Synthesis and Antibacterial Activity of Certain β-Aminoketones

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A series of β-aminoketones has been synthesized under the conditions of the Mannich reaction. Most of the compounds have exhibited antibacterial activity.

β-AMINOKETONES (Mannich bases) have been synthesized and screened as antispasmodics, local anesthetics, analgesics, and antibacterial agents (1–11). In a recent article from this laboratory the authors described the synthesis of a group of β-aminoketones derived from 1-(*N*-β-hydroxyethyl-4-piperidyl)-3-(4-piperidyl) propane (12). Several of these compounds have exhibited antibacterial and antiviral activity (13). In this communication the synthesis and antibacterial activity of β-aminoketones obtained from 4-(3-phenylpropyl)-piperidine is described.

BIOLOGICAL DATA

The β-aminoketones listed in Table I were screened *in vitro* against four organisms: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Mycobacterium smegmatis*, and *Klebsiella pneumoniae* by agar diffusion technique. Filter paper disks (6.35 mm. diameter) saturated with the solution (20 mg./ml.) of the test compound were placed on the agar. After 72 hr. of incubation, the zones of inhibition around the disks were measured. The results are recorded in Table I. A negative sign indicates no observable inhibition.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were observed on a Perkin-Elmer model 137 spectrophotometer in Nujol mull. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

β-Aminoketone Hydrochlorides—*Procedure A*—4-Phenylpropylpiperidine (5.07 Gm.; 0.025 mole) was dissolved in 5 ml. of ethanol. To this solution concentrated hydrochloric acid (2.5 ml.) was added followed by 5 ml. of 37% formalin and 0.025 mole of the appropriate ketone. The resulting reaction mixture was refluxed for 4 hr. At the end of this period some solvent was evaporated under vacuum. The contents were then diluted with 50 ml. of acetone. Refrigeration of the contents yielded the desired product.

Procedure B—A mixture of 0.025 mole of 4-(3-phenylpropyl)piperidine hydrochloride, 0.025 mole of the ketone, and 1 Gm. of paraformaldehyde in 10 ml. of ethanol containing two drops of concentrated hydrochloric acid was heated under reflux for 2 hr. Another 0.5 Gm. of paraformaldehyde was added, and the refluxing continued for 3 hr. At the end of this period the contents were poured into 50 ml. of acetone, after removing some solvent. The product obtained after overnight refrigeration was recrystallized from a suitable solvent.

4-Phenylpropylpiperidinoethyl-4-bromophenylcarbinol Hydrochloride (Compound 14)—β-4-(3-Phenylpropyl)-piperidine-4-bromopropiophenone hydrochloride (13.5 Gm., 0.03 mole) was neutralized with 10% aqueous sodium hydroxide with cooling. The product obtained was filtered and washed thoroughly with cold water until washings were free from alkali. After air drying, the product was suspended in 100 ml. of methanol in a 1-L. flask. Three and eight-tenths grams of sodium borohydride, dissolved in 50 ml. of methanol, was added slowly with stirring. During the additions the temperature was kept below 50°. The reaction mixture was stirred for an additional 2 hr. and then left at room temperature overnight. It was filtered and the filtrate evaporated to dryness under vacuum. Fifty milliliters of water was then added to the residual solid. The resulting mixture was extracted with ether. The extract, after washing with water, drying over magnesium sulfate, and evaporating the ether, yielded a viscous oil which soon solidified. It was dissolved in 10 ml. of ethanol, acidified with concentrated hydrochloric acid, and poured into 100 ml. of acetone. Overnight refrigeration of the acidified solution gave the desired product. An analytical sample was prepared by recrystallizing from ethanol-acetone, m.p. 173–174°; yield, 4.05 Gm. (30%). IR: 3333 cm.$^{-1}$ (OH).

Anal.—Calcd. for $C_{23}H_{31}BrClNO$: C, 61.00; H, 6.90; N, 3.09. Found: C, 61.29; H, 7.14; N, 3.00.

