The Use of Amino Acids in the Mannich Reaction

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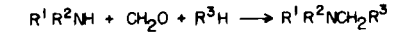
Amino acids have been found to participate as the amine component in the Mannich reaction with both ketones and phenols. The phenolic Mannich bases may be cyclized with sulfuric acid to 1,2-dihydro-4(3*H*)isoquinolones. In the presence of thionyl chloride the same Mannich bases undergo lactonization to benz[*f*]-1,4-oxazepin-4(3*H*)ones.

The Mannich reaction has been exploited extensively for synthesis of many types of new compounds. The reaction consists of the interaction of ammonia, a primary or a secondary amine (**1**) with formaldehyde (**2**) or other aldehyde and an active hydrogen compound (**3**) such as a ketone containing at least one alpha hydrogen or a phenol containing at least one hydrogen in an *ortho* or *para* position. The new amine is represented by **4**. The number of amines which have been utilized in this reaction is vast. However



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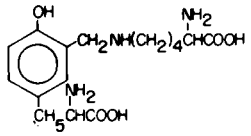
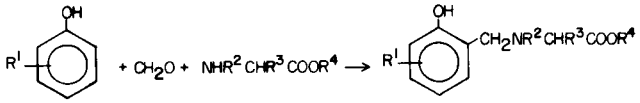
one important class of compounds possessing an amino group has been neglected as components in the Mannich reaction. Very few references are found describing the use of amino acids in this reaction.

Two compounds have been prepared utilizing amino acids with phenols in the Mannich reaction. *N*-Acetyltyrosine, formaldehyde, and α-*N*-acetyllysine gave **5** after hydrolysis (2). The same product was obtained when lysine



was used, which might indicate that the α-amino group might be unreactive in the Mannich reaction. However from 2,4-dimethylphenol (**6**, R^1 = 2,4-di-CH_3), formaldehyde, and threonine (**7**, R^2 = R^4 = H, R^3 = CH_3CHOH) the expected Mannich base, *N*-(2-hydroxy-3,5-dimethylbenzyl)threonine (**8**, R^1 = 2,4-dimethyl, R^2 = R^4 = H, R^3 = CH_3CHOH) was obtained (3).



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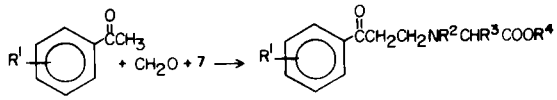
One example utilizing a ketone has been reported in a patent (4). Acetophenone (**9**, R^1 = H), formaldehyde, and glycine ethyl ester (**7**, R^2 = R^3 = H, R^4 = C_2H_5) hydrochloride gave the expected product, *N*-(2-benzoylethyl)-glycine ethyl ester (**10**, R^1 = R^2 = R^3 = H, R^4 = C_2H_5) hydrochloride. The free acid (**10**, R^1 = R^2 = R^3 = R^4 = H) was obtained after hydrolysis.



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The purpose of the work described in this paper is to determine if the common amino acids will participate in the Mannich reaction, and to explore the possibility of utilizing these new Mannich bases as intermediates for preparing certain heterocyclic compounds.

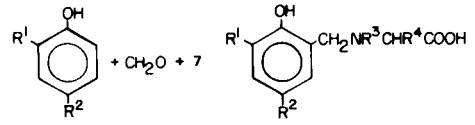
The reaction of 4-methoxyacetophenone (**9**, R^1 = 4-CH_3O) with formaldehyde and glycine ethyl ester (**7**, R^2 = R^3 = H, R^4 = C_2H_5) gave the expected product, the ethyl ester of *N*-2-(4-methoxybenzoyl)-ethyl glycine (**10**, R^1 = 4-CH_3O, R^2 = R^3 = H, R^4 = C_2H_5). Hydrolysis of the ester with dilute hydrochloric acid gave the corresponding acid (**10**, R^1 = 4-CH_3O, R^2 = R^3 = R^4 = H).

The use of alanine ethyl ester, phenylalanine ethyl ester, and valine ethyl ester in the Mannich reaction was successful. Other ketones which were used were acetophenone, 3-nitroacetophenone, 4-hydroxy-3-methoxyacetophenone, and 3,4,5-trimethoxyacetophenone.

The reactions can be carried out in the usual manner in

refluxing ethanol, but better yields are obtained when the reaction medium is cyclohexane-*t*-butyl alcohol with removal of the water as it is formed. Ten such aminoketones are collected in Table I.

The reaction was also explored using phenols as the active hydrogen component. Formaldehyde, 2,4-dimethylphenol (**11**, $R^1 = R^2 = CH_3$) and methionine were allowed

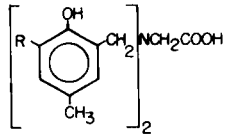


11 **12**

to react, and the desired product, *N*-(2,4-dimethylbenzyl)-methionine (**12**, $R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3SCH_2CH_2$) was obtained. The reaction with 2,4-dimethylphenol was also successful utilizing alanine, glycine, glutamic acid, and serine. The desired *N*-benzyl-*N*-methylglycines were also obtained from sarcosine and 2,4-dimethylphenol, 2-methoxy-4-methylphenol, and 2,4-dichlorophenol.

