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Autoxidation and Hydrolysis Kinetics of the Sodium Salt of Phenylbutazone in Aqueous Solution

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Abstract □ The present investigation offers experimental results concerning the degradation kinetics of the sodium salt of phenylbutazone based on a reliable HPLC procedure. The method allows the simultaneous determination of the parent compound and its main decomposition products. The degradation kinetics at 37°C were compared at pH 7.9 and 10.0 and under oxygen and nitrogen atmospheres. Parallel tests were carried out in the dark and under photolytic conditions for the aforementioned conditions. The influence of traces of iron and a chelating agent of iron on the degradation was studied. At pH 7.9 and pH 10.0 the main degradation products are 3-hydroxy-2-oxohexanoic acid 1,2-diphenylhydrazide and 3-carboxy-2-oxohexanoic acid 1,2-diphenylhydrazide. Azobenzene is formed only at pH 10.0. At pH 7.9, in the dark, the degradation proceeds with a lag phase. In contrast, no lag phase is observed under photolytic conditions. The process of autoxidation and hydrolysis is catalyzed by traces of iron both in the dark and under irradiation conditions. An unexpected increase in the degradation is observed in the presence of iron(III) and EDTA in aerobic conditions and under irradiation.

Keyphrases □ Phenylbutazone—autoxidation, hydrolysis, degradation, degradation products, effects of light and pH

Numerous accounts on the stability of phenylbutazone (I) in drugs have been reported (1–7). A degradation pathway has been suggested which involves oxidation and hydrolysis (4). Furthermore, Schmid (8) has shown that the hydrolysis of I to IV is reversible.

Kinetics of the degradation of the sodium salt of phenylbutazone in aqueous solution have been previously investigated (9, 10) using UV spectrophotometry. The procedure was only valid for the determination of the parent compound; the kinetics of formation of the degradation products were not evaluated.

Since II, VIII, and IX (see *Scheme I* of the immediately preceding paper for the structures of the degradation products) have been suspected to have noxious properties (11, 12) it is useful to investigate, under different conditions, the degradation kinetics of I together with the formation of all its decomposition products. In the present work, a reliable HPLC procedure (13) has been used to follow simultaneously the kinetics of the breakdown of the parent compound and the formation of six main degradation compounds, using experimental conditions which complement previous work (9, 10).

EXPERIMENTAL SECTION

Materials, Reagents, and Solutions—Phenylbutazone and its decomposition products (II[1], III[1], IV[1], VI[1], VIII, and IX) were used as received (see *Scheme I* of the immediately preceding paper for the structures of the degradation products). All chemicals were analytical reagent grade and water was glass distilled.

The study was conducted at pH 7.9 or 10.0 using a 3.24×10^{-3} M concentration of I and an ionic strength of $\mu = 0.5$. The solutions were prepared in 0.2 M ammonium acetate buffer (when a buffer effect was studied at pH 7.9 the buffer concentrations were 0.1, 0.2, and 0.3 M). The experiments were carried out at pH 7.9 and 10.0 without additives, and at pH 7.9 in the presence of iron and iron and EDTA.

For each set of experiments, the sodium salt of phenylbutazone solution (solution A) was prepared in a volumetric flask (100 mL) by dissolving phenylbutazone (100 mg) in a minimum amount of concentrated NaOH (~4 M). Solution A was then added to a volume of 100 mL as described below.

For experiments at pH 7.9 and 10.0, without additives, an acetic acid solution was added to solution A to get a 0.2 M (or 0.1 M, or 0.3 M) final acetate concentration. The pH was adjusted[2] to 7.9 or 10.0 with ammonium hydroxide. Potassium chloride and water were added to a volume of 100 mL to have an ionic strength of $\mu = 0.5$.

For experiments in the presence of iron, a saturated solution of iron(III) chloride in the buffer was prepared by shaking (in a water bath at 40°C) iron(III) chloride in the buffer for 48 h. The filtered solution was added to solution A to make 100 mL. The iron concentration was determined in the filtrate by atomic absorption spectrophotometry[3] using a graphite furnace. The concentrations of the solution was 0.008×10^{-3} M iron(III).

For experiments in the presence of iron and EDTA, an appropriate amount of EDTA was added to an aliquot of the solution described above. The concentrations of the solutions were 0.008×10^{-3} M and 10.52×10^{-3} M with respect to iron(III) and EDTA.

