present study of 1.95 hours. It would appear that disappearance of acetaminophen's pharmacologic effects bears little relationship to the rate with which this drug is metabolized and excreted, even though a kinetic relationship may exist between these quantities.

Biological Variations and Body Surface Area of Test Subjects.—Expected biological variation was found in the individual values of either the half-life or rate constant for disposal of acetaminophen. Since the rates of other physiological processes are sometimes related to body surface area, it was of interest to examine the present results to determine whether these were factors in causing the variation observed. There was no evidence of a relationship between surface area and rate constant when these quantities were plotted.

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Aryl Indolizines I

Synthesis and Properties of Some Phenylindolizines

By VINCENT S. VENTURELLA†

Several aromatically substituted indolizines were prepared for possible psychotropic activity utilizing the Tschitschibabin method, and the susceptibility of the nucleophilic position toward benzoyl chloride was established. The properties of the prepared compounds indicated that those with an aromatic halide are not susceptible to nucleophilic attack such as the formation of alkoxy derivatives and also that those compounds containing the *p*-nitrophenyl group could be reduced to the corresponding amino compounds only under drastic conditions not normally expected of such compounds.

THE PHYSIOLOGICAL ACTIVITY of serotonin analogs (1) and reserpine (2) suggests that the structurally similar diphenylindolizines may possess psychotropic activity. In addition, it has been reported (3) that several alkylindolizines have a convulsant activity which would tend to indicate a profound effect on the central nervous system. It is hoped that the use of aryl substituents will moderate this activity thus producing compounds having the desired effect.

It is possible to prepare substituted indolizines by methods developed by Tschitschibabin (4), Barrett (5), or Scholtz (6), the former being most desirable because of ease of formation, good yields, and availability of starting materials. A modification of the method of Moser and Bradsher (7) permitted easy quaternization of the corresponding aryl pyridine with a substituted phenacyl halide to produce a solid product (Table I) in the absence of solvent followed by cyclization according to the scheme shown in Eq. 1.

When 2-parachlorobenzylpyridine was employed, the conditions necessary for the quaternization forced a spontaneous cyclization to occur, thus making it difficult to isolate these intermediates. Considerable decomposition of the tar base, which was always present in excess, was evident in the quaternization step either with 2-benzylpyridine or the *p*-chloro analog. The indolizines prepared are summarized in Table II.

The resonating system of the indolizines in the active state results in an alternating system of electron density (8) which causes nucleophile activity at position 1 or at position 3 if the former is substituted, leading to facile attack by electrophilic reagents. Thus treat-

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TABLE I.—SUBSTITUTED 2-BENZYLPYRIDINIUM ACETOPHENONE BROMIDES

Compd.	Condensation Temp., °C.	Time, min.	Leaching Solv.	Recryst. Solv.	M.p., °C.	Yield, %	Anal., % Calcd. C	H	N	Found C	H	N
IA	40	20	EtOH	Hot H_2O	236–238, dec.	54	53.78	3.81	3.14	53.48	3.80	3.40
IB	50	20	MeOH	Aq. MeOH (cold) 10%	211–212.5, dec.	85	58.10	4.12	6.78	57.78	4.18	7.00
IC	60	35	EtOH (cold)	Aq. MeOH (hot) 50%	248–251, dec.	48	70.30	4.96	3.16	70.32	4.91	3.13

TABLE II.—ARYL INDOLIZINES

Compd.	Reflux Time, hr.	Recryst. Solv.	M.p., °C.	Yield, %	Anal., % Calcd. C	H	N	Found C	H	N
IIA	3	Aq. MeOH (hot)	138 to 139.5	89[a]	69.00	4.02	4.02	68.63	3.98	4.19
IIB	2	Boiling Me_2CO	166–167, dec.	94[a]	76.50	4.46	8.92	75.63	4.62	9.00
IIC	2	Boiling EtOH	196–197, dec.	93[a]	90.25	5.79	4.05	89.72	5.78	4.03
IID	5	Me_2CO-H_2O	178–180, dec.	63[b]	62.99	3.41	3.68	62.69	3.55	3.66
IIE	7	Me_2CO-H_2O	214–216	49[b]	68.97	3.74	8.05	68.99	3.69	8.05
IIF	8	Me_2CO-H_2O	195–196	30[b]	82.32	4.75	3.69	82.41	4.99	3.60

[a] Based on pyridinium salt. [b] Based on starting substituted acetophenone.

ment with benzoyl chloride gave fair to good yields of the corresponding benzoyl derivatives by a modification of the procedure of Holland (9). The benzoyl compounds are peculiar in their lack of reactivity toward carbonyl reagents, but are said to form 2,4-dinitrophenylhydrazones readily (10). However, the compounds prepared in the present study formed these derivatives in poor yields and only after several hours of heating. In addition, the prepared benzoyl compounds have an infrared spectrum which would tend to preclude the presence of the carbonyl group. The effect of adjacent aromatic groups on the wavelength of absorption (11) coupled with reports that alkyl formyl derivatives (12) absorb at 6.1 μ tends to substantiate the fact that the carbonyl compounds of the present study had an absorption at 6.3 to 6.4 μ.

