Determination and Thin-Layer Chromatography of Phenylbutazone in the Presence of Decomposition Products

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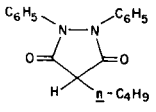
An assay procedure for phenylbutazone involving acid and base shake-out followed by UV spectrophotometric measurement at 264 and 232 mμ is described. The method enables potentially interfering substances such as other medicaments, excipients, and dyes to be removed, and the quantities of phenylbutazone and its decomposition products to be determined. A thin-layer chromatographic system involving cyclohexane, chloroform, methanol, and acetic acid (60:30:5:5) on Silica Gel GF is applied to screening phenylbutazone preparation and semiquantitative estimation of decomposition products present.

THE WIDE USAGE of the antiarthritic and analgesic compound phenylbutazone (4-*n*-butyl-1,2-diphenylpyrazolidine-3,5-dione) (I) has given rise to a large body of data on its *in vivo* properties (1). Parallel to this, a varied collection of analytical procedures for determining the drug in pharmaceutical and biological media has appeared.

Phenylbutazone was analyzed polarographically by Kalvoda and Zyka (2), while hydrolysis of the drug followed by color formation of the resulting products was employed by Pulver (3), Pemberton (4), Hoehlein (5), and recently by Maggiorelli *et al.* (6). Simple colorimetric (7, 8), halometric (9–11), and gravimetric (12) procedures have been utilized also. Direct UV analysis (13–16) including the automated procedure employed by Ahuja *et al.* (17), titrimetry against chloramines (18), and base (19, 20) also have been applied to phenylbutazone analysis.

Titration of phenylbutazone with sodium hydroxide has been adopted as the official method of analysis by the British Pharmacopoeia 1963 (21) and the National Formulary XII (22). The compendial methods suffer from some shortcomings.[1] The required initial extraction of the drug from tablets with acetone and/or ethanol as designated often does not give complete recoveries. Traces of tablet-coating dyes occasionally are extracted also so that the titration end point—phenolphthalein pink—is obscured. Moreover, nonofficial phenylbutazone–aluminum hydroxide combinations cannot be assayed by the official method. The BP and NF assays are inadequate too in that they are not specific for phenylbutazone. That is, common decomposition products, such as the carboxylic acid II and the α-hydroxycarboxylic acid III, are titratable and will afford higher than actual assay results if present. Current spectrophotometric analyses of phenylbutazone similarly are nonspecific. Herrmann recognized this in his work on phenylbutazone metabolism (23). In formulations, decomposition of the drug can give rise to 4-hydroxyphenylbutazone (IV) and *n*-caproylhydrazobenzene (V) in addition to Compounds II and III, all of which can interfere with a UV spectrophotometric assay.



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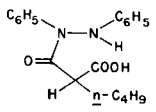

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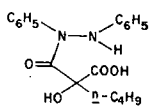

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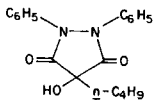

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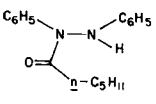

V

To overcome the problems generated by the presence of decomposition products, other medicinal agents and interfering dyes, a specific, precise, and accurate method of analysis for phenylbutazone and its preparations, involving acid–base shake-out followed by UV spectrophotometric measurement was sought. In addition, a thin-layer chromatographic procedure suitable for semiquantitative estimation of any decomposition products present was investigated.

EXPERIMENTAL

Chloroform employed in the studies was analytical reagent grade used without further purification.

A Beckman model DU spectrophotometer was

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[1] The NF assay procedure was revised in the First Interim Revision Announcement to NF XII, p. 4.

utilized for all analyses. When determining a (absorptivity) values for decomposition products at 264 mμ (11.07) and 232 mμ (48.4) the instrument was standardized against 1.439×10^{-4} M potassium dichromate in 0.01 N H_2SO_4 (0.04235 g. $K_2Cr_2O_7$/1. acid). Dichromate readings, when a values quoted in parentheses above were determined, were 0.522 at 232 mμ and 0.570 at 264 mμ.

Reference standard phenylbutazone was medicinal grade bulk drug which analyzed 100% by both the BP and NF procedures, and was shown by TLC to be free of both contaminants and decomposition products.

