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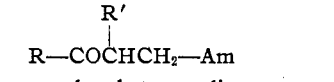
Antispasmodics. I. Substituted β-Amino Ketones

BY J. J. DENTON, R. J. TURNER, W. B. NEIER, VIRGINIA A. LAWSON AND H. P. SCHEDL

Recorded in the literature are numerous synthetic analogs of atropine and papaverine, prepared for pharmacological testing as antispasmodic agents. Of these two types, atropine analogs, basic esters of carboxylic acids, seem the more important and therefore have received more attention from workers in this field.

Recognizing the disadvantage of these compounds in medical use due to the instability of the ester grouping to hydrolytic conditions, we became interested in the preparation of compounds with antispasmodic activity but having no ester group.

Certain substituted β-aminoalkyl aryl ketones have been reported to show antispasmodic action, but the quantitative pharmacological evaluation and the correlation of antispasmodic activity with chemical structure appear to be lacking. We therefore undertook the synthesis and study of the basic ketones having almost exclusively the general structure



R is an aryl or heterocyclic group
R′ is a hydrogen or phenyl group
Am is a substituted amino group

Substituted β-amino ketones of this type may most readily be prepared by means of the Mannich reaction, the literature of which has been reviewed recently by Blicke.[1] Of all the starting ketones which we have utilized in the Mannich reaction, only one, 6-acetyl-1,4-benzodioxane, has not been thoroughly described in the literature.

An acetyl-1,4-benzodioxane[2] has been mentioned, but the position of the acetyl group was not definitely stated. By means of a Friedel–Crafts reaction on 1,4-benzodioxane we have prepared 6-acetyl-1,4-benzodioxane. The position of the acetyl group was established by oxidation of this ketone, according to the method of Kröhnke,[3] to 1,4-benzodioxane-6-carboxylic acid, a compound prepared by Fittig and Macalpine[4] and later by Gattermann.[5]

Table I gives the substituted β-amino ketones prepared in this study. A superscript in the name column of this table refers to a previous preparation of this compound in the literature, while a capital letter in the procedure column refers to our own preparation in the experimental part. Where both reference and procedure are given for any compound, a difference in physical properties between the compound which we have prepared and that disclosed in the literature is indicated.

Pharmacological Activity

The antispasmodic activity, recorded in the table, is based on the relaxing action of the compound on a section of an isolated rabbit intestine made spastic with furfuryltrimethylammonium iodide (Furmethide) and is graded in a quantitative manner by allowing four plus to represent the greatest activity and a minus to indicate only slight or no activity. β-Diethylaminoethyl diphenylacetate hydrochloride (Trasentin) and papaverine hydrochloride have been included at the end of the table for the sake of comparison. For the determination of the pharmacological activity of these compounds, we wish to express our great indebtedness to Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants of the Pharmacology Department of the Lederle Laboratories Division. A detailed discussion of the antispasmodic testing method by which the activity was determined will be published[6] elsewhere.

In Table I it is interesting to note the changes in antispasmodic activity which result from variations within the general structure of these substituted amino ketones. The most effective amino group in this series of compounds is the piperidyl group. It is outstanding in the propiophenones having no ring or side-chain substituents (I-VI) as well as in the thenoyl compounds (XXIX-XXXI), and it is as effective as any other amino group in the propionaphthones (XX-XXVI). Morpholinyl derivatives are, in general, the least active.

The introduction of substituents into the aromatic-ring of the propiophenones (IV-XIX) decreased the antispasmodic activity, except in Compound XVIII.

The addition of a phenyl group to the side chain had no effect on the activity in the dimethylamino compound (XXXIII) or in the piperidyl compound (XXXIV), as compared with compounds I and III, respectively; while this same transformation resulted in an increase in activity in the morpholinyl compound (XXXV).

Six of the thirty-seven substituted amino ketones equalled β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin) in antispasmodic rating; these were Compounds III, VII, XXX, XXXIV, XXXV and XXXVII.