Anomolus behavior of the aryl indolizines prepared was found to exist in two instances. First, a fair degree of basicity should be evident because many of literature compounds form salts with mineral acid (10). In all cases of the present study, the compounds could be dissolved in concentrated mineral acid, but quantitatively precipitated upon dilution with even minute amounts of water. This anomoly is most logically attributed to the presence of multiple resonating systems which inactivate the available electrons on the tertiary nitrogen. Although a report (13) indicates that the presence of an aryl nitro group retards hydrolysis of 1-acyl groups, it was found that if a *p*-nitrophenyl group and a *p*-chlorophenyl group were at positions 2 and 3, respectively, the benzoyl derivative could not be isolated. The evidence discounts the possibility that hydrolysis occurs during reaction or processing. The only other explanation for this result is that the presence of a *p*-chlorophenyl group in the 3-position increases the neighboring group neutralizing effect of the resonance form of the *p*-nitrophenyl group, thereby preventing a nucleophilic center from being established.

Preliminary studies on the reactivity of the *p*-chlorophenyl group indicated that it has a low order of reactivity because it failed to undergo nucleophilic substitution in refluxing methanolic sodium methoxide.

EXPERIMENTAL[1]

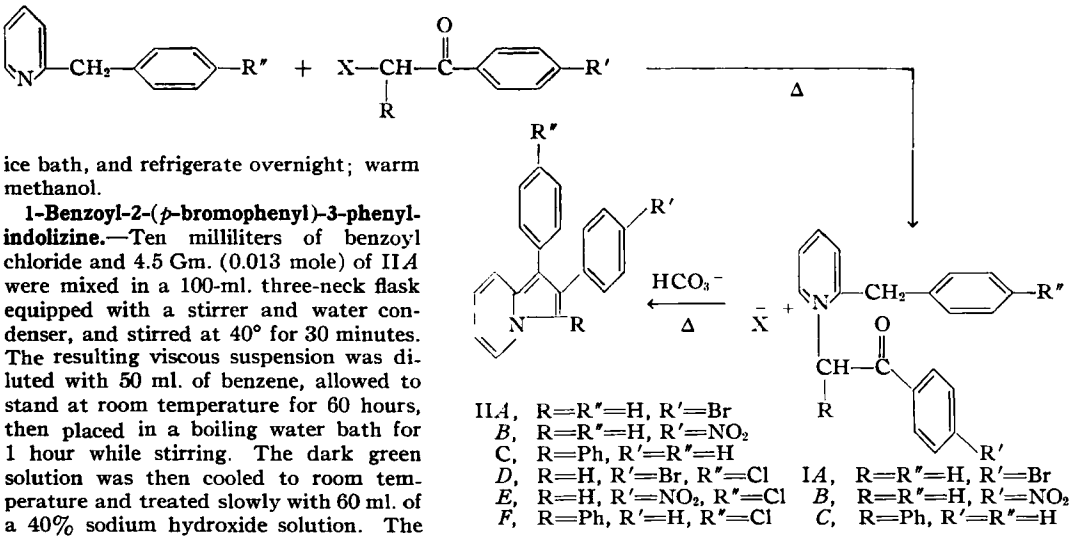
The first two parts of the Experimental are general procedures, the details of which are presented in Tables I and II.

2-Benzylpyridinium Acetophenone Bromides.—The appropriate bromoacetophenone was mixed with 3 equiv. of 2-benzylpyridine and warmed to the required temperature on a water bath with constant agitation until solidification occurred. The resulting product was refrigerated for 2 days. The solid was then fragmented, leached, removed by filtration, and recrystallized.

Cyclodehydration of the Pyridinium Salts.—The pyridinium salt was placed in a three-neck flask equipped with a stirrer and water condenser and treated with a saturated solution of sodium bicarbonate (20 Gm./500 ml.) and 10 ml. of ethanol. The mixture was refluxed with constant stirring for the required period of time. The resulting slurry was filtered hot, the solid washed several times with hot water, dried by suction, and recrystallized.