Sample Processing—For each experiment, 3-mL aliquots of the solution were transferred to 10-mL standard antibiotic vials. The vials were closed with a rubber seal. The solutions were bubbled for 3 min with either oxygen or nitrogen through the rubber cap using inlet and outlet syringe needles.

Sets of vials corresponding to the different experiments were placed in the same incubator at 37 ± 1°C. The ceiling of the incubator was fitted with a distributed light source delivering a radiative power ~1% of that emitted by the sun on a bright day. The amount of near UV and visible radiation received by the solutions was estimated using actinometry[4] and was found to be 800 $\mu W/cm^2$. The set of vials to be studied in the dark was enclosed in a light-tight

[1] Gifts from Geigy Laboratories, Basel, Switzerland. These compounds were described in G. Pawelczyk and R. Wachowiak, *Diss. Pharm. Pharmacol.*, **20**, 653 (1968).
[2] Potentiograph Metrohm E 436.
[3] Model 420 equipped with an H.G.A. graphite furnace; Perkin-Elmer.
[4] In a first step, the spectral power distribution of a lamp was measured by means of a calibrated spectroradiometer. Then, a graph of the yield in Fe^{2+} ions *versus* lamp power was obtained using potassium ferrioxalate actinometry. Actinometer preparation and final titration followed the Parker and Hatchard procedure (C. A. Parker and C. G. Hatchard, *J. Phys. Chem.*, **63**, 22 (1959); see also C. A. Parker in "Photoluminescence of Solutions," American Elsevier, New York, N.Y. 1968, p. 210). The irradiation step only was different, since we used the full spectrum of the lamp. The last step was the measurement of the actual sample in the incubator. Once the absorbed power was measured, yield was obtained following standard procedures using the power distribution of the lamp, the yield *versus* wavelength quantum yield change of the actinometer, and the absorption curve of the sample.

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box. The contents of the vials were mixed by a gentle motion once a day.

Analytical Procedure—The samples were analyzed by HPLC on a home-made Lichrosorb RP 18 column (5 μm, 15 cm × 0.4 cm) under the chromatographic conditions previously described[5,6] (13). A wavelength of 237 nm was selected for the detection of I–IV, VI, and VIII; 314 nm was used for IX. Determinations were carried out in duplicate on two separate vials withdrawn at suitable time intervals. The samples were assayed immediately after dilution with the mobile phase. The reaction was stopped at 50% completion. At this point, 0.315 mL of oxygen was consumed of the 7 mL present in the vial (on the average) since the total oxidation of 3.0 mg of I requires 0.63 mL of oxygen. The observed differences between the values measured for a duplicate pair of vials were ~3% for I for 95% of the samples. For the remaining 5%, differences as high as 5%, and rarely 10%, were noted. We tentatively attribute the latter to defective sealing and/or degradation of the stopper which permitted entry of oxygen. At the end of each experiment pH values were measured: no significant variation was observed.

RESULTS AND DISCUSSION

All experiments relate to 3.24×10^{-3} M solutions of I in a 0.2 M acetate buffer at an ionic strength of 0.5 μ and a temperature of 37°C, except where otherwise stated.

Aerobic Conditions—*Qualitative Results*—Typical chromatograms of phenylbutazone solutions withdrawn at ~30–40% decomposition level (at pH 7.9) under photolytic conditions are given in Figs. 1a and b. The chromatogram obtained at pH 10.0 is similar with one exception: product U_2 is not present in the latter. The same decomposition pattern for the identified products was obtained in the dark.

At pH 7.9, the main decomposition product is III; IV is formed in a smaller amount. Compound II is detected but is not quantifiable because it is readily hydrolyzed to III which is the major degradation product in aerobic conditions. Compound VI was not detected because it probably is not formed in our working temperature range (8, 14). No authentic samples of V and VII were available to identify on the chromatogram, but under our experimental conditions, the decarboxylation of III leading to V and VII seems improbable.

Two unknown degradation products (U_1 and U_2) are found at a low and nearly constant level. Product U_1 is detectable after 15% decomposition of I under illumination; U_2 is detectable after 20 and 25% decomposition of I under illumination and in the dark, respectively. Based on starting product I, the percent yields of U_1 and U_2 are supposed to have the same molecular absorption coefficient as I, and are, respectively, 0.7% (pH 7.9) or 1.15% (pH 10) and 0.56% (pH 7.9). Products VIII and IX are not involved in the pH range near neutrality (4) and are not formed.