Analysis of Phenylbutazone—*Preparation of Samples*—Weigh 20 tablets, calculate the average weight per unit, and grind to 80 mesh. For capsules determine the weight of the contents of 20 capsules, calculate the average weight, and mix thoroughly. Analyze bulk drug and reference standard samples without further treatment.

Determination—*Formulations*—Accurately weigh a portion of powdered tablet or capsule fill equivalent to about 40 mg. phenylbutazone, and quantitatively transfer to a 250-ml. separator containing 20 ml. 0.1 N NaOH. Add 12 ml. $CHCl_3$ and rotate gently. Draw off the clear $CHCl_3$ layer and extract this with six 15-ml. portions of 0.1 N NaOH. Combine all NaOH solutions (discarding the $CHCl_3$). Acidify the aqueous alkaline phase with 1.5 ml. concentrated HCl. Extract the acidified solution with six 25-ml. portions of $CHCl_3$, combining the $CHCl_3$ solutions in a 250-ml. volumetric flask. Make to volume with $CHCl_3$ and mix thoroughly. Filter this solution through Whatman paper No. 30 or equivalent, discarding the first 10 ml. of filtrate. Evaporate an accurately measured 10-ml. aliquot of the filtrate to dryness with a rotary film evaporator. With the aid of 0.1 N NaOH quantitatively transfer the residue into a 200-ml. volumetric flask. Make up to volume with 0.1 N NaOH and mix.

Standard and Bulk Drug—Accurately weigh out about 40 mg. of standard phenylbutazone or bulk drug and proceed as above. Alternatively, dissolve the sample in 65 ml. $CHCl_3$ in a 250-ml. volumetric flask. Make up to volume with freshly prepared acid-washed $CHCl_3$ (200 ml. $CHCl_3$ treated with 1.5 ml. concentrated HCl) and mix. Proceed as above, starting at "Filter this solution...."

Measure the absorbance of both reference standard and sample solutions against a blank of 0.1 N NaOH at 232 and 264 mμ.

Calculation—Solve for X and Y

$$A \cdot X + 11.07\ Y = W \qquad \text{(Eq. 1)}$$

$$B \cdot X + 48.4\ Y = Z \qquad \text{(Eq. 2)}$$

where

A = a of phenylbutazone standard at 264 mμ
B = a of phenylbutazone standard at 232 mμ
W = absorbance of sample solution at 264 mμ
Z = absorbance of sample solution at 232 mμ
11.07 = a of decomposition product at 264 mμ
48.4 = a of decomposition product at 232 mμ

$$X \times \frac{250}{10} \times \frac{200}{1000} \times \frac{\text{av. wt. per unit}}{\text{wt. of sample taken}} = \text{g. phenylbutazone per unit} \qquad \text{(Eq. 3)}$$

$$Y \times \frac{250}{10} \times \frac{200}{1000} \times \frac{\text{av. wt. per unit}}{\text{wt. of sample taken}} = \text{g. decomposition product present} \qquad \text{(Eq. 4)}$$

Percent phenylbutazone on basis of total drug and decomposition products present at time of formulation is:

$$\frac{X}{X + Y} \times 100$$

Percent decomposition product on basis of total drug and decomposition products present at time of formulation is:

$$\frac{Y}{X + Y} \times 100$$

Thin-Layer Chromatography—*Preparation of Layers*—Prepare chromatoplates with standard equipment for TLC (24). To obtain five plates 20 × 20 cm., mix 25 g. Silica Gel GF (Merck) with 50 ml. water. Apply the slurry to plates (layer thickness *ca.* 250 μ), air dry, and then activate the chromatoplates at 110° for 20 min.

Solvent System—Cyclohexane–chloroform–methanol–glacial acetic acid (60:30:5:5).

Detection Reagents—1. Short-wavelength UV light.

2. Chlorine/*o*-toluidine (*a*) Chlorination: treat the developed dry chromatoplate with a Cl_2 atmosphere. When employing Cl_2 gas from a cylinder, chlorinate the plate for 5–10 min. If the gas is generated from equal volumes of 10% HCl and 1.5% $KMnO_4$, expose the plate for 15–20 min. (*b*) Spray reagent: dissolve 0.16 g. *o*-toluidine in 30 ml. glacial acetic acid, make up to 500 ml. with distilled water. Dissolve 1 g. KI in this solution. (*c*) Procedure: after chlorination allow the plate to stand in the air for 3–5 min. to remove excess Cl_2. Cautiously spray a corner of the chromatogram. If the background does not turn blue, complete the spraying process. Otherwise wait a few moments before proceeding.

