matic protons), 5.7 (1H, s, CH—C_6H_5), and 3.77 and 3.01 ppm (each 1H, d, J = 13.5 Hz, CH_2). Found: C 72.3; H 4.6; N 10.7; S 8.1%; M 397. $C_{24}H_{19}N_3OS$. Calculated: C 72.5; H 4.7; N 10.5; S 8.0%; M 397.

5-Acetamido-4-benzyl-1,3-diphenylpyrazole (VII). A mixture of 7.8 g (0.02 mole) of pyrazolothiazepine V and 20 of Raney nickel in 50 ml of ethanol was refluxed for 4 h, after which the hot mixture was filtered, and the catalyst was washed with 10 ml of hot ethanol. The filtrate was evaporated in vacuo, and the residue was recrystallized from ethanol to give 4.8 g (65%) of pyrazole VII with mp 214-215°C and R_f 0.27. IR spectrum: 1690 (C=O) and 3245 cm^{-1} (NH). PMR spectrum (d_6-DMSO): 7.1-7.8 (15H, m, aromatic protons), 3.9 (2H, s, CH_2—C_6H_5), and 1.93 ppm (3H, s, CH_3—C=O). Found: C 78.3; H 5.5; N 11.3%; M 367. $C_{24}H_{21}N_3O$. Calculated: C 78.4; H 5.7; N 11.4%; M 367.

5-Amino-4-benzyl-1,3-diphenylpyrazole (VIII). A 3.6-g (0.01 mole) sample of pyrazole VII was heated in 10 ml of concentrated HCl on a boiling-water bath for 1 h, after which the mixture was cooled to room temperature, neutralized with dilute sodium carbonate solution, and extracted three times with ether. The extract was dried with magnesium sulfate, the solvent was removed by distillation, and the residue was recrystallized from ether—petroleum ether (1:1) to give 2.5 g (78%) of pyrazole VIII with mp 104-105°C and R_f 0.7. IR spectrum: 3290 and 3425 cm^{-1} (NH_2). PMR spectrum ($CDCl_3$): 7.2-7.8 (15H, m, aromatic protons), 3.87 (2H, s, CH_2—C_6H_5), and 3.5 ppm (2H, s, NH_2). Found: C 81.3; H 5.9; N 12.7%; M 325. $C_{22}H_{19}N_3$. Calculated: C 81.2; H 5.8; N 12.9%; M 325.

LITERATURE CITED

1. L. R. Swett and J. D. Ratajczyk, West German Patent No. 1939007; Chem. Abstr., 72, 121602 (1970).
2. L. R. Swett, US Patent No. 3891630 (1975); Chem. Abstr., 83, 147510 (1975).
3. L. R. Swett, J. D. Ratajczyk, C. W. Norden, and G. H. Aunilian, J. Heterocycl. Chem., 12, 1137 (1975).
4. C. Joshi Krishna, N. Pathak Vigai, and Garg Urmila, J. Heterocycl. Chem., 17, 789 (1980).
5. C. Joshi Krishna, Dubej Kalpana, and Dandia Aushu, Heterocycles, 16, 71 (1981).

INDOLE DERIVATIVES.

124.* 5-(2-PHENYLETHENYL)INDOLINES AND 5-(2-PHENYLETHENYL)INDOLES

L. N. Chupina, V. F. Shner, G. I. Gritsina, A. I. Terekhina, and N. N. Suvorov

UDC 547.753'754'212'313.2'53.024.07:543.422'51

5-(2-Phenylethenyl)indolines, the dehydrogenation of which leads to the formation of the corresponding compounds of the indole series, were obtained from 5-formyl-1-methyl(or benzyl)indolines via the Grignard reaction with benzylmagnesium chloride and subsequent dehydration. The hormonal activity of the synthesized compounds was studied.

Indole and indoline derivatives that contain a 2-phenylethenyl substituent in the benzene part of the molecule are unkown in the literature. These compounds are heterocyclic analogs of diarylethylenes, which display biological activity (estrogenic activity, for example [2, 3]).