Sarcosine and formaldehyde alkylated the 4-posiiton of 2,6-dichlorophenol and 2,6-dimethoxyphenol. Alkylation of both *ortho* positions occurred when sarcosine and formaldehyde were allowed to react with 4-methoxyphenol. Alkylation of 2-naphthol occurred at the 1-position.

When glycine and formaldehyde were allowed to react with 2,4-dimethylphenol and with 2-methoxy-4-methylphenol, the *N*,*N*-bis-benzyl derivatives (**13**, R = CH_3, R = CH_3O) were obtained. The other primary amino acids gave only secondary amines as products.



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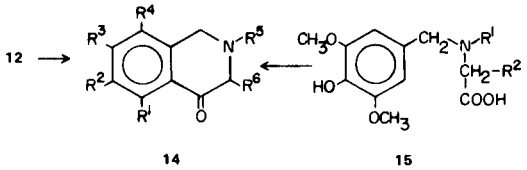
N-Benzylamino acids similar to **12** have been prepared from benzylamines and derivatives of ethyl α-chloroacetate, and have been cyclized to derivatives of 1,2,-dihydro-4(3*H*)-isoquinolone (5) (**14**).



14 **15**

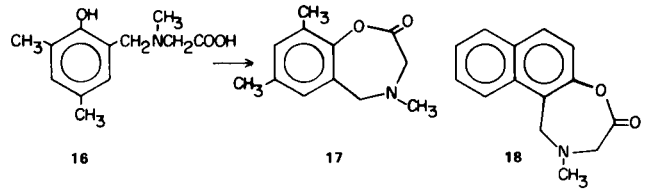
N-(2-Hydroxy-3-methoxy-5-methylbenzyl)sarcosine (**12**, $R^1 = CH_3O$, $R^2 = R^3 = CH_3$, $R^4 = H$) readily underwent cyclization in the presence of sulfuric acid to give 1,2-dihydro-8-hydroxy-7-methoxy-2,5-dimethyl-4(3*H*)isoquinolone (**14**, $R^1 = R^5 = CH_3$, $R^2 = H$, $R^3 = CH_3O$, $R^4 = HO$, $R^6 = H$).

N-(3,5-Dimethoxy-4-hydroxybenzyl)sarcosine (**15**, $R^1 = CH_3$, $R^2 = H$) was subjected to the cyclization procedure, and a product was obtained which contained one less methyl group than expected. The new compound proved to be, based on its nmr spectrum, 1,2-dihydro-5,6-dihydorxy-7-methoxy-2-methyl-4(3*H*)isoquinolone (**14**, $R^1 = R^2 = HO$, $R^3 = CH_3O$, $R^4 = R^6 = H$, $R^5 = CH_3$).

The latter compound was converted to its oxime which failed to undergo the Beckmann rearrangement to give the corresponding benzodiazepinone. The oxime, however, did undergo reduction over platinum oxide to give the expected amine, 4-amino-5,6-dihydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride.

The Mannich base from alanine, formaldehyde, and 2,6-dimethoxyphenol (**15**, $R^1 = H$, $R^2 = CH_3$) also suffered demethylation during cyclization to give 1,2-dihydro-5,6-dihydroxy-7-methoxy-3-methyl-4(3*H*)isoquinolone (**14**, $R^1 = R^2 = OH$, $R^3 = CH_3O$, $R^4 = R^5 = H$, $R^6 = CH_3$).

The phenolic Mannich base in which an *ortho* hydrogen has been substituted possesses the potential of lactonization to form benzoxazepinones. Two compounds of this type were prepared. The treatment of *N*-(3,5-dimethyl-2-hydroxybenzyl)sarcosine (**16**) with thionyl chloride gave the desired compound, 1,2-dihydro-2,6,8-trimethylbenz[*f*]-1,4-oxazepin-4(3*H*)one (**17**). In a like manner, 1,2-dihydro-2-methylnaphth[1,2-*f*]-1,4-oxazepin-4(3*H*)one (**18**) was prepared.



16 **17** **18**

N-[2-(4-Methoxybenzoyl)ethyl]glycine (**10**, $R^1 = 4\text{-}CH_3O$, $R^2 = R^3 = R^4 = H$) was reduced with sodium borohydride to the corresponding alcohol, *N*-[3-hydroxy-3-(4-methoxyphenyl)propyl]glycine.

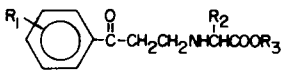
Previously, we have shown that benzylamines of the Mannich base type can alkylate cyanide ion to give phenylacetonitriles (6). The Mannich bases used were exclusively *N*,*N*-dimethyl derivatives (*i.e.*, the amine component was dimethylamine). In the one example investigated, the presence of the carboxy substituent does not prevent alkylation. The reaction between *N*-(2-hydroxy-1-naphthyl)-sarcosine and cyanide ion gave 2-hydroxy-1-naphthylacetonitrile. The nitrile was readily reduced to 2-(2-hydroxy-1-naphthyl)ethylamine.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are corrected. Spectral data were obtained from a