3. Folin-Ciocalteu (FCR) (*a*) Stock solution: to a solution of 10 g. sodium tungstate and 2.5 g. sodium molybdate in 70 ml. water add successively 5 ml. 85% phosphoric acid and 10 ml. concentrated HCl. Reflux for 10 hr. then add 15 g. lithium sulfate, 5 ml. water, and 1 drop bromine. Boil this solution for 15 min. Cool and make up to 100 ml. in a volumetric flask. (*b*) Spray reagent I: 20% aqueous Na_2CO_3. Spray reagent II: dilute 1 volume stock solution with 3 volumes water. (*c*) Procedure: spray with I, air dry, and spray with II.

Preparation of Sample—Weigh 20 tablets or capsules and determine the average weight per unit. Powder five tablets or mix the contents of five capsules, and transfer a weighed portion equivalent to one unit to a 40-ml. centrifuge tube. Add 5 ml. 80% ethanol containing 1% concentrated HCl. Mix thoroughly for 1 min. and centrifuge.

Chromatographic Procedure for Decomposition Products—On duplicate plates, spot 10 μl. of solution to be examined adjacent to each of decomposition product standards equivalent to 3, 6, 9, 12, 15, 18, and 21% of label claim for phenylbutazone. Insert the plate in a suitable jar previously equilibrated with solvent, and allow the solvent to rise to a height of 15 cm. (time, about 40 min.). Air dry the plates and examine under UV light and/or treat each plate with one of the two spray reagents. Compare spot areas and color intensity.

TABLE I—ANALYSIS OF PHENYLBUTAZONE SAMPLES

	Label Claim, mg.	Label Claim Compendial Procedure, %		Label Claim Determined by Peak Height Measurement at 264 mμ		Determinations by Simultaneous Equation			
		As Stated	Modified[a]	Found, %	SD^b	Label Claim Found, %	SD^b	Decomposition Product Present Found, %	SD^b
Simulated phenylbutazone-alka	100	84–88	97–100	100.71	1.62	99.48	1.54	7.98[c]	1.06
Formulation A containing $Al(OH)_3$	100	87–93	94–97	100.86	0.70	100.24	0.62	3.88	0.92
Formulation B containing $Al(OH)_3$	50			100.34	0.32	99.24	0.32	6.72	0.62
Formulation B[d] containing $Al(OH)_3$	50			74.16	0.78	68.08	1.91	28.06	0.34
Formulation C containing $Al(OH)_3$	100			99.37	0.33	99.35	0.33	0.98	0.83
Formulation C[d] containing $Al(OH)_3$	100			94.00	0.56	93.52	0.57	2.95	0.29
Formulation D containing $Al(OH)_3$	100			97.64	0.73	96.48	0.79	7.51	0.58
Formulation D[d] containing $Al(OH)_3$	100			85.88	0.30	81.63	0.24	24.61	1.76
Formulation E containing $Al(OH)_3$	100	10–15	17–24	97.84	0.46	97.42	0.49	2.99	0.22
Formulation F[d] containing $Al(OH)_3$	100			88.70	0.30	87.06	0.37	10.20	0.54

[a] By increasing amount of solvent utilized in extracting phenylbutazone. [b] Four determinations. [c] Theoretical: 7.0%. [d] Sample at least 5 years old.

DISCUSSION

During routine analysis of both normal and alka[2] phenylbutazone formulations a number of difficulties were encountered and some doubts as to the reliability of official analytical methods and the suitability of published assays were raised. Both the BP (21) and the NF (22) procedures were applied and although simulated alka tablets gave satisfactory results (Table I) data for commercial formulations exhibited a broad analytical range. In addition, values often were low, but these could be elevated when volumes of solvent greatly in excess of those stipulated in the monographs were utilized.

The reliability of the compendial method could be questioned further when seven out of 16 brands of phenylbutazone, labeled BP or NF, which were obtained for analysis, could not be analyzed by the official methods.[3] This was due, apparently, to dyes extracted from tablet coatings interfering with the pink phenolphthalein end point of the compendial procedure. The dyes turned a dark blue color during titration. Skepticism regarding the pharmacopial procedure was heightened when examination of the two decomposition products (II and III) confirmed that these were extractable from the tablet mass of decomposed phenylbutazone (I) and, as expected, were titratable with sodium hydroxide. Thus, samples of drugs containing these would give higher than actual assay values.

