

Reaction of Phenolic Mannich Bases with Enamines. General Synthesis of Pyran-Containing Fused Ring Systems.

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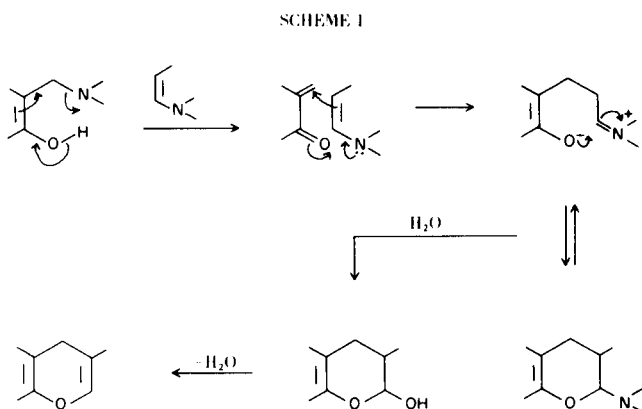
The reaction of *o*-phenolic Mannich bases with enamines yields cyclic *O,N*-acetals having a 2-aminodihydropyran or a spiropyranopiperidine structure in common. The 2-aminodihydropyrans are easily converted to 2-hydroxydihydropyrans and to pyrans. The preparation of a large variety of pyran-containing fused ring systems is reported.

The alkylation of enamines with Mannich bases proved to be a useful tool for introduction of substituents in position α to the carbonyl (1-4). Our exploration of this reaction (4,5) has shown that in the case of *ortho*-phenolic Mannich bases the alkylation is accompanied by a spontaneous cyclization.

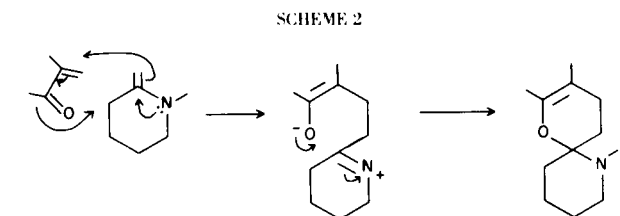
The objective of the present communication is to demonstrate that the reaction of enamines with *ortho*-phenolic Mannich bases is a general and versatile method for the preparation of pyran-containing fused ring systems.

When phenolic Mannich bases were allowed to react with enamines, cyclic *O,N*-acetals or ketals having the pyran nucleus were obtained. The reaction may be formally represented to proceed through loss of the amine portion from the Mannich base followed by a cycloaddition of the resulting *o*-methylenequinone to the enamine (Scheme 1) (6). The initial products, 2-amino-

reaction lies in its simplicity, generally good yields, the abundance of readily prepared (7) or commercially available starting materials as well as in its broad scope. As seen in Table I, the synthesis is applicable to enamines derived from both aldehydes and ketones. The use of heterocyclic ketones permits the preparation of pyrans fused to heterocyclic rings. The Mannich bases vary from those with aromatic and quinoid nuclei to heteroaromatic ones derived from pyridine, coumarin, indole, quinoline, carbazole, etc. Partially reduced heterocyclic systems which embody an endocyclic enamine function undergo an analogous reaction. The products obtained are cyclic *O,N*-ketals with a common spiropyrano piperidine structure (Scheme 2). For example, pyrano[2,3-*i*]quinolizidines



dihydropyrans, were readily hydrolyzed to 2-hydroxydihydropyrans which in turn were easily dehydrated to pyrans. Examples of heterocyclic nuclei prepared by this method are given in Table I. The particular value of this



were obtained from the reaction with $\Delta^{5,10}$ -dehydroquinolizidine (8) (Table II, Compounds **26-31**). Spiropyranotetrahydroisoquinolines or spiropyranotetrahydro- β -carbolines were formed when 1,2,3,4-tetrahydro-2-methyl-1-methyleneisoquinoline (9) or the corresponding β -carboline (10) was allowed to react with phenolic Mannich bases (Table II, Compounds **32-38**).

The cyclic nature of the products was confirmed by the absence of phenolic OH, C=O or C=C-N stretching frequencies in the infrared spectra. The compounds were base insoluble, and the ferric chloride test for phenols was negative. Additional support for the assigned structures was derived from the ability of 2-hydroxydihydropyrans to be dehydrated (Table I, Compounds **23-25**) or etherified (**39**).

