[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

# Mannich Bases from Benzalacetones

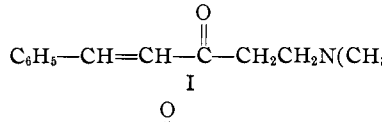
BY J. H. BURCKHALTER AND SAM H. JOHNSON, JR.[1]

Mannich bases from benzalacetone were prepared as vinylogs of γ-phenylpropylamines (specifically, β-aminopropiophenones) in an attempt to enhance the analgetic effect of the latter class of compounds. These vinylogous bases, while devoid of analgetic activity, were found to possess *in vitro* action against bacteria. As a result the toxic groups, nitro, chloro and methoxy, were substituted in the benzene ring in attempting to increase the biological effect. However, the antibacterial effect was not improved.

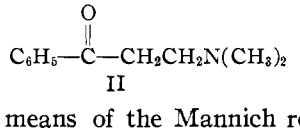
## Discussion

Attempts to find better agents for the relief of pain among the γ-phenylpropylamines have been described in the foregoing publications.[2] Incidental to these studies, we became interested in learning whether vinylogs of certain γ-phenylpropylamines would possess any analgetic effect. As the similarity in chemical reactivity of a compound and its vinylog is well known,[3] continued investigations into the pharmacology and chemotherapy of vinylogous substances appeared to be warranted.[4]

5-Dimethylamino-1-phenyl-1-penten-3-one (I), first prepared from benzalacetone by means of the Mannich reaction,[5] is a vinylog of II which possesses a γ-phenylpropylamine structure. II, also readily



I

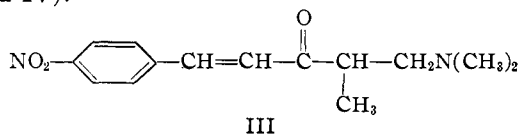


II

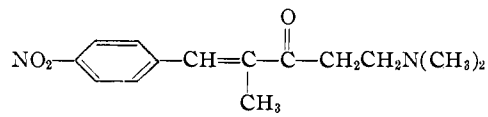
prepared by means of the Mannich reaction,[6] has been classed as a spasmolytic agent by Denton, *et al.*[7] Further, it is well known that spasmolytic and analgetic activities are frequently resident in the same molecule. Despite these relationships, I and its analogs have failed to exhibit analgetic effect.[8] However, it is known that certain α,β-unsaturated ketones possess an antibacterial effect, and I was found to be active against various bacteria.[9]

In view of the wide range of effectiveness of the antibiotic Chloromycetin, which possesses the *p*-nitro group,[10] it was decided to introduce this group into I and to make certain other structural changes in attempts to enhance its antibacterial effectiveness. The thirteen compounds listed in Table I are the result of these structural variations.

Two other bases having a methyl group substituted on each side of the carbonyl were also made (III and IV).



III



IV

These fifteen related keto bases were all prepared by means of the Mannich reaction, employing paraformaldehyde with the appropriate benzalacetone and secondary amine.[5,11]

The starting chloro- and dimethoxybenzalacetones were prepared by the Claisen–Schmidt method,[12] while the nitro substituents were introduced by nitration of the benzalacetones.[13]

5-Diethylamino-1-(2,3-dimethoxyphenyl)-1-penten-3-one hydrochloride (Table I, no. 2) was reduced catalytically to the pentanone with the object of finding any difference in biological activity between the two compounds.

The structural variations in I failed to improve its antibacterial effectiveness.

**Acknowledgment.**—The authors are grateful to Parke, Davis and Company for financial aid.

## Experimental[14]

**2,3-Dimethoxybenzalacetone.**—Following the procedure of Drake and Allen[11] used in the preparation of benzalacetone, 83 g. (0.5 mole) of freshly distilled 2,3-dimethoxybenzaldehyde, 174 g. (3 moles) of acetone and 20 ml. of 10% sodium hydroxide solution gave 75 g. (73% yield) of a yellow viscous oil, b.p. 142–145° (1.5 mm.), $n^{20}D$ 1.5854.

*Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.50; H, 6.86.

**The 2,4-dinitrophenylhydrazone** upon recrystallization from a chloroform–alcohol mixture melted at 217°.

*Anal.* Calcd. for $C_{18}H_{18}N_4O_6$: C, 55.84; H, 4.69. Found: C, 55.58; H, 4.67.

***o*-Nitrobenzalacetone.**—After the procedure for the preparation and isolation of *p*-nitrobenzalacetone had been followed,[13] the alcoholic filtrate was dissolved in ether and the solution washed well with water. The ether extract was dried over potassium carbonate, the ether was removed and the residue was distilled as a yellow oil at 148–152° (0.3 mm.), 18% yield. Upon cooling the product solidified, m.p. 53°.[13] Near the end of the distillation care must be taken to prevent decomposition of the residue.