The BP and NF procedures were found to be inapplicable to the analysis of alka phenylbutazone formulations. Application of the methods to these preparations afforded extremely low assay values—sometimes in the 20% range. This was probably due to the insolubility of the drug-antacid complex in the formulation.

Because of the shortcomings of the official method, the possibility of performing UV spectrophotometric analysis on phenylbutazone formulations in a manner similar to that of the other workers (16, 17, 20) was explored. However, this technique too appeared fraught with pitfalls. In addition to decomposition products II and III, which would interfere with the assay if present, two additional ones, IV and V, also could be present and would give rise to interference. In neutral ethanolic solutions, UV spectra of the four degradation products were found to exhibit $\lambda_{max.}$ 236 mμ while phenylbutazone showed $\lambda_{max.}$ 247 mμ. In basic solution the latter was found to undergo bathochromic and hyperchromic shifts to 264 mμ[4] while the decomposition products suffered hypsochromic and hypochromic shifts to 232 mμ (Table II). Nevertheless, these artifacts still showed absorbance at 264 mμ.

Assay of phenylbutazone in the presence of decomposition products can be expected to indicate slightly higher than actual values for the drug if only direct spectrophotometric measurement at 264 mμ is employed. Data in Table III indicate that near 100% phenylbutazone, the error introduced by decomposition products will be small, but as the concentration levels of the decomposition products increase the deviation becomes highly significant. For instance

[2] The term alka is used to designate those preparations containing phenylbutazone formulated with aluminum hydroxide and magnesium carbonate or magnesium oxide.

[3] See Footnote 1, p. 1952.

[4] This maximum also was observed with neutral aqueous solutions and the 255 mμ maximum reported by other workers (16) could not be reproduced.

TABLE II—MOLAR ABSORPTIVITY VALUES OF PHENYLBUTAZONE AND ITS DECOMPOSITION PRODUCTS

Compound	Neutral Solution $\lambda_{max.}$ mμ	$\epsilon_{max.}$	0.01 *N* NaOH $\lambda_{max.}$ mμ	$\epsilon_{max.}$	0.1 *N* NaOH • 264 mμ
I	247	15,360	264	20,925	20,925
II	236	18,810	232	15,425	3,550
III	236	19,000	232	16,550	3,915
IV	236	17,385	232	16,400	3,835
V	236	18,455	236	14,890	3,080

a decomposed sample of phenylbutazone assaying 92–93% active ingredient will appear to be at lower pharmacopeial limits but, in fact, will be subpotent. This discrepancy becomes still more significant when analysis of phenylbutazone by measuring the absorbance at 264 mμ is utilized in accelerated stability and shelf-life studies. Data based on highly decomposed samples analyzed in this way will indicate that the drug is much more stable than is actually the case.

Initial investigation indicated that the 264- and 232-mμ absorbances of both phenylbutazone and the decomposition products obeyed Beer's law. As expected, addition of known amounts of decomposition products to a standardized phenylbutazone solution exhibited a direct additive effect on absorbancy at these wavelengths. Thus it appeared that simultaneous equations could be applied to the calculation of phenylbutazone in the presence of decomposition products. Values for standard phenylbutazone and decomposition product would be constant in this, while the variables would be the observed absorbance value at 264 and 232 mμ for the sample solution. Variations in the standard would be compensated for by altering these constants in calculations.

Table II indicates the molar absorptivity (ϵ) of decomposition products II to IV. *n*-Caproylhydrazobenzene (V) has a lower value, but is eliminated during the analytical procedure. As this amide is a very minor decomposition product, no appreciable error is introduced in doing this. Variation in composition with accompanying changes in ϵ values at 264 mμ between the decomposition products could introduce differences of up to 0.05% at this wavelength, and of 0.2% at 232 mμ for a sample containing 97% phenylbutazone and 3% of only the highest (III) as compared to the lowest absorbing decomposition product (II). In a 10% decomposed sample this comparison would show up as 0.185 and 0.93% differences, respectively, for determinations at the two wavelengths. Since TLC work (see below) has shown that decomposed samples seldom contain only one decomposition product, the error introduced by variation in molecular extinction values will be considerably less than the figures quoted. To virtually eliminate the possibility of introducing such errors, an intermediate arbitrary value of ϵ that is 15,950 at 232mμ (a 48.4) and 3,700 at 264 mμ (a 11.07) for the contribution due to decomposition products was chosen. This reflects the fact that in decomposed phenylbutazone samples the carboxylic acid II is usually present in quantities comparable to the α-hydroxy analog III together with considerably smaller amounts of product IV.