TABLE I (a)
Compounds Prepared by Reaction of Phenolic Mannich Bases with Enamines

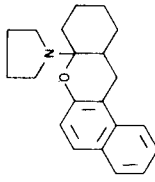
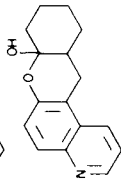
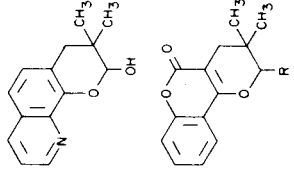


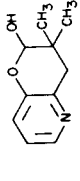
Compound	M.p., °C	Empirical Formula	Yield, % (b)	Calcd., %		Found, %			
				C	H	C	H	N(S)(c)	N(S)(c)
1 	90-95	C ₂₁ H ₂₅ NO	52	82.04	8.20	81.79	8.28	4.56	4.50
2 	238-240	C ₁₆ H ₁₇ NO ₂	83	75.27	6.71	75.18	6.95	5.49	5.50
3 	183-186	C ₁₄ H ₁₅ NO ₂	13	73.34	6.59	73.27	6.78	6.11	6.34
4 R = OH	135-139	C ₁₄ H ₁₄ O ₄	41	68.28	5.73	68.55	5.91		
5 R = 	142-144	C ₁₈ H ₂₁ NO ₄	38	68.55	6.71	68.66	6.84	4.44	4.72
6 R = OH	191-193	C ₁₅ H ₁₄ O ₄	43	69.75	5.46	70.04	5.63		
7 R = 	153-155	C ₁₉ H ₂₁ NO ₄	43	69.70	6.43	69.85	6.63	4.28	3.98
8 	114-117	C ₁₀ H ₁₃ NO ₂	66	67.02	7.31	67.17	7.38	7.82	7.86

TABLE I - Continued

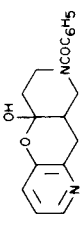
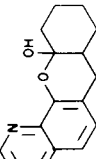
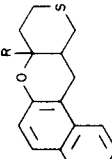

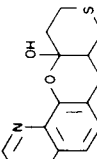
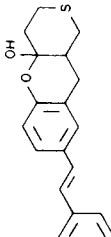
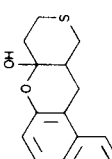
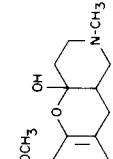
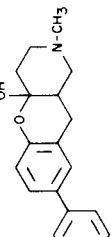
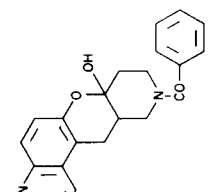
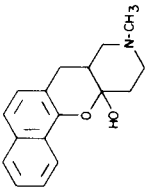
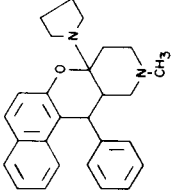
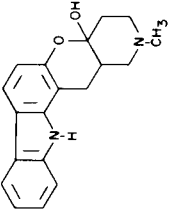
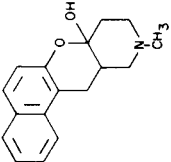
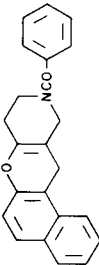
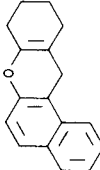
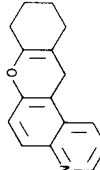
9		176-178	C ₁₈ H ₁₈ N ₂ O ₃	31	69.66	5.85	9.03	69.39	5.70	9.26
10		132-135	C ₁₆ H ₁₇ NO ₂	20	75.27	6.71	5.49	75.37	6.85	5.40
11		149-153	C ₁₆ H ₁₆ O ₂ S	38	74.30	7.42	(9.44)	74.21	7.42	(9.43)
12	R = OH 	147-149	C ₂₁ H ₂₅ NSO	59	70.56	5.92	(11.77)	70.49	6.03	(11.69)
13		140-143	C ₁₅ H ₁₅ NO ₂ S	19	65.91	5.53	(11.73)	66.00	5.72	(11.56)
14		170-173	C ₂₀ H ₂₀ O ₂ S	19	74.04	6.21	(9.88)	73.93	6.12	(9.81)
15		238-241	C ₁₅ H ₁₅ NO ₂ S	29	65.91	5.53	(11.73)	65.96	5.74	(11.52)
16		125-127	C ₁₄ H ₁₉ NO ₃	44	67.44	7.68	5.62	67.46	7.63	5.60
17		181-183	C ₁₉ H ₂₁ NO ₂	11	77.26	7.17	4.74	77.16	7.16	4.87
18		249-252	C ₂₂ H ₂₀ N ₂ O ₃	89	73.31	5.59	7.77	73.31	5.72	7.70