The antispasmodic activity, itself, and the changes in activity with the above variations in chemical structure interested us in studying further transformations on this structure. These studies will be reported in subsequent publications.

(1) F. F. Blicke, in Adams, "Organic Reactions," Vol. I, John Wiley Sons, Inc., New York, N. Y., 1942, p. 303.
(2) Martin, Hirt and Meracher, U. S. Patent 2,383,874 (1945).
(3) Kröhnke, *Ber.*, **66**, 604 (1933).
(4) Fittig and Macalpine, *Ann.*, **168**, 99 (1873).
(5) Gattermann, *ibid.*, **357**, 374 (1907).
(6) Cunningham, Harned, *et al.*, in press.

TABLE I

Number	Hydrochlorides	Activity
	Propiophenone	
I	β-Dimethylamino-[11]	+
II	β-Diethylamino-[7]	+
III	β-(1-Piperidyl)-[12]	++
IV	β-(4-Morpholinyl)-[9]	−
V	β-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-[12]	+
VI	β-[1-(4-Methylpiperazyl)]-	+
VII	β,β′-Methylimino-bis-[7,11]	++
IX	β-(1-Piperidyl)-4-chloro-	−
X	β-(1-Piperidyl)-4-bromo-	+
XI	β-(1-Piperidyl)-4-methyl-	+
XII	β-(4-Morpholinyl)-4-methyl-	−
XIII	β-(1-Piperidyl)-4-ethyl-	+
XIV	β-(1-Piperidyl)-4-methoxy-[12]	−
XV	β-(1-Piperidyl)-3,4-methylenedioxy-	+
XVI	β-(1-Piperidyl)-3,4-dimethoxy-[12]	−
XIX	β-(1-Piperidyl)-4-acetamido-	−
XXXIII	β-Dimethylamino-α-phenyl-	+
XXXIV	β-(1-Piperidyl)-α-phenyl-[12]	++
XXXV	β-(4-Morpholinyl)-α-phenyl-	++
	1,4-Benzodioxane	
XVII	6-(β-(1-Piperidyl)-propionyl)-	+
XVIII	6-[β-(4-Morpholinyl)-propionyl]-	+
	Propionaphthone	
XX	β-Dimethylamino-2-[8]	+
XXI	β-Diethylamino-2-	+
XXII	β-(1-Piperidyl)-1-	+
XXIII	β-(1-Piperidyl)-2-[8]	+
XXIV	β-(4-Morpholinyl)-1-	−
XXV	β-(4-Morpholinyl)-2-	−
XXVI	β-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-2-	+
XXVII	β-(1-Piperidyl)-4-chloro-1-	+
XXVIII	β-(4-Morpholinyl)-4-chloro-1-	+
	Miscellaneous	
VIII	1,4-bis-(2-Benzoylethyl)-piperazine[12]	−
XXIX	2-(2-Thenoyl)-ethyldimethylamine[7,10]	−
XXX	1-[2-(2-Thenoyl)-ethyl]-piperidine[7,10]	++
XXXI	4-[2-(2-Thenoyl)-ethyl]-morpholine[9]	−
XXXII	2,4-Dimethyl-5-(β-(1-piperidyl)-propionyl) pyrimidine	−
XXXVI	bis-(1-Piperidylmethyl)-methyl-3-pyridyl ketone	−
XXXVII	β,β′-bis-(1-Piperidyl)-pivalophenone	++
	β-Diethylaminoethyl diphenyla etate (Trasentin)	++
	Papaverine	+

