *tert*-butyl ester.[12] Preparation of the requisite *tert*-butyl ester XXIb by condensation of molar equivalents of dichloroquinone XVIII and *tert*-butyl 3-aminocrotonate XIXb[12] proceeded in only 30% yield when effected in a 15% solution of acetic acid in ethanol but afforded a respectable 60% yield when carried out in glacial acetic acid. Heating *tert*-butyl ester XXIb with *p*-toluenesulfonic acid in refluxing toluene then smoothly furnished 4,7-dichloro-5-hydroxy-2-methylindole (XXIII) (Scheme III).

Scheme III



a series, $R = C_2H_5$
b series, $R = t\text{-}C_4H_9$

The isolation of only the 1:2 hydroquinone adduct XX from the reaction of quinone XVIII with a 50% excess of aminocrotonate in contrast to the isolation of indole XXI in the absence of excess crotonate is worthy of comment. We suggest that the intramolecular cyclization of XXIV to quinonimine XXII, ultimately providing indole XXI, is hindered by the *o*-chlorine atom allowing, in the presence of excess crotonate, an alternative reaction course to the observed 1:2 adduct XX. (For a discussion of the mechanism of the Nenitzescu reaction, see ref 13.) That steric factors can indeed play a role is well documented.[2] The apparent failure to form XX in the absence of excess crotonate presumably reflects the much more rapid rate of the initial crotonate to quinone condensation.

Unfortunately, several attempts to effect dechlorination of 4,7-dichloro-5-hydroxyindole (XXIII) by treatment with sodium borohydride or lithium aluminum hydride in reflux-

‡Preferential or concomitant dechlorination at C_7 *via* complex formationof the hydride reagent with the *peri*-nitrogen was considered less likely on the basis of the relative acidities of the two possible assisting functions.

ing tetrahydrofuran were ineffective and led only to the recovery of starting dichloroindole.§

Biological Evaluation. Lead compound IX significantly suppressed carrageenin-induced edema of the rat paw;[14] by the oral route it was about equipotent (ED_{50} = 150 mg/kg) with aspirin (130 mg/kg) but substantially less potent than phenylbutazone (51 mg/kg) or indomethacin (16 mg/kg).# Its duration of effect was about the same as that observed for aspirin. Unlike aspirin, IX was ineffective in suppressing carrageenin-induced edema in adrenalectomized rats, which suggests that its mode of action may be mediated *via* the adrenals. Compound IX significantly suppressed yeast-induced pyrexia[15] in rats at 83 mg/kg (oral) but also produced hypothermia at higher doses, which aspirin did not.# When evaluated in the guinea pig erythema assay,[16] IX was only effective at toxic doses, whereas aspirin showed good inhibition at several nontoxic dose levels. In the rat adjuvant-arthritis assay[17] IX was inactive.

Low order activity was observed in the inflamed rat paw test.[18] In this assay the dose required to elevate the pain threshold to 160 mm (control animals react at 100-110 mm) was 30 mg/kg (four doses, ten mice/dose) by interperitoneal administration. The peak effect at the highest dose (200 mg/kg, ten mice) tested was twice that of control. The effect at 100 mg/kg ip (ten mice) is produced quickly (30 min) and is short-lived (30 min). Activity on oral administration was not observed. In the mouse hot plate assay,[19] animals treated with IX at 125 mg/kg oral (five doses, ten mice/dose) and 87 mg/kg ip (four doses, ten mice/dose) showed elevated reaction times twice that of control animals. In the quinone-induced writhing assay,[20] the ED_{50} for IX was 12 mg/kg ip (three doses, ten mice/dose) and 71 mg/kg oral (five doses, ten mice/dose). Finally, the single oral dose LD_{50} for IX was 787 mg/kg (14-day observation, 95% confidence limits; 609-3060 mg/kg).

Biological activity proved to be quite specific to IX and none of the congeners (see Tables IV-VI) approached IX in interest. In all instances these substances were found to have a narrower activity spectrum, failing to produce an acceptable effect in one or more of the assays in which IX had been shown to be active. Moreover, with the exception of the 2-ethyl (**87**), 6-methyl-7-demethyl (**90**), and the 1-methyl members of the series, the congeners of Table VI and also the gramine-type derivative failed to show activity in the primary carrageenin assay (250 mg/kg, oral) and these exceptions were, at best, less potent than IX. [The 6,7-dimethyl (**92**) and 5-hydroxy (**83**) analogs, which were not submitted to the carrageenin assay, failed in the quinone writhing test at an oral dose of 200 mg/kg.] Most of the azabicyclononane derivatives were also ineffective in the paw pain assay (200 mg/kg, oral). The two 5-methoxy-2,7-dimethyltryptamines involving other bicyclic amines (**73** and **74**) and the homopiperidine derivative **71** were less interesting than IX in the carrageenin assay and were inactive in the guinea pig erythema and paw pain tests at 250 and 200 mg/kg orally, respectively.

Experimental Section

General. Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Each analytical sample had ir, uv, and nmr spectra compatible with their assigned structures.

§ 7-Chloro-5-methoxy-2-methylindole was ultimately prepared *via* a Nenitzescu reaction with 2-chloro-5-trifluoromethyl-1,4-benzoquinone (see ref 12).

See Experimental Section for details.

Spectra were obtained on Cary 11 (uv), Perkin-Elmer 21 (KBr disks) (ir), and Varian Associates Model A-60 and HA-100-D (nmr) instruments. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of their values. The petroleum ether used was that fraction boiling at 30-60°.

Solutions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Tlc was carried out on silica gel GF plates, using in most cases C_6H_6-Me_2CO-H_2O (2:1:2) as solvent system.

