SUMMARY

The healing retardation action of anti-inflammatory agents, phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin, has been demonstrated in rats.

Topical application of retinoic acid can reverse the healing inhibitory action of these anti-inflammatory agents.

The mechanism of action of these agents has been discussed.

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New Compounds: Some Potential Chemotherapeutic Agents Derived from Aralkyl Ketones

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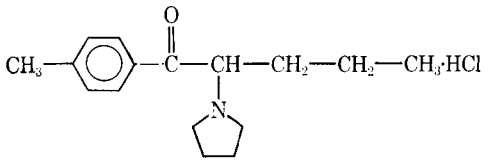
Abstract □ The Mannich reaction has been successfully applied to some aralkyl ketones, valerophenone and caprophenone, and their substituted derivatives in efforts to find efficient agents to be screened for possible CNS stimulant, analgesic, or antispasmodic activity. The aminoketones (Mannich bases) were converted to the γ-amino secondary alcohols by treatment with sodium borohydride. The synthesis of a series of γ-amino tertiary alcohols was achieved by the application of the Grignard reaction to the corresponding Mannich bases. The last section of the study involved the preparation of γ-amino alkyl esters from the corresponding secondary and tertiary alcohols.

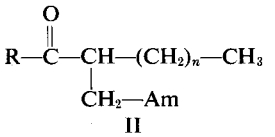
Keyphrases □ Chemotherapeutic agents—aralkyl ketone derivatives, synthesis □ Aralkyl ketone derivatives—synthesis, structure–activity relationships □ Mannich reaction—synthesis □ Grignard reaction—synthesis

The significant action of pyrovalerone hydrochloride (I) as a CNS stimulant has been reported (1):



I

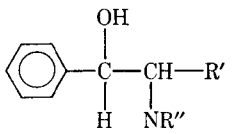
In view of this activity, the authors undertook the synthesis and study of aminoketones having the following structure (II):



II

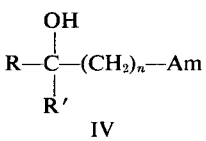
Am = substituted amino group
R = aryl group or substituted aryl group
n = 2,3

To investigate a possible structure–activity relationship, a number of analogs and derivatives were prepared. Recorded in the literature (2–5) are numerous ketonic Mannich bases prepared for pharmacological testing, such as antispasmodic, analgesic, local anesthetic, or chemotherapeutic agents. From the correlation of the chemical structure of these ketones with their antispasmodic activities, the following conclusions were drawn: (*a*) Activity is enhanced by the introduction of a phenyl group into the α-position of the propiophenones. (*b*) The piperidyl group was the most active amino group, while the morpholino group was the least active amino moiety. (*c*) Simple substituents in the *p*-position of the aromatic rings of the propiophenones decreased activity (5). Since some of the structural modifications in these various ketones had an effect on the physiological activity, the transformation of the ketones to the corresponding alcohols might possibly have a greater effect; also the amino alcohols are generally much more stable than the corresponding ketones (6). Lutz *et al.* (7) have reported the preparation and screening of 184 amino alcohols against avian malaria. The general structure (III) of the secondary alcohols is represented as follows:



III

These compounds included examples of 50 variations in the benzene nucleus and over 60 variations in the *N*,*N*-dialkyl groups on the nitrogen. The change in activity with variation in chemical structure led Denton *et al.* (8) to prepare more than 100 γ-amino tertiary alcohols; a majority of them have exhibited pharmacological activity. The general structure (IV) of the amino tertiary alcohols prepared by these workers is reported as follows:



IV

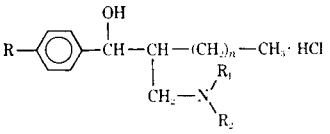


Table I—γ-Amino Secondary Alcohols (Hydrochloride Salts)