	Formula	M. p.,[a] °C.	Yield,[b] %	Procedure	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
VI	$C_{14}H_{20}N_2O\cdot 2HCl\cdot 0.75H_2O$	187.1–188.5 dec.	15.7	A	55.81[c]	55.6	8.49	8.5	8.14	8.15	25.9	26.0
IX	$C_{14}H_{18}ClNO\cdot HCl$	186.0–187.2	18.8	B	58.34	58.1	6.65	6.64	4.86	4.89	24.60	24.6
X	$C_{14}H_{18}BrNO\cdot HCl$	206.0–207.5	62.0	B	50.9[d]	50.7	5.8	6.0	4.24	4.42	10.74	10.7
XA[e]	$C_{14}H_{18}BrNO$	52.3–54.1			56.76[f]	56.5	6.12	6.21	4.76	4.59		
XI	$C_{15}H_{21}NO\cdot HCl$	171.3–172.5	46.6	A	67.26	67.2	8.28	8.40	5.23	5.13	13.24	13.2
XII	$C_{14}H_{19}NO_2\cdot HCl$	224.3[g]	69.0	A	62.33	62.3	7.47	7.62	5.19	5.24	13.14	13.3
XIII	$C_{16}H_{23}NO\cdot HCl$	177.9–178.8	45.5	A	68.19	68.3	8.58	8.85	4.97	4.97	12.58	12.7
XV	$C_{15}H_{19}NO_3\cdot HCl\cdot 0.5H_2O$	212.0–212.8	39.3	A	58.6[h]	58.5	6.89	7.06	4.56	4.72	11.56	11.6
XVII	$C_{16}H_{21}NO_3\cdot HCl\cdot 0.5H_2O$	219.5–220.0	41.0	A	59.9[i]	60.1	7.2	7.19	4.36	4.19	11.09	11.1
XVIII	$C_{15}H_{19}NO_4\cdot HCl$	218.1–219.0	52.2	A	57.4	57.2	6.43	6.18	4.47	4.57	11.31	11.3
XIX	$C_{16}H_{22}N_2O_2\cdot HCl$	263.5[j]	28.3	A	61.83	61.6	7.46	7.69	9.01	9 25	11.41	11.3
XX	$C_{15}H_{17}NO\cdot HCl\cdot H_2O$	165.0–166.0	51.0	B	63.8[k]	63.3	7.12	7.05	4.96	5.51	12.59	12.9
XXI	$C_{17}H_{21}NO\cdot HCl$	146.5–147.9	23.5	B	69.97	70.1	7.60	7.76	4.80	4.99	12.15	12.3
XXII	$C_{18}H_{21}NO\cdot HCl$	181.8–182.5	28.2	B	71.15	71.1	7.30	7.34	4.61	4.66	11.67	11.7
XXIII	$C_{18}H_{21}NO\cdot HCl$	194.6–195.0	63.0	B	71.15	71.2	7.30	7.19	4.61	4.56	11.67	11.8
XXIV	$C_{17}H_{19}NO_2\cdot HCl$	164.7–167.3	28.5	B	66.77	66.9	6.59	6.44	4.56	4.63	11.59	11.6
XXV	$C_{17}H_{19}NO_2\cdot HCl$	197.7–198.2	51.5	B	66.77	66.5	6.59	6.51	4.58	4.62	11.59	11.8
XXVI	$C_{22}H_{21}NO\cdot HCl$	201.2–202.0	34.6	B	75.09	74.8	6.30	6.25	3.98	4.02	10.08	10.3
XXVII	$C_{18}H_{20}ClNO\cdot HCl$	183–185	54.0	C	63.91	63.6	6.26	6.41	4.14	4.35	20.96	20.6
XXVIII	$C_{17}H_{18}ClNO_2\cdot HCl$	181–183	47.0	C	58.87[l]	58.5	5.52	5.79	4.04	4.22	20.45	21.0
XXXII	$C_{14}H_{21}N_3O\cdot HCl$	148.0–148.8	5.2	A	59.4	59.1	7.76	8.00	14.8	14.9	12.5	12.6
XXXIII	$C_{17}H_{19}NO\cdot HCl$	157.2–158.5	49.6	D	70.28[m]	70.0	6.97	7.00	4.82	4.90	12.21	12.1
XXXV	$C_{19}H_{21}NO_2\cdot HCl$	166.8–167.0	50.1	D	68.77	68.8	6.68	6.77	4.22	4.32	10.69	10.7
XXXVA[e]	$C_{19}H_{21}NO_2$	125.0–125.5			77.26	77.0	7.17	7.26	4.74	4.84		
XXXVI	$C_{19}H_{29}N_3O\cdot 2HCl$	125–206 dec.		D							18.2	18.5
XXXVIA[e]	$C_{19}H_{29}N_3O$	82.3–83.3	68		72.33	72.2	9.26	9.3	13.32	12.9		
XXXVII	$C_{21}H_{32}N_2O\cdot 2HCl$	169.0–170.0	43.0	A	62.84	62.2	8.54	8.8	6.98	6.85	17.66	17.2