(1) Parke, Davis and Company Fellow, 1948–1950. Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) Burckhalter and Johnson, THIS JOURNAL, **73**, 4827, 4830, 4832 (1951).

(3) Fuson, *Chem. Revs.*, **16**, 1 (1935).

(4) For such studies with local anesthetics, reference may be made to the interesting results with vinylogous compounds prepared by Gilman, *et al.*, THIS JOURNAL, **47**, 245 (1925), **50**, 437 (1928); Bailey and McElvain, *ibid.*, **52**, 2007 (1930); Weizmann, *et al.*, *ibid.*, **71**, 2315 (1949); and Clinton, Salvador and Laskowski, *ibid.*, **71**, 1300 (1949).

(5) Mannich and Schütz, *Arch. Pharm.*, **265**, 684 (1917).

(6) Mannich and Heilner, *Ber.*, **65**, 356 (1922).

(7) Denton, *et al.*, THIS JOURNAL, **71**, 2048 (1949).

(8) Unpublished results by Dr. C. V. Winder, Parke, Davis and Co., Detroit.

(9) Unpublished results by Schlingman, Fox and Sarber, Parke, Davis and Co., Detroit.

(10) Rebstock, *et al.*, THIS JOURNAL, **71**, 2458 (1949).

(11) Lutz, *et al.*, *J. Org. Chem.*, **14**, 993 (1949), have prepared Mannich bases from *p*-halobenzalacetones.

(12) Drake and Allen, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 77.

(13) Baeyer and Drewsen, *Ber.*, **15**, 2856 (1882).

(14) C and H analyses by Mr. Charles Beazley, Skokie, Illinois.

TABLE I

5-DIALKYLAMINO-1-(SUBSTITUTED PHENYL)-1-PENTEN-3-ONES (ANALOGS OF I)

| No. | Phenyl substituents | Amino group | M.p., °C. | Yield,[a] % | Formula | Chlorine, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 1 | 2,3-Dimethoxy | Dimethyl | 140 | 43[b] | $C_{15}H_{21}NO_3 \cdot HCl$ | 11.82 | 11.72 |
| 2 | 2,3-Dimethoxy | Diethyl | 110 | 53[c] | $C_{17}H_{25}NO_3 \cdot HCl$ | 10.82 | 10.88 |
| 3 | 2,3-Dimethoxy | Morpholinyl | 154 | 33[d] | $C_{17}H_{23}NO_4 \cdot HCl$ | 10.40 | 10.47 |
| 4 | *p*-Nitro[g] | Dimethyl | 187 | 68[e] | $C_{13}H_{16}N_2O_3 \cdot HCl$ | 12.45 | 12.49 |
| 5 | *p*-Nitro[g] | Diethyl | 150 | 50[f] | $C_{15}H_{20}N_2O_3 \cdot HCl$ | 11.33 | 11.44 |
| 6 | *p*-Nitro[g] | Morpholinyl | 219 | 63[b] | $C_{15}H_{18}N_2O_4 \cdot HCl$ | 10.86 | 10.94 |
| 7 | *p*-Nitro[g] | Piperidyl | 209 | 62[b] | $C_{16}H_{20}N_2O_3 \cdot HCl$ | 10.92 | 11.02 |
| 8 | *o*-Nitro | Dimethyl | 167 | 34[f] | $C_{13}H_{16}N_2O_3 \cdot HCl$ | 12.45 | 12.53 |
| 9 | *o*-Nitro | Morpholinyl | 172 | 35[f] | $C_{15}H_{18}N_2O_4 \cdot HCl$ | 10.86 | 10.98 |
| 10 | *o*-Nitro | Piperidyl | 178 | 47[f] | $C_{16}H_{20}N_2O_3 \cdot HCl$ | 10.92 | 11.04 |
| 11 | *o*-Chloro[h] | Dimethyl | 168 | 20[b] | $C_{13}H_{16}ClNO \cdot HCl$ | 12.93 | 13.04 |
| 12 | *o*-Chloro[h] | Morpholinyl | 161 | 36[f] | $C_{15}H_{18}ClNO_2 \cdot HCl$ | 11.48 | 11.46 |
| 13 | *o*-Chloro[h] | Piperidyl | 168 | 46[f] | $C_{16}H_{20}ClNO \cdot HCl$ | 11.29 | 11.38 |

[a] Based upon the substituted benzalacetone. [b] From ethanol. [c] From mixture of isopropyl alcohol, acetone and ether. [d] From ethanol–acetone. [e] From acetone–ether. [f] From ethanol–ether. [g] For intermediate *p*-nitrobenzalacetone, see ref. 13. [h] For intermediate *o*-chlorobenzalacetone, see Vorländer, *Ann.*, **294**, 291 (1897).