Quaternization with 2-*p*-Chlorobenzylpyridine.—In each case, the substituted pyridine was mixed with the bromoacetophenone and heated as described for the 2-benzylpyridinium salt. The temperature, time of condensation, and the leaching solvent for the *p*-chloro analogs of compounds *IA*, *IB*, and *IC*, respectively, were as follows: 50° for 10 minutes, stand at room temperature for 3 days; ethanol: 60° until reddish brown and syrupy, shake until solid, and refrigerate 3 days; methanol: steam bath until dark brown and syrupy, shake until solid, immediately cool in an

[1] All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Microanalyses by Schwartzkopf Microanalytical Laboratories, Woodside, N. Y.



IIA, R=R″=H, R′=Br
B, R=R″=H, R′=NO2
C, R=Ph, R′=R″=H
D, R=H, R′=Br, R″=Cl
E, R=H, R′=NO2, R″=Cl
F, R=Ph, R′=H, R″=Cl

IA, R=R″=H, R′=Br
B, R=R″=H, R′=NO2
C, R=Ph, R′=R″=H

(Eq. 1)

ice bath, and refrigerate overnight; warm methanol.

1-Benzoyl-2-(*p*-bromophenyl)-3-phenylindolizine.—Ten milliliters of benzoyl chloride and 4.5 Gm. (0.013 mole) of II*A* were mixed in a 100-ml. three-neck flask equipped with a stirrer and water condenser, and stirred at 40° for 30 minutes. The resulting viscous suspension was diluted with 50 ml. of benzene, allowed to stand at room temperature for 60 hours, then placed in a boiling water bath for 1 hour while stirring. The dark green solution was then cooled to room temperature and treated slowly with 60 ml. of a 40% sodium hydroxide solution. The benzene layer was removed, washed with 60 ml. of water, and the combined aqueous layers washed with benzene until the benzene washings were colorless. The benzene layers were then dried over anhydrous sodium sulfate and evaporated under reduced pressure to a thick green syrup. The addition of 50 ml. of petroleum ether (30–60°) to the syrup caused precipitation of a greenish brown solid. The solid was removed by filtration, washed with two 50-ml. portions of petroleum ether, and suction dried to give 4.0 Gm. (68%) of a bright green powder. It crystallized from boiling ethanol as needles, m.p. 196–198°.

Anal.—Calcd. for $C_{27}H_{18}BrNO$: C, 71.68; H, 3.98; N, 3.10. Found: C, 71.48; H, 3.98; N 3.10.

2,4-Dinitrophenylhydrazone.—Red-brown scales (95% ethanol), m.p. 140–142°.

Anal.—Calcd. for $C_{33}H_{22}BrN_5O_4$: N, 11.07. Found: N, 11.52.

1-Benzoyl-2-(*p*-bromophenyl)-3-(*p*-chlorophenyl)indolizine.—Five grams (0.013 mole) of the corresponding indolizine was mixed at 60° (water bath) with 12.5 ml. of benzoyl chloride, stirred for 1 hour, diluted with 25 ml. of benzene, and kept at this temperature for 2 additional hours. After standing for 48 hours at room temperature, the green solution was diluted with 50 ml. benzene, made basic with a 40% solution of sodium hydroxide, and the liquids were separated. Processing as previously described gave a green solid which was washed twice with ice-cold acetone and suction dried to give 4.5 Gm. (70%) of a crystalline solid. Recrystallization from hot acetone gave yellowish-green flakes, m.p. 235–237°.

Anal.—Calcd. for $C_{27}H_{17}BrClNO$: C, 66.81; H, 3.51; N, 2.88. Found: C, 66.78; H, 3.76; N, 2.22.

2,4-Dinitrophenylhydrazone.—Orange-red needles (70% ethanol), m.p. 185–187°.

Anal.—Calcd. for $C_{33}H_{21}BrClN_5O_4$: N, 10.55. Found: N, 10.99.

1-Benzoyl-2-(*p*-nitrophenyl)-3-phenylindolizine.—Five grams (0.016 mole) of II*B* was mixed with 12.3 ml. of benzoyl chloride and heated on a water bath at 60° for 30 minutes, giving a dark greenish-brown syrup. Ten milliliters of benzene was added, followed by refluxing for 1 hour. The mixture was stirred at room temperature for 20 hours and allowed to stand for 3 days. Processing followed by the addition of petroleum ether (30–60°) gave a dark oil which crystallized when triturated with cold ethyl acetate. Filtration and washing with petroleum ether gave 3.5 Gm. (53%) of a green solid which recrystallized as plates from boiling ethanol, m.p. 253–257°.