Separation of Ethyl 5-Hydroxy-2,6-dimethylindole-3-carboxylate (III) from Ethyl 5-Hydroxy-2,7-dimethylindole-3-carboxylate (IV). The crude mixture (192 g) from 300 g of ethyl 3-aminocrotonate (II) and 283 g of toluquinone (I),[2] was stirred in 1 l. of MeOH-H_2O (15:6) for 40 min and then was filtered. The residual solids obtained after concentration of the filtrate were slurried with 50% Me_2CO-H_2O and filtered to give 30 g of solid, tlc of which indicated a mixture of the 7-methyl isomer IV and ethyl 3-amino-2-(2,5-dihydroxy-*p*-tolyl)crotonate. The solid was then slurried in EtOAc and filtered from the uncyclized hydroquinone. The Me_2CO-H_2O filtrate was concentrated and the residue was recrystallized from Me_2CO to give 14.5 g of IV, mp 197-200°. This process was repeated with the crude material remaining after the first MeOH-H_2O slurry until most of the 7 isomer was removed as judged by tlc. The residual crude III was washed several times with MeOH-H_2O (15:6) to remove the remaining 7 isomer and recrystallization from Me_2CO gave essentially pure 6 isomer, mp 224-228°. Both the 6 and 7 isomers thus obtained were used without further purification. In several such separations the yields were 10-15% for the 7 isomer and 15-20% for the 6 isomer.

5-Methoxy-2,7-dimethylindole (VIa). This compound was obtained from 5-hydroxy-2,7-dimethylindole[2] by treatment with NaOH and Me_2SO_4. A product of suitable purity for subsequent work was obtained in 80% yield. A sample was recrystallized from Et_2O-petroleum ether to give white crystals, mp 76-77°. *Anal.* ($C_{11}H_{13}NO$) C, H, N.

Preparation of Tryptamines. The various tryptamines were prepared by the method described[3] by Speeter and Anthony except where otherwise noted. The following experiments illustrate the general procedure. A solution of 2.5 ml (0.0252 mol) of $(COCl)_2$ in 10 ml of Et_2O was added dropwise, under N_2, to an ice-cold, magnetically stirred solution of 3 g (0.0172 mol) of 2,7-dimethyl-5-methoxyindole (VIa) in 60 ml of Et_2O. The mixture was stirred for 30 min, diluted with petroleum ether, and filtered to give 2.67 g (80%) of solid, mp 165-168°.

Without further purification, this acid chloride was converted to the glyoxamide by addition to a stirred solution of 500 ml of Et_2O containing 10 g (0.080 mol) of 3-azabicyclo[3.2.2]nonane. After stirring for 1 hr, the white **3-(5-methoxy-2,7-dimethyl-3-indoleglyoxyloyl)-3-azabicyclo[3.2.2]nonane** (see VIII) was collected, washed with Et_2O and H_2O, and dried to give 3.66 g (75%), mp 242-243° The characterization of this substance and the other indole glyoxamides prepared in a similar manner is given in Tables I-III.

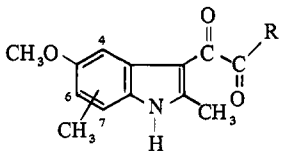
Conversion of the glyoxamide to the corresponding tryptamine was accomplished in accord with the following example. To a stirred solution of 2.4 g (6.7 mmol) of the above glyoxamide in 300 ml of THF was added portionwise, under N_2, 2.58 g (67 mmol) of $LiAlH_4$. The resulting mixture was stirred and refluxed for 24 hr. The reaction was cooled and 17 ml of saturated sodium potassium tartrate solution was added dropwise. The inorganic salts were filtered and washed with THF. The combined filtrates were dried and evaporated to give 2.02 g (92%) of **3-[2-(2,7-dimethyl-5-methoxy-3-indolyl)ethyl]-3-azabicyclo[3.2.2]nonane (IX)** as an oil which solidified on standing. Recrystallization from Et_2O-petroleum ether gave white crystals, mp 110-113°. The characterization of this substance and other tryptamines prepared in a similar manner is given in Tables IV-VI.

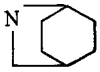
3-Azabicyclo[3.2.2]nonylacetyl-5-methoxy-2-methylindole. 3-Chloroacetyl-5-methoxy-2-methylindole was prepared, according to the method of Sanna,[6] from the bromomagnesium salt of 5-methoxy-2-methylindole and chloracetyl chloride to give a product that was not characterized but proved suitable for further use.

A mixture of 3.0 g (0.0126 mol) of 3-chloroacetyl-5-methoxy-2-methylindole and 6.0 g (0.049 mol) of 3-azabicyclo[3.2.2]nonane in 100 ml of *i*-PrOH was heated at reflux for 1.5 hr. The solvent was concentrated to a small volume and H_2O was then added to precipitated tan solid. The solid was collected and air-dried to give 3.4 g (82%), mp 191-196°, of 3-azabicyclo[3.2.2]nonylacetyl-5-methoxy-2-methylindole. Recrystallization from *i*-PrOH afforded an analytical sample, mp 209-210°. *Anal.* ($C_{20}H_{26}N_2O_2$) C, H, N.