*See [1] for communication 123.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119815. Scientific-Research Institute for the Biological Testing of Chemical Compounds, Kupavna, Moscow Province.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 466-469, April, 1984. Original article submitted July 27, 1983.

0009-3122/84/2004-0372$08.50

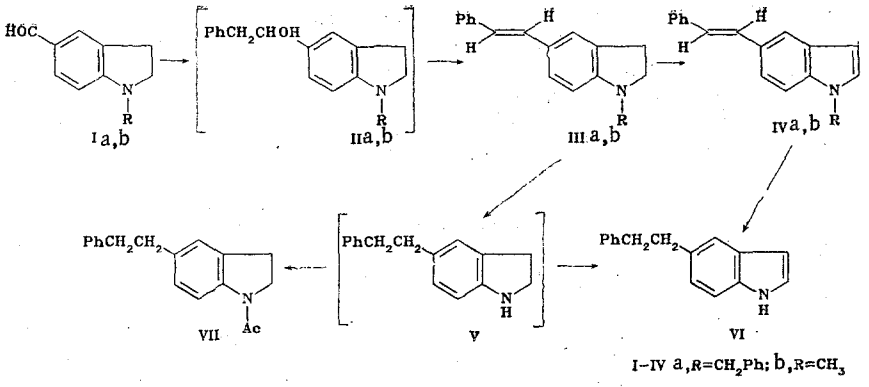
The aim of the present research was to develop a method for the synthesis of 5-(2-phenylethenyl)indolines and 5-(2-phenylethenyl)indoles and to study their hormonal activity.

The construction of an ethylene bridge between the phenyl and indole parts of the molecule was based on the Grignard reaction of aldehydes of the indoline series (Ia, b) [4] with benzylmagnesium chloride. Carbinols IIa, b were unstable. Having noted the formation of these compounds by thin-layer chromatography (TLC), we therefore subjected them to dehydration with sulfosalicylic acid and obtained olefins IIIa, b. The trans configuration of IIIa, b was confirmed by the observation in the PMR spectra of signals of olefin protons with a characteristic spin-spin coupling constant (J = 17 Hz) [5].

The dehydrogenation [6] of IIIa, b by the action of active manganese dioxide prepared by the method in [7] leads to the corresponding indole derivatives IVa, b in high yields. The dehydrogenation of indoline IIIb with chloroanil does not proceed as satisfactorily: The yield of indole IVb is ∿20%, and large amounts of impurities are formed, according to TLC. The trans configuration of IVa, b was established by PMR spectroscopy as in the preceding case.

The debenzylation of IIIa, and IVa with lithium in liquid ammonia is accompanied by reduction of the ethylene fragment and leads to the formation of the corresponding saturated compounds V and VI. The structure of indoline V, which was characterized in the form of acetyl derivative VII, was confirmed by dehydrogenation of indole VI. We were unable to carry out the selective debenzylation of IIIa by hydrogenolysis over a palladium catalyst in acetic acid in the presence of HCl: According to the mass-spectrometric data, the principal reaction product, regardless of the activity of the catalyst, is saturated compound V, and the corresponding olefin is formed in only trace amounts. The PMR spectra of VI and VII do not contain signals of N-benzyl and olefin protons, but signals of protons of the aliphatic part of the molecule appear in the spectrum, in agreement with the proposed structure.

The hormonal activity (androgenic, anabolic, estrogenic, thymolytic [8], antiandrogenic [9], and antiestrogenic [10]) of the synthesized IIIa, b and IVa, b was studied by means of



known tests. The compounds did not display activity in any of these tests. It should be noted that the presence of hydroxy and alkoxy groups in the molecules is characteristic for diarylethylenes that have estrogenic activity [2, 3]. The absence of activity in the case of III and IV is possibly associated with this. We noted that the investigated compounds administered subcutaneously in a daily dose of 20 mg/kg for 4 days caused an ∿20% increase in the mass of the adrenal glands.

