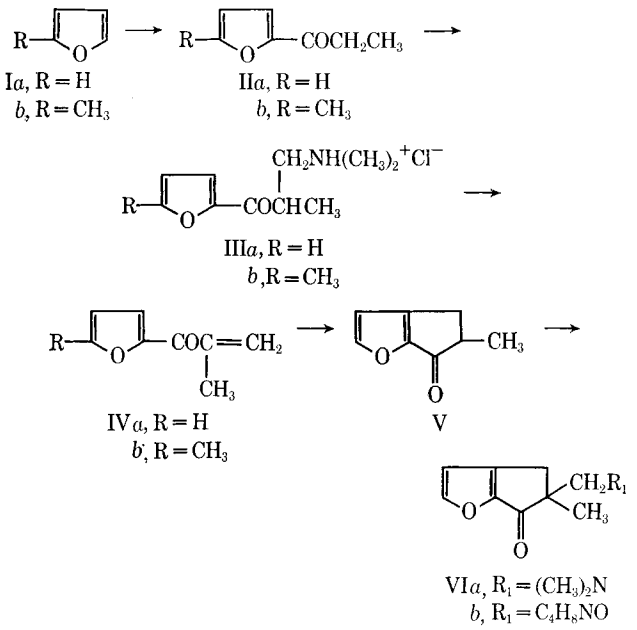
Preparation of Some Mannich Bases of Bicyclic Furans

J. SAM and J. R. MOZINGO, JR.*

Abstract □ The Mannich bases of 6(4H)cyclopenta[b] furanone (V) and substituted 6,7-dihydro-4(5H) benzofuranones (VIII) were synthesized and subjected to general biological screening procedures. No significant activity was noted.

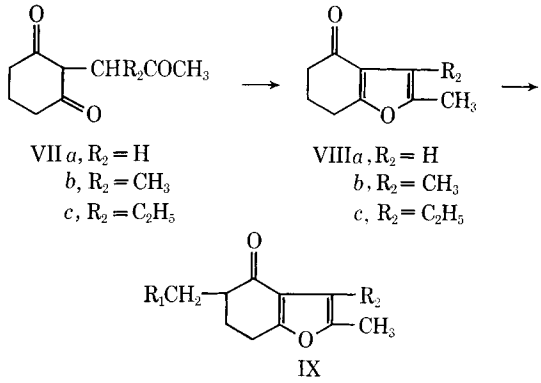
Keyphrases □ Mannich bases, bicyclic furans—synthesis □ Pharmacological screening—bicyclic furan Mannich bases □ GLC—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Previous investigators (1–4) have shown that the Mannich bases of tetralone, thiaindanones, 4-keto-4,5,6,7-tetrahydrothionaphthene, and substituted indole-4(5H)-ones possess CNS depressant properties. In a continuation of interest in the chemistry and the development of biologically active compounds, several Mannich bases of 6(4H)cyclopenta[b]furanone (V) and substituted 6,7-dihydro4-(5H)benzofuranones (VIII) have been synthesized.



The propionylfurans (II) were prepared by the treatment of an appropriate furan with propionic anhydride. Paraformaldehyde and dimethylamine hydrochloride when refluxed in ethanol with II offered excellent yields of the Mannich bases (III*a* and III*b*). The latter on steam distillation provided IV*a* and IV*b*, respectively. Furans are known to be susceptible to acid decomposition (5); nevertheless, attempts were made to cyclize IV*a* to V using various mixtures (1:4, 1:3, 1:1) of sulfuric and fuming sulfuric acid as well as 100% fuming sulfuric acid and concentrated sulfuric acid. Only when conducting the cyclization with concentrated sulfuric acid within 3–4 min. was any appreciable product (14%) obtained. Shorter or longer reaction periods provided negligible yields of V. Utilizing the same conditions, IV*b* under went decomposition and polymerization; neither starting material nor cyclization product were isolated.

The general procedure of von Stetter and Lauterbach (6) was followed for the synthesis of substituted 6,7-dihydro-4(5H)benzofuranones (VIII).



Little difficulty was encountered in the preparation of the Mannich bases (VI and IX, Table I) when freshly distilled V and VIII were used. The latter compounds when allowed to age, however, decompose, and then yield Mannich bases difficult to purify.

IR and NMR data of the Mannich bases are presented in Table II.

PHARMACOLOGY[1]

The compounds were tested for CNS, cardiovascular, autonomic, endocrine, anti-inflammatory, antiallergic, and metabolic activities. In addition, most of the compounds described in this paper were screened for analgesic, hypoglycemic, hypocholesterolemic, diuretic reticuloendothelial, local anesthetic, antispasmotic, antithrombotic, anti-Parkinson, anorexic, antibacterial, antifungal, and antiprotozoan properties. Most tests were carried out following oral administration of the test compound.