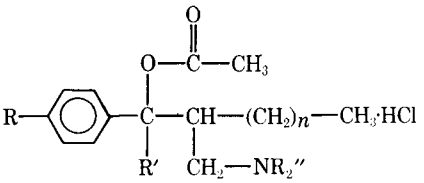
No.[a]	R	NR_1R_2	n	Yield, %	M.p.[b]	Formula	Anal.[c] Calcd.	Anal.[c] Found
1	Hydrogen	1-Methyl piperazino	2	75	233–235°	$C_{17}H_{30}Cl_2N_2O$	C, 56.97 H, 8.71 N, 7.81	C, 56.87 H, 8.79 N, 7.48
2	Methyl	Morpholino	2	77	175°	$C_{17}H_{28}ClNO_2$	C, 65.05 H, 8.98 N, 4.46	C, 64.71 H, 9.08 N, 4.58
3	Methyl	1-Methyl piperazino	3	59	235°	$C_{19}H_{34}ClN_2O$	C, 60.19 H, 9.07 N, 7.42	C, 59.95 H, 9.10 N, 7.15
4	Methoxy	Piperidino	2	77	193°	$C_{18}H_{30}ClNO_2$	C, 65.92 H, 9.22 N, 4.27	C, 65.93 H, 9.08 N, 4.43
5	Hydrogen	Dimethyl amino	2	52	168°	$C_{16}H_{24}ClNO$	C, 65.23 H, 9.38 N, 5.42	C, 64.92 H, 9.53 N, 5.66
6	Methoxy	Morpholino	2	66	190°	$C_{17}H_{28}ClNO_3$	C, 61.89 H, 8.55 N, 4.24	C, 61.61 H, 8.48 N, 4.36

[a] All the γ-amino secondary alcohols in this table were recrystallized from ethanol or ethanol–ethyl acetate solution. [b] All melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Alfred Bernhardt, 433, Mulheim (Ruhr), West Germany.

where R is usually aryl; R′ is alkyl, cycloalkyl, or aryl; and the amino group is, most commonly, dimethyl amino, pyrrolidino, piperidino, and morpholino.

Compounds in which $n = 1$ or 3 usually showed reduced antispasmodic activity. The compound trihexyphenidyl hydrochloride (Artane, Lederle Laboratories), prepared by Cunningham (9), was found to be a potent antispasmodic. The pyrrolidine homolog (Kemadrin, Burroughs Wellcome & Co.) was prepared by an analogous procedure. In large doses, these compounds stimulated the CNS in a manner similar to that of atropine.

A number of esters of 4-dialkyl amino-1,2-diphenylbutanol have been reported to possess a high order of analgesic activity in animals (10). One of these isomers, dextropropoxyphene (Darvon, Eli Lilly and Co.), has been found to be an effective analgesic in human beings (11). In view of these studies, the authors decided to prepare some related open-chain esters. The general structure (V) of the aminoalkyl esters is represented as follows:



V

DISCUSSION

The first group of compounds described in this research is related to the CNS stimulant pyrovalerone hydrochloride, Compound I; the structures described in Tables I–III represent, in a general way, the variations applied to the antispasmodic and analgesic agents. In any event, the analogy of pyrovalerone hydrochloride to Type II compounds does not seem remote. Upon inspection of molecular models, certain points of resemblance stand out and the spatial similarity of pyrovalerone hydrochloride becomes

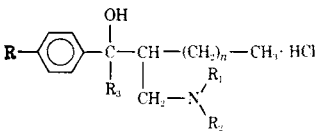


Table II—γ-Amino Tertiary Alcohols (Hydrochloride Salts)