EXPERIMENTAL

The UV spectra of solutions of the compounds in 95% alcohol were recorded with an EPS-3 recording spectrophotometer. The PMR spectra of solutions in d-chloroform and d_6-acetone were obtained with a Varian XL-200 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-112 spectrometer at an ionizing voltage of 70 eV with direct introduction of the samples. The reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates. The compounds obtained were purified by filtration of solutions in benzene through a layer of L 40/100 silica gel.

TABLE 1. Properties of the Synthesized Compounds

Compound	mp,[a] °C	PMR spectrum, ppm				
		CH_2	CH_3	2-H_2	3-H_2	CH=CH
IIIa	100,5—101,5	4,32 s (benzyl)		2,92 t	3,33 t	7,08 d, 6,97 d (J=17 Hz)
IIIb	107,0—108,5		2,74 s	2,92 t	3,31 t	6,98 d, 6,89 d (J=17 Hz)
IVa	111,5—113,0	5,42 s (benzyl)			6,43 q	7,16 d[b] (J=17 Hz)
IVb	142,0—143,5		3,84 s		6,45 q	7,18 d[b] (J=17 Hz)
VI[c]	77,5—78,5	2,93 m (aliph.)			6,43 m	
VII[d]	196,5—198,0	2,88 s (aliph.)	2,21 s (acetyl)	3,15 t	4,04 t	

TABLE 1 (continued)

Compound	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIIa	210 (4,5), 244 (4,1), 260 (3,9), 350 (4,4)	88,7	7,0	4,5	$C_{23}H_{21}N$	88,7	6,8	4,5	96
IIIb	206 (4,5), 240 (4,2), 263 (3,9), 345 (4,4)	86,4	7,3	6,0	$C_{17}H_{17}N$	86,8	7,3	6,0	62
IVa	208 (4,5), 234 (4,2), 240 (4,1), 266 (4,4), 276 (4,4), 322 (4,4)	89,1	6,5	4,3	$C_{23}H_{19}N$	89,3	6,2	4,5	77
IVb	206 (4,5), 234 (4,2), 240 (4,1), 268 (4,4), 275 (4,5), 286 (4,5), 324 (4,5)	87,4	6,5	5,8	$C_{17}H_{15}N$	87,5	6,5	6,0	88
VI[c]	210 (4,4), 224 (4,5), 273 (3,7), 286 (3,6), 297 (3,4)	86,8	6,8	6,2	$C_{16}H_{15}N$	86,8	6,8	6,3	69 (A), 64 (B)
VII[d]	212 (4,5), 257 (4,3), 262 (4,2), 286 (3,7), 297 (3,6)	81,7	7,5	5,2	$C_{18}H_{19}NO$	81,2	7,2	5,3	71

[a]The compounds were recrystallized: III and IV from ethanol, VI from benzene—heptane (1:1), and VII from benzene—hexane (1:1). [b]The signal of the second olefinic proton is overlapped by the signals of the aromatic protons. [c]Found: M^+221. Calculated: M 221. [d]Found: M^+ 265. Calculated: M 265.

1-Benzyl-5-(trans-2-phenyl-1-ethenyl)indoline (IIIa). A solution of 5 g (21.1 mmole) of 1-benzyl-5-formylindoline (Ia) in 35 ml of anhydrous tetrahydrofuran (THF) was added dropwise with stirring at 0°C to a solution of benzylmagnesium chloride prepared from 3.9 ml (33.9 mmole) of benzyl chloride and 0.76 g (31.3 mmole) of magnesium in 10 ml of anhydrous ether, and the mixture was stirred at 0°C for 15 min and at 20°C for 15 min, cooled to 10°C, and treated with a solution of 15 g of ammonium chloride in 45 ml of water. The organic layer was separated, and the aqueous layer was extracted with chloroform (two 50-ml portions). The combined extract was washed with water and dried, and the solvent was evaporated. A 6.5-g sample of sulfosalicyclic acid and 100 ml of benzene were added to the residue (8.5 g), and the mixture was refluxed with a Dean—Stark adapter for 1 h. A 100-ml sample of a 2% solution of sodium carbonate was added, and the mixture was heated with stirring until the precipitate dissolved. The organic layer was separated, and the aqueous layer was extracted with chloroform (two 50-ml portions). The combined extract was dried, the solvent was evaporated, and the residue was dissolved in benzene. The solution was filtered through silica gel to give IIIa.