[a] All melting points are corrected. [b] Yields refer to pure hydrochlorides and are based on starting ketones. [c] Calcd. H_2O, 2.62; found (by Karl Fischer method), 2.84. [d] Calcd. Br, 24.2; found, 24.3. [e] Refers to free amine corresponding to preceding hydrochloride. [f] Calcd. Br, 26.98; found, 26.4. [g] Decomposed in approx. ten seconds when inserted in bath at 224.3°. [h] Calcd. H_2O, 2.93; found (by Karl Fischer method), 2.97. [i] Calcd. H_2O, 2.8; found (by Karl Fischer method), 2.8. [j] Melted in approx. ten seconds when immersed in bath at 263.5°. [k] Calcd. H_2O, 6.4; found (by Karl Fischer method), 6.3. [l] Karl Fischer moisture determination showed presence of 1.9% water. Calculations are based on this amount of water. [m] Calculations are based on a Karl Fischer moisture analysis showing presence of 0.25% water.

(7) Blicke and Burckhalter, THIS JOURNAL, **64**, 451 (1942).
(8) Blicke and Maxwell, *ibid.*, **64**, 428 (1942).
(9) Haradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).
(10) Levvy and Nisbet, *J. Chem. Soc.*, 1053 (1938).
(11) Mannich and Heilner, *Ber.*, **55**, 356 (1922).
(12) Mannich and Lammering, *ibid.*, **55**, 3510 (1922).

Experimental

Procedure A.—A mixture of molar proportions of amine hydrochloride and ketone, 1.5 moles of paraformaldehyde and a slight excess of hydrogen chloride was refluxed in ethanol for one to two hours. An additional one-mole portion of paraformaldehyde was then added, and refluxing

was continued for two to four hours. Where the product crystallized well from the cooled reaction mixture, it was collected on a filter and dried. More soluble products were precipitated by the addition of ether, acetone or isopropyl acetate.

Procedure B.—A mixture of molar proportions of amine hydrochloride and ketone, 1.1 moles of paraformaldehyde, and a slight excess of hydrogen chloride was refluxed in mixed amyl alcohols (Pentasol) for two to four hours. The product was isolated as in procedure A.

Procedure C.—This method is essentially that of Winstein and co-workers.[13] The reaction times were held to a minimum.

Procedure D.—One mole of formaldehyde (35% aqueous solution) was added dropwise to one mole of amine in dilute ethanol at 5–10°. The stirred mixture was allowed to warm to room temperature over a period of about one hour. One mole of the ketone was added. After one hour, the stirred reaction mixture was refluxed for one to four and one-half hours. Dilution with water caused precipitation of the amino ketone as a solid. It was collected, dried and converted to its hydrochloride.