At pH 10.0, the main decomposition product is III; IV is formed in a smaller amount and, as expected at this pH value, IX appears but at trace levels after 25% decomposition of I (Fig. 2). Both in the dark and under photolytic conditions, IX is present as *trans*-azobenzene (relative retention time of *trans*- to *cis*-azobenzene is 2.9 min with the mobile phase described in footnote 6). Although a photostationary mixture of *cis*- and *trans*-azobenzene should be formed under illumination, the competing thermal isomerization efficiency (*cis* to *trans*) at 37°C and the low incident light flux result in undetectable amounts of the *cis* isomer (15). These observations for experiments at pH 7.9 and 10.0 are in good agreement with degradation Scheme I of the immediately preceding paper.

Quantitative Results—Kinetics of decomposition of phenylbutazone were studied at two different pH values (7.9 and 10.0). The influence of pH on the degradation is shown in Figs. 3a (in the dark) and b (under irradiation). The degradation pattern under irradiation at both pH values, and in the dark at pH 10.0, results in a single straight line. In contrast, at pH 7.9 in the dark, two linear relationships are observed; the effect is more evident with product III. In the dark and under irradiation, the degradation of I is faster at pH 7.9 than at 10.0. The formation of III is a sensitive function of pH, in contrast to IV. This means that only degradation pathway 1 is dependent on pH.

In the dark, attempts to determine the reaction order at pH 7.9, by a graphical method, show that the degradation process does not follow a simple order and that a complex reaction is involved. A fractional order probably occurs in the dark at pH 7.9. The half-lives (Table I) show an acceleration of the degradation at pH 7.9 compared with pH 10.0. At pH 10.0, zero-order kinetics are observed ($r = 0.994$).

Under photolytic conditions, the degradation process follows zero-order kinetics at pH 7.9 ($r = 0.994$) and at pH 10.0 ($r = 0.999$). The rate constants

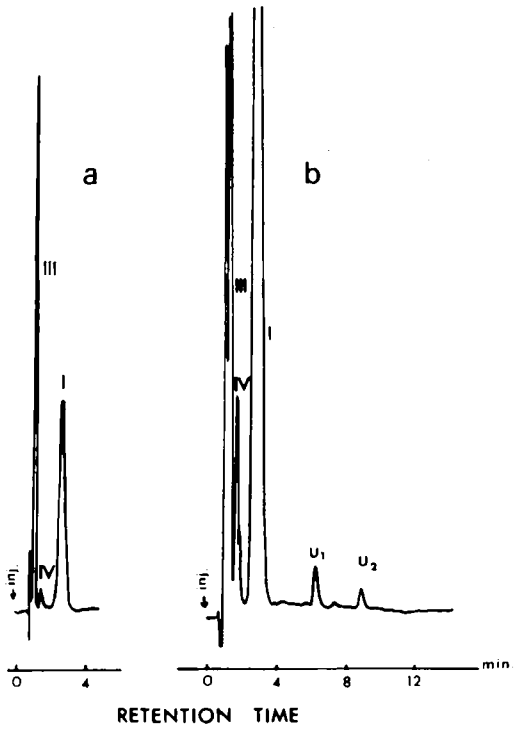

Figure 1—*Chromatograms of a 2.34 × 10^{-3} M phenylbutazone solution diluted 1 to 20 (a) and diluted 1 to 2 (b), withdrawn at ~30–40% degradation at pH 7.9. Kinetic determinations were made in aerobic conditions and under irradiation, determined at 237 nm.*

calculated from the slopes and the half-lives given in Table I clearly show an increase of the degradation at pH 7.9 compared with pH 10.0.

In contrast to pH 7.9, where the sum of I and its decomposition products is always ~100% (with respect to the initial concentration of I), this sum is lowered to 90% at pH 10.0. This apparent loss under photolytic conditions can be explained by the formation of non-UV-absorbing species.

The influence of the buffer concentration on the decomposition was carried out at pH 7.9 in the dark and under irradiation. No significant differences were found between the slopes obtained for each concentration. The influence of a buffer concentration change which could be expected to appear in the hydrolysis step is negligible.