TABLE I

Mannich Bases from Ketones, Formaldehyde and Amino Acid Esters

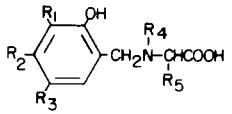


Cmpd. No.	R_1	R_2	R_3	Method	Yield	M.p., °C	Recryst. Solvent	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	4-CH_3O	H	C_2H_5	A B	78 38	189-191 (a)	Ethanol	$C_{14}H_{19}NO_4 \cdot HCl$	55.72	6.68	4.64	55.65	6.72	4.73
2	4-CH_3O	H	CH_3	B	24	180-182 (b)	Ethanol	$C_{13}H_{17}NO_4 \cdot HCl$	54.26	6.31	4.87	54.33	6.56	4.96
3	4-CH_3O	H	H	C	32	200-201.5 (c)	Aq. Ethanol	$C_{12}H_{15}NO_4 \cdot HCl$	52.66	5.89	5.12	52.63	5.91	5.21
4	4-CH_3O	ϕCH_2	C_2H_5	B	18	182-184 (d)	Ethanol	$C_{21}H_{25}NO_4 \cdot HCl$	64.53	6.45	3.58	64.30	6.61	3.76
5	4-CH_3O	CH_3	C_2H_5	B	66	116-118 (e)	Ethyl Acetate	$C_{15}H_{21}NO_4 \cdot HCl$	57.05	7.02	4.43	57.20	6.99	4.23
6	4-CH_3O	$(CH_3)_2CH$	C_2H_5	B	42	139-141 (f)	Acetone	$C_{17}H_{25}NO_4 \cdot HCl$	59.38	7.62	4.07	59.29	7.46	3.88
7	4-HO-3-CH_3O	H	C_2H_5	B	18	84-86 (g)	Aq. Acetone	$C_{14}H_{19}NO_5 \cdot HCl \cdot \frac{1}{2} H_2O$	51.46	6.48	4.29	51.53	6.54	4.43
8	3-NO_2	H	CH_3	B	26	142-145 (h)	Ethanol	$C_{12}H_{14}N_2O_5 \cdot HCl$	47.61	5.00	9.25	47.81	4.96	9.20
9	H	H	C_2H_5	B	15	236-238 (i)	Acetic Acid	$C_{11}H_{15}NO_3$	63.14	7.23	6.69	63.14	7.09	6.70
10	3,4,5-CH_3O	H	C_2H_5	B	43	167-169 (j)	Ethanol	$C_{10}H_{23}NO_6 \cdot HCl$	53.11	6.69	3.87	53.35	6.85	3.66

(a) Ir (nujol): 2600 (broad band), 1740, 1576, 1600, 1510 cm^{-1}; nmr (deuterium oxide): δ 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 4.35 (q, J = 7 Hz, 2), 4.13 (s, 2), 3.92 (s, 3), 3.59 (s, 4), 1.35 (t, J = 7 Hz, 3) ppm. (b) Ir (potassium bromide): 2600 (broad band), 1750, 1680, 1600, 1515 cm^{-1}; nmr (deuterium oxide): δ 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 4.25 (s, 2), 4.00 (s, 3), 3.97 (s, 3), 3.65 (s, 4) ppm. (c) Ir (potassium bromide): 2900 (broad band), 1750, 1660, 1600, 1570, 1500 cm^{-1}; nmr (deuterio DMSO): δ 9.83 (broad s, 2), 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 3.93 (s, 2), 3.83 (s, 3), 3.43 (m, 4) ppm. (d) Ir (potassium bromide): 2600 (broad band), 1740, 1665, 1600, 1580, 1500 cm^{-1}; nmr (deuterio DMSO): δ 9.67 (broad s, 2), 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.37 (s, 5), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 4.42 (m, 1), 4.10 (q, J = 7 Hz, 2), 3.90 (s, 3), 3.47 (m, 4), 1.07 (t, J = 7 Hz, 3) ppm. (e) Ir (potassium bromide): 2700 (broad band), 1740, 1680, 1600, 1580, 1530, 1510 cm^{-1}; nmr (deuterio DMSO): δ 10.00 (broad s, 2), 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 4.27 (q, J = 7 Hz, 2), 4.17 (m, 1), 3.88 (s, 3), 3.49 (m, 4), 3.22 (d, J = 7 Hz, 2), 2.93 (t, J = 7 Hz, 3) ppm. (f) Ir (potassium bromide): 2750 (broad band), 1720, 1670, 1590 cm^{-1}; nmr (deuterium oxide): δ 8.00 (d, $J_{1,2}$ = 8 Hz, 2), 7.07 (d, $J_{1',2'}$ = 8 Hz, 2), 4.42 (q, J = 7 Hz, 2), 4.10 (d, J = 4 Hz, 1), 4.00 (s, 3), 3.63 (s, 4), 2.37 (m, 1), 2.93 (m, 9) ppm. (g) Ir (potassium bromide): 3200 (broad band), 1750, 1680, 1600, 1520 cm^{-1}; nmr (deuterio DMSO): δ 10.00 (broad s, 3), 7.57 (d, $J_{1,2}$ = 8 Hz, 2), 7.03 (d, $J_{1',2'}$ = 8 Hz, 1), 4.25 (q, J = 7 Hz, 2), 4.02 (s, 2), 3.83 (s, 3), 3.40 (m, 4), 1.23 (t, J = 7 Hz, 3). (h) Ir (potassium bromide): 2700 (broad band), 1760, 1700, 1610, 1530, 1350 cm^{-1}; nmr (deuterium oxide): δ 3.75 (s, 1), 8.45 (m, 2), 7.75 (t, J = 8 Hz, 1), 4.17 (s, 2), 3.93 (s, 3), 3.63 (s, 4) ppm. (i) Ir (chloroform): 2650 (broad band), 1750, 1685, 1600, 1450 cm^{-1}; nmr (deuterium oxide): δ 8.62 (m, 2), 8.25 (m, 3), 4.88 (q, J = 7 Hz, 2), 4.62 (s, 2), 4.13 (s, 4), 1.80 (t, J = 7 Hz, 3) ppm. (j) Ir (potassium bromide): 2950 (broad band), 1760, 1690, 1590, 1510 cm^{-1}; nmr (deuterium oxide): δ 7.27 (s, 2), 4.40 (q, J = 7 Hz, 2), 4.17 (s, 2), 4.00 (s, 6), 3.90 (s, 3), 3.60 (s, 4), 1.35 (t, J = 7 Hz, 3) ppm.