3-[2-(5-Methoxy-1,2,7-trimethyl-3-indolyl)ethyl]-3-azabicyclo-

Table I. 5-Methoxy-2,6- (or 2,7-) dimethyl-3-indolylglyoxamides



Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
			A. 6-Methyl Series			
1	NH_2	86	MeOH	281-283	$C_{13}H_{14}N_2O_3$	C, H, N
2	$NHCH_2C(CH_3)=CH_2$	58	MeOH	205-207	$C_{17}H_{20}N_2O_3$	C, H, N
3	$N(CH_3)_2$	66	MeOH	168-169	$C_{15}H_{18}N_2O_3$	C, H, N
4	$N(C_2H_5)_2$	78	CH_2Cl_2-Et_2O	179-180	$C_{17}H_{22}N_2O_3$	C, H, N
5		57	Me_2CO	190-192	$C_{17}H_{18}N_2O_3$	C, H, N
6	c-NC_5H_{10}	60	EtOH	247-250	$C_{18}H_{22}N_2O_3$	C, H, N
7	c-$N(CH_2CH_2)_2O$	73	MeOH	290-293	$C_{17}H_{20}N_2O_4$	C, H, N
			B. 5-Ethoxy-6-methyl Derivative			
8	$N(CH_3)_2$	80	MeOH	177-179	$C_{16}H_{20}N_2O_3$	C, H, N
			C. 7-Methyl Series			
9	NH_2	73	Me_2CO	251-253	$C_{13}H_{14}N_2O_3$	C, H, N
10	$NHCH_3$	80	Me_2CO	242-245	$C_{14}H_{16}N_2O_3$	C, H, N
11	NHC_4H_9	75	Me_2CO	203-205	$C_{17}H_{22}N_2O_3$	C, H, N
12	NHC_6H_{11}	41	MeOH-H_2O	159-161	$C_{19}H_{24}N_2O_3$	H, N; C[a]
13	$NHCH_2CH=CH_2$	47	Me_2CO	196-198	$C_{16}H_{18}N_2O_3$	C, H, N
14	$NHCH_2C(CH_3)=CH_2$	70	MeOH-H_2O	163-165	$C_{17}H_{20}N_2O_3$	C, H, N
15	$NHCH_2CH_2SC_2H_5$	80	Me_2CO-H_2O	83-85	$C_{17}H_{22}N_2O_3S$	C, H, N, S
16	$N(CH_3)_2$	77	MeOH	252-254	$C_{15}H_{18}N_2O_3$	C, H, N
17	$N(C_2H_5)_2$	80	CH_2Cl_2-Et_2O	184-185	$C_{17}H_{22}N_2O_3$	C, H, N
18	$N(C_2H_5)CH_2CH=CH_2$	57	Me_2CO-H_2O	173-174	$C_{18}H_{22}N_2O_3$	C, H, N
19	$N(CH_2CH=CH_2)_2$	80	MeOH	181-182	$C_{19}H_{22}N_2O_3$	C, H, N
20	c-NC_4H_8	79	CH_2Cl_2-Et_2O	191-192	$C_{17}H_{20}N_2O_3$	C, H, N
21		76	Me_2CO	214-215	$C_{17}H_{18}N_2O_3$	C, H, N
22	c-NC_5H_{10}	81	CH_2Cl_2-MeOH	113-116	$C_{18}H_{22}N_2O_3$	C, H, N
23		58	Me_2CO	191-192	$C_{18}H_{20}N_2O_3$	C, H, N
24	c-$N(CH_2CH_2)_2O$	76	MeOH	220-222	$C_{17}H_{20}N_2O_4$	C, H, N
25	c-NC_5H_{10}	51	EtOH-H_2O	90-110, 142	$C_{19}H_{24}N_2O_3$	C, H, N
26		71	Me_2CO	242-246	$C_{23}H_{30}N_2O_3$	C, H, N
27		80	MeOH	255-257	$C_{20}H_{24}N_2O_3$	C, H, N
28		58	Me_2CO-MeOH	142-145, 185-190	$C_{21}H_{26}N_2O_3 \cdot MeOH$	C, H, N
			D. 4-Chloro-7-methyl Derivative			
29		73	Me_2CO	248-250	$C_{17}H_{17}ClN_2O_3$	C, H, Cl, N

[a]C: calcd, 69.49; found, 70.08.

[3.2.2]nonane. A solution of 1.66 g (5.1 mmol) of 3-[2-(2,7-dimethyl-5-methoxy-3-indolyl)ethyl]-3-azabicyclo[3.2.2]nonane (IX) in 10 ml of DMSO was added to a cold solution of methylsulfinyl carbanion[21] prepared from NaH (5.1 mmol as a 57.2% dispersion in mineral oil) and 15 ml of DMSO.[22] The resulting solution was stirred at room temperature for 1 hr, after which time 725 mg (5.1 mmol) of MeI was added. In 15 min a precipitate appeared. The mixture was stirred for 3 hr and filtered, and the solids were washed with H_2O and dried to give 1.44 g (83.5%, mp 148-152°). Recrystallization from Et_2O furnished white crystals, mp 152-153°. *Anal.* ($C_{22}H_{32}N_2O$) C, H, N.

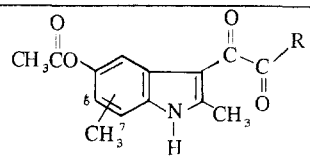
5-Acetoxy-2,6-dimethylindole. A solution of 5.0 g (0.031 mol) of 2,6-dimethyl-5-hydroxyindole,[2] 7.8 ml of Ac_2O, and 50 ml of pyridine was allowed to stand at room temperature for 18 hr. The reaction solution was diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with saline, dried, and concentrated. The residue was chromatographed on Florisil;** the product was eluted with C_6H_6 and was recrystallized from Et_2O-petroleum ether to give 3.645 g (58%), mp 105-106°. A second recrystallization gave white crystals, mp 106-107°. *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

5-Acetoxy-2,7-dimethylindole. This compound was prepared from 2,7-dimethyl-5-hydroxyindole[2] as described directly above for the 6-methyl series. The product was obtained in 81% yield as white crystals, mp 94-95°. *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