No.[a]	R	NR_1R_2	R_3	n	Yield, %	M.p.[b]	Formula	Anal.[c] Calcd.	Anal.[c] Found
1	Hydrogen	1-Methyl piperazino	Methyl	2	42	220°	$C_{18}H_{32}Cl_2N_2O$	C, 59.49 H, 8.88	C, 59.27 H, 9.24
2	Methyl	Pyrrolidino	Ethyl	2	50	205°	$C_{19}H_{32}ClNO$	C, 66.91 H, 9.89 N, 4.29	C, 66.82 H, 9.92 N, 4.33
3	Hydrogen	Pyrrolidino	Ethyl	2	50	203°	$C_{18}H_{30}ClNO$	C, 69.41 H, 9.71 N, 4.49	C, 69.27 H, 9.75 N, 4.27
4	Methyl	Dimethyl amino	Benzyl	2	21.4	243°	$C_{22}H_{32}ClNO$	C, 73.12 H, 8.64 N, 3.84	C, 72.84 H, 8.98 N, 3.96

[a] All the γ-amino tertiary alcohols in this table were recrystallized from ethanol–ethyl acetate, methanol–ethyl acetate, and benzene solutions. [b] All the melting points are uncorrected. [c] The carbon, hydrogen, nitrogen analyses are through the courtesy of Dr. Alfred Bernhardt, 433, Mulheim (Ruhr), West Germany.

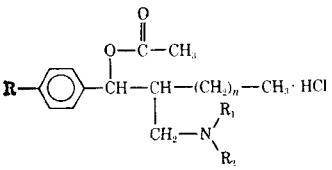


Table III—γ-Aminoalkyl Esters (Hydrochloride Salts)

No.[a]	R	NR_1R_2	*n*	Yield, %	M.p.[b]	Formula	Anal.[c] Calcd.	Anal.[c] Found
1	Hydrogen	Dimethyl amino	2	71	237.5°	$C_{16}H_{26}ClNO$	C, 64.04 H, 8.73 N, 4.60	C, 63.71 H, 8.54 N, 4.86
2	Hydrogen	1-Methyl piperazino	2	40	220°	$C_{19}H_{32}Cl_2N_2O_2$	C, 57.11 H, 8.07 N, 7.01	C, 56.83 H, 8.35 N, 7.02
3	Methyl	1-Methyl piperazino	2	75	208°	$C_{20}H_{34}Cl_2N_2O_2$	C, 56.86 H, 8.35 N, 6.63	C, 56.63 H, 8.47 N, 6.42
4	Methyl	Morpholino	3	55	135–136°	$C_{20}H_{32}ClNO_3$	C, 64.77 H, 8.94 N, 3.77	C, 64.70 H, 8.56 N, 4.01
5	Methyl	1-Methyl piperazino	3	48	193–194°	$C_{21}H_{36}Cl_2N_2O_2$	C, 55.57 H, 8.44 N, 6.17	C, 55.56 H, 8.81 N, 6.42

[a] All the γ-aminoalkyl esters in this table were recrystallized from methanol–ethyl acetate and ethanol–ethyl acetate solutions. [b] All melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Alfred Bernhardt, 433, Mulheim (Ruhr), West Germany.

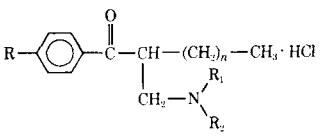


Table IV—β-Amino Ketones (Hydrochloride Salts)

