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SYNTHESIS OF BENZ[G]INDOLE AMINOMETHYL DERIVATIVES

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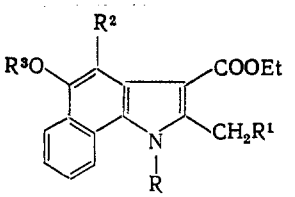
Aminomethyl derivatives of indole have been found to include compounds with a high degree of antiviral [6] and antitubercular activity [4] as well as compounds which exhibit antiarrhythmic, antifibrillatory, and anticonvulsive activity [5]. At the same time there has been little study of the aminomethyl derivatives in the benz[g]indole series. A description has been given for the synthesis of N-methyl and N-phenyl-2-methyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-oxybenz[g]indoles by treating corresponding derivatives of 5-oxybenz-[g]indoles with bisdimethylaminomethane [1]. However, information about their biological activity is lacking.

We synthesized the benz[g]indoles [III-XVIII] in order to test the antiviral activity of the aminomethyl derivatives of 2-methyl-3-ethoxycarbonylbenz[g]indole.



I—XVIII

R = Me (I, V, VI, XVIII), Ph (II—IV, VII—XVII); R^1 = H (I—VII, XVIII), Br (VIII), NMe_2 (IX, XII), $N(CH_2CH_2)_2O$ (X, XIII, XV), $N(CH_2)_5$ (XI, XIV, XVI), SPh (XVII); R^2 = H (I, II, VII—XIV, XVII, XVIII), CH_2NMe_2 (III), $CH_2N(CH_2CH_2)_2O$ (IV, VI, XV), $CH_2N(CH_2)_5$ (V, XVI); R^3 = H (I—VI, XII—XVII), Ac (VII—XI, XVIII).

The aminomethyl derivatives III-VI are formed upon the aminomethylation of 5-oxybenz[g] indoles I and II by method [1]. The substituent in position 2 was modified through the bromide of VIII which was obtained reacting bromosuccinimide with 2-methyl-5-acetoxybenz[g]indole VII. The treatment of compound VII with secondary amines results in the synthesis of 2-aminomethyl derivatives IX-XI whose hydrolysis and subsequent aminomethylation of the intermediate 5-oxybenz[g]indoles result in the formation of 2,4-diaminomethylbenz[g]indoles XV and XVI. The reaction between potassium thiophenolate and 2-bromomethylbenz[g]indole VIII is accompanied by the hydrolysis of the acetyl group which results in the formation of 2-thiophenylmethyl-3-ethoxycarbonyl-5-oxybenz[g]indole XVII which we were not able to aminomethylate on position 4. One should note that when we reacted bromosuccinimide with 1,2-dimethyl-5-acetoxybenz[g]indole XVIII [2], we did not observe the formation of the corresponding 2-bromomethyl derivative. It is generally known that the antiviral activity of this series of compounds is associated with the presence of an o-quinoline structure [3].

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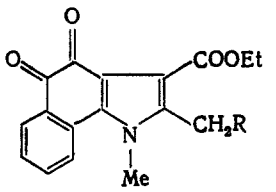
TABLE 1. Characteristics of Synthesized Compounds III-VI, IX-XIV

Compound	mp, °C	Yield, %	Empirical formula	mp, °C of hydrochloride
III	—	38	$C_{28}H_{27}N_3O_3$	202(decomposition)
IV	—	68	$C_{27}H_{28}N_2O_4$	191—2
V	173—5	68	$C_{28}H_{28}N_2O_3$	206(decomposition)
VI	138—9	60,5	$C_{22}H_{26}N_2O_4$	212—3
IX	143—4	78	$C_{26}H_{26}N_2O_4$	—
X	192—8	69	$C_{25}H_{23}N_2O_3$	—
XI	152—3	74	$C_{29}H_{30}N_2O_4$	—
XII	143—4	31,3	$C_{18}H_{19}N_2O_3$	220
XIII	234—5	42	$C_{24}H_{26}N_2O_4$	255(decomposition)
XIV	203—5	67	$C_{27}H_{29}N_2O_3$	240(decomposition)



XIX—XXI

R = H (XIX), Br (XX), $N(CH_2CH_2)_2O$ (XXI).

In order to examine the antiviral activity of the 2-aminomethyl derivatives of benz[g]indole that contain an o-quinone fragment, we synthesized 2-morpholinomethyl-3-ethoxycarbonylbenz[g]indole-4,5-dione (XXI) by brominating the known 1,2-dimethylbenz[g]indole-4,5-dione (XIX) [2] and by treating the resultant bromomethyl derivative (XX) with morpholine.

EXPERIMENTAL (CHEMISTRY)

IR-spectra were recorded on a Perkin-Elmer 599 (USA) spectrophotometer in the form of a suspension in petroleum jelly. Reaction progress and synthesized compound purity were controlled by TLC on Silufol UV-254 plates in a 9:1 benzene-acetone and $CHCl_3$ systems. Development in UV light. Characteristics of compounds III-VI and IX-XIV are given in the Table. Found element analysis values corresponded to the calculated values.