Anal.—Calcd. for $C_{27}H_{18}N_2O_3$: C, 77.52; H, 4.31; N, 6.69. Found: C, 77.53; H, 4.30; N, 6.77.

2,4-Dinitrophenylhydrazone.—Orange-brown granules(ethanol), m.p. 198–201°, dec.

Anal.—Calcd. for $C_{33}H_{22}N_6O_6$: N, 14.10. Found: N, 14.79.

2 - (*p* - Aminophenyl) - 3 - phenylindolizine.—Ten grams (0.031 moles) of II*B* was placed in a 250-ml. three-neck flask equipped with a stirrer and water condenser and mixed with 9 equiv. of concentrated hydrochloric acid (28 Gm.), stirred, and diluted with water to 80 ml. The stirred suspension was then heated to 60° while 0.124 moles of granular tin was added portionwise over 1.5 hours. At the end of 5 hours of heating, the suspension was cooled, allowed to stand overnight at room temperature, and filtered. The filtrate was made alkaline with 10 *N* sodium hydroxide solution. Stirring for 1 hour, followed by filtration and water washing gave 7.2 Gm. (71%) of a tan microcrystalline material. The solid was recrystallized from hot aqueous acetone and dried at 100°, m.p. 153 to 154.5°.

Anal.—Calcd. for $C_{20}H_{16}N_2$: C, 84.51; H, 5.63; N, 9.86. Found: C, 84.59; H, 5.76; N, 9.74.

2 - (*p* - Aminophenyl) - 3 - (*p* - chlorophenyl)indolizine.—Ten grams of II*E* was reduced in the same manner as II*B* to give 4.5 Gm. (49%) of product, m.p. 165–167° after recrystallization from ethanol-water.

Anal.—Calcd. for $C_{20}H_{15}ClN_2$: C, 75.47; H, 4.72; N, 8.80; Cl, 11.01. Found: C, 74.97; H, 4.67; N, 8.57; Cl, 10.94.

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Critical *In Vitro* Factors in Evaluation of Gastric Antacids I

Polypeptide Inhibition

By SAURABH DESAI, MILO GIBALDI, and JOSEPH L. KANIG

In vitro **investigation of a wide range of antacid materials contained in various commercially available dosage forms has indicated demonstrable differences in both the degree and rate of neutralization and in buffering capacities. Results obtained by using pH-titration curves reveal that the type of dosage form exerts an influence on the antacid properties of the same chemical compound. Inhibition of antacid activity of some compounds was observed when polypeptides were added to the artificial gastric fluid. It is thus conceivable that antacid activity could be completely curtailed if similar conditions are encountered in the human system.**

ANTACIDS are the object of considerable interest in therapeutics and in pharmacological and pharmaceutical research. Because of their widespread use in the treatment of peptic ulcers, hyperacidity, and gastric distress, numerous *in vitro* investigations have been instituted to evaluate antacid activity (1–11).

The increasing popularity of antacid therapy has led to the marketing of a large number of products which are based on the principle of neutralization of excess gastric acid. These commercially available products may be broadly divided into systemic and nonsystemic preparations. According to Fuchs (12) systemic antacids are defined as those which react with hydrochloric acid in the stomach to form by-products which are readily absorbed and, in turn, induce a systemic alkalosis by shifting the buffer balance of the blood. Nonsystemic antacids are said to form by-products which are insoluble in body fluids and therefore will not induce an alkalosis.

In vivo excretion data obtained from another study currently being conducted in our laboratories offer evidence that the supposed nonsystemic antacids may induce a mild but nevertheless measurable systemic alkalosis. Furthermore, almost all of the products in this category will react with HCl to form water soluble by-products such as magnesium chloride, calcium chloride, and aluminum chloride which are equally soluble in body fluids.

Since the possibility exists that the so-called nonsystemic antacids might induce systemic effects and to avoid conceptual misunderstandings because of erroneous terminology, antacids have been classified in this investigation on an entirely different basis. A study of the currently marketed antacids indicated that all products could be divided into two major product types—effervescent and noneffervescent.

Although a number of comparative studies in recent years have been reported (1–3, 7–10, 13) regarding antacid efficiency, a lack of information still exists on comparisons between (*a*) effervescent and noneffervescent antacids, (*b*) antacid products using doses recommended by manufacturers rather than equal weights of similar products or other arbitrary levels, (*c*) the different dosage forms of the same products at the recommended dosage levels for each.

Since it has the greatest effect on results, one of the most critical *in vitro* factors is the composition of the test fluid. Almost invariably a dif-

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