DISCUSSION

4-(3-Phenylpropyl)-piperidine was converted to the hydrochloride salt and condensed with formaldehyde and several substituted ketones. Paraformaldehyde, as well as aqueous formalin, yielded satisfactory products. The Mannich base hydrochlorides were usually isolated from the reaction mixture

TABLE I—ANTIBACTERIAL ACTIVITY OF β-AMINOKETONES: MICROBIAL SPECTRUM

Compound No.[a]	*S. aureus* K257	*P. aeruginosa*	*K. pneumoniae* ATCC 8052	*M. smegmatis*
1	+	+	+	+
2	+	+	−	+
3	−	+	−	−
4	+	+	+	+
5	+	+	+	+
6	+	+	+	+
7	−	−	−	−
8	−	−	+	+
9	−	−	−	−
10	+	+	−	+
11	+	+	+	+
12	−	+	+	+
13	+	+	+	+
14	+	+	+	+

[a] As in Table II. A negative sign indicates no inhibition.

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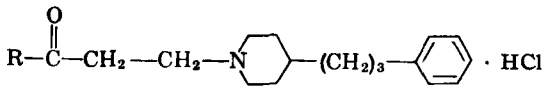
TABLE II—β-AMINOKETONES



Compound No.	R	Formula	% Analysis Calcd.	% Analysis Found	Yield,[a] %	M.p., °C.	Infrared C=O	Infrared +NH
1	Phenyl	$C_{23}H_{30}ClNO$[b]	C, 74.26 H, 8.13 N, 3.77	74.48 8.25 3.76	53	173–174	1685	2475
2	4-Chlorophenyl	$C_{23}H_{29}Cl_2NO$[c]	C, 67.96 H, 7.19 N, 3.45	67.72 7.22 3.47	64	190–192	1680	2450
3	4-Methylphenyl	$C_{24}H_{32}ClNO$[d]	C, 74.66 H, 8.36 N, 3.63	74.47 8.20 3.62	46	190	1680	2450
4	4-Fluorophenyl	$C_{23}H_{29}ClFNO$[d]	C, 70.85 H, 7.50 N, 3.59	70.87 7.68 3.70	44	179–181	1675	2500
5	4-Nitrophenyl	$C_{23}H_{29}ClN_2O_3$[b]	C, 66.25 H, 7.01 N, 6.72	66.12 7.18 6.56	48	175–176	1680	2400
6	4-Ethoxyphenyl	$C_{25}H_{34}ClNO_2$[b]	C, 72.16 H, 8.24 N, 3.37	71.95 8.22 3.41	60	190–191	1670	2530
7	4-Phenylphenyl	$C_{29}H_{34}ClNO$[c]	C, 77.75 H, 7.65 N, 3.13	77.51 7.49 3.15	44	199–200	1670	2500
8	3-Nitrophenyl	$C_{23}H_{29}ClN_2O_3$[d]	C, 66.25 H, 7.01 N, 6.72	66.46 7.25 6.60	40	159–161	1695	2600
9	4-Hydroxyphenyl	$C_{23}H_{30}ClNO_2$[c]	C, 71.20 H, 7.80 N, 3.61	71.49 7.84 3.49	51	208–209	1670	2600
10	3-Hydroxyphenyl	$C_{23}H_{30}ClNO_2$[b]	C, 71.20 H, 7.80 N, 3.61	71.14 7.99 3.50	49	176–178	1690	2600
11	3,4,5-Trimethoxyphenyl	$C_{26}H_{36}ClNO_4$[d]	C, 67.61 H, 7.86 N, 3.03	67.50 8.02 3.04	52	171–172	1665	2400
12	4-Bromophenyl	$C_{23}H_{29}BrClNO$[c]	C, 61.25 H, 6.48 N, 3.11	61.08 6.50 3.09	51	192–193	1695	2500
13	2-Thenyl	$C_{21}H_{28}ClNOS^1/_2H_2O$[b]	C, 65.16 H, 7.55 N, 3.62	65.55 7.72 3.77	33	165–166	1650	2500

[a] Yields are of the products obtained after first recrystallization. [b] Recrystallized from ethanol. [c] Recrystallized from aqueous ethanol–acetone. [d] Recrystallized from ethanol–acetone.

by adding acetone to it and refrigerating overnight. It was observed that while using 4-phenylacetophenone, the best results were obtained when some of the solvent was distilled from the reaction mixture before the addition of acetone. The period required to refrigerate the reaction mixture in order to get a solid product varied considerably. While using 3-nitroacetophenone, a solid product was obtained after 4 days of refrigeration. Prolonged refrigeration resulted in improved yields. The β-aminoketone from 4-bromoacetophenone was reduced to the corresponding γ-amino secondary alcohol by sodium borohydride. Infrared spectra of the β-aminoketones exhibited characteristic absorption bands for carbonyl and $\overset{+}{N}H$ (14). No carbonyl absorption was observed in the infrared spectrum of the aminoalcohol; instead, absorption due to OH group, as expected, was observed.