TABLE I - Continued

19		192-195	$C_{17}H_{19}NO_2$	40	75.81	7.11	5.20	76.08	7.20	5.39
20		203-207	$C_{27}H_{30}NO_2$	55	81.37	7.59	7.03	81.31	7.55	6.99
21		201-203	$C_{19}H_{20}N_2O_2$	5	74.00	6.54	9.09	73.75	6.60	9.14
22		167-171	$C_{17}H_{19}NO_2$	60	75.81	7.11	5.20	75.55	7.22	4.96
23		152-153	$C_{23}H_{19}NO_2$	42	80.91	5.61	4.10	80.62	5.63	3.90
24		93-95	$C_{17}H_{16}O$	79	86.40	6.83		86.53	6.94	
25		130-132	$C_{16}H_{15}NO$	63	80.98	6.37	5.90	81.09	6.37	5.80

(a) For additional examples, see ref. 5. (b) The yields stated in the table represent materials of analytical purity. They reflect losses incurred by recrystallization to constant melting point. (c) Sulfur values are given in place of nitrogen for all compounds containing sulfur.

TABLE II

Compounds Prepared by Reaction of Phenolic Mannich Bases
with Partially Hydrogenated Heterocyclic Systems Having the Vinylamine Function

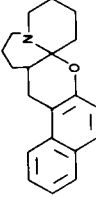
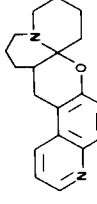
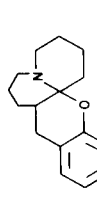
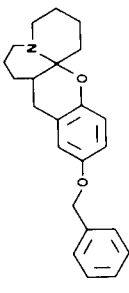
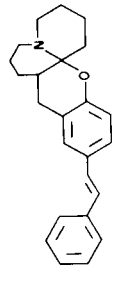
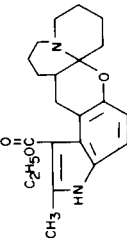
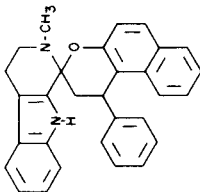
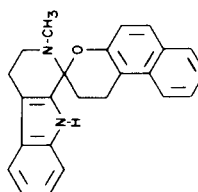
Compound	M.p., °C	Empirical Formula	Yield, % (a)	Calcd., %			Found, %		
				C	H	N	C	H	N
	209-212	C ₂₀ H ₂₃ NO	17	81.87	7.90	4.77	82.07	7.93	4.77
	178-181	C ₁₉ H ₂₂ N ₂ O	51	77.53	7.53	9.52	77.25	7.65	9.30
	93-95	C ₁₇ H ₂₃ NO ₂	50	74.69	8.48	5.12	74.71	8.41	4.97
	66-67	C ₂₃ H ₂₇ NO ₂	27	79.05	7.79	4.01	79.24	8.07	3.92
	88-93	C ₂₄ H ₂₇ NO	29	83.44	7.88	4.04	83.69	7.88	4.15
	166-169	C ₂₂ H ₂₈ N ₂ O ₃	60	71.71	7.66	7.60	71.67	7.70	7.66

TABLE II - Continued

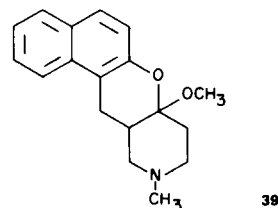
32		171-174	C ₂₂ H ₂₀ BrNO	71	67.01	5.11	3.55	67.18	5.07	3.73
33		164-167	C ₂₁ H ₂₀ N ₂ O	63	79.71	6.37	8.85	79.93	6.39	8.63
34		172-173	C ₂₈ H ₂₅ NO	43	85.90	6.44	3.58	85.73	6.39	3.40
35		134-139	C ₂₆ H ₂₆ N ₂ O ₃	12	75.34	6.32	6.76	75.14	6.34	6.92
36		176-178	C ₂₆ H ₃₀ N ₂ O ₅	28	69.31	6.71	6.22	69.24	6.94	6.16

