Triarylpyridylethanols and Triarylpyridylethylenes. Chemistry and Antifertility Effects

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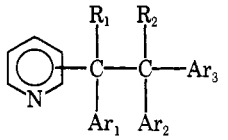
Triarylpyridylethanols were prepared by condensing the corresponding diaryl ketones and diarylmethanes. The ethylenes were obtained by the acid-catalyzed elimination of H_2O from the ethanols. In the absence of electron-donating substituents, acid treatment of the carbinols resulted in predominant cleavage to starting ketone. The compounds were tested for their antifertility effects in pregnant hamsters. The most active compound was carbinol **3**, which, at 30 mg/kg, prevented all of the treated animals from maintaining their pregnancies.

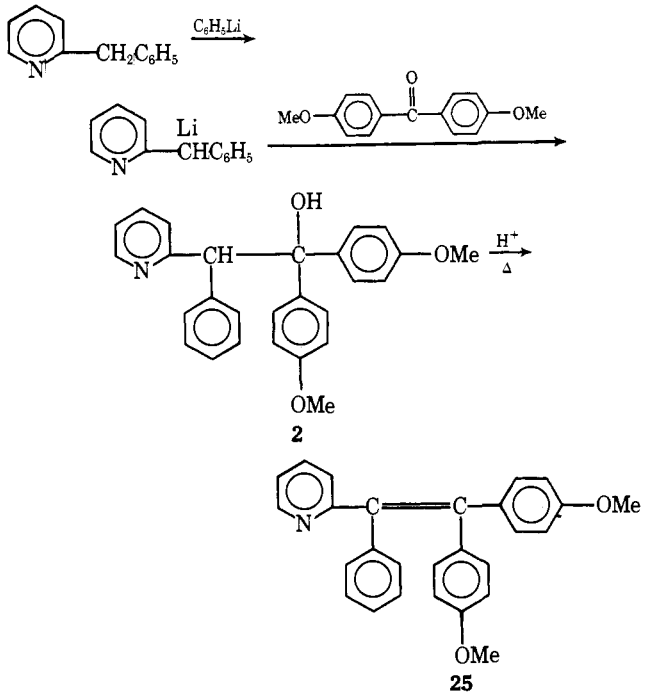
Stilbenes and their triaryl analogs are recognized as endocrine-active substances, particularly in the area of reproductive physiology.[1] The compounds described in this article were synthesized to provide new polyaromatic materials of potential usefulness in the antifertility field. The structures studied were of three general types: pyridineethanols (I), pyridinemethanols (II), and the ethylenes (III) derived from I and II.



I, $R_1 = H$; $R_2 = OH$
II, $R_1 = OH$; $R_2 = H$
III, $R_1 + R_2 =$ bond

Chemistry. The syntheses of these compounds are illustrated by the example given in Scheme I. The experimental

Scheme I



methods cited in Tables I and II were usually the only procedures employed in the synthesis of the cited compound. In a few cases, however, where reactions were unsuccessful or where low yields resulted, some modifications of the procedure were made.

By increasing the ratio of the organometallic reagent to ketone to 2:1, the yields of certain pyridineethanols (I) could often be improved; thus, where attempted, method B was usually an improvement over method A. With basic ether substituted ketones, however, a 4:1 ratio of organometallic to ketone was more beneficial than lower ratios, i.e., method E as opposed to methods A or B. The condensation of 9-fluorenone or 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one with 2-benzylpyridyllithium was unsuccessful by these methods.

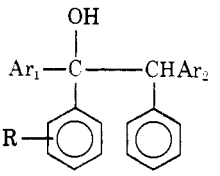
The formation of the lithio derivative of diphenylmethane occurred at a much slower rate than that of 2- or 4-benzylpyridine. Because of this, some experimentation was done to determine reaction conditions for optimum yields of **10** from diphenylmethyllithium. If one allows only 2 hr for organometallic formation, then a 4:1 ratio of lithio reagent to ketone is required for an optimal yield, regardless of the reaction time. If, however, the organometallic is allowed to form overnight, one may attain a similar yield by using 2 mol of organometallic per mole of ketone. When ice-bath temperature was used during organometallic formation, the subsequent yield of **10** was low but concomitant formation of the corresponding methanol was significant (40%). When phenyl 4-pyridyl ketone was employed under these conditions, no **16** formed but α,α-diphenyl-4-pyridinemethanol was isolated in 53% yield. These data indicate the low reactivity of C_6H_5Li toward diphenylmethane at 0°; thus, the C_6H_5Li becomes available for condensation with the ketone.