5-[(5-Methoxy-2,7-dimethyl-3-indolyl)methyl]-3-azabicyclo[3.2.2]nonane. A solution containing 12.5 ml of dioxane, 12.5 ml of AcOH, 0.94 ml of 37% aqueous formaldehyde, and 1.52 g of

**Florisil is the trademark of the Floridin Co. for a magnesia-silica gel adsorbent.

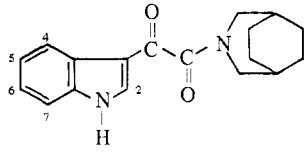
Table II. 5-Acetoxy-2,6- (or 2,7-) dimethyl-3-indolylglyoxamides



Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
			A. 6-Methyl Series			
30	NHC_2H_5	79	MeOH	238-240	$C_{16}H_{18}N_2O_4$	C, H, N
31	$N(CH_3)_2$	47	MeOH	208-210	$C_{16}H_{18}N_2O_4$	C, N; H[a]
			B. 7-Methyl Series			
32	NH_2	59	MeOH	251-253	$C_{14}H_{14}N_2O_4$	C, H, N
33		85	MeOH	244-246	$C_{22}H_{26}N_2O_4$	C, H, N

[a]H: calcd, 6.00; found, 6.50.

Table III. Substituted 3-Indoleglyoxyloyl-3-azabicyclo[3.2.2]nonanes



Compd	Substituents	Yield, %	Recrystn, solvent	Mp, °C	Formula	Analyses
34	5-MeO-2,7-diMe	40	EtOH	243-244	$C_{21}H_{26}N_2O_3$	C, H, N
35	5-AcO-2,7-diMe	85	MeOH	246-248	$C_{22}H_{26}N_2O_4$	C, H, N
36	5-MeO	65	MeOH	225-226	$C_{19}H_{22}N_2O_3$	C, H, N
37	2,7-diMe	36	EtOH	200-201	$C_{20}H_{24}N_2O_2$	C, H, N
38	5-MeO-2-Et-7-Me	51	MeOH	113-116	$C_{22}H_{28}N_2O_3 \cdot MeOH$	C, H, N
39	5-EtO-2,7-diMe	77	MeOH	250-251	$C_{22}H_{28}N_2O_3$	C, H, N
40	5-MeO-2,6-diMe	90	EtOH	238-240	$C_{21}H_{26}N_2O_3$	C, H, N
41	5-MeO-2,7-diMe-4-Cl	91	THF	281-282	$C_{21}H_{25}ClN_2O_3$	C, H, Cl, N
42	5-MeO-2-Me-4,7-diCl	51	Me_2CO	290-292	$C_{20}H_{22}Cl_2N_2O_3$	C, H, Cl, N

3-azabicyclo[3.2.2]nonane was cooled to 5° and a solution of 1.75 g (10 mmol) of 2,7-dimethyl-5-methoxyindole (VIa) in 22 ml of dioxane was added in 30 min. The reaction mixture was kept at 5° for 2 hr and then allowed to stand overnight at room temperature. The solution was diluted with 125 ml of H_2O, filtered, and made alkaline with 10 *N* NaOH. The resulting mixture was cooled and filtered. The dried solid was washed several times with hot hexane and dried to give 1.83 g (58%) of crude solid. Recrystallization from Et_2O gave off-white crystals, mp 168-170°. *Anal.* ($C_{20}H_{28}N_2O$) C, H, N.

7-Ethyl-5-methoxy-2-methylindole. This compound was prepared by the sequence previously described[7] for the corresponding 7-methyl derivative *via* a Nenitzescu condensation between *tert*-butyl 3-aminocrotonate[12] and **5-chloro-2-ethyl-1,4-benzoquinone** (mp 65-66°, used in the crude form) prepared in 42% overall yield by addition of HCl gas to ethyl-1,4-benzoquinone followed by Ag_2O oxidation according to the procedure of Hodgson and Moore.[23] The Nenitzescu product, ***tert*-butyl 4-chloro-7-ethyl-5-hydroxy-2-methylindole-3-carboxylate** [55%, mp 181-182° (Me_2CO). *Anal.* ($C_{16}H_{20}ClNO_3$) C, H, Cl, N] was transformed to the subject compound by the following sequence: O-methylation to ***tert*-butyl 4-chloro-7-ethyl-5-methoxy-2-methylindole-3-carboxylate** (84%, mp 145-147°, used crude); decarbalkoxylation to **4-chloro-7-ethyl-5-methoxy-2-methylindole** [78%, mp 90-91° (Et_2O-petroleum ether). *Anal.* ($C_{12}H_{14}ClNO$) C, H, Cl, N]; and finally catalytic Pd/C dechlorination to 7-ethyl-5-methoxy-2-methylindole [90%, mp 70-72° (Et_2O-petroleum ether). *Anal.* ($C_{12}H_{15}NO$) C, H, N].