6-Acetyl-1,4-benzodioxane.—To a flask equipped with stirrer, dropping funnel and condenser, were added 200 g. (1.5 moles) of aluminum chloride and 800 cc. of carbon disulfide. A mixture of 136 g. (1 mole) of 1,4-benzodioxane and 105 g. (1.34 moles) of acetyl chloride was added dropwise with stirring over a period of two hours. After the addition was completed, the reaction mixture was heated under reflux for four hours. The carbon disulfide was then removed by distillation, and the residue decomposed with ice and water. The solid which formed was collected on a filter and washed thoroughly with water. After one recrystallization from dilute alcohol, the light tan material weighed 152 g. (85.5% of the theory); m. p. 78–81°. Further recrystallization from alcohol gave the product in the form of colorless plates; m. p. 84–85°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.62. Found: C, 67.5; H, 5.69.

(13) Winstein, Jacobs, Seymour and Linden, *J. Org. Chem.*, **11**, 218 (1946).

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Summary

1. Thirty-seven substituted β-aminoalkyl aryl and heterocyclic ketones, of which twenty-two are new compounds, have been prepared by means of the Mannich reaction.

2. Correlation of the chemical structures of the above ketones with their antispasmodic activities has shown the following to be generally true: (a) Substituted β-aminopropiophenones and propionaphthones are active; (b) the piperidyl group is the most effective while the morpholinyl group is the least effective amino group; (c) simple substituents in the para-positions of the aromatic rings of the propiophenones decrease the activity; (d) enhancement of activity results from the introduction of a phenyl group into the α-position of only some of these propiophenones.

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Antispasmodics. II. Tertiary β-Amino Alcohols

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In the first paper of this series,[1] it was shown that several substituted β-amino ketones exhibited interesting antispasmodic activity. Since some of the structural modifications reported in that paper had an effect on the activity, it was considered that the transformation of these ketones to alcohols, principally tertiary alcohols, might possibly have a greater effect. The synthesis and study of a number of tertiary amino alcohols having generally the following structure were therefore undertaken:

$RR'C(OH)CH(R'')CH_2Am$
R is an aryl or heterocyclic group
R′ is an alkyl or phenyl group
R″ is hydrogen, a methyl, or phenyl group
Am is a tertiary amino group

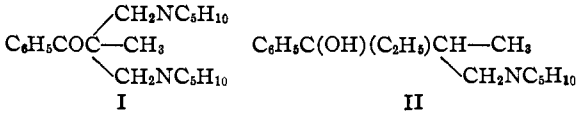
This paper deals principally with certain variations in R, recorded in Table A, and in R″, recorded in Table B.

We have prepared these tertiary alcohols by the addition of a Grignard reagent to some of the substituted β-amino ketones previously reported,[1] according to the reaction

$$RCOCH(R'')CH_2Am \xrightarrow{R'MgX} RR'C(OH)CH(R'')CH_2Am$$

During the course of this work, other investigators[2] have reported the preparation of compounds of the same general formula by the above method. In using this method we have obtained the expected tertiary alcohol from every ketone except one.

Treatment of β,β′-bis-(1-piperidyl)-pivalophenone (I) with an excess of ethylmagnesium bromide did not give the expected tertiary alcohol which would result from the simple addition of the Grignard reagent. Instead it gave 1-(1-piperidyl)-2-methyl-3-phenyl-3-pentanol (II), a tertiary alcohol lacking one of the piperidylmethyl groups originally present in the ketone (I).



I II

(1) Denton, Turner, Neier, Lawson and Schedl, THIS JOURNAL, **71**, 2048 (1949).

(2) (a) Spaeth, Geissman and Jacobs, *J. Org. Chem.*, **11**, 399 (1946). (b) Ruddy and Buckley, Abstracts of Papers, 110th Meeting, A. C. S., Sept. 1946, p. 14K. (c) Becker, Ananenko, Glenwood and Miller, *Federation Proc.*, **5**, 163 (1946). (d) Kleiderer, Rice, Conquest and Williams, Report No. PB-981, Office of the Publication Board, Dept. of Commerce, Washington, 1945, p. 38.