TABLE II - Continued

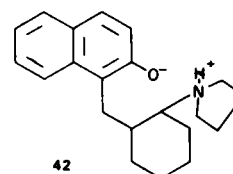
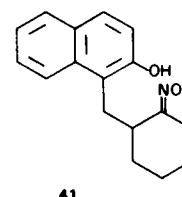
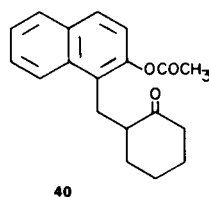
197-200	$C_{30}H_{26}N_2O$	62	83.69	6.09	6.51	83.65	6.06	6.41
178-181	$C_{24}H_{22}N_2O$	38	81.32	6.26	7.90	81.26	6.40	7.85

	
37	38

(a) See Table I, footnote (b).



Since products derived from enamines of cyclic ketones or $\Delta^{5,10}$ -dehydroquinolizidine possess a minimum of two chiral centers, the occurrence of diastereoisomers was anticipated. However, under standard conditions, only one isomer was isolated in crystalline form (11a,b). This is perhaps not surprising since, in analogy to sugars, hemiketals and hemiacetals are capable of anomerization *via* the phenol-ketone or phenol-aldehyde form. In the case of *O,N*-acetals, the epimerization may involve the phenoxymmonium zwitterion. In either situation, the more insoluble isomer is expected to crystallize out. The presence of the open form in solution was suggested by the reactions with acetic anhydride, hydroxylamine, and lithium aluminum hydride which resulted in the acetoxyketone **40**, phenol-oxime **41**, and the phenolamine **42**, respectively.



In conclusion, we wish to draw attention to related reactions. Quagliaro *et al.* (12) have prepared a hexahydro-12-hydroxyxanthenol by heating *o*-dimethylamino-methylphenol with cyclohexanone at 200° for 2 hours. Paquette and Stucki (13) have described a synthesis of 2,4-dihydroxypyran from enamines and salicylic aldehydes. Boyd *et al.* (14) and Miyano (15) obtained 4-pyrone from the reaction of enamines with salicylic acid derivatives.

EXPERIMENTAL (16)

2-Hydroxydihydropyrans.

A solution of 0.1 mole of enamine and 0.1 mole of the phenolic Mannich base in 100 ml. of dioxane was refluxed with a gentle sweep of nitrogen. When after 2-8 hours the evolution of basic

fumes had subsided, 20 ml. of water was added and the refluxing was continued for 1-2 hours. The solvents were evaporated under reduced pressure and the residue was crystallized from ethanol (Compounds **2**, **3**, **6**, **9**, **10**, **12**, **15**, **17**, **18**), acetonitrile (**13**, **14**, **16**, **21**), ethyl acetate (**4**, **8**, **22**), and methanol (**19**).

Spectral Data for Compound **8**:

λ max (ethanol), $m\mu$ (ϵ) 219 (11,100), 258 (4,625), 280 (3,600), 326 (3,180); δ (deuteriochloroform) 6H singlet at 1.08 ppm [$(\text{CH}_3)_2\text{C} <$], 2H singlet at 2.88 ppm (benzylic $-\text{CH}_2-$), 1H singlet at 5.37 ppm ($-\text{O}-\overset{\text{I}}{\text{C}}-\text{O}-$), 2H at 7.09 and 1H at 7.92 ppm (pyridine protons), 1H singlet at 8.92 ppm ($-\text{OH}$); ν max (nujol), cm^{-1} 708, 798, 950, 1090, 1100, 1185, 1238, 1450, 1578 (w), 1592 (w), 2900, 3050.

2-Aminodihydropyrans (Compounds **1**, **5**, **7**, **11**, **20**), Spirodihydropyranoquinolizidines (**26-31**), Spirodihydropyranoisoquinolines (**32-36**), and Spirodihydropyrano- β -carbolines (**37-38**).