Aminomethyl Derivatives of 1,2-Dimethyl-3-ethoxycarbonyl-5-oxybenz[g]indole (V, VI) and 1-Phenyl-2-methyl-3-ethoxycarbonyl-5-oxybenz[g]indole (III, IV). A solution of 5 mmole of 1,2-dimethyl-3-ethoxycarbonyl-5-oxybenz[g]indole (I) or 1-phenyl-2-methyl-3-ethoxycarbonyl-5-oxybenz[g]indole (II) in 30 ml of dioxane and a corresponding bisaminomethane was heated for 4 h at 80°C. The dioxane and excess amine were vacuum-evaporated and the residue was recrystallized from alcohol. Reaction with an ether solution of HCl converted the bases of III-VI to hydrochlorides which were recrystallized from an acetone-methanol-ether mixture.

1-Phenyl-2-bromomethyl-3-ethoxycarbonyl-5-acetoxybenz[g]indole (VIII). A 0.9 g (6 mmole) portion of bromosuccinimide was added to a solution of 1.9 g (5 mmole) of 1-phenyl-2-methyl-3-ethoxycarbonyl-5-acetoxybenz[g]indole VII [2] in 30 ml of CCl_4. The mixture was boiled for 4 h after the hot reaction mixture was filtered and the mother liquor was vacuum-evaporated. The resultant yield of 1.95 g (84.5%) of compound VIII was used for subsequent conversions without additional purification.

Aminomethyl Derivatives of 1-Phenyl-3-ethoxycarbonyl-5-acetoxybenz[g]indole (IX-XI). A 5 mmole portion of an appropriate amine was added to a solution of 2.5 mmole of 2-bromomethyl-3-ethoxycarbonyl-5-acetoxybenz[g]indole VIII in 20 ml of abs. benzene. The mixture was then kept at room temperature for 20 h after which the separated amine bromohydrate precipitate was filtered off and the mother liquor was vacuum-evaporated. The residue was then crystallized from aq. acetone.

Aminomethyl Derivatives of 1-Phenyl-3-ethoxycarbonyl-5-oxybenz[g]indole (XII-XIV). A solution of 0.28 g (5 mmole) of KOH in 10 ml of abs. alcohol was added to a suspension of 2.5 mmole of appropriate 5-acetoxybenz[g]indoles (IX-XI) in 20 ml of abs. alcohol. The mixture was then heated for 1 h at 60°C, cooled to 20°C after which 30 ml of water was added. The mixture was then acidified with diluted HCl to pH 5.0, then cooled. The separated precipitate was filtered off and recrystallized from aq. acetone. The bases XII-XIV were converted to hydrochlorides which were recrystallized from an acetone-methanol-ether mixture.

1-Phenyl-2,4-dimorpholinomethyl-3-ethoxycarbonyl-5-oxybenz[g]indole HCl (XV). A solution of 0.7 g (1.6 mmole) of 2-morpholinomethylbenz[g]indole (XIII) in 20 ml of dioxane and 1 ml (5 mmole) of bismorpholinomethane was boiled for 1 h and the solvent was vacuum-evaporated. The residue was dissolved in 10 ml of 50% alcohol, cooled, and the water-alcohol layer was separated from the resultant oil. The oil was dissolved in ether, dried with $CaCl_2$ and treated with an ether solution of HCl. The separated XV HCl precipitate was filtered off and recrystallized from a 9:1 acetone-methanol mixture. Yield of XV was 0.35 g ´35.5%), mp 121°C (with decomposition). $C_{33}H_{37}N_3O_5 \cdot 2HCl$.

1-Phenyl-2,4-dipiperidinomethyl-3-ethoxycarbonyl-5-oxybenz[g]indole dihydrochloride (XVI) was obtained in the same way that XV was obtained from XIV, to yield 0.34 g (35%), mp 187°C (with decomposition, acetone-methanol, 9:1). $C_{33}H_{39}N_3O_3 \cdot 2HCl$.

1-Phenyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-oxybenz[g]indole (XVII). A 0.51 ml (5 mmole) portion of thiophenol was added to a solution of 0.86 g (15 mmole) of KOH in 7 ml of alcohol. The mixture was kept at room temperature for 0.5 h after which a suspension of 2.33 g (5 mmole) of VIII in 30 ml of abs. alcohol was added to the mixture. The mixture was stirred at room temperature for 1.5 h, and for 1 h at 40°C. Then 20 ml of the solvent was distilled off the reaction mixture after which 30 ml of water containing 1.35 ml of AcOH was added to the reaction mass. The mixture was then stirred for 0.5 h at 20°C and cooled, and the separated precipitate was filtered off and recrystallized from 50% alcohol. Yield of XVII was 1.35 g (55%), mp 201-202°C. $C_{28}H_{23}NO_3S$. IR-spectrum, ν_{max}, cm^{-1}: 1660 (C=O), 3280 (OH).