The acid-catalyzed dehydration of the carbinols was attempted with **1–3**, **5**, **8**, **9**, **12**, **18**, and a mixture of **14** and **15**. Of these, compounds **2**, **3**, **9**, **12**, **14**, and **15** gave the desired product. These are all *p*-alkoxy-substituted carbinols. Compound **5** gave the original ketone as a cleavage product and **1** was recovered unchanged. Compounds **8** and **18** were partly cleaved to ketone and partly recovered under these conditions.

In another experiment, **1** was refluxed with Ac_2O after which the cleavage products, benzophenone and 2-benzylpyridine, were recovered. Although **9** gave the desired ethylene (**28**) the yield was low and cleavage also occurred. As determined by NMR analysis, the acid treatment of **9** gave the desired ethylene and the ketone cleavage product in a ratio of about 1:2, respectively. These data suggest that at least one and preferably two strongly electron-donating groups are necessary for the stabilization of the carbonium ion IV in the reaction sequence (Scheme II). Without the stabilization of IV, cleavage predominates and occurs via V. Under the cited reaction conditions, the dimethylamino groups in **18** are most probably in the protonated form during the equilibrium. The stabilization of IV is therefore not possible and the ethylene is not formed.

Biological Screening Results. A pregnant hamster test system, varying slightly from those reported[3] by others, was used to study the antifertility effects of these compounds. The animals (eight per test group) were treated daily by the subcutaneous administration (olive oil vehicle) of compound on days 3–8 of pregnancy. The control group

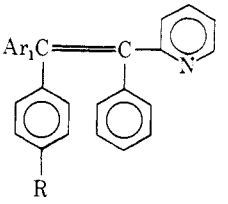
Table I. Carbinols



No.	Ar_1	R	Ar_2	Mp, °C	Yield, %	Method	Formula[a]	Recrystn solvent
1	C_6H_5	H	2-Pyridyl	193–194[b]	60	A	$C_{25}H_{21}NO$	2-Butanone
					85	B[c]		
2	4-$MeOC_6H_4$	4-MeO	2-Pyridyl	171.5–172.0	69	A	$C_{27}H_{25}NO_3$	C_6H_6
3	4-$Et_2NCH_2CH_2OC_6H_4$	4-$Et_2NCH_2CH_2O$	2-Pyridyl	111.5–112.0	25	A	$C_{37}H_{47}N_3O_3$	Petr ether
4	C_6H_5	H	4-Pyridyl	185.5–188.0	29	A	$C_{25}H_{21}NO$	C_6H_6
5	4-MeC_6H_4	4-Me	2-Pyridyl	169.5–171.0	41	A	$C_{27}H_{25}NO$	C_6H_6
6	4-$MeOC_6H_4$	4-MeO	4-Pyridyl	179–182	9	A[d]	$C_{27}H_{25}NO_3$	EtOH[e]
7	4-$Et_2NCH_2CH_2OC_6H_4$	H	4-Pyridyl	179–180	3	B	$C_{31}H_{34}N_2O_2$	C_6H_6
8	4-ClC_6H_4	4-Cl	2-Pyridyl	154–155	54	B	$C_{25}H_{19}Cl_2NO$	C_6H_6
9	4-$Et_2NCH_2CH_2OC_6H_4$	H	2-Pyridyl	111–120	16	B[c]	$C_{31}H_{34}N_2O_2$	C_6H_6
					4	A		
					46	E		
10[f]	2-Pyridyl	H	C_6H_5	236–238	24	C[c]	$C_{25}H_{21}NO$	C_6H_6
					31	D		
11	3-Pyridyl	H	C_6H_5	193–194	11	C	$C_{25}H_{21}NO$	C_6H_6
12	4-$Et_2NCH_2CH_2OC_6H_4$	4-MeO	2-Pyridyl	117–133	29	B[g]	$C_{32}H_{36}N_2O_3$	EtOH[h]
13	3-ClC_6H_4	3-Cl	2-Pyridyl	159.0–159.5	58	B	$C_{25}H_{19}Cl_2NO$	EtOH
14[i]	4-$MeOC_6H_4$	H	2-Pyridyl	155–156	36	B	$C_{26}H_{23}NO_2$	EtOH[j]
15[i]	4-$MeOC_6H_4$	H	2-Pyridyl	161–162	9	B	$C_{26}H_{23}NO_2$	EtOH[j]
16	4-Pyridyl	H	C_6H_5	235.5–236.0	53	D	$C_{25}H_{21}NO$	C_6H_6
17	2-Pyridyl	H	2-Pyridyl	191.5–193.5	71	B	$C_{24}H_{20}N_2O$	EtOH
18	4-$Me_2NC_6H_4$	4-Me_2N	2-Pyridyl	160.5–161.0	48	B	$C_{29}H_{31}N_3O$	C_6H_6
19	3-Pyridyl	H	2-Pyridyl	178–179	58	B	$C_{24}H_{20}N_2O$	C_6H_6
20	4-Pyridyl	H	2-Pyridyl	183–184	72	B	$C_{24}H_{20}N_2O$	C_6H_6
21	2-Pyridyl	4-MeO	C_6H_5	181.5–184.5	12	C	$C_{26}H_{23}NO_2$	CCl_4[k]
22	α-(9-Fluorenyl)-α-phenyl-2-pyridinemethanol			223–225	86	B	$C_{25}H_{19}NO$	C_6H_6
23	α-(9-Fluorenyl)-α-phenyl-3-pyridinemethanol			210.5–211.0	86	B	$C_{25}H_{19}NO$	C_6H_6
24	α-(9-Fluorenyl)-α-phenyl-4-pyridinemethanol			237.0–238.5	65	B	$C_{25}H_{19}NO$	C_6H_6