The only compound showing any activity was IX*c* (Table I) which exhibited smooth muscle relaxant activity at 10 mcg./ml. in primary testing. However, the level of activity of this compound was insufficient to justify further investigation.

EXPERIMENTAL[2]

The intermediates 2-propionylfuran (7), 5-methyl-2-propionylfuran (7), 1-bromo-2-pentanone (8), 3-bromo-2-butanone (9), 3-bromo-2-pentanone (8), 2-(2-oxopropyl)cyclohexane-1,3-dione (6), 2-(1-methyl-2-oxopropyl)cyclohexane-1,3-dione (6), 6,7-dihydro-2-

[1] The authors are grateful to Dr. H. Leo Dickison of Bristol Laboratories, Syracuse, N. Y. for the pharmacological data.

[2] All melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. IR spectra were determined with a Perkin-Elmer 137B IR spectrophotometer using potassium bromide pellets and liquid films. NMR spectra were determined on a Varian A-60A spectrophotometer using tetramethylsilane and D_2O as internal standards. GLC were taken on an Aerograph Autoprep A-700 equipped with a thermal conductivity detector and containing a 0.62-cm. × 4.9-m. (0.25-in. × 16-ft.) column packed with 20% Carbowax 1540 on 60–80 mesh Chromasorb W.

Table I—Mannich Bases Derived from Benzofuranones (IX) and Cyclopenta[b]furanones (VI)

No.	R_1	R_2	Yield, %	M.p., °C.[a]	Molecular Formula[b]	Anal., % Calcd.	Found
VI*a*	$(CH_3)_2N$	—	63	228–228.5(A)	$C_{11}H_{16}ClNO_2$	C, 57.51 H, 7.02 N, 6.10	C, 57.56 H, 7.11 N, 6.30
VI*b*	C_4H_8NO[c]	—	74	192–194(E)	$C_{13}H_{18}ClNO_3$	C, 57.46 H, 6.68 N, 5.15	C, 57.58 H, 6.79 N, 5.31
IX*a*	$(CH_3)_2N$	H	40	167–167.5(A)	$C_{12}H_{18}ClNO_2$	C, 59.14 H, 7.44 N, 5.75	C, 58.85 H, 7.43 N, 5.85
IX*b*	C_4H_8NO[c]	H	70	179–181(EE)	$C_{14}H_{20}ClNO_3$	C, 58.84 H, 7.06 N, 4.90	C, 58.70 H, 6.99 N, 4.90
IX*c*	$(CH_3)_2N$	CH_3	40	186–189(A)	$C_{13}H_{20}ClNO_2$	C, 60.57 H, 7.82 N, 5.44	C, 60.21 H, 7.92 N, 5.58
IX*d*	C_4H_8NO[c]	CH_3	31	213–215(A)	$C_{15}H_{22}ClNO_3$[d]	C, 60.09 H, 7.40 N, 4.67	C, 58.60 H, 7.32 N, 4.97
IX*e*	$(CH_3)_2N$	C_2H_5	24	197–197.5(Ac)	$C_{14}H_{22}ClNO_2$[d]	C, 58.16 H, 8.95 N, 5.65	C, 61.04 H, 8.15 N, 4.69
IX*f*	C_4H_8NO[c]	C_2H_5	8	172–172.5(Ac)	$C_{16}H_{24}ClNO_3$	C, 61.23 H, 7.71 N, 4.46	C, 61.05 H, 7.75 N, 4.37

[a] Recrystallization solvent; A = acetonitrile, E = ethanol, EE = ethanol-ether, Ac = acetone. [b] Hydrochloride. [c] Morpholino. [d] Although good elemental analysis was not obtained, the IR and NMR spectra were consistent with the structure proposed.

methyl-4(5H)benzofuranone (6), and 6,7-dihydro-2,3-dimethyl-4(5H) benzofuranone (6) were prepared according to procedures described in the literature.

N,N-Dimethyl-2-(2-furoyl)propylamine Hydrochloride (IIIa)—A mixture of 52.0 g. (0.42 mole) of 2-propionylfuran, 20.0 g. (0.60 mole) of paraformaldehyde, 36.0 g. (0.44 mole) of dimethylamine hydrochloride, 1 ml. of hydrochloric acid, and 80 ml. of ethanol was refluxed for 4 hr. The solvent was distilled under reduced pressure; the solid residue was washed with 200 ml. of ether to remove the unchanged starting materials. The salt was recrystallized from acetonitrile to give 86.5 g. (95%) of white crystals, m.p. 168.5–169°, $\lambda_{max.}$ (KBr) 1,660 cm.$^{-1}$; NMR (D_2O), 1.39–1.55 δ (3H, doublet), 3.00–3.05 (6H, singlet), 3.16–3.95 (3H, multiplet), 6.68–6.72 (1H, multiplet), 7.55–7.68 (1H, doublet), 7.82–7.89 (1H, doublet).