The influence of light on the kinetic behavior of phenylbutazone solution without additives at pH 7.9 and 10.0 is shown in Figs. 4a and b, respectively.

Figure 2—*Chromatogram of a undiluted 2.34 × 10^{-3} M phenylbutazone solution withdrawn at ~30–40% degradation at pH 10.0. Kinetic conditions are the same as Fig. 1. Detection wavelength was at 314 nm.*

[5] Mobile phase: 0.1 M Tris-citrate buffer (pH 5.25)–acetonitrile (52:48); flow rate: 2.0 mL/min.

[6] Mobile phase: 0.1 M Tris-citrate buffer (pH 5.25)–acetonitrile (40:60); flow rate: 2.0 mL/min.

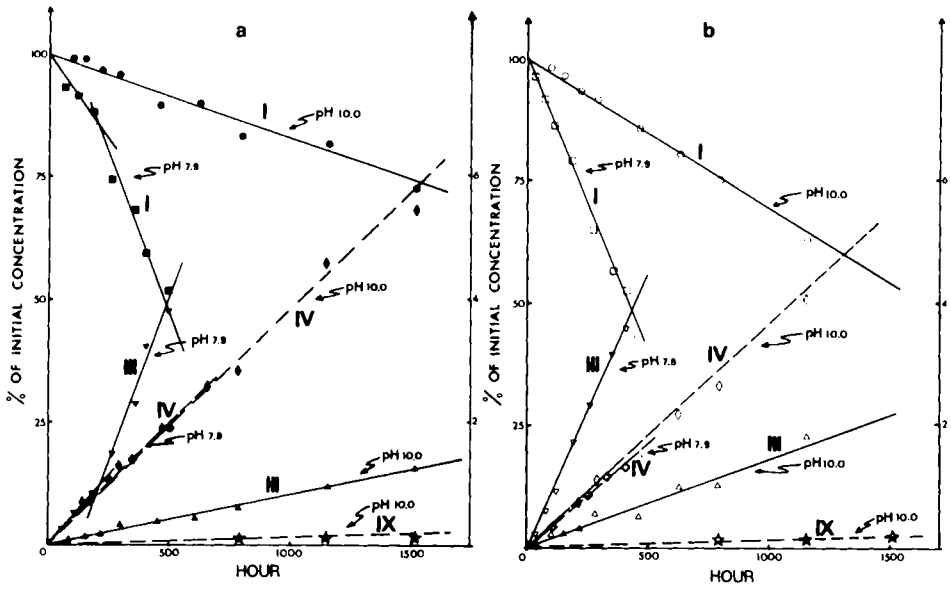

Figure 3—*Influence of pH on the percentage of I, III, IV, and IX as a function of time during the decomposition of phenylbutazone in aerobic conditions in the dark (a) and under photolytic conditions (b) (open symbols). Key: at pH 7.9—(■) I; (▼) III; (◆) IV; and at pH 10.0—(●) I; (▲) III; (♦) IV; (★) IX. (Right ordinate refers to IV and IX.)*

Table I—Half-lives ($t_{1/2}$) and Rate Constants (k) under the Degradation of Phenylbutazone under Aerobic Conditions

		$t_{1/2}$, h		k, g/L/h
pH	Additive	In the Dark	Under Irradiation	Under Irradiation
10.0	None	3000	1500	0.034
7.9	None	473	458	0.120
7.9	Iron	300	220	0.234
7.9	Iron + EDTA	450	170	0.281

Exposure to light increases the decomposition of I. (Compare half-lives in the dark and under irradiation at both pH values in Table I.)

For decomposition in the dark at pH 7.9 (Fig. 4a), the process shows a lag phase which is not observed under photolytic conditions. This induction phase suggests that radical formation is even taking place in the dark. At pH 7.9, 1 in 10^3 phenylbutazone sodium salt molecules [p$K \sim 4.6$ (16)] is in its acid form. In this form, the proton available next to the carbonyl group could be the site of the homolytic process. As the presence of oxygen is necessary to observe a photochemical degradation, it seems likely that some activated form of molecular oxygen is involved. The primary species would be either singlet $^1O_2$ or superoxide $O_2^{\cdot}$. The latter, in aqueous solution, would first react to give $^{\cdot}OOH$ radicals. These could be identical to the species generated in the thermal activation and explain why the observed decomposition products distribution is the same (10). The activation of molecular oxygen could be sensitized by I since the latter absorbs part of the exciting light.