2-Ethyl-7-methyl-5-methoxyindole. This compound was obtained *via* Nenitzescu condensation of 5-chloro-2-methyl-1,4-benzoquinone[23] with ethyl 3-amino-2-pentenoate[24,25] by the sequence described[7] earlier for the corresponding 2-methyl derivative. The Nenitzescu product, **ethyl 2-ethyl-4-chloro-5-hydroxy-7-methylindole-3-carboxylate** [41%, mp 130-131° (C_6H_6). *Anal.* ($C_{14}H_{16}ClNO_3$) C, H, Cl, N] was O-methylated to **ethyl 2-ethyl-4-chloro-5-methoxy-7-methylindole-3-carboxylate** [82%, mp 143-145° (Me_2CO). *Anal.* ($C_{15}H_{18}ClNO_3$) C, H, Cl, N]; decarbethoxylated to **2-ethyl-4-chloro-5-methoxy-7-methylindole** [81%, mp 100-102° (Et_2O-petroleum ether). *Anal.* ($C_{12}H_{14}ClNO$) C, H, Cl, N] by heating 500 mg of ester with a solution of 1.07 g of KOH in 1 ml of H_2O and 5 ml of 95% *i*-BuOH for 48 hr, drowning in H_2O, extracting with Et_2O, evaporating the solvent, chromatographing on silica gel, and eluting with C_6H_6; and dechlorinated to **2-ethyl-7-methyl-5-methoxyindole** [96% as an oil; picrate mp 119-120° (Et_2O-petroleum ether); brick red crystals. *Anal.* ($C_{18}H_{18}N_4O_8$) C, H, N].

5-Ethoxy-2,7-dimethylindole. Treatment of 5-hydroxy-2,7-dimethylindole (Va) with Et_2SO_4 by the procedure described above for VIa gave yellow crystals (46%, mp 90-93°) of suitable purity for further work. A sample was recrystallized from Et_2O-petroleum ether to give crystals, mp 90-93°. *Anal.* ($C_{12}H_{15}NO$) C, H, N.

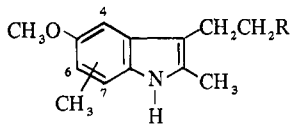
5-Ethoxy-2,6-dimethylindole. This compound was prepared by the procedure described above for VIa from 5-hydroxy-2,6-dimethylindole,[2] NaOH, and Et_2SO_4 and was obtained as yellow crystals (52%, mp 120-121°). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

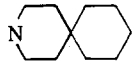
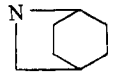
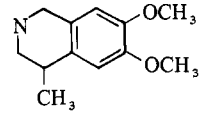
Ethyl 5-Methoxy-2,6,7-trimethylindole-3-carboxylate. This compound was obtained (96%) as a white solid, mp 184-185° (Me_2CO-hexane) from ethyl 5-hydroxy-2,6,7-trimethylindole-3-carboxylate,[26] NaOH, and Me_2SO_4 as described above for VIa. *Anal.* ($C_{15}H_{19}NO_3$) C, H, N.

5-Methoxy-2,6,7-trimethylindole. A stirred mixture of ethyl 5-methoxy-2,6,7-trimethylindole-3-carboxylate (1 g, 3.83 mmol), 2.42 g (43.1 mmol) of KOH, and 2.3 ml of H_2O in 11.3 ml of 95% *i*-BuOH was heated at reflux for 20 hr. The reaction mixture was cooled, diluted with H_2O, and extracted with EtOAc. The combined extracts were dried and concentrated. The residue was chromatographed on silica gel and the product was eluted with C_6H_6 and recrystallized from Et_2O-petroleum ether to give 285 mg (40%, mp 90-91°). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

Ethyl 4,7-Dichloro-5-hydroxy-2-methylindole-3-carboxylate (XXIa). To a hot solution of 2.5 g (0.0141 mol) of 2,5-dichloro-1,4-benzoquinone (XVIII) in 75 ml of EtOH was added 1.80 g (0.0139 mol) of ethyl 3-aminocrotonate (XIXa) and 2.5 ml of AcOH and the solution was refluxed for 0.5 hr. The solvent was removed and the residue was triturated with CH_2Cl_2 to give 2.10 g (40%) of the indole as a complex with 0.5 mol of 2,5-dichlorohydroquinone, mp 175-