Anal.—Calcd. for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; Cl, 16.29; N, 6.44. Found: C, 54.99; H, 7.40; Cl, 16.09; N, 6.52.

N,N-Dimethyl-2(5-methyl-2-furoyl)propylamine Hydrochloride (IIIb)—The procedure outlined for the preparation of III*a* was used. Beginning with 27.6 g. (0.2 mole) of 2-methyl-5-propionylfuran, 9.0 g (0.3 mole) of paraformaldehyde, 17.1 g. (0.21 mole) of dimethylamine hydrochloride, 1 ml. concentrated hydrochloric acid and 60 ml. of ethanol, a yield of 39.8 g. (86%) of white crystals, m.p. 167–167.5° was obtained; $\lambda_{max.}$ (KBr) 1,650 cm.$^{-1}$; NMR (D_2O), 1.16–1.38 (3H, doublet), 2.29–2.36 (3H, singlet), 2.78–2.87 (6H, singlet), 3.00–3.74 (3H, multiplet), 6.20–6.33 (1H, doublet), 7.37–7.48 (1H, doublet).

Anal.—Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; Cl; 15.30; N, 6.05. Found: C, 56.95; H, 7.96; Cl, 15.29; N, 6.14.

2-(α-Methylacrylo)furan (IVa)—A solution composed of 323.5 g. (1.49 moles) of *N,N*-dimethyl-2-(2-furoyl)propylamine hydrochloride and a minimum amount of water was steam-distilled. The distillate was extracted with three 200-ml. portions of ether, combined and dried over anhydrous magnesium sulfate. The solvent was distilled under reduced pressure and the residue distilled to give 108 g. (53.5%) of product, b.p. 39–44°/0.1 mm., n_D^{30} 1.5169, $\lambda_{max.}$ (liquid film) 1,630 cm.$^{-1}$; NMR ($CDCl_3$), 1.99–2.10 (3H, doublet), 5.72–6.00 (2H, multiplet), 6.42–6.57 (1H, multiplet), 7.05–7.18 (1H, multiplet), 7.60–7.70 (1H, multiplet). Poor stability of the compound would not allow elemental analysis. Purity and structure were confirmed by GLC, NMR, and IR.

2-(α-Methylacrylo)-5-methylfuran (IVb)—The procedure outlined for the preparation of IV*a* was followed using 229.0 g. (0.99 mole) of *N,N*-dimethyl-2-(5-methyl-2-furoyl)propylamine hydrochloride, which provided a yield of 47.0 g. (31.4%) b.p. 104–105°/29 mm.,

Table II—IR and NMR Spectra Data of the Mannich Bases of Table I

No.	max. (KBr), cm.$^{-1}$	NMR Solvent	δ[a]
VI*a*	2510, 1690 1580	D_2O	1.27–1.34 (3H, s), 2.79–2.86 (6H, s), 2.89–2.98 (2H, d), 3.39–3.46 (2H, s), 6.61–6.68 (1H, d), 7.96–8.02 (1H, d)
VI*b*	2500, 1680 1590	D_2O	1.35–1.39 (3H, s), 2.95–3.10 (2H, d), 3.17–3.40 (4H, m), 3.47–3.54 (2H, s), 3.80–4.02 (4H, m), 6.57–6.65 (1H, d), 7.90–7.97 (1H, d)
IX*a*	2500, 1650 1580	$CDCl_3$	2.21–2.35 (3H, s), 2.71–3.25 (12H, m), 3.50–4.00 (1H, m), 6.15–6.25 (1H, s)
IX*b*	2400, 1660 1580	D_2O	2.15–2.28 (3H, s), 2.78–3.56 (10H, m), 3.74–4.08 (5H, m), 6.08–6.18 (1H, s)
IX*c*	2600, 1650 1580	D_2O	1.93–2.14 (6H, d), 2.66–3.61 (13H, m)
IX*d*	2550, 1650 1580	D_2O	1.86–2.14 (6H, d), 2.75–3.10 (4H, m), 3.12–3.48 (7H, m), 3.83–4.03 (4H, m)
IX*e*	2600, 1650 1580	$CDCl_3$	0.93–1.26 (3H, t), 2.15–2.26 (3H, s), 2.40–4.10 (15H, m)
IX*f*	2450, 1650 1580	$CDCl_3$	0.87–1.21 (3H, t), 2.11–2.28 (3H, s), 2.35–2.72 (6H, m), 2.78–3.52 (6H, m), 3.58–3.90 (1H, m), 3.95–4.35 (4H, m)

