INDOLE DERIVATIVES.

CX.* 3-(AMINOMETHYL)INDOLES

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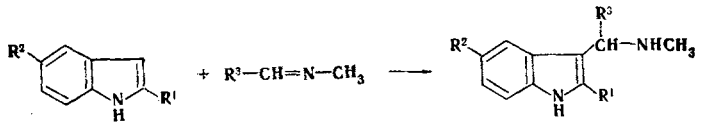
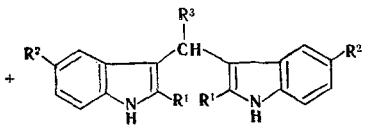
α-Aryl-substituted 3-(aminomethyl)indoles were obtained by reaction of indole with arylidenemethylamines. The compounds have weak bacteriostatic and fungistatic activity.

α-Alkyl-substituted 3-(aminomethyl)indoles are widely used in the synthesis of various compounds of the indole series [2-4]. Some of these compounds are of interest as possible agents for the treatment of diabetes [5]. In addition, up until now the α-aryl-substituted analogs have been difficult to obtain and little study has been devoted to them. Under the conditions of the synthesis of alkyl-substituted aminomethylindoles [5] (heating in a solvent with an acid catalyst) indole reacts with aromatic aldimines to give exclusively diindolylmethane derivatives [6].

We have found that aryl-substituted aminomethylindoles (Ia-f) can be obtained in good yields (70-80%) by using mixed aldimines (for example, benzalmethylamine) and carrying out the reaction at room temperature in the absence of a solvent [7]. However, the reaction proceeds very slowly under these conditions. By carrying out the reaction at 40-70°C, we shortened the reaction time to 20-40 h. At higher temperatures the reaction proceeds with resinification and the percentage of diindolylmethane derivatives IIa-f increases. The reaction time cannot be decreased and the yield of reaction product cannot be raised by the use of a solvent or an acid catalyst. As in the case of completely aromatic aldimines, primarily diindolylmethane derivatives IIa-f are obtained under these conditions.



Ia-f



IIa-f

I, II a $R^1=R^2=H$, $R^3=C_6H_5$; b $R^1=R^2=H$, $R^3=C_6H_4OCH_3$-*p*; c $R^1=H$, $R^2=OCH_3$, $R^3=C_6H_5$; d $R^1=R^2=H$, $R^3=$ 2-thienyl e $R^1=CH_3$, $R^2=H$, $R^3=C_6H_5$; f $R^1=R^2=H$, $R^3=C_6H_4NO_2$-*p*

The UV spectra of Ia-f are similar to the spectra of alkylindoles. Substituting in the para position (OCH_3, NO_2) of the phenyl ring (Ib,e) is manifested by a small bathochromic shift of the long-wave absorption band (Table 1). The IR spectra of these compounds contain a broad low-intensity absorption band with a maximum at 3340 cm^{-1} ($NHCH_3$) and a high-intensity band at 3490 cm^{-1} (indole NH). Compounds Ia-f were also characterized by their PMR spectra (Table 2).

*See [1] for communication CIX.

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TABLE 1. Substituted 3-(Aminomethyl)indoles

Compound	mp, °C[a]	Found, %			Empirical formula	Calc., %			UV spectrum		Yield, %
		C	H	N		C	H	N	λ_{max}, nm	lg ε	
Ia	140—141	81,4	6,8	12,0	$C_{16}H_{16}N_2$	81,4	6,8	11,8	280, 290	3,81, 3,74	81
Ib	57—59[b]	76,6	7,1	10,6	$C_{17}H_{18}N_2O$	76,6	6,8	10,5	280—282	4,03	68
Ic	125—126	76,8	6,9	10,3	$C_{17}H_{18}N_2O$	76,6	6,8	10,5	276—278	3,78	80
Id	112—114	69,1	6,1	11,5	$C_{14}H_{15}N_2S$[c]	69,1	6,2	11,5	281, 288	3,83, 3,76	65
Ie	118—120	81,9	7,2	10,7	$C_{17}H_{18}N_2$	81,6	7,2	11,2	281, 288	3,90, 3,84	82
If	139—141	68,4	5,3	15,1	$C_{16}H_{15}N_3O_2$	68,3	5,4	14,9	270—272	4,16	72

[a]From benzene. [b]From benzene—petroleum ether. [c]Found: S 13.2%. Calculated: S 13.2%.

TABLE 2. PMR Spectra of Aryl-Substituted 3-(Aminomethyl)-indoles

Compound	δ, ppm			
	α-CH	NCH_3	heteroaromatic and aromatic protons	substituent protons
Ia	5,0	2,39	10,1 (1-H), 7,2 (2-H), 6,8—7,6	
Ib	4,91	2,35	10,0(1-H), 7,1(2-H), 6,8—7,4	OCH_3 3,69
Ic	4,91	2,33	9,8(1-H), 7,08(2-H), 6,8—7,7	OCH_3 3,65
Id	5,23	2,31	10,0(1,H), 7,18(2-H), 6,8—7,6	
Ie	5,03	2,37	9,7(1-H), 6,8—7,7	2-CH_3 2,45
If	5,11	2,37	10,1 (1-H), 7,2 (2-H), 6,9—8,1	

Aryl-substituted aminomethylindoles are unstable in solution and are easily hydrolyzed, particularly in acidic media, to give diindolylmethane derivatives.