Phenylbutazone solutions containing known amounts of decomposition products were assayed by UV absorptivity at 264 and 232 mμ. Table III tabulates single analysis data obtained by direct measurement at 264 mμ only, and results found by inserting spectrophotometer readings obtained at both wavelengths in the simultaneous equation and calculating the amount of phenylbutazone (see *Experimental*). The results indicate that values based on the one wavelength invariably are high.

One of the major shortcomings of the BP and NF methods was the problem of isolating all the phenylbutazone present in the sample. More than the specified volume of solvent often was required to effect complete isolation of the drug. Continuous extraction in a continuous extraction apparatus also was effective for regular phenylbutazone tablets. However, the drug could not be completely isolated from formulations containing aluminum hydroxide with this procedure (25). The solution appeared to lie in breaking up drug-excipient complexes. This could be accomplished by dissolving the sample in 0.1 *N* acid or base. Subsequent isolation of drug by solvent extraction indicated that the procedure afforded quantitative recovery.

Extraction was desirable from the point of view that it was a means of removing interfering dyes and other medicaments from the phenylbutazone formulation. By dissolving the specimen being assayed in 0.1 *N* base and extracting the resultant solution with chloroform, chloroform-soluble dyes, alkaloids, steroids, and other neutral and basic components could be removed from the formulation. The aqueous phase could then be made acidic and phenylbutazone and decomposition products recovered, by extracting the acidic solution with $CHCl_3$ followed by evaporation of the organic solvent. Water-

TABLE III—RECOVERIES OF PHENYLBUTAZONE IN PRESENCE OF DECOMPOSITION PRODUCTS[a]

Theoretical Content, mg.	Simultaneous Equation Found, mg.	Simultaneous Equation Recovery, %	264 mμ Peak Measurement Found, mg.	264 mμ Peak Measurement Recovery, %
100.00	100.00	100.00	100.00	100.00
88.88	88.37	99.42	90.23	101.52
87.50	88.34	100.96	90.52	103.45
85.71	85.58	99.85	87.44	102.02
80.00	78.27	97.84	81.52	101.90
77.77	76.61	98.51	79.96	102.81
72.72	70.91	97.51	75.21	103.42
70.00	68.55	97.93	73.03	104.33
66.66	65.75	98.63	71.04	106.57

[a] To demonstrate the validity of the simultaneous equation, Compound II was used as the decomposition product.

TABLE IV—COMPOUND R_f VALUES (×100) OF PHENYLBUTAZONE AND RELATED COMPOUNDS

Compound	R_f
I	49
II	18
III	13
IV	25
V	39
N-(α-Hydroxycaproyl)-hydrazobenzene	35
Oxyphenbutazone	20
Hydroazobenzene	75

soluble dyes and quaternary alkaloidal material remain in the aqueous phase. The thus-recovered drug and related compounds would then be determined by UV spectrophotometry in 0.1 *N* NaOH. Application of this procedure was found to give complete recovery of drug and decomposition products concomitant with removal of the interfering substances. The procedure, too, was effective in removing traces of the seldom-encountered *n*-caproylhydrazobenzene (V) decomposition product.

For routine use the initial (NaOH solution) stage of the extraction procedure often can be by-passed without affecting recovery, accuracy, or precision. If the sample contains no known neutral medicaments, is capsule material, or is tablet material whose dye is not $CHCl_3$ soluble (a small amount of powdered tablet in a test tube with $CHCl_3$ readily indicates this), simple sample dispersion in 0.1 *N* HCl followed by $CHCl_3$ extraction affords recovery of all phenylbutazone and decomposition products present. The final stage of the determination is then performed in a manner identical to the two-stage shake-out, as described in the *Experimental* section.

Alka formulations containing no medicaments other than phenylbutazone (and aluminum hydroxide gel) or alkali-soluble dyes can be assayed directly at 264 and 232 mμ after dissolving and diluting the samples in 0.1 *N* NaOH.