[a] s = singlet, d = doublet, m = unresolvable multiplet, t = triplet.

n_D^{25} 1.5280, $\lambda_{max.}$ (liquid film) 1,645 cm.$^{-1}$; NMR (CCl_4), 1.95–2.05 (3H, singlet), 2.35–2.43 (3H, singlet), 5.75–6.00 (2H, multiplet), 6.20–6.33 (1H, multiplet), 7.05–7.15 (1H, multiplet), Poor stability would not allow elemental analysis. Purity and structure were determined by GLC, NMR and IR.

5-Methyl-6(4H)cyclopenta[b]furanone (V)—To 250 ml. of concentrated sulfuric acid, 72.0 g. (0.53 mole) of 2-(α-methylacrylo) furan was added dropwise and stirred for 3 min. The mixture was cooled and poured into 1,500 ml. of crushed ice, extracted with ether, and the extracts dried over magnesium sulfate. The solvent was distilled under reduced pressure and the residue distilled to give 9.8 g. (13.5%) of product, b.p. 56–56.5°/0.03 mm., n_D^{24} 1.5283, $\lambda_{max.}$ (liquid film) 1,690 cm.$^{-1}$; NMR ($CDCl_3$) 1.21–1.40 (3H, doublet), 2.02–2.57 (2H, doublet), 2.80–3.37 (1H, multiplet), 6.52–6.60 (1H, doublet), 7.81–7.90 (1H doublet).

A 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethanol-ethyl acetate, m.p. 229–230°.

Anal.—Calcd. for $C_{14}H_{12}N_4O_5$: C, 53.17; H, 3.82; N, 17.71. Found: C, 52.85; H, 3.84; N, 17.18.

2-(1-Ethyl-2-oxopropyl)cyclohexane-1,3-dione (VIIc)—Following the procedure outlined by Schaeffer and Vince (10), a solution of 54.0 g. (1.0 mole) of sodium methoxide, 116 g. (1.04 mole) of 1,3-cyclohexanedione, and 183 g. (1.11 mole) of 3-bromo-2-pentanone in 580 ml. of ethanol was refluxed for 15 min. and then cooled. The sodium bromide formed during the reaction was removed by filtration and the filtrate concentrated under reduced pressure on a steam bath. The residual syrup was dissolved in 500 ml. of a 1:1 mixture of chloroform and 10% sodium hydroxide solution. The aqueous phase was separated and extracted with 250 ml. of chloroform. After cooling the aqueous solution in an ice bath and acidifying with concentrated hydrochloric acid, the aqueous solution was extracted with three 250-ml. portions of chloroform. After drying the chloroform extract over anhydrous magnesium sulfate, the solvent was distilled under reduced pressure. All attempts to purify the residual oil failed; however, 196 g. (74.5%) of the crude product was isolated.

6,7-Dihydro-3-ethyl-2-methyl-4(5H)benzofuranone (VIIIc)—Concentrated sulfuric acid (1,000 ml.) was treated dropwise with stirring with 150.0 g. (0.77 mole) of 2-(1-ethyl-2-oxopropyl)cyclohexane-1, 3-dione (VIIc). After 3 min., the mixture was poured over approximately 3,000 ml. of crushed ice. After the cold aqueous solution was extracted with three 200-ml. portions of chloroform, the organic layers were combined and dried over anhydrous magnesium sulfate. The solvent was distilled under reduced pressure and the residue distilled to afford 27.8 g. (21%) of product, b.p. 85–88°/1.5 mm., n_D^{24} 1.5143, $\lambda_{max.}$ (liquid film) 1,650 cm.$^{-1}$; NMR ($CDCl_3$), 0.90–1.27 δ (3H, singlet); 2.18–2.23 (3H, singlet), 2.19–2.96 (8H, multiplet).

Mannich Bases (Tables I and II)—A mixture of 0.05 mole of the ketone, 0.05 mole of paraformaldehyde, 0.05 mole of the appropriate amine hydrochloride, 5 ml. of ethanol, and 1 drop of concentrated hydrochloric acid was refluxed for 8 hr. The alcohol was distilled under reduced pressure and the residual material was washed several times with ether. If a solid appeared, it was recrystallized from an appropriate solvent. If an oil remained, it was treated with a 10% sodium bicarbonate solution and extracted with ether. The ether solution was washed with water and then dried over magnesium sulfate. Dry hydrogen chloride was bubbled through the ether extract; the resulting crystals were removed by filtration and recrystallized from an appropriate solvent.

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