[a] All compounds analyzed within ±0.4% of theoretical values for C, H, and N. [b] Reference 2 gives mp 186–189°. [c] Reaction was allowed to proceed for 3 days. [d] Reaction was allowed to proceed overnight. [e] First recrystallization was from C_6H_5. [f] See Chemistry. [g] Reaction was allowed to proceed for 1 hr. [h] First recrystallization was from heptane. [i] Diastereomers. [j] Compounds 14 and 15 were separated and purified by fractional recrystallization. [k] First recrystallization was from EtOH.

Table II. Ethylenes

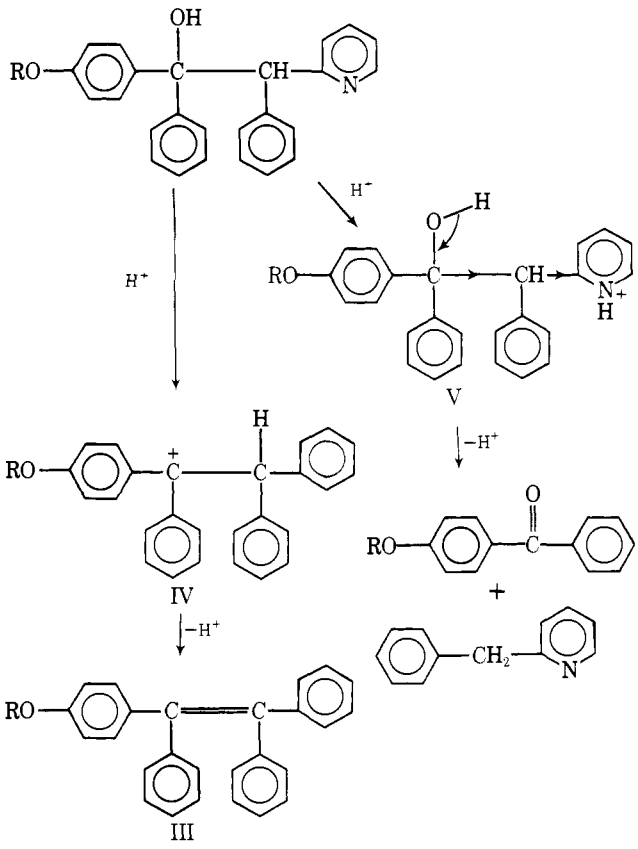


No.	Ar_1	R	Mp, °C	Yield, %	Formula[a]
25	4-$MeOC_6H_4$	MeO	139–141	41[b]	$C_{27}H_{33}NO_2$
26	4-$Et_2NCH_2CH_2OC_6H_4$	$Et_2NCH_2CH_2O$	Oil	48[c]	$C_{37}H_{45}N_3O_2$
27	4-$MeOC_6H_4$	H	124–127	35[d]	$C_{26}H_{21}NO$
28	4-$Et_2NCH_2CH_2OC_6H_4$	H	90.5–92.5	4[e]	$C_{31}H_{32}N_2O$
29	4-$Et_2NCH_2CH_2OC_6H_4$	MeO	95–113[f]	13[f,g]	$C_{32}H_{34}N_2O_2$