Table IV. 5-Methoxy-2,6- (or 2,7-) dimethyltryptamines



Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses	Ataxia, RWD, mg/kg ip
			A. 6-Methyl Series				
43	NH_2	16	$EtOH-Et_2O$	174-176	$C_{13}H_{18}N_2O \cdot C_4H_4O_4$[a]	C, H, N	130
44	$NHCH_3$	32[b]	Me_2CO-Et_2O	152-154	$C_{14}H_{20}N_2O \cdot C_4H_4O_4$[a]	C, H, N	80
45	$NHCH_2C(CH_3)=CH_2$	87	$EtOH-Et_2O$	187-188	$C_{17}H_{24}N_2O \cdot C_4H_4O_4$[a]	C, H, N	
46	$N(CH_3)_2$	50	Me_2CO-Et_2O	150-151	$C_{15}H_{22}N_2O \cdot C_4H_4O_4$[a]	C, H, N	
47	$N(C_2H_5)_2$	80	$EtOH-Et_2O$	130-132	$C_{17}H_{26}N_2O \cdot C_4H_4O_4$[a]	H, N; C[c]	22
48		85	$EtOH-Et_2O$	182-185	$C_{17}H_{22}N_2O \cdot C_4H_4O_4$[d]	C, H, N	
49	$c-NC_5H_{10}$	67	Et_2O	121-123	$C_{18}H_{26}N_2O$	C, H, N	
50	$c-N(CH_2CH_2)_2O$	55	EtOH	156-157	$C_{17}H_{24}N_2O_2 \cdot C_4H_4O_4$[a]	C, H, N	
			B. 5-Ethoxy-6-methyl Derivative				
51	$N(CH_3)_2$	67	EtOH	191-192	$C_{16}H_{24}N_2O \cdot C_4H_4O_4$[a]	C, H, N	76
			C. 7-Methyl Series				
52	NH_2	33	$CH_2Cl_2-Et_2O$	133-137	$C_{13}H_{18}N_2O$	C, H, N	72
53	$NHCH_3$	14	Ether-petroleum ether	110-112	$C_{14}H_{20}N_2O$	C, H, N	48
54	NHC_4H_9	47	$EtOH-Et_2O$	127-128	$C_{17}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N	70
55	NHC_6H_{11}	29	$EtOH-Et_2O$	186-188	$C_{19}H_{28}N_2O \cdot C_4H_4O_4$[a]	C, H, N	72
56	$NHCH_2CH=CH_2$	37	$EtOH-Et_2O$	165-168	$C_{16}H_{22}N_2O \cdot C_4H_4O_4$[d]	C, H, N	
57	$NHCH_2C(CH_3)=CH_2$	65	$EtOH-Et_2O$	157-158	$C_{17}H_{24}N_2O \cdot C_4H_4O_4$[a]	C, H, N	68
58	$NHCH_2CH_2SC_2H_5$	57	EtOH	188-190	$C_{17}H_{26}N_2OS \cdot 0.5C_4H_4O_4$[d]	C, H, N, S	68
59	$N(CH_3)_2$	86	Et_2O	115-116	$C_{15}H_{22}N_2O$	C, H, N	26
60	$N(C_2H_5)_2$	60	$MeOH-Et_2O$	118-120	$C_{17}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N	22
61	$N(C_3H_7)_2$	53[b]	$EtOH-Et_2O$	141-144	$C_{19}H_{30}N_2O \cdot C_4H_4O_4$[a]	C, H, N	25
62	$N(C_2H_5)CH_2CH=CH_2$	75	$EtOH-Et_2O$	110-112	$C_{18}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N	
63	$N(CH_2CH=CH_2)_2$	81	$EtOH-Et_2O$	123-125	$C_{19}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N	52
64	$c-NC_4H_8$	50	$EtOH-Et_2O$	121-122	$C_{16}H_{22}N_2O \cdot C_4H_4O_4$[a]	C, H, N	18
65		68	Et_2O	135-137	$C_{17}H_{22}N_2O$	C, H, N	68
66	$c-NC_5H_{10}$	55	$EtOH-Et_2O$	150-152	$C_{18}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N	14
67		88	$EtOH-Et_2O$	122-123	$C_{18}H_{24}N_2O \cdot C_4H_4O_4$[a]	C, H, N	
68	$2-Et-c-NC_5H_9$	24[b]	$EtOH-Et_2O$	242-243	$C_{20}H_{30}N_2O \cdot 0.5C_4H_4O_4$[d]	C, H, N	
69	$3-Me-c-NC_5H_9$	32[b]	$EtOH-Et_2O$	203-205	$C_{19}H_{28}N_2O \cdot 0.5C_4H_4O_4$[d]	C, H, N	34
70	$c-N(CH_2CH_2)_2O$	48	$EtOH-Et_2O$	137-138	$C_{17}H_{24}N_2O_2 \cdot C_4H_4O_4$[a]	C, H, N	86
71	$c-NC_6H_{12}$	79	$EtOH-Et_2O$	127-129	$C_{19}H_{28}N_2O \cdot C_4H_4O_4$[a]	H, N; C[e]	20
72		80	EtOH	251-253	$C_{23}H_{34}N_2O \cdot 0.5C_4H_4O_4$[d]	C, H, N	>100
73		84	EtOH	190-192	$C_{20}H_{28}N_2O \cdot C_4H_4O_4$[d]	C, H, N	
74		67	EtOH	189-193	$C_{21}H_{30}N_2O \cdot 0.5C_4H_4O_4 \cdot C_2H_5OH$[d]	C, H, N	
75		33[b]	$EtOH-Et_2O$	216-218	$C_{25}H_{32}N_2O_3 \cdot C_4H_4O_4$[d]	C, H, N	
			D. 4-Chloro-7-methyl Derivative				
76		73	EtOH	183-184	$C_{17}H_{21}ClN_2O_6 \cdot C_4H_4O_4$[d]	C, H, N	

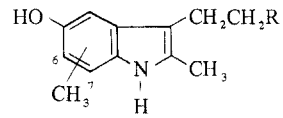
[a]Maleate. [b]Overall yield for two steps from 5-methoxy-2,6- (or 2,7-) dimethylindole. [c]C: calcd, 64.59; found, 65.08. [d]Fumarate. [e]C: calcd, 66.32; found, 65.30.

180°; the nmr was characterized by a 2-proton singlet at δ 7.17. *Anal.* ($C_{15}H_{13}Cl_3NO_4$) C, H, Cl, N.

A mixture of 274 mg of the indole-hydroquinone complex, 400 mg of Ag_2O, and 1.75 g of Na_2SO_4 in 56 ml of Et_2O was stirred at room temperature for 20 min. The mixture was filtered and the filtrate evaporated. The residue was extracted with boiling petroleum ether and then triturated with C_6H_6 to give the free indole XXIa. Recrystallization from Me_2CO-hexane gave 110 mg (48%), mp 147-149°. *Anal.* ($C_{12}H_{11}Cl_2NO_3 \cdot 0.5C_6H_6$) C, H, Cl, N.