1-(*p*-**Nitrophenyl**)-1-**penten-3-one**.—1-Phenyl-1-penten-3-one was obtained in 66% yield by the Claisen–Schmidt method from benzaldehyde and methyl ethyl ketone.[15] Fifty grams was slowly added to 150 g. of concentrated sulfuric acid kept at 0°. The temperature of the stirred solution was kept below −20° while a mixture of 26 ml. of concentrated nitric and 50 g. of concentrated sulfuric acids was slowly added. Stirring was continued for ten minutes after the addition was completed, and the mixture was poured into 1.5 kg. of cracked ice. A gummy material solidified after three hours. It was collected upon a filter, washed well with water and air dried. After recrystallization from alcohol, 30 g. (50% yield) of a light yellow solid, m.p. 107°, was obtained.

*Anal.* Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.44. Found: C, 64.50; H, 5.50.

By addition of water to the filtrate, a solid of wide melting range was isolated. Treatment with charcoal and several recrystallizations from alcohol gave a substance considered to be the *o*-nitro isomer which, melting around 42°, was still impure.

**2-Methyl-1-(*p*-nitrophenyl)-1-buten-3-one**.—2-Methyl-1-phenyl-1-buten-3-one was obtained in 51% yield through the saturation of a mixture of benzaldehyde and methyl ethyl ketone with dry hydrogen chloride.[15] By the nitration procedure of the foregoing experiment, 50 g. of this ketone was converted into 45 g. (70% yield) of a nearly white, fluffy solid, m.p. 109° (from alcohol).

*Anal.* Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.44. Found: C, 64.41; H, 5.45.

Dilution of the alcoholic filtrate with water and distillation of the crude precipitated solid gave only an additional quantity of the para isomer. The structure was confirmed by alkaline permanganate oxidation to *p*-nitrobenzoic acid, m.p. 238°.[16]

(15) Harris and Mueller, *Ber.*, **35**, 970 (1902).

(16) Beilstein and Kuhlberg, *Ann.*, **163**, 128 (1872), reported 238°.

**Mannich Bases (Table I)**.—The keto bases were prepared by the general procedure of heating at reflux temperature 0.1 mole of the benzalacetone with 0.1 mole of paraformaldehyde and 0.11 mole of the appropriate amine hydrochloride in 15 ml. of alcohol. After 30 minutes, two drops of concentrated hydrochloric acid was added. (Under these conditions, compound 6 crystallized even from the hot alcoholic solution.) At the end of two hours, the solution was poured into 50 ml. of acetone and the mixture cooled in an ice-chest for four hours. The solid product was recrystallized.

**5-Dimethylamino-4-methyl-1-(*p*-nitrophenyl)-1-penten-3-one (III) Hydrochloride**.—By the foregoing procedure, a 61% yield of pure light yellow III hydrochloride was obtained, m.p. 161°. The product was recrystallized first from isopropyl alcohol and then from acetone.

*Anal.* Calcd. for $C_{14}H_{19}N_2O_3 \cdot HCl$: Cl, 11.87. Found: Cl, 11.86.

**5-Dimethylamino-2-methyl-1-(*p*-nitrophenyl)-1-penten-3-one (IV) Hydrochloride**.—By the same general procedure, a 65% yield of pure light yellow IV hydrochloride was obtained, m.p. 189°. Recrystallization was effected from absolute alcohol by means of a Soxhlet extractor.

*Anal.* Calcd. for $C_{14}H_{19}N_2O_3 \cdot HCl$: Cl, 11.87. Found: Cl, 11.93.

**5-Diethylamino-1-(2,3-dimethoxyphenyl)-pentan-3-one Hydrochloride**.—A mixture of 13.5 g. of 5-diethylamino-1-(2,3-dimethoxyphenyl)-1-penten-3-one hydrochloride (Table I, no. 2), 75 ml. of alcohol and 0.1 g. of Adams catalyst was shaken in a Parr hydrogenator until one molecular equivalent of hydrogen had been absorbed. After removal of the catalyst and the solvent, the solid residue was recrystallized from an acetone–isopropyl alcohol mixture to give 9 g. (67% yield) of the white crystalline pentanone, m.p. 106°.

*Anal.* Calcd. for $C_{17}H_{27}NO_3 \cdot HCl$: Cl, 10.75. Found: C, 10.87.

LAWRENCE, KANSAS RECEIVED MARCH 26, 1951