SUMMARY

Thirteen β-aminoketones have been synthesized using 4-(3-phenylpropyl)-piperidine and several ketones under Mannich reaction conditions. One β-aminoketone (No. 12, Table II) has been reduced to the corresponding γ-amino secondary alcohol by sodium borohydride. Antibacterial activities have been determined for all compounds described herein.

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Keyphrases

β-Aminoketones—synthesis
Antibacterial activity—β-aminoketones
IR spectrophotometry—structure

Influence of Starch Concentration on the Disintegration Time of Tolbutamide Tablets

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Disintegration tests were performed on tablets compressed from 16/20, 40/60, and 60/80 mesh granulations prepared by the method of dry granulation to contain 250 mg. of tolbutamide and corn starch concentrations of 6, 7, 8, 9, and 10 percent in each granulation size. It might be expected that disintegration time would decrease as the percentage of starch in the tablet increased. This does not appear to be the case for tolbutamide tablets. Instead, there appears to be a critical starch concentration for different granulation sizes.

In a number of instances, poor tablet formulation has been shown to cause a significant variation in gastrointestinal absorption and physiological availability of the active ingredient (1–3). Variables in the formulation and processing include such factors as particle size and shape, binders, diluents, disintegrating agents, lubricants, compression rate, and compression pressure as well as physical features of the dosage form itself. Alteration of any of these factors may influence the disintegration time, dissolution rate, and clinical effectiveness of compressed tablets.

Disintegrating agents have been widely used in compressed tablets as substances or mixtures of substances added to a tablet to facilitate its breakup or disintegration following administration (4). There have been many classifications of disintegrating agents but one of the more recent is that of Feinstein and Bartilucci (5) who divided them into starches, clays, celluloses, algins, or gums. Fakouhi *et al.* (6) point out that disintegrating agents generally fall into three classes: (*a*) agents that react with moisture to constitute a foam, (*b*) effervescent substances that react with moisture to form a gas, and (*c*) substances that react with moisture to swell (most common). The most commonly used agent has been starch from various sources but particularly corn or potato starch.

A study was undertaken to determine the influence of corn starch concentration on the disintegration of tolbutamide tablets prepared from various size granules by direct compression.

EXPERIMENTAL

Tolbutamide powder (USP XVI, 100 mesh) was dried at 100° for 24 hr. Approximately 1 Gm. of powder at a time was compressed at 10,000 lb. gauge pressure in a Carver hydraulic press using 3/4-in. flat-face punches. The slugs were granulated using a Fitzpatrick mill and the granules sieved for 5 min. through 16, 20, 40, 60, and 80-mesh screens using an automatic sieve shaker. Granule sizes were designated 16/20, 40/60, and 60/80 which refers to a passage through the first sieve size number designation and retention on the second sieve. The tolbutamide granules and corn starch (USP XVI, moisture content 9.2% w/w) were thoroughly mixed to give granulation-starch mixtures containing 6, 7, 8, 9, and 10% corn starch. Compressed tablets of 250-mg. tolbutamide content were prepared from the various granule-starch combinations using 3/8-in. shallow concave punches at 2,000 lb. gauge pressure in the Carver press. Tablets and granules were assayed, and disintegration tests performed, using the methods as outlined in the USP XVII (7).

RESULTS AND DISCUSSION

Table I shows the average disintegration time of compressed tablets prepared from different granule sizes and containing varying percentages of corn starch. This information is presented graphically in Fig. 1.

It might be expected that disintegration time would decrease as the percentage of starch in the tablet is increased. This does not appear to be the case for tolbutamide tablets. Instead, there appears to be a critical starch concentration for different granulation sizes when granulations are prepared by methods involving dry granulation and com-

Table I—Average Disintegration Times in Minutes of Tolbutamide Tablets

Starch Concn., %	Granule Size 16/20	20/40	40/60	60/80
6	>30	>30	—	—
7	2.3	22.3	>30	>30
8	1.1	8.8	28.8	>30
9	0.4	0.3	1.9	2.1
10	—	—	0.7	1.0

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