TABLE II

Mannich Bases from Phenols, Formaldehyde and Amino Acids



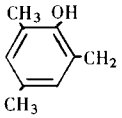
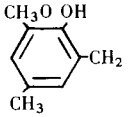
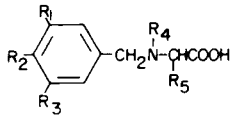
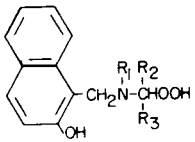
Compd. No.	R_1	R_2	R_3	R_4	R_5	Method	Yield (%)	M.p., °C	Recryst. Solvent	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	CH_3	H	CH_3	H	$CH_2CH_2SCH_3$	D	50	200-201 dec. (b)	Aq. Acetic Acid	$C_{14}H_{21}NO_3S$	59.34	7.46	4.94	59.48	7.66	5.00
2	CH_3	H	CH_3	H	CH_3	D	42	240-242 dec. (c)	Ethanol	$C_{12}H_{17}NO_3$	64.55	7.68	6.27	64.27	7.45	6.16
3	CH_3	H	CH_3	H	H	D	21	238-239 dec. (d)	Aq. Pyridine	$C_{11}H_{15}NO_3$	63.14	7.23	6.69	63.14	7.09	6.70
4	CH_3	H	CH_3		H	D	34	218-220 dec. (e)	Aq. Pyridine	$C_{20}H_{25}NO_4$	69.95	7.34	4.08	70.10	7.29	4.05
5	CH_3	H	CH_3	H	$HOCCH_2$ (O)	D	25	222-225 dec. (f)	Water	$C_{13}H_{17}NO_5$	58.42	6.41	5.24	58.46	6.43	5.43
6	CH_3	H	CH_3	H	$HOCH_2$	D	60	215-217 dec. (g)	Aq. Methanol	$C_{12}H_{17}NO_4$	60.24	7.16	5.85	59.96	7.20	5.67
7	CH_3	H	CH_3	CH_3	H	D	53	160-162 (h)	Ethanol	$C_{12}H_{17}NO_3$	64.55	7.68	6.27	64.48	7.81	6.32
8	CH_3O	H	CH_3	H	H	D	5	237-239 dec. (i)	Acetic Acid	$C_{11}H_{15}NO_4$	58.65	6.71	6.22	58.72	6.73	6.08
9	CH_3O	H	CH_3		H	D	25	180-182 dec. (j)	Aq. Methanol	$C_{20}H_{25}NO_6$	63.98	6.71	3.73	63.75	6.94	3.53
10	CH_3O	H	CH_3	CH_3	H	D	30	175-176 (k)	IPA	$C_{12}H_{17}NO_4$	60.24	7.16	5.85	60.19	7.18	5.45
11	Cl	H	Cl	CH_3	H	D	15	148-150 (l)	Water	$C_{10}H_{11}Cl_2NO_3$	45.48	4.20	5.30	45.76	4.38	5.11
12	H	CH_3O	HO	CH_3	H	D	100	200-205 dec. (m)	(a)	$C_{11}H_{15}NO_5$	54.76	6.27	5.81	54.73	6.51	5.76
13	H	CH_3O	HO	H	$CH_2CH_2SCH_3$	D	50	210-213 dec. (n)	(a)	$C_{13}H_{19}NO_5S$	51.81	6.36	4.65	51.43	6.51	4.66
14	CH_3O	H	CHO	CH_3	H	D	55	188-189 dec. (o)	Water	$C_{12}H_{15}NO_5$	56.91	5.97	5.53	56.90	6.10	5.61
15	CH_3O	H	COOH	CH_3	H	D	60	210-213 dec. (p)	Acetic Acid	$C_{12}H_{15}NO_6$	53.53	5.62	5.20	53.28	5.78	5.06
16	CH_2NCH_2COOH (CH$_3$)	H	OCH_3	CH_3	H	D	41	193-195 dec. (q)	DMF	$C_{15}H_{22}N_2O_6$	55.20	6.80	8.58	55.37	6.90	8.53

TABLE II (Continued)