1-Methyl-2-bromomethyl-3-ethoxycarbonyl-4,5-dihydrobenz[g]indole-4,5-dione (XX). A suspension of 0.6 g (2 mmole) of 1,2-dimethyl-3-ethoxycarbonyl-4,5-dihydrobenz[g]indol-4,5-dione (XIX) [2] in 20 ml of CCl_4, 0.3 g (2.5 mmole) of bromosuccinimide, and a catalytic quantity of benzoyl peroxide was boiled for 10 h. The mixture was then cooled, the separated precipitate was filtered off, and the mother liquor was vacuum-evaporated and recrystallized from acetone. Yield of XX was 0.35 g (45.7%), mp 176-178°C. $C_{17}H_{14}NBrO_4$.

1-Methyl-2-morpholinomethyl-3-ethoxycarbonyl-4,5-dihydrobenz[g]indol-4,5-dione (XXI). A 0.13 ml (8 mmole) portion of morpholine was added to a solution of 0.16 g (4 mmole) of 2-bromomethylbenz[g]indole-4,5-dione (XX) in 10 ml of dioxane. The mixture was kept for 24 h at 20°C and the separated precipitate was filtered off, the mother liquor was vacuum-evaporated, and the residue was rrecrystallized from methanol. Yield of XXI was 0.1 g (61.5%), mp 174-175°C. $C_{21}H_{22}N_2O_5$. Reacting the base of XXI with an ether solution of HCl converted it to the hydrochloride which was recrystallized from alcohol. Yield of the hydrochloride XXI was 1 g (97%), mp 175°C (with decomposition). $C_{21}H_{22}N_2O_5 \cdot HCl$.

EXPERIMENTAL (BIOLOGY)

The antiviral activity of the compounds was tested against influenza A viruses strain A/FPV (H7N7) and A/Bethesda/63 (H2N2).

The virus-inhibiting activity of the substances was evaluated in a primary-trypsitinized culture of chick embryo fibroblasts (CEF) inoculated with 10-100 50% tissue cytopathic doses (TCD_{50}) of the virus. In preliminary experiments we determined the maximum tolerated concentration (MTC) of the test substances for a culture of CEF cells after which the compounds were employed at concentrations that were $\frac{1}{4}$ and $\frac{1}{8}$ of the MTC.

The therapeutic action of the compounds was tested on a mouse influenza pneumonia model induced by an intranasal influenza virus infection. The activity of the compounds was judged by the reduction in the virus' infections titer in vitro and animal mortality in vivo in comparison to the control groups.

Of the tested compounds (III–VI, XIII–XVII, XXI), slight virus-inhibiting activity against the influenza virus was exhibited by compounds IV, XIII, and XIV which reduced the virus' infectious titer by 0.75 lg TCD_{50} at a concentration of 5 and 2.5 μg/ml. The tested compounds were not observed to have any activity in the mouse influenza pneumonia model.

Thus, among the new aminomethyl derivatives in the benz[g]indole series we have found substances that exhibit virus-inhibiting activity against the influenza virus, although to a lesser degree than the corresponding derivatives in the indole series. The annelation of the benzene ring at position 7 and 8 of the indole ring can be assumed to reduce antiviral activity.

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SYNTHESIS OF 8-ARYLMORPHONES AND 8-ARYLCODONES AND STUDY OF THEIR ANALGESIC ACTIVITY

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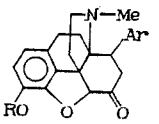
Introduction of substituents into the C ring of morphine alkaloids leads to a substantial change in their analgetic effects [2]. We synthesized several 8-arylmorphones and 8-arylcodones (I-VII) and studied the effect of the introduction of a phenyl and o-, m- and p-methoxyphenyl groups on the analgetic activity of the corresponding morphones and codones. The preparation of 8-arylcodone by the reaction of codeinone with Ph_2CuLi has already been reported in [3], but the physical characteristics of the compound obtained were not given.

The 3-hydroxy- and 3-methoxy-4,5-epoxy-6-oxo-8-aryl-17-methylmorphinanes (I-VII) were synthesized by arylation of morphine and codeine by aryl iodides under conditions for palladium catalysis, similarly to the corresponding reactions of allyl halides with allyl alcohols [5].



I-VII

R = Me (I, III, V, VI), H (II, IV, VII);
Ar = Ph (I, II), C_6H_4OMe-p (III, IV)
C_6H_4OMe-o (V, VII), C_6H_4OMe-m (VI).

EXPERIMENTAL (CHEMISTRY)

The reaction was carried out in MeCN at 80°C at a molar ratio of the reagents: morphine (codeine), ArI, $Pd(OAc)_2$ and Et_3N 125:130:2.2:125. The course of the reaction was monitored by TLC. The physical constants of the compounds obtained are given in Table 1. The data from the elemental analyses correspond to the calculated values.

General Method of Arylation of Codeine or Morphine. A 0.01 mole portion of Et_3N, 40 mg of $Pd(OAc)_2$, and 30 ml of MeCN is added with stirring to 0.01 mole of morphine (codeine); then 0.0104 mole of ArI is added dropwise. At the end of the addition of ArI, the reaction mixture is heated with stirring for 3 h at 80°C in an argon atmosphere. At the end of the

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