[a] All compounds analyzed within ±0.4% of theoretical values for C, H, and N except 28 which was characterized by NMR in lieu of analysis. [b] After chromatography (Al_2O_3, CH_2Cl_2–petroleum ether 1:3) and recrystallization from EtOH. [c] After chromatography (Al_2O_3, CH_2Cl_2). [d] After drying first on a porous plate and then in vacuo. [e] After chromatography (Al_2O_3, hexane) and recrystallization from hexane. [f] As the dihydrogen citrate hemihydrate. [g] After recrystallization from MeOH–Et_2O.

received the vehicle only. All animals were sacrificed on the 15th day of pregnancy and the uteri were observed for signs of pregnancy. Animals with one or more live fetuses were considered pregnant regardless of whether or not resorption sites were observable. The results were recorded in terms of the percent of animals still pregnant at the time of sacrifice which was 1 day prior to expected normal parturition.

Scheme II



The antifertility effects of these compounds were determined at the dose of 30 mg/kg/day. The most active compound was carbinol **3** which caused complete cessation of pregnancy at this dose although 70% of the controls were pregnant at sacrifice. Of the ethylenes **25–29** the most active compound was **26** which is the product of the dehydration of **3**. Compound **26** reduced the pregnancy rate to 14% whereas 60% of the controls were pregnant. None of the other compounds produced significant differences in the pregnancy rates of the test animals compared with those of their respective controls.

The results with the pregnant hamster test system indicate the importance of bis(diethylaminoethoxy) substitution as a determinant of the antifertility activity of these compounds.

Experimental Section

The following compounds were prepared according to the cited references: 4-(β-diethylaminoethoxy)benzophenone,[4] 4,4′-bis(β-diethylaminoethoxy)benzophenone,[5] 4-(β-diethylaminoethoxy)-4′-methoxybenzophenone,[6] and 3,3′-dichlorobenzophenone.[7] The 4-methoxyphenyl 2-pyridyl ketone was prepared as described below. Other starting materials were commercially available. The melting points were taken on a Thomas-Hoover melting point apparatus. NMR spectra were measured in $CDCl_3$ using a Varian A-60A spectrometer with TMS as an internal standard.

4-Methoxyphenyl 2-Pyridyl Ketone. Butyllithium (2.8 mol) was prepared from BuBr and Li in Et_2O (500 ml), cooled to −20°, and treated with 365 g (2.3 mol) of 2-bromopyridine (Aldrich) in 1 l. of Et_2O. A solution of 200 g (1.5 mol) of anisonitrile (Aldrich) in 1 l. of C_6H_6 was added and stirring was continued until the mixture reached room temperature. It was treated with aqueous NH_4Cl, heated on a steam bath, and extracted with Et_2O. The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was recrystallized twice from EtOH to give colorless needles: 134 g (42%); mp 96.5–97.5°; picrate mp 186–189°.

General Methods for Preparing the Pyridylcarbinols. A. A 1 *M* solution of phenyllithium was prepared in Et_2O from Li and C_6H_5Br. To this was added an equimolar amount of the active hydrogen compound at room temperature. The dark red solution was stirred for 45 min after which it was cooled in an ice bath. The ketone was then added as a solution (ca. 0.5 *M*) in Et_2O or as a slurry where such a solution was not possible. The ice bath was removed and the reaction mixture was stirred for ca. 1 hr. It was once again cooled in an ice bath and hydrolyzed with aqueous NH_4Cl. The desired carbinol was obtained by filtration or by evaporation of the organic layer. The crystallization solvents are given in Table I.

B. This method is a modification of method A using 2 mol of organometallic reagent per mole of ketone. The reaction mixture was stirred overnight at room temperature prior to hydrolysis.