Compd. No.	R_1	R_2	R_3	R_4	R_5	Method	Yield (%)	M.p., °C	Recryst. Solvent	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
17	CH_3O	HO	CH_3O	CH_3	H	D	61	191-193 (r)	Methanol	$C_{12}H_{17}NO_5$	56.40	6.71	5.49	56.36	6.75	5.54
18	Cl	HO	Cl	CH_3	H	D	39	172-174 (s)	Aq. Methanol	$C_{10}H_{11}Cl_2NO_3$	45.48	4.20	5.30	45.53	4.54	5.16



19	CH_3	H	H	---	---	D	57	184-185 dec. (t)	Methanol	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.38	6.25	5.50
20	H	CH_3	H	---	---	D	89	248-250 dec. (u)	(a)	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.76	6.29	5.56
21	H	$HOCH_2$	H	---	---	D	99	227-230 dec. (v)	(a)	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.33	5.54	5.58
22	H	CH_3	CH_3	---	---	D	87	288-290 dec. (w)	(a)	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	69.65	6.42	5.20

(a) Crystallized from reaction medium - analytically pure. (b) Ir (potassium bromide): 3000 (broad band), 1630, 1500 cm^{-1}; nmr (trifluoroacetic acid): δ 7.27 (s, 1), 7.10 (s, 1), 4.57 (m, 3), 2.70 (m, 4), 2.33 (s, 6), 2.23 (s, 3) ppm. (c) Ir (potassium bromide): 3000 (broad band), 1630, 1490 cm^{-1}; nmr: could not be obtained due to insolubility of compound in nmr solvents. (d) Ir (Nujol): 3300 (broad band), 2700 (broad band), 1620, 1570, 1480 cm^{-1}: nmr (trifluoroacetic acid): δ 7.83 (broad s, 2), 7.25 (s, 1), 7.05 (s, 1), 4.60 (t, J = 7 Hz, 2), 4.25 (t, 7 Hz, 2), 2.30 (s, 6) ppm. (e) Ir (Nujol): 3000 (broad band), 1630, 1590, 1480 cm^{-1}; nmr (deuterio DMSO): δ 7.50 (broad s, 2), 6.95 (s, 2), 6.87 (s, 2), 3.80 (s, 4), 3.28 (s, 2), 2.18 (s, 6), 2.17 (s, 6) ppm. (f) Ir (potassium bromide): 3425 (broad band), 2600 (broad band), 1700, 1590, 1500 cm^{-1}: nmr (trifluoroacetic acid): δ 8.67 (broad s, 4), 6.95 (s, 2), 4.06 (s, 2), 3.73 (t, J = 7 Hz, 1), 2.73 (d, J = 7 Hz, 2), 2.17 (s, 6) ppm. (g) Ir (potassium bromide): 3250 (broad band), 1630, 1590, 1490 cm^{-1}: nmr: could not be obtained due to insolubility of compound in nmr solvents. (h) Ir (potassium bromide): 3000 (broad band), 1635, 1500 cm^{-1}; nmr (deuterium oxide): δ 7.18 (s, 1), 7.15 (s, 1), 4.38 (s, 2), 3.78 (s, 2), 2.93 (s, 3), 2.25 (s, 6) ppm. (i) Ir (potassium bromide): 3060 (broad band), 1640, 1610, 1505 cm^{-1}; nmr (trifluoroacetic acid): δ 7.90 (broad s, 2), 6.93 (s, 1), 6.73 (s, 1), 4.52 (t, J = 5 Hz, 2), 4.18 (t, J = 5 Hz, 2), 3.93 (s, 3), 2.25 (s, 3) ppm. (j) Ir (potassium bromide): 3500 (broad band), 2950 (broad band), 1640, 1600, 1510 cm^{-1}; nmr (deuterio DMSO): δ 6.70 (s, 2), 6.53 (s, 2), 3.73 (s, 10), 3.17 (s, 2), 2.17 (s, 6) ppm. (k) Ir (potassium bromide): 3450 Broad band), 2300 (broad band), 1640, 1610, 1510 cm^{-1}; nmr: could not be determined due to insolubility in nmr solvents. (l) Ir (potassium bromide): 3000 (broad band), 1640, 1580, 1480 cm^{-1}: nmr (deuterio DMSO): δ 7.45 (d, J = 1 Hz, 1), 7.18 (d, J = 1 Hz, 1), 3.85 (s, 2), 3.40 (s, 2), 2.27 (s, 3) ppm. (m) Ir (potassium bromide): 3130 (broad band), 1640, 1625, 1525, 1400, 1210 cm^{-1}; nmr: could not be determined due to insolubility in nmr solvents. (n) Ir (potassium bromide): 3150 (broad band), 1635, 1525, 1445, 1200 cm^{-1}: nmr (deuterio DMSO): δ 8.02 (broad s, 4), 6.75 (s, 1), 6.58 (s, 1), 3.90 (s, 2), 3.72 (s, 3), 3.33 (m, 1), 2.66 (m, assumed to be 2, partially obscured by DMSO), 2.03 (s, 5) ppm. (o) Ir (potassium bromide): 3000 (broad band), 1675, 1640, 1590, 1500 cm^{-1}: nmr: could not be determined because of insolubility in nmr solvents. (p) Ir (potassium bromide): 3520, 3000 (broad band), 1700, 1630, 1610, 1510, 1400 cm^{-1}; nmr (deuterio DMSO): δ 11.00 (broad s, 3), 7.60 (m, 2), 3.97 (s, 2), 3.90 (s, 3), 3.42 (s, 2), 2.43 (s, 3) ppm. (q) Ir (potassium bromide): 3000 (broad band), 1700, 1630, 1490 cm^{-1}; nmr (deuterium oxide): δ 7.23 (s, 2), 4.47 (s, 4), 3.90 and 3.89 (s, 7), 2.95 (s, 6) ppm. (r) Ir (potassium bromide): 3490, 3080 (broad band), 1640, 1600, 1530, 1470, 1400 cm^{-1}; nmr (deuterio DMSO): δ 6.72 (s, 2), 5.82 (broad s, 2), 3.78 (s, 8), 3.22 (s, 2), 2.43 (s, 3) ppm. (s) Ir (potassium bromide): 3440, 3030 (broad band), 1620, 1570, 1500, 1400 cm^{-1}; nmr (trifluoroacetic acid): δ 7.78 (broad s, 2), 7.53 (s, 2), 4.33 (m, 4), 3.20 (t, J = 4 Hz, 3) ppm. (t) Ir (potassium bromide): 2500 (broad band), 1620, 1580, 1515 cm^{-1}; nmr (deuterio DMSO): δ 7.67 (m, 6), 6.60 (broad s, 2), 4.40 (s, 2), 3.48 (s, 2), 2.47 (s, 3) ppm. (u) Ir (potassium bromide): 3170, 2600 (broad band), 1620, 1580, 1525, 1450, 1400 cm^{-1}; nmr: could not be obtained due to insolubility of compound in nmr solvents. (v) Ir (potassium bromide): 3200, 2625 (broad band), 1620, 1560, 1525, 1450, 1380 cm^{-1}: nmr: could not be determined due to insolubility of compound in nmr solvents. (w) Ir (potassium bromide): 3180, 2600 (broad band), 1620, 1600, 1570, 1515, 1440, 1400 cm^{-1}: nmr: could not be determined due to insolubility of compound in nmr solvents.