No.[a]	R	NR_1R_2	*n*	Method	Yield, %	M.p.[b]	Formula	Anal.[c] Calcd.	Anal.[c] Found
1	Hydrogen	Dimethyl amino	2	A	22	159–160°	$C_{14}H_{22}ClNO$	C, 63.50 H, 8.74	C, 63.62 H, 8.84
2	Hydrogen	Pyrrolidino	2	B	21	139–140°	$C_{16}H_{24}ClNO$	C, 68.86 H, 8.54 N, 4.96	C, 69.03 H, 8.66 N, 4.92
3	Hydrogen	1-Methyl piperazino	2	B	40	198–200°	$C_{17}H_{28}Cl_2NO$	C, 58.78 H, 8.11 N, 8.11	C, 58.77 H, 8.27 N, 8.46
4	Methyl	Morpholino	2	A,B	55	170–171°	$C_{17}H_{26}ClNO_2$	C, 65.42 H, 8.40 N, 4.50	C, 65.26 H, 8.61 N, 4.68
5	Methyl	Piperidino	2	A,B	22	158–160°	$C_{18}H_{28}ClNO$	C, 67.76 H, 8.85 N, 4.38	C, 67.78 H, 9.04 N, 4.30
6	Methyl	Pyrrolidino	2	B	20	178–180°	$C_{17}H_{26}ClNO$	C, 66.97 H, 8.46 N, 4.59	C, 67.24 H, 8.85 N, 4.82
7	Methyl	1-Methyl piperazino	2	B	48	191–193°	$C_{18}H_{30}Cl_2N_2O$	C, 56.70 H, 8.82 N, 7.71	C, 56.75 H, 8.70 N, 7.79
8	Hydrogen	Dimethyl amino	3	A	11.5	130–131°	$C_{15}H_{24}ClNO$	C, 66.31 H, 8.96 N, 5.18	C, 66.62 H, 8.84 N, 5.34
9	Methyl	Dimethyl amino	3	A	50	142–143°	$C_{16}H_{26}ClNO$	C, 66.70 H, 9.18 N, 4.82	C, 66.71 H, 9.34 N, 5.22
10	Methyl	Morpholino	3	B	76	170°	$C_{18}H_{28}ClNO_2$	C, 66.34 H, 8.66 N, 4.29	C, 66.11 H, 8.49 N, 4.70
11	Methyl	1-Methyl piperazino	3	B	34	188–190°	$C_{19}H_{32}Cl_2N_2O$	C, 58.08 H, 8.71 N, 7.41	C, 58.27 H, 8.72 N, 7.11
12	Hydroxy	Morpholino	2	B	66	180°	$C_{16}H_{24}ClNO_3$	C, 58.90 H, 7.73 N, 4.30	C, 59.03 H, 7.78 N, 4.73
13	Hydroxy	Piperidino	2	B	65	153–154°	$C_{17}H_{20}ClNO_2$	C, 65.26 H, 9.93 N, 4.47	C, 64.86 H, 8.69 N, 4.79

[a] All the Mannich bases in this table were recrystallized from ethanol–ethyl acetate, ethanol–ether, and benzene solutions. [b] All the melting points are uncorrected. [c] The carbon, hydrogen, nitrogen analyses are through the courtesy of Dr. Alfred Bernhardt, 433, Mulheim (Ruhr), West Germany.

apparent. 2-(1-Pyrrolidino methyl)-4′-methyl valerophenone hydrochloride (Compound 6, Table IV) bears a strong resemblance to pyrovalerone hydrochloride. A practical variation of this compound in which the methyl group on the aromatic nucleus was replaced by a methoxy group and also the introduction of an acetoxy methyl in place of the carbonyl group in the alkyl chain has been devised. The acetoxy group may help in favorably altering the distribution of the compound in the animal body and also in increasing the concentrations in the brain. Moreover, such a change as the replacement of the pyrrolidino group by the morpholino group may be effective for the increased activity, possibly because of a certain attraction between the cation head and the unshared pair of electrons on oxygen. The reduction of the keto group to the carbinols may show parallel results, the latter being more stable to the biological reactions.

Aralkyl ketones (valerophenone and caprophenone) and their substituted derivatives were prepared as indicated in the *Experimental* section. The Mannich bases and the corresponding secondary and tertiary alcohols were obtained by modifying the methods in the literature (12–14). The preparation of aminoalkyl esters was patterned after the work of Burckhalter and Johnson (15) and that of Pohland and Sullivan (10). A number of procedures (15–17) and their modifications were attempted to bring about the successful esterification of the tertiary amino alcohols. Each attempt met with failure. An examination of the IR spectrum of each reaction product did not reveal the presence of the characteristic alkyl ester absorption in the region of 1735–1750 $cm.^{-1}$, indicating no reaction had taken place. Similar difficulties in obtaining the acyl derivatives of tertiary amino alcohols have been recorded (13, 18), one of the possible explanations for the failure to bring about this esterification being steric inhibition.