1-Methyl-5-(trans-2-phenyl-1-ethenyl)indoline (IIIb). Compound IIIb was similarly obtained from 5 g of 1-methyl-5-formylindoline (Ib).

1-Benzyl-5-(trans-2-phenyl-1-ethenyl)indole (IVa). A 2.2-g sample of IIIa was added in portions with stirring at room temperature to a suspension of 11 g of manganese dioxide in 60 ml of benzene. After 3 h, the precipitate was removed by filtration and washed with

benzene and chloroform. The combined filtrate was dried, and the solvent was evaporated in vacuo to give IVa.

1-Methyl-5-(trans-2-phenyl-1-ethenyl)indole (IVb). Compound IVb was similarly obtained from 2.05 g of IIIb and 11.4 g of manganese dioxide.

5-(2-Phenyl-1-ethyl)indole (VI). A) A solution of 1.6 g (5.2 mmole) of IVa in 10 ml of anhydrous THF was added with stirring to 100 ml of liquid ammonia, after which 0.14 g (20.2 mmole) of lithium metal was added in portions. After 15 min, 2.3 g of ammonium chloride was added, and the mixture was stirred for 1 h until the ammonia had evaporated completely. Water (100 ml) was added to the residue, and the mixture was extracted with benzene (two 100-ml portions). The extract was dried, the solvent was evaporated, and the residue (1.2 g) was worked up to give VI.

B) A solution of 0.11 g of crude V in 2 ml of benzene was stirred with 0.55 g of manganese dioxide at room temperature for 1 h, after which the mixture was filtered, and the precipitate was washed with chloroform. Workup of the combined filtrate gave VI, which was identical to the sample obtained by method A.

1-Acetyl-5-(2-phenyl-1-ethyl)indoline (VII). A solution of 1.4 g (4.5 mmole) of IIIa in 20 ml of THF and 100 ml of liquid ammonia was reduced with 0.12 g (17.2 mmole) of lithium to give 0.95 g of V in the form of an oil. The oil was triturated with 1 ml of acetic anhydride, and the precipitate was removed by filtration, washed with water, dried, and recrystallized to give VII.

LITERATURE CITED

1. V. S. Rozhkov, Yu. I. Smushkevich, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 3, 372 (1981).
2. U. Solmsen, Chem. Rev., 45, 481 (1945).
3. J. Grundy, Chem. Rev., 57, 281 (1957).
4. A. P. Terent'ev, Ke Pang-Lun, and M. N. Preobrazhenskaya, Zh. Obshch. Khim., 32, 1335 (1962).
5. N. Bhacca and D. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden-Day (1964).
6. M. N. Preobrazhenskaya, Usp. Khim., 36, 1760 (1967).
7. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, K. H. Evans, B. A. Huns, A. B. A. Jansen, and T. Walker, J. Chem. Soc., 1094 (1952).
8. A. I. Terekhina, L. M. Mikhailovskaya, I. V. Ganina, E. A. Perfil'eva, and É. A. Rudzit, Khim.-farm. Zh., No. 2, 75 (1977).
9. L. O. Rondall and J. J. Selitto, J. Endocrinol., 62, 693 (1958).
10. K. Nakamura, Y. Masuda, H. Nakamura, N. Habano, and K. Nakabsuji, Arzneim.-Forsch., 18, 909 (1968).