Perkin-Elmer 521 IR spectrometer and a Varian A-60 or T-60 nmr spectrometer. Mass Spectra were determined on a Jeol MS-9.

Preparation of Mannich Bases from Ketones, Formaldehyde, and Amino Acid Esters. Method A.

The ketone (0.15 mole), D,L-amino acid ester hydrochloride (0.15 mole), and paraformaldehyde (4.5 g., 0.3 mole) was heated under reflux in 100 ml. of *t*-butyl alcohol and 100 ml. of cyclohexane for 24 hours. The water formed was collected in a Dean-Stark trap. The solvent was removed under vacuum and the residual oil was taken up in the appropriate solvent to allow the product to crystallize. The aminoketones are described in Table I.

Method B.

The procedure was the same as Method A except that the solvent was ethanol and the paraformaldehyde was replaced with one equivalent of formalin.

Hydrolysis of Mannich Base Esters. Method C.

The ester was dissolved in 1*N* hydrochloric acid (30 ml./g.) and the resulting solution was heated under reflux for 1.5 hours. The hot solution was filtered and concentrated.

Preparation of Mannich Bases from Phenols, Formaldehyde, and Amino Acids. Method D.

The phenol (0.3 mole), D,L-amino acid (0.3 mole), and formalin (40 ml., 0.4 mole) was heated under reflux in 60-100% ethanol for 18 hours or until the product precipitated. Purification was effected by crystallization from a suitable solvent. The aminophenols are collected in Table II.

Cyclization of Phenolic Mannich Bases with Sulfuric Acid. Method E.

The *N*-benzoylamino acid (0.1 mole) was heated on the steam bath in 50 ml. sulfuric acid for 2.5-18 hours. The dark solution was poured onto ice and neutralized with 50% sodium hydroxide. The solid which precipitated was collected on a filter, crystallized from an appropriate solvent, or converted to the hydrochloride salt and crystallized from an appropriate solvent. The isoquinolones are described in Table III.

1,2-Dihydro-5,6-dihydroxy-7-methoxy-2-methylisoquinol-4(3*H*)one Oxime Hydrochloride.

A solution of 1,2-dihydro-5,6-dihydroxy-7-methoxy-2-methylisoquinol-4(3*H*)one (21.8 g., 0.092 mole) and hydroxylamine hydrochloride (7.0 g., 0.1 mole) in 200 ml. of ethanol and 50 ml. of water was heated under reflux for 5.5 hours. A light green solid precipitated upon chilling. The solid was washed with acetone and crystallized from 95% ethanol to give 18.7 g. (74%) of the light green oxime, m.p. 280°; ir (Nujol): 3550, 1620 cm^{-1}; nmr (deuterio DMSO): δ 12.15 (broad s, 1), 10.87 (broad s, 1), 6.58 (s, 1), 4.43 (s, 2), 4.33 (s, 2), 3.78 (s, 3), 2.90 (s, 3) ppm.

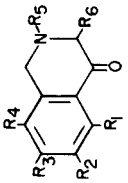
Anal. Calcd. for $C_{11}H_{14}N_2O_4 \cdot HCl$: C, 48.10; H, 5.50; N, 10.20. Found: C, 47.79; H, 5.80; N, 10.16.

4-Amino-5,6-dihydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolone.