EXPERIMENTAL

Aralkyl ketones were prepared according to the methods described in the literature (19–21).

***p*-Methyl Caprophenone**—Eighty grams (0.06 mole) of *n*-hexanoyl chloride was gradually added to a mixture of 184.0 g. (2.0 moles) of dry toluene and the 131.0 g. (1.0 mole) of powdered anhydrous aluminum chloride. The reaction mixture was stirred for 12 hr. at room temperature and thereafter refluxed for 3 hr. The dark-colored reaction mixture was cooled and then decomposed in a solution of ice and concentrated HCl. The organic layer was separated and washed with 10% NaOH and water, respectively. The product was dried over anhydrous $MgSO_4$ and distilled at 280°. Redistillation yielded 70.0 g. (40%) of a clear liquid, b.p. 280°.

Anal.—Calcd. for $C_{13}H_{18}O$: C, 82.01; H, 9.58. Found: C, 82.13; H, 9.41.

Mannich Bases—Three methods were investigated; Procedure A, as will be noted, was the general method for the preparation of the compounds in Table IV.

2-(1-Pyrrolidinomethyl)-valerophenone Hydrochloride—*Method A*—A solution of 3.35 g. (0.05 mole) of pyrrolidine in 50 ml. of absolute alcohol was cooled and treated with concentrated HCl until the final solution was acidic. Valerophenone (8.10 g., 0.05 mole) and paraformaldehyde (1.80 g., 0.05 mole) were then added and the reaction mixture was refluxed for 8 hr. Two further additions (0.90 g., 0.03 mole) of paraformaldehyde were also made. The solvent was distilled *in vacuo*, and the residue was treated with 30 ml. of water and extracted with ether. The ether portion was discarded. The aqueous layer was made alkaline with 30% NH_4OH and ether extracted. The ether portion was washed with water, dried over anhydrous $MgSO_4$, and treated with gaseous HCl, producing an oil. The oil solidified after refrigeration for 48 hr. Recrystallization from benzene yielded 3.0 g. (21%) of white crystals, m.p. 139–140°.

γ-Amino Secondary Alcohols—2-(1-Morpholinomethyl)-1-(4-methylphenyl)-1-pentan-1-ol Hydrochloride—A solution of 1.10 g. (0.03 mole) of sodium borohydride in 100 ml. of 50% MeOH was cooled to 20°. To this was added gradually a solution of 8.25 g. (0.03 mole) of 2-(1-morpholinomethyl)-4-methylvalerophenone in 50% MeOH with stirring for several hours. The temperature was then raised to 50–60° to decompose excess sodium borohydride. The solvent was distilled *in vacuo*. The residue was dissolved in ether and washed with 50-ml. portions of water. The ether portion was dried ($MgSO_4$) and treated with gaseous HCl, producing a solid product. Recrystallization of HCl salt from ethanol–ethyl acetate mixture yielded 7.0 g. (77%) of product, m.p. 175°.

γ-Amino Tertiary Alcohols—2-(1-Piperidinomethyl)-1,1-Diphenylhexan-1-ol Hydrochloride—This preparation was chosen as a representative of all the Grignard reactions reported in this research. To a solution of 0.06 mole of phenyl magnesium bromide in 100 ml. dry ether was gradually added 5.36 g. (0.02 mole) of 2-(1-piperidinomethyl)caprophenone. The reaction mixture was stirred overnight. The mixture was then decomposed by the dropwise addition of a saturated ammonium chloride solution; the temperature was regulated with an ice bath. The ether solution was decanted from the granular material, and the solid material was washed with 50 ml. of ether. The combined ether solutions were dried ($MgSO_4$) and treated with gaseous HCl, producing a sticky mass which solidified after refrigeration for 24 hr. Recrystallization from methanol–ethyl acetate mixture yielded 3.5 g. (42%) of product, m.p. 210–211°.

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