The reaction was carried out as above without addition of water. The products were crystallized from ethanol (Compounds **27**, **29**, **33**, **36**), ethyl acetate (**1**, **5**, **7**, **20**, **34**, **35**), acetonitrile (**11**, **28**, **30**, **31**, **32**, **37**, **38**), and Skelly B (**26**).

Spectral Data for Compound **1**:

λ max (ethanol), $m\mu$ (ϵ) 232 (75,600), 266 (4,200), 277 (5,000), 289 (3,900), 317 (2,100), 333 (2,600); δ (deuteriochloroform) 12H at 1.67 ppm ($-\text{CH}_2-$), 1H at 2.3 ppm ($\cong \text{CH}$), 6H at 2.84 ppm ($-\text{CH}_2\text{N} <$, and benzylic $-\text{CH}_2-$), 6H in the 6.9-7.9 ppm region (aromatic protons); ν max (nujol), cm^{-1} 740, 765, 808, 840, 880, 910, 942, 968, 993, 1072, 1145, 1212, 1232, 1265, 1372, 1392, 1430, 1465, 1600, 1620, 2900.

Spectral Data for Compound **26**:

λ max (ethanol), 235 (78,000), 267 (4,550), 278 (5,150), 289 (3,700), 321 (2,300), 333 (2,700); δ (deuteriochloroform) 10H envelope at 1.55 ppm ($-\text{CH}_2-$), 1H at 2.05 ppm ($\cong \text{CH}$), 2H at 2.60 ppm (benzylic $-\text{CH}_2-$), 4H at 3.0 ppm ($-\text{CH}_2\overset{\text{I}}{\text{N}}\text{CH}_2-$), 6H in the 7-7.85 region (aromatic protons); ν max (nujol), cm^{-1} 745, 755, 770, 795, 810 (s), 865 (v.s.), 945, 983, 1038, 1083, 1125, 1150, 1185, 1233 (v.s.), 1358, 1385, 1430, 1458, 1595, 1615, 7900.

Pyrans (Compounds **23-25**).

A solution of 5 g. of 2-hydroxydihydropyran and 5 g. of anhydrous sodium acetate in 50 ml. of glacial acetic acid was refluxed for 5 hours and poured into an ice-water mixture. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

Spectral Data for Compound **24**:

δ (deuteriochloroform) 2H singlet at 3.44 ppm (benzylic methylene), λ max (ethanol) $m\mu$ (ϵ) 215 sh (46,000), 219 (51,000), 244 (19,400), 283 (4000), 322 (1600), 336 (1700). 8,9,10,11,11a,12-Hexahydro-7a-methoxy-10-methyl-7aH-naphthol-[1',2':5,6]pyrano[3,2-c]pyridine (**39**)

A solution of 50 g. of **22** in 50 ml. of methanolic hydrogen chloride was refluxed for 3 hours, poured into ice-water, and made basic with cold 10% sodium hydroxide. The resulting gummy precipitate was extracted with four 50 ml. portions of chloroform. The combined extracts were dried over sodium sulfate and evaporated under reduced pressure. The residual gum crystallized on standing and was recrystallized from ethanol, yield 28% m.p.

124-125°; ν max (nujol), 1075 cm^{-1} ($\text{C}-\text{O}-\text{CH}_3$); δ (deuteriochloroform) 3.33 ppm (OCH_3).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_2$: C, 76.29; H, 7.49; N, 4.94. Found: C, 76.10; H, 7.55; N, 4.86.

2-[(2-Acetoxy-1-naphthyl)methyl]cyclohexanone (**40**).

A solution of 1 g. of 8,9,10,11,11a,12-hexahydro-7aH-benzo[*a*]xanthen-7a-ol (**4**) in 10 ml. of pyridine and 5 ml. of acetic anhydride were allowed to stand for 24 hours at room temperature, poured into 250 ml. of sodium carbonate solution and stirred for 0.5 hour. The mixture was extracted with three 50 ml. portions of methylene chloride. The combined extracts were washed with 1 *N* hydrochloric acid solution, dried over sodium sulfate and evaporated under reduced pressure. The residual gum was recrystallized from Skelly B, yield 20%; m.p. 86-91° (Lit. (17) 88-90°); ν max (nujol), 1695 cm^{-1} (ketone) 1750 cm^{-1} (phenolic ester).

Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{O}_3$: C, 77.00; H, 6.80. Found: C, 77.13; H, 6.77.

2-(Hydroxy-1-naphthyl)methylcyclohexanone Oxime (**41**).

A solution of 5.08 g. (0.02 mole) of 8,9,10,11,11a,12-hexahydro-7aH-benzo[*a*]xanthen-7a-ol (**4**) and 2.1 g. (0.02 mole) of hydroxylamine hydrochloride in 50 ml. ethanol was refluxed for 5 hours and poured into 500 ml. of ice-water. The mixture was made strongly basic with 50% potassium hydroxide and filtered. The pH of the filtrate was lowered to ca. 7 with acetic acid. The precipitated product was filtered off, washed with water, and recrystallized from acetonitrile, m.p. 205-209°; ν max (nujol), 1668 cm^{-1} ($>\text{C}=\text{N}-$), 3380 cm^{-1} ($-\text{OH}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.93; H, 7.27; N, 5.45.

1-(2-Pyrrolidinyl)cyclohexylmethyl-2-naphthol (**42**).

A solution of 1 g. of **1** in 10 ml. of tetrahydrofuran was added dropwise with stirring to a suspension of 1 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran. After 5 hours reflux, the mixture was chilled and the excess reagent was decomposed by dropwise addition of water. The mixture was filtered and the solids were washed several times with hot tetrahydrofuran. Combined filtrates were concentrated under reduced pressure. The residual gum crystallized on standing and was recrystallized from acetonitrile; yield 50%, m.p. 123-125°; ν max (nujol), 2500 cm^{-1} ($\cong \overset{\text{+}}{\text{NH}}$).

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}$: C, 81.50; H, 8.79; N, 4.53. Found: C, 81.75; H, 8.78; N, 4.31.

Starting Materials.

The amine fragments of the enamines were as follows: pyrrolidine (used in preparations of compounds **1**, **2**, **9**, **10**, and **20-22**), dimethylamine (in **3**, **4**, **6**, and **8**), piperidine (in **11-15**), and morpholine (in **5** and **7**). The amine part of the Mannich bases was exclusively dimethylamino.

The previously undescribed 6-bromo-1-dimethylaminomethyl-2-naphthol (**43**), 4-benzyloxy-2-dimethylaminomethylphenol (**44**), 3-dimethylaminomethyl-4-stilbenol (**45**), and 1-dimethylamino-methyl-2-hydroxycarbazole (**46**) were prepared by the following procedure: A solution of 0.1 mole of the phenolic starting material, 5.4 g. of dimethylamine, and 8.5 ml. of 37% formaldehyde in 200 ml. of ethanol was refluxed for 5 hours (0.5 hour in the case of **43**), and allowed to stand overnight at 0-5°. The precipitated product was filtered off and recrystallized from anhydrous ethanol. In the case of **44**, the reaction mixture was

concentrated under reduced pressure to 1/4 of its volume and the residue was poured into 1 l. of ice-water. The precipitated oil was extracted with four 100 ml. portions of ether. The combined ether solutions were extracted with three 40 ml. portions of 3 *N* hydrochloric acid. The combined acidic extracts were made basic in the cold with ammonium hydroxide. The precipitated oil crystallized on chilling and scratching. The crystals were filtered off, washed with ice-cold water and recrystallized from anhydrous ethanol.

The compounds obtained had the following analytical and physical data.

Compound **43**, yield 60%, m.p. 93-94°.

Anal. Calcd. for C₁₃H₁₄BrNO: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.69; H, 5.14; N, 5.04.

Compound **44**, yield 64%, m.p. 50-52°.

Anal. Calcd. for C₁₆H₁₉NO₂: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.63; H, 7.59; N, 5.37.

Compound **45**, yield 68%, m.p. 95-97°.

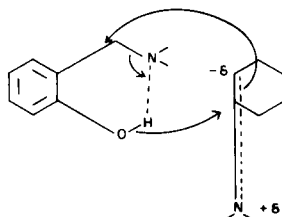
Anal. Calcd. for C₁₇H₁₉NO: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.83; H, 7.65; N, 5.59.

Compound **46**, yield 50%, m.p. 167-169°.

Anal. Calcd. for C₁₅H₁₆N₂O: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.96; H, 6.86; N, 11.71.

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