The above oxime (2.75 g., 0.01 mole) was reduced in 100 ml. of 50% acetic acid at low pressure over 0.27 g. of platinum oxide. Uptake of hydrogen was complete in 1.5 hours. The catalyst and solvent were removed and the residue was converted to the hydrochloride salt with ethanolic hydrochloric acid. The salt was crystallized from water-acetone (1-3) to give 1.4 g. (47%) of white solid, m.p. 245°; ir (Nujol): 3450, 1630, 1600, 1550, 1500 cm^{-1};

TABLE III

Isoquinolones



Cmpd. No.	R_1	R_2	R_3	R_4	R_5	R_6	Method	Yield (%)	M.p., °C	Recryst. Solvent	Formula	Analyses Calcd. C	H	N	Found C	H	N
1	OH	OH	OCH_3	H	CH_3	H	E	60	272-275 (a)	Water	$C_{11}H_{13}NO_4 \cdot HCl$	50.88	5.44	5.39	51.04	5.50	5.12
2	CH_3	OCH_3	H	OH	CH_3	H	E	29	144-146 (b)	Aq. Methanol	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	65.04	6.84	6.17
3	OH	OH	OCH_3	H	H	CH_3	E	13	215-218 (c)	Aq. Methanol	$C_{11}H_{13}NO_4$	59.18	5.87	6.28	59.20	5.84	6.44

(a) Ir (Nujol): 3460, 2570 (broad band), 1630, 1590, 1515 cm^{-1}; nmr (deuterio DMSO): δ 11.87 (broad s, 1), 8.67 (broad s, 1), 6.60 (s, 1), 3.92 (s, 3), 3.65 (s, 2), 3.32 (s, 2), 2.38 (s, 3) ppm. (b) Ir (chloroform): 3520, 2920, 2760, 1660, 1490 cm^{-1}; nmr (deuteriochloroform): δ 8.83 (broad s, 1), 6.92 (s, 1), 4.02 (s, 3), 3.68 (s, 2), 3.20 (s, 2), 2.65 (s, 3), 2.47 (s, 3) ppm. (c) Ir (potassium bromide): 3240, 2550 (broad band), 1630, 1580, 1510 cm^{-1}; nmr (deuterio DMSO): δ 6.55 (s, 1), 3.98 (s, 2), 3.90 (s, 3), 3.77 (m, 4), 1.27 (d, J = 7 Hz, 3) ppm.

nmr (deuterium oxide): δ 6.57 (s, 1), 4.10 (m, 1), 4.38 (d, J = 2Hz, 2), 3.83 (s, 5), 3.08 (s, 2) ppm.

Anal. Calcd. for $C_{11}H_{16}N_2O_3 \cdot 2HCl$: C, 44.96; H, 6.10; N, 9.43. Found: C, 44.66; H, 5.65; N, 9.36.

N-[3-Hydroxy-3-(*p*-methoxyphenyl)propyl]glycine.

To a stirred suspension of ethyl *N*-[2-(*p*-methoxybenzoyl)ethyl]-glycinate·HCl (30.2 g., 0.1 mole) and potassium carbonate (7 g., 0.55 mole) in 200 ml. of 50% ethanol was slowly added sodium borohydride (7.4 g., 0.2 mole). Stirring was continued at room temperature overnight and then the reaction mixture was acidified with acetic acid. The solution was placed on a strong acid (Dowex 50/50W) ion exchange column and washed with distilled water until chloride ion was no longer detected in the eluent. The product was removed by washing with 1*N* ammonia water, and was crystallized from methanol-ether. The yield of amino alcohol, m.p. 182-184°; was 10 g., (42%); ir (Nujol): 1600, 1580, 1500 cm^{-1}; nmr (deuterium oxide): δ 7.07 (m, 4), 4.70 (s, 1), 3.75 (s, 3), 3.50 (s, 2), 3.03 (m, 2), 2.13 (m, 2) ppm.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.40; H, 7.10; N, 5.89.

N-(3,5-Dimethyl-2-hydroxybenzyl)glycine and *N,N*-bis-(3,5-Dimethyl-2-hydroxybenzyl)glycine.

To a solution of 2,4-dimethylphenol (36.6 g., 0.3 mole) in 200 ml. of ethanol was added a solution of glycine (29.6 g., 0.4 mole) in 200 ml. of water and formalin (50 ml., 0.5 mole). The reaction mixture was heated under reflux for 24 hours, and then evaporated. The residual solid was washed with water and hot acetone, and then crystallized once from 50% acetic acid and once from 25% pyridine to give the mono adduct.

The mother liquors were concentrated to about one-third their original volume, and the bis adduct obtained after chilling, was purified by dissolving in 15% sodium hydroxide solution and reprecipitating by slow addition of acetic acid followed by crystallization from acetone. Both products are described in Table II.

N-(2-Hydroxy-3-methoxy-5-methylbenzyl)glycine and *N,N*-bis-(2-Hydroxy-3-methoxy-5-methylbenzyl)glycine.

A mixture of 2-methoxy-4-methylphenol (41.4 g., 0.3 mole), glycine (29.6 g., 0.4 mole) in 400 ml. of 50% ethanol and formalin (50 ml., 0.5 mole) was warmed to effect solution and left at room temperature for one week. The solid which precipitated was collected on a filter and dissolved in hot 50% acetone and filtered to give the mono adduct which was crystallized from glacial acetic acid.