When the above reaction was carried out in $CHCl_3$ using 2.5 g of 2,5-dichloro-1,4-benzoquinone (XVIII) and a 50% molar excess of ethyl 3-aminocrotonate (XIXa) according to the method of Grinev, *et al.*,[10] 978 mg (23% based on aminocrotonate) of the 1:2 hydroquinone adduct XX was obtained, mp >300° dec. *Anal.*

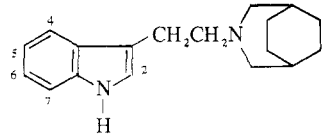
Table V. 5-Hydroxy-2,6- (or 2,7-) dimethyltryptamines



Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses	Ataxia, RWD, mg/kg ip
			A. 6-Methyl Series				
77	NH_2	8[b]	MeOH-Et_2O	166-168	$C_{12}H_{16}N_3O \cdot C_4H_4O_4$[a]	C, H, N	
78	NHC_2H_5	21	EtOH-Et_2O	160-161	$C_{14}H_{20}N_2O \cdot C_4H_4O_4$[a]	C, H, N	160
79	$N(C_2H_5)_2$	60	MeOH-H_2O	219-221	$C_{14}H_{20}N_2O$	C, H, N	
			B. 7-Methyl Series				
80	NH_2	19	MeOH-Et_2O	180-181	$C_{12}H_{16}N_2O \cdot C_4H_4O_4$[a]	C, H, N	
81	$N(CH_3)_2$	3[b]	EtOH-Et_2O	144-147	$C_{14}H_{20}N_2O \cdot C_4H_4O_4$[a]	C, H, N	

[a]Maleate salt. [b]Based on 5-acetoxy-2,6- (or 2,7-) methylindole, the last pure intermediate.

Table VI. 3-[2-(3-Indolyl)ethyl]-3-azabicyclo[3.2.2]nonanes



Compd	Substituents	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
82	5-MeO-2,7-diMe	67	Et_2O-petroleum ether	110-113	$C_{21}H_{30}N_2O$	C, H, N
83	5-HO-2,7-diMe	60	Et_2O-petroleum ether	103-106	$C_{20}H_{28}N_2O$	C, H, N
84	5-MeO-2-Me	69	EtOH-Et_2O	167-168	$C_{20}H_{28}N_2O \cdot C_4H_4O_4$[a]	C, H, N
85	5-MeO	70	EtOH-Et_2O	182-184	$C_{19}H_{26}N_2O \cdot C_4H_4O_4$[a]	C, H, N
86	2,7-diMe	34	EtOH-Et_2O	95-96	$C_{20}H_{28}N_2 \cdot C_4H_4O_4 \cdot C_2H_5OH$[a]	C, H, N
87	5-MeO-2-Et-7-Me	83	Et_2O-petroleum ether	108-110	$C_{22}H_{32}N_2O$	C, H, N
88	5-MeO-2-Me-7-Et	53[b]	EtOH-Et_2O	173-174	$C_{22}H_{32}N_2O \cdot C_4H_4O_4$[a]	C, H, N
89	5-EtO-2,7-diMe	66	EtOH-Et_2O	200-202	$C_{22}H_{32}N_2O \cdot C_4H_4O_4$[a]	C, H, N
90	5-MeO-2,6-diMe	84	Et_2O-petroleum ether	146-148	$C_{21}H_{30}N_2O$	C, H, N
91	5-MeO-2-Me-7-Cl	12[b,c]	EtOH-Et_2O	166-168	$C_{20}H_{27}ClN_2O \cdot C_4H_4O_4$[a]	C, H, Cl, N
92	5-MeO-2,6,7-triMe	44[b]	EtOH-Et_2O	211-213	$C_{22}H_{32}N_2O \cdot C_4H_4O_4$[a]	C, H, N
93	5-MeO-2,7-diMe-4-Cl	82	EtOH-Et_2O	206-208	$C_{21}H_{29}ClN_2O \cdot C_4H_4O_4$[a]	C, H, Cl, N
94	5-MeO-2-Me-4,7-diCl	25[b]	EtOH-Et_2O	214-216	$C_{20}H_{26}Cl_2N_2O \cdot C_4H_4O_4$[a]	C, H, Cl, N

[a]Maleate. [b]Overall yield for two stages from the appropriately substituted 5-methoxyindole. [c]Purified by partition chromatography on diatomaceous silica using a heptane-2-methoxyethanol (1:1) system; the product was eluted at peak HBV 2.5 (Vm/Vs = 2.07). Compound 84 (22%) was obtained from the fraction eluted at peak HBV 4.0.

($C_{18}H_{22}Cl_2N_2O_6$) C, H, Cl, N. The assignment of a trans relationship to the methyl and carbethoxy functions in structure XX is based on previous experience with this class.[2]

***tert*-Butyl 4,7-Dichloro-5-hydroxy-2-methylindole-3-carboxylate (XXIb).** A magnetically stirred mixture of 3.0 g (0.017 mol) of 2,5-dichloro-1,4-benzoquinone (XVIII) in 20 ml of AcOH was heated to solution, 2.66 g (0.0109 mol) of *tert*-butyl 3-aminocrotonate (XIXb)[12] was added, and stirring was continued without further heating for 0.5 hr. The mixture was cooled and the precipitated solid was filtered, washed with cold AcOH, and dried to give 3.12 g (60%) of product XXIb, mp 192-194°.

When this reaction was carried out in a 15% AcOH-EtOH solution 30% of product XXIb was obtained. An analytical sample, mp 194-195°, was prepared by recrystallization from CH_2Cl_2-Et_2O. *Anal.* ($C_{14}H_{15}Cl_2NO_3$) C, H, N.

4,7-Dichloro-5-hydroxy-2-methylindole (XXIII). A solution of 3.025 g (9.55 mmol) of *tert*-butyl 4,7-dichloro-5-hydroxy-2-methylindole-3-carboxylate (XXIb) and 5.5 mg of PTSA in 225 ml of toluene was refluxed for 1 hr and filtered, and the filtrate was concentrated. The residue was dissolved in Et_2O, washed with H_2O, dried, and concentrated to a residue which was chromatographed on silica gel. Elution with C_6H_6 gave, after crystallization from Et_2O-petroleum ether, 1.116 g (53%) of product XXIII, mp 122-123° *Anal.* ($C_9H_7Cl_2NO$) C, H, N, Cl.