The bacteriostatic activity of Ia-f in the base form with respect to 10 forms of inducers of bacterial infections (including tuberculosis mycobacteria) and five forms of pathogenic fungi was studied. According to the data of T. N. Zykova and T. A. Gus'kova (Department of Chemotherapy, S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute), the investigated compounds have weak bacteriostatic and fungistatic activity.

EXPERIMENTAL

The IR spectra of 0.5% chloroform solutions of the compounds were recorded with a UR-20 spectrometer. The UR spectra of alcohol solutions were recorded with an SF-4A spectrophotometer. The PMR spectra of deuteroacetone solutions were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard.

4-Nitrobenzalmethylamine. A total of 8 ml (0.066 mole) of a 25% aqueous solution of methylamine was added to a solution of 5 g (0.033 mole) of 4-nitrobenzaldehyde in 20 ml of benzene, and the mixture was heated at 70° for 1 h. It was then cooled, and the resulting precipitate was removed by filtration and recrystallized from cyclohexane to give 4 g (74%) of the aldimine with mp 107-108°. Found: C 58.3; H 4.6; N 17.6%. $C_8H_8N_2O_2$. Calculated: C 58.5; H 4.9; N 17.1%.

2-Formylthiophene Methylimine. This compound, with bp 194-196°, was obtained in 57% yield by the method used to prepare benzalmethylamine [8]. Found: C 58.5; H 5.5; N 11.5; S 25.2%. C_6H_7NS. Calculated: C 57.6; H 5.6; N 11.2; S 25.6%.

3-(α-Methylaminobenzyl)indole (Ia). A solution of 30 g (0.26 mole) of indole in 36.8 g (0.31 mole) of benzalmethylamine was heated at 70° for 40 h and allowed to stand at room temperature until crystallization was complete (∿15 h). The solid material was removed by filtration, washed thoroughly with benzene, and recrystallized from benzene to give a colorless crystalline substance that turned pink in air. The product was obtained in 81% yield and had mp 140-141°.

Substituted indoles Ib-e were similarly obtained (see Table 1). The optimum temperature for 3-[1-methylamino-1-(2-thienyl)methyl]indole (Id) was 30-40°.

3-(α-Methylamino-4-nitrobenzyl)indole (If). A mixture of 2.3 g (0.2 mole) of indole and 3.3 g (0.2 mole) of 4-nitrobenzalmethylamine in 3 ml of benzene was heated at 70° for 30 h, after which it was allowed to stand at room temperature until crystallization was complete. The yellow crystalline product was recrystallized from benzene to give 4 g (72%) of If with mp 139-141°.

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INDOLE DERIVATIVES.

CXI.* INTRODUCTION OF A 3-INDOLYL GROUP IN CH ACIDS

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A method for the introduction of a 3-indolyl group in compounds with an active methylene group was developed. The corresponding 3-indolyl diketones were obtained by condensation of 1-acetyl-3-indolinone with dimedone, 4-hydroxycoumarin, 1,2-diphenyl-3,5-pyrazolinedione, and barbituric and thiobarbituric acids and subsequent alkaline hydrolysis of the condensation products. The existence of cyclic six-membered 3-indolyl diketones in the enol form and of cyclic five-membered 3-indoly diketones in the keto form was shown by IR and UV spectroscopy. Depending on the conditions, (1-acetyl-3-indolyl)cyanoacetamide, 1,3-bis(1-acetyl-3-indolyl)-1,3,3-tricyano-2-amino-1-propene, and 1-acetyl-3-indolylmalononitrile are obtained in the condensation of 1-acetyl-3-indolinone with malononitrile. 1-Acetyl-3-indolylmalononitrile exists in equilibrium with the keteneimine form and in protic solvents is converted to 3-cyano-8-acetylpyrrolo[2,3-b]indole by intramolecular cyclization.

No methods have been developed for the introduction of a 3-indolyl group in compounds with an active methylene group. The basis of the method used in the present research was condensation of 1-acetyl-3-indolinone (acetylindoxyl) (I) with a number of CH acids that differ with respect to their acidity constants (pK_a). 1-Acetylindoxyl rather than indoxyl was selected as the carbonyl component because of its high accessibility and stability.

The condensation of 1-acetylindoxyl (I) with cyanoacetic acid was first used for the preparation of 3-indolylacetonitrile [2]. The reaction was carried out under severe con-

*See [1] for communication CX.

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