C. This method is also a modification of method A. Organometallic reagent (2 mol) was used per mole of ketone. After the active hydrogen compound was added to the phenyllithium in Et_2O, an equal volume of THF was introduced and the mixture was stirred for 2 hr prior to the addition of ketone. The reaction mixture was stirred overnight at room temperature prior to hydrolysis.

D. This method is a modification of method C. The active hydrogen compound and phenyllithium were stirred in Et_2O–THF overnight prior to the addition of ketone.

E. This is a modification of method A using 4 mol of organometallic reagent per mole of ketone.

Separation of the Diastereomers 14 and 15. A 42.4-g (0.20 mol) quantity of 4-methoxybenzophenone (Aldrich) was condensed with 2-benzylpyridyllithium according to method B. The crude carbinol (78.9 g, mp 126–140°) was then fractionally recrystallized from EtOH to give **14** (27.0 g, mp 155–156°) and **15** (7.0 g, mp 161–162°). A mixture melting point of **14** and **15** was depressed and the NMR spectra (60 mHz, $CDCl_3$) allowed differentiation.

14: MeO, δ 3.66 (singlet); benzylic H, 5.04 (singlet); aromatic (anisyl) A_2B_2, 6.61 (doublet, H ortho to MeO) and 7.58 (multiplet, H meta to MeO); OH, 8.02 (singlet, disappears after D exchange).

15: MeO, δ 3.70 (singlet); benzylic H, 5.04 (singlet); aromatic (anisyl) A_2B_2, 6.72 (doublet, H ortho to MeO) and 7.51 (doublet, H meta to MeO); OH, 8.07 (singlet, disappears after D exchange).

Preparation of the Ethylenes. A 0.3 *M* solution of the carbinol in EtOH–HCl was stirred and refluxed for 1.5–2 hr. The solvent was removed in vacuo and the residue was dissolved in H_2O. This solution was made alkaline with 10% aqueous NaOH and extracted with Et_2O. The desired compound was obtained by evaporating the dried ($MgSO_4$) Et_2O solution and purifying as indicated in Table II.

Acknowledgments. The author wishes to thank Mr. K. T. Stewart who prepared the 4-methoxyphenyl 2-pyridyl ketone and Mr. M. Gordon and his coworkers for the microanalyses and NMR spectra.

References and Notes

(1) (a) U. V. Solmssen, *Chem. Rev.*, **37**, 481 (1945); (b) J. Grundy, *ibid.*, **57**, 281 (1957); (c) C. R. Thompson and H. W. Werner, *Proc. Soc. Exp. Biol. Med.*, **77**, 494 (1951); (d) M. R. Callentine, *Clin. Obstet. Gynecol.*, **10**, 74 (1967); (e) F. P. Palopoli, V. J. Feil, R. E. Allen, D. E. Holtkamp, and A. Richardson, Jr., *J. Med. Chem.*, **10**, 84 (1967).

(2) J. H. Burckhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. R. Dice, G. Rodney, and D. H. Kaump, *J. Med. Chem.*, **10**, 565 (1967).

(3) (a) J. O. Johnston and K. K. Hunter, *Physiologist*, **13**, 235 (1970); (b) G. D. Gutknecht, L. J. Wyngarden, and B. B. Pharriss, *Proc. Soc. Exp. Biol. Med.*, **136**, 1151 (1971); (c) A. P. Labhsetwar, *Nature (London)*, **230**, 528 (1971); (d) A. P. Labhsetwar, *J. Endocrinol.*, **53**, 201 (1972).

(4) R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. Van Campen, U.S. Patent 2,914,562 (1959); *Chem. Abstr.*, **54**, 5581*e* (1960).

(5) F. P. Palopoli, D. E. Holtkamp, and J. L. Schaar, U.S. Patent 3,243,461 (1966); *Chem. Abstr.*, **64**, 17488*f* (1966).

(6) British Patent 929,254 (1963); *Chem. Abstr.*, **60**, 2827*g* (1964).

(7) H. L. Haller, P. D. Bartlett, N. L. Drake, M. S. Newman, S. J. Cristol, C. M. Eaker, R. A. Hayes, G. W. Kilmer, B. Magerlein, G. P. Mueller, A. Schneider, and W. Wheatley, *J. Am. Chem. Soc.*, **67**, 1591 (1945).