The bis adduct was obtained by evaporation of the acetone filtrate. The solid residue was dissolved in the minimum volume of ethanol, and water was added until the solution became cloudy. Both products are described in Table II.

2-Hydroxy-1-naphthylacetonitrile.

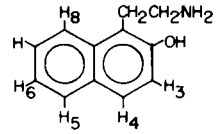
A solution of *N*-(2-hydroxy-1-naphthylmethyl)sarcosine (33 g., 0.13 mole) and potassium cyanide (13 g., 0.2 mole) in 250 ml. of dimethyl formamide was heated at 100-110° under nitrogen for 2 hours. The solid which had precipitated was collected and proved to be sarcosine. The filtrate was evaporated, and the resulting oil was crystallized from ethanol with the aid of charcoal to give 8.0 g. (34%) of the nitrile, m.p. 185-186.5°; reported (7) m.p. 177°; ir (Nujol): 3300, 2245, 1620, 1500 cm^{-1}; nmr (deutero DMSO): δ 10.30 (broad s, 1), 7.67 (m, 6), 4.23 (s, 2) ppm.

Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.78; H, 4.86; N, 7.69.

2-(2-Hydroxy-1-naphthyl)ethylamine Hydrochloride.

A solution of 2-hydroxy-1-naphthylacetonitrile (32 g., 0.17 mole) in 250 ml. of 2-methoxyethanol and 20 ml. of concentrated hydrochloric acid was reduced at low pressure with 5% Pd-C (6.5 g.). After hydrogen uptake had ceased, the catalyst and solvent were removed and the residual solid was washed with acetone. Two crystallizations from methanol-ether gave 15.2 g. (30%) of the amine hydrochloride, m.p. 230-233°.

A 2 g. portion of the hydrochloride was converted to the free base which melted at 163-165° after crystallization from ethanol. The yield was 1.0 g. The free base was treated with hydrobromic acid and the salt obtained melted at 236-237°. Reported (8) m.p. 220° dec.; ir (potassium bromide) of free base: 2700 (broad band), 1610, 1590, 1500, 1450 cm^{-1}; nmr (deuterio DMSO) 100 MHz: chemical shifts [Chemical shift assignments made by analogy with published model compounds (9).] (δ), aromatic protons, H_3, 7.12 ($J_{3,4}$ = 9.0); H_4, 7.61 ($J_{5,6}$ = 8.0); H_5, 7.74 ($J_{5,7}$ = 1.5); H_6, 7.21 ($J_{6,7}$ = 7.0); H_7, 7.40 ($J_{6,8}$ = 1.5); H_8, 7.92 ($J_{7,8}$ = 8.0); 3.09 (m, 2), 2.86 (m, 2) ppm.



Anal. Calcd. for $C_{12}H_{13}NO \cdot HCl$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.28; H, 6.61; N, 6.23.

1,2-Dihydro-2-methylnapth[1,2-*f*]-1,4-oxazepin-4(3*H*)one.

A mixture of *N*-(2-hydroxy-1-naphthylmethyl)sarcosine (56.7 g., 0.23 mole) in thionyl chloride (25 ml., 0.34 mole) and 300 ml. of benzene was heated under reflux for 3 hours, chilled and filtered. The product was washed with benzene and then with acetone. The lactone hydrochloride m.p. 190-195°, was slowly added to a sodium bicarbonate solution, and then extracted with ether. The solution was dried over magnesium sulfate. The residue which remained after evaporation was crystallized from a small volume of ether to give 11.0 g. (21%) of the lactone, m.p. 110-112°; ir (chloroform): 1760, 1600, 1500, 1460 cm^{-1}; nmr (deuteriochloroform): δ 7.70 (m, 6), 4.10 (s, 2), 3.30 (s, 2), 2.56 (s, 3) ppm.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.20; H, 5.93; N, 5.94.

1,2-Dihydro-2,6,8-trimethylbenz[*f*]-1,4-oxazepin-4(3*H*)one.

A suspension of *N*-(3,5-dimethyl-2-hydroxybenzyl)sarcosine (33.6 g., 0.15 mole) in thionyl chloride (15 ml., 0.2 mole) and 200 ml. of benzene was heated under reflux for 1.5 hours. A solid formed, was collected on a filter, and washed with acetone. The lactone hydrochloride, m.p. 208-210°, was converted to the free base in sodium bicarbonate solution. The base was taken up in ether, dried, evaporated, and the residue was crystallized from Skellysolve B to give 23.5 g. (77%) of the lactone, m.p. 63-66°; ir (chloroform): 1740, 1600, 1470 cm^{-1}; nmr (deuterio DMSO) of hydrochloride salt: δ 12.16 (broad s, 1), 7.07 (d, 2), 4.23 (s, 2), 3.80 (s, 2), 2.80 (s, 3), 2.27 (s, 3), 2.20 (s, 3) ppm; mass spectrum: 205 (calcd. 205), 177 (loss of C≡O), 162 (loss of CH_3 from 177 fragment), 134 (loss of CH_2=N-CH_3 from 177 fragment), 106 (loss of C≡O from 134 fragment).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.01; H, 7.21; N, 6.66.

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