At pH 10.0 no lag time is observed in the dark in the decomposition process, but the same pattern as for pH 7.9 for the evolution of III and IV is observed (Figs. 4a and b).

In the course of our kinetic run, we observed that the rate of formation of IV is not affected by irradiation at both pH values studied (Figs. 4a and b) whereas that of III is increased. In the presence of oxygen, the effect of light is to cause the reaction to proceed faster along path 1.

The influence of the additives iron and EDTA was investigated at pH 7.9. Figures 5a (in the dark) and b (under photolytic conditions) show the influence of traces of iron(III) alone and in the presence of EDTA, compared with the kinetics without iron. These graphs and the calculated values of rate constants and half-lives (Table I) show the catalytic role of iron(III) on the decomposition.

EDTA is a strong complexing agent for iron at pH 7.9. As can be seen, a large increase in the degradation is observed in the presence of iron(III) and EDTA, under irradiation (Figs. 5a and b, Table I). This result is unexpected since EDTA is used in commercial formulations for its "stabilization properties." Similar accelerating effects on the degradation rates have been previously observed with another chelating agent in the oxidation kinetics of epinephrine, carried out in the dark (17). The effect of EDTA in our system cannot be elucidated at present. Recent studies (18) have shown that the well-known decomposition of peroxides by iron(III) EDTA involves formation of active $^{\cdot}OH$ radicals.

Anaerobic Conditions—Determinations were carried out with nitrogen bubbled samples to compare with the oxygen-flushed samples. The results given in Table II show that in the presence of nitrogen, the degradation is largely decreased compared with the degradation in aerobic conditions, at

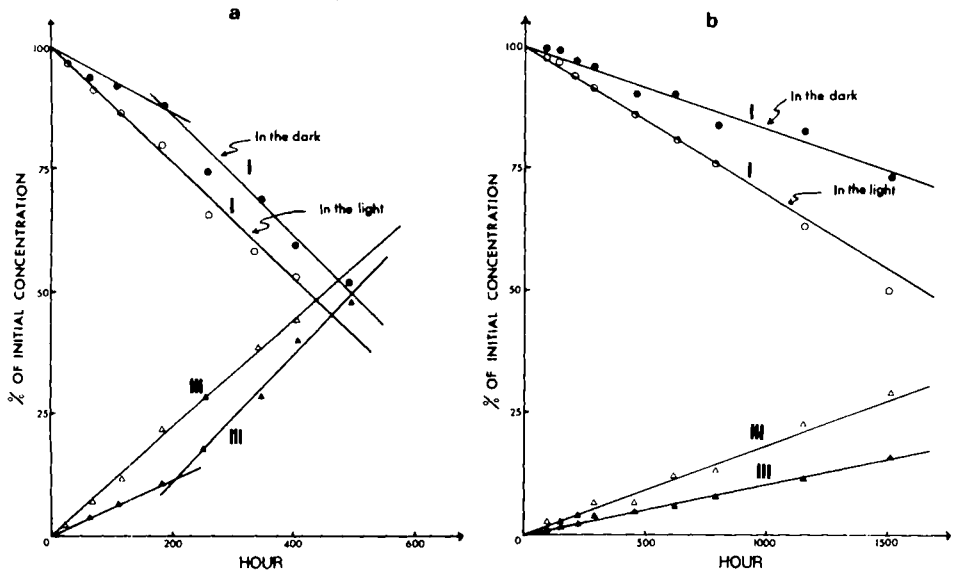

Figure 4—*Influence of light on the decomposition of phenylbutazone in aerobic conditions at pH 7.9 (a) and pH 10.0 (b).*