4,7-Dichloro-5-methoxy-2-methylindole. This compound was prepared from reaction of 4,7-dichloro-5-hydroxy-2-methylindole with alkaline Me_2SO_4. The product was obtained as crystals (71%), mp 108-110°, from Et_2O-petroleum ether. *Anal.* ($C_{10}H_9Cl_2NO$) H, Cl, N; C: calcd, 52.2; found, 51.7.

7-Chloro-5-methoxy-2-methylindole. This compound was prepared by treatment of 7-chloro-5-hydroxy-2-methylindole[12] with dimethyl sulfate by the method reported above for the preparation of VIa. The product was obtained as an oil (65% yield) and identified as the picrate, mp 137-138°. *Anal.* ($C_{16}H_{13}ClN_4O_8$) C, H, N, Cl.

Biological Evaluation. Carrageenin-Induced Edema of the Rat Paw.[14] The reported ED_{50} values were obtained from the following data [oral dose mg/kg, control/treated (95% confidence limits), number of rats]. For IX: 250, 2.4 (1.5-3.7), 4; 83, 1.7 (1.2-2.5), 12; 27, 1.0 (0.7-1.4), 12. For aspirin: 250, 2.5 (1.7-3.7), 12; 83, 1.5 (1.0-2.1), 12; 28, 1.3 (0.9-1.9), 12; 9, 0.9 (0.6-1.2), 12. For phenylbutazone: 250, 2.3 (1.6-3.4), 12; 83, 2.7 (1.8-3.9), 12; 28, 1.9 (1.3-2.7), 12: 9, 1.2 (0.8-1.8), 12. For indomethacin: 250, 3.2 (2.2-4.7), 12; 8?, 2.6 (1.8-3.7), 12; 28, 2.1 (1.4-3.0), 12; 9, 2.2 (1.5-3.2), 12; ?, 1.9 (1.3-2.8), 12; 1, 1.3 (0.09-1.8), 12.

Suppression of Yeast-Induced Pyrexia.[15] Effect of IX (oral dose mg/kg, number of rats): 34.4° (250, 3); 36.6° (83, 9); 37.6° (27, 9); 38.2° (9, 9); 38.3° (control, 156); 36.8° (normal temperature). The value for the 250 mg/kg dose was significantly lower than normal temperature ($p < 0.05$ by Student's t test), and that observed for the 83 mg/kg dose was significantly lower than that noted for the pyretic controls ($p < 0.05$ by Student's t test).

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Syntheses and Biological Activities of 7-Ethyl-8-chloro-10-(1′-D-ribityl)isoalloxazine and 7-Chloro-8-ethyl-10-(1′-D-ribityl)isoalloxazine, Analogs of Riboflavin†

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The riboflavin analogs 7-ethyl-8-chloro-10-(1′-D-ribityl)isoalloxazine and 7-chloro-8-ethyl-10-(1′-D-ribityl)-isoalloxazine have been synthesized starting with *o*-aminoethylbenzene. The former analog is devoid of biological activity in the riboflavin-deficient rat but it was found to be a strong, reversible antagonist of riboflavin in *Lactobacillus casei.* The latter analog produced good growth response and caused the complete recovery of the visually observable signs of deficiency in the riboflavin-deficient rat and thus shows that it possesses riboflavin-like activity. The latter analog was found to be a potent antagonist in the rat in that when 150 μg/day or more was administered, most of the experimental animals died. This analog also inhibited the action of administered riboflavin in the growth of the rat. Both the lethality of and the inhibition of the growth-promoting properties of riboflavin by this analog could be counteracted by the administration of sufficient riboflavin, thus demonstrating that these activities are properties of an antagonist of riboflavin. The latter analog was found to be a strong, reversible antagonist of riboflavin in *L. casei.*

When a young riboflavin-deficient rat is given riboflavin, it increases its food consumption, improves its food utilization, increases in weight, lives longer, and shows recovery from the visually observable signs of the deficiency. When riboflavin is given with adequate food, these responses are always intimately linked in such animals. If following the administration of any chemical compound, especially if it be an analog of riboflavin, one observes one or more of the above changes to take place, it is entirely reasonable to attribute to such a compound riboflavin-like or vitamin-like activity. If following the administration of such a compound the animal's condition with respect to one or more of the above criteria is worsened, it is reasonable to suspect that the compound might be an antagonist of riboflavin. However, if the activities of the suspected antagonist are prevented or reversed by the simultaneous administration of riboflavin, it is entirely reasonable to ascribe antiriboflavin or riboflavin antagonistic properties to the compound.

This report, as well as others we have published and will publish in the future, has as an important aim the recording of overwhelming evidence that among homologs and analogs of riboflavin which we have synthesized are some possessing almost exclusively riboflavin-like properties. Others possess almost exclusively riboflavin antagonistic activities, and still others which now are several in number clearly display mixed properties, both vitamin-like with regard to some of the above criteria and riboflavin antagonist properties with regard to some of the above criteria.

For an analog of riboflavin to possess significant biological activity it must bear a D-ribityl side chain at position 10 of the isoalloxazine or flavin nucleus. Starting with that basic structural unit, alterations of the substituents at positions 7 and 8 lead to compounds with activities ranging from zero to extremely potent vitamin-like or antagonistic activities. For a clear understanding of this report it will be necessary to review briefly the findings reported for compounds possessing combinations of alkyl and halogen groups in these two positions.

Dichlororiboflavin [7,8-dichloro-10-(1′-D-ribityl)isoalloxazine] was synthesized specifically to test it for riboflavin antagonist properties.[1,2] It proved, however, to be devoid

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