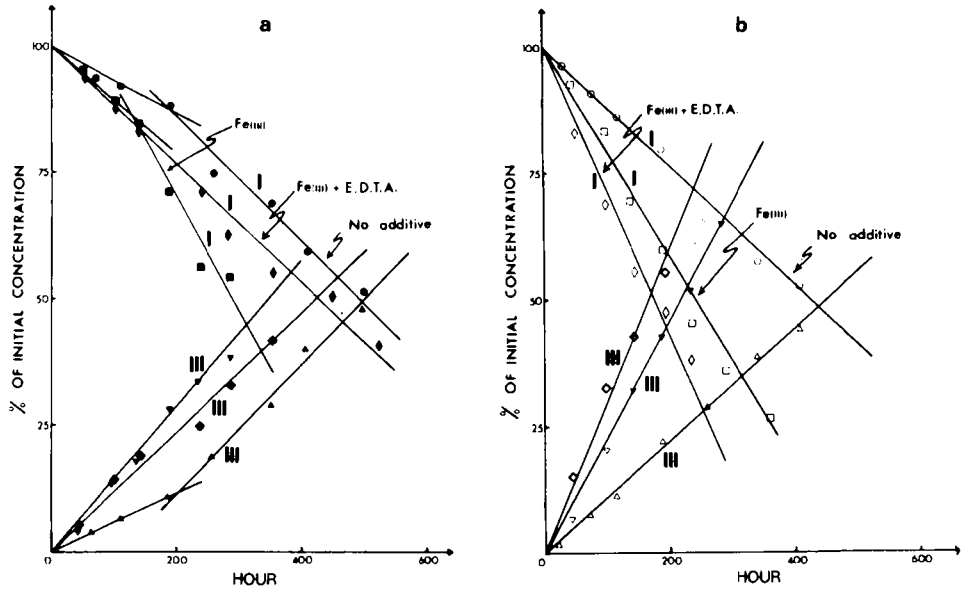

Figure 5—*Influence of iron(III) (0.008 × 10^{-3} M) in the presence of EDTA (10.52 × 10^{-3} M) on the decomposition of phenylbutazone at pH 7.9, in aerobic conditions in the dark (a) and under photolytic conditions (b) (open symbols). Key: without additive—(●) I; (▲) III; with iron—(■) I; (▼) III; with iron and EDTA—(♦) I; (◆) III.*

Table II—Comparative Degradation of Phenylbutazone (I) at Different Time Intervals

pH	Time, h	Compound[a]	Initial Concentration of I, %, with N_2		Initial Concentration of I, %, with O_2	
			In the Dark	Under Irradiation	In the Dark	Under Irradiation
		I	100.49	97.23	94.50	91.50
7.9	71	III	N.D.[d]	N.D.	4.00	7.50
		IV	0.35	0.34	0.24	0.24
		I	100.47	97.88	87.50	77.00
7.9	191	III	N.D.	N.D.	10.00	21.00
		IV	1.06	1.02	0.72	0.64
		I	98.36	97.40	66.00	57.50
7.9	357	III	0.67	1.27	31.00	39.50
		IV	1.82	1.68	1.40	1.22
		I	98.22	93.72	—	—
7.9	520.50	III	0.70	1.35	—	—
		IV	2.62	2.52	—	—
		I	95.25	90.16	88.00[b]	78.50[c]
10.0	699	III	0.45	0.93	7.00[b]	12.50[c]
		IV	2.14	2.06	2.70[b]	2.60[c]
		IX	N.D.	N.D.	N.D.	N.D.
		I	91.84	85.22	72.44	47.98
		III	0.81	1.92	16.13	9.87
10.0	1510	IV	6.38	6.08	5.24	4.37
		IX	N.D.	N.D.	0.064	0.14

[a] See Scheme I. [b] Calculated from Fig. 3a. [c] Calculated from Fig. 3b. [d] Not detected.

both pH values. In these samples, the main degradation route is 2 which, through hydrolysis, leads to IV. Compound III is also formed in small amounts. (The formation of III might be due to the fact that the deaerating procedure is not totally effective.) The removal of oxygen shows up clearly in the variation of the ratio IV:III in the dark as well as under irradiation (Table II).

The effect of additives (Table III) can be analyzed as follows: iron(III) alone induces some degradation whereas the addition of iron(III) and EDTA has no clear stabilizing effect in the dark. The effect of light is only to increase decomposition when it exists in the dark.

Table III—Effect of Additives on the Decomposition of Phenylbutazone under Anaerobic Conditions

Time, h	Additive	Phenylbutazone Remaining, %	
		In the Dark	Under Irradiation
	None	100.47	98.88
191	Iron	98.88	90.45
	Iron + EDTA	98.58	96.59
	None	98.22	93.72
530	Iron	83.00	78.52
	Iron + EDTA	92.30	90.76

CONCLUSIONS

The results we obtained at pH 7.9 and pH 10.0 are in good agreement with the general degradation scheme proposed by Awang *et al.* (4): evidence for two main degradation paths corresponding to hydrolysis (path 2) and autoxidation followed by hydrolysis (path 1) have been disclosed by HPLC analysis.

Kinetic results in aerobic conditions showed that only the oxidation path is affected by pH. This agrees with the findings of Pawelczyk and Wachowiak (2). In the dark at pH 7.9, a lag phase is observed. This was not found by Pawelczyk and Wachowiak who worked at a higher temperature which offset the induction time. This means that one cannot use data obtained between 60°C and 100°C to predict the shelf life of phenylbutazone samples.

The influence of light as well as the catalytic effect of iron traces have been shown to increase the rate of degradation of I through the oxidation pathway. HPLC analysis permitted the determination of trace amount of IX. We have found that it would only be formed at pH 10.0 and after ~25% decomposition of I. Compound IX, a potential carcinogen, could be formed in pharmaceutical formulations where autoxidation and hydrolysis are found at such pH conditions; the problem could arise for injections. In fact, Pawelczyk and Wachowiak report the formation of IX in injectable formulations, but only beyond their storage limit (3). In tablet and capsules, hydrolysis would be so impeded that formation of IX is highly improbable. Compound IX has been detected

in solid formulations only after sustained heating at 60°C after a prolonged storage time (5).

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Controlled Long-Term Release of Small Peptide Hormones Using a New Microporous Polypropylene Polymer: Its Application for Vasopressin in the Brattleboro Rat and Potential Perinatal Use

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Received June 13, 1983, from the *Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands.* Accepted for publication January 25, 1984.

Abstract □ Based on drug release by microporous hollow fibers and the recent introduction of microporous polymers, a new technique was developed for controlled delivery of peptides. Small-diameter microporous polypropylene tubing, lumen-loaded with microgram quantities of vasopressin, and coated with collodion, releases vasopressin after *in vitro* immersion slowly (1–100 ng/d) and constantly for months. The mechanism of pseudo-zero-order delivery is based on high adsorption of vasopressin, keeping the void volume concentration of dissolved vasopressin constant, which is consequently a constant driving force of outward diffusion. The collodion coating prevents the entry of proteinaceous compounds which would result in rapid desorption of vasopressin. The present delivery module provides a lasting release for other peptides as well (lysine-vasopressin, oxytocin, α-melanocyte-stimulating hormone and, to a lesser extent, Met-enkephalin). The microporous polymer-collodion device is biocompatible and, loaded with vasopressin, successfully alleviates the diabetes insipidus of Brattleboro rats deficient for vasopressin. Subcutaneous implantation normalized diuresis for a period of 60 d and constant urine vasopressin excretion is observed. When the commercially available osmotic minipump is too large for implantation, the small size of the present controlled-delivery system allows peptide treatment of young and immature laboratory rats, even if located *in utero*.

Keyphrases □ Controlled drug delivery—vasopressin, microporous polymers, Brattleboro rat □ Vasopressin—controlled drug delivery, microporous polymers, Brattleboro rat □ Brattleboro rat—vasopressin, controlled delivery, microporous polymers

Peptide hormones and many other substances must be administered in a long-term continuous fashion and within a specified range of concentrations in order to bring about physiological changes. Effective dosages can be given by injections, but because of the short half-life of hormone peptides, high doses often have to be administered, resulting in a sawtooth pattern of peptide levels. As a consequence, side effects frequently occur. Several controlled-release techniques have been developed, ensuring a continuous and constant application for a variety of substances (1–5). Most of these techniques are based either on the principle of: (*a*) constant diffusion of substances (mostly hydrophobic steroids and drugs) through polymer matrices (6) or (*b*) constant delivery of a liquid volume containing the physiologically active agents from an osmotically active core (3). A widely used osmotic minipump—an example of the second approach—has the advantage that it is suitable for all types of compounds (including peptide hormones). However, because of its size, implantation cannot be performed in small laboratory animals or fetuses.

Recently we encountered problems when vasopressin supplementation had to be given to vasopressin-deficient newborn Brattleboro rats (7). Based on the possibilities of drug release by the use of hollow fibers (6) and the recent introduction of a new microporous polymer matrix[1] (8, 9), a technique has now been developed through which controlled delivery of peptides can be obtained. It is small enough to allow the use in immature rats. Preliminary results both on the development and on the applications of the present technique have been partially in-

[1] Accurel polypropylene.

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