Table I gives the results obtained for commercial and simulated phenylbutazone formulations. Both peak height measurement and simultaneous equation values are given. The data show that although most preparations contain a "reasonable" amount of phenylbutazone (*i.e.*, at least 92.5% of the labeled amount) formulations may contain surprisingly large amounts of decomposition products.

Investigation showed that cyclohexane–chloroform–methanol–acetic acid (60:30:5:5) on Silica Gel GF was an ideal system for resolving and semiquantitatively estimating phenylbutazone (I), its decomposition products II to V, and hydrazobenzene, if present. Table IV lists the R_f values obtained for phenylbutazone (I) decomposition products II to V, and a fifth degradation product shown as *N*-(α-hydroxycaproyl)-hydrazobenzene. In addition, R_f values for hydrazobenzene, a potential oxidation product, oxyphenbutazone (4-*n*-butyl-2 - (4 - hydroxyphenyl) - 1 - phenylpyrazolidine-3,5-dione), and diethyl-*n*-butylamatonate, a synthesis intermediate, are included although none of these were detected in the samples examined.

Viewing plates under short-wavelength UV light indicates immediately the presence of phenylbutazone and most of the decomposition products in the sample. Chlorine/*o*-toluidine gives blue- to violet-colored spots with II, III, and V, with a sensitivity level well below 1 mcg. Phenylbutazone stains yellow while 4-hydroxyphenylbutazone (IV) gives only a weak color reaction even at very high concentrations. FCR affords colors with all of the compounds. Although it is not as sensitive as chlorine/*o*-toluidine for Compounds II and III, requires time for some spots to develop, and gives halos around spots often making quantitation difficult, FCR is useful in indicating the presence of components which could be overlooked by both UV light and chlorine/*o*-toluidine. Estimation of 4-hydroxyphenylbutazone (IV) is facilitated by FCR. This visualizer also shows that a seemingly minor (by UV and chlorine/*o*-toluidine) decomposition product appearing at R_f 0.35 in some samples is present in significant quantities.

Calibration experiments indicated that the level of decomposition products, II to V, could be determined with an accuracy of 3% by the semiquantitative procedures employed. To assure that decomposition was not occurring in solution during TLC analysis, duplicate solutions of phenylbutazone tablets, alka formulations, and bulk drug in the spotting solvent were stored in a refrigerator and at

TABLE V—DECOMPOSITION PRODUCT CONTENT OF PREPARATIONS CONTAINING $Al(OH)_3$

Formulation	TLC Method % Decomposition Product II	III	IV	V	[a]	Total	Simultaneous Equation Value for Total % Decomposition Present
A (contains alkaloids)	2	2	—	—	—	4	3.88
B (contains steroid and alkaloid)	2	2	—	—	+	4	6.70
B (contains steroid and alkaloid)[b]	15	6	—	—	+	21	28.06
C	1	1	<1	2	—	4	0.98
C[b]	1	1	<1	1	—	3	2.95
D (contains alkaloids)	< 1	<1	1	3	+	4	7.51
D (contains alkaloids)[b]	7	3	6	1	+	17	24.61
E	1	<1	2	—		3	2.99
F[b]	4	<1	1	7	—	11	10.20

[a] + indicates presence of *N*-(α-hydroxycaproyl)-hydrazobenzene. No quantitation performed on this compound due to lack of sufficient standard. [b] Sample at least 5 years old.

room temperature. Refrigerated solutions showed no decomposition of phenylbutazone after 24 hr. while those kept at room temperature showed some deterioration. Phenylbutazone samples spotted on TLC plates were found to be stable. "Half-developing" a chromatoplate, drying it in a warm air stream, and then rechromatographing produced no detectable shadow or decomposition spots.

Thirty-three brands of phenylbutazone tablets were examined with the TLC system. Thirty-two of these (labeled BP, NF, USP, and many without compendial designations) including 13 which were at least 5 years old exhibited only trace amounts (well under 0.5%) of decomposition products, II to V, relative to phenylbutazone. One of them contained about 6% decomposition products. In no case did the dyes present in tablet coatings interfere with the TLC method. Four samples of bulk drug, including one which was 10 years old, also were analyzed by TLC. One of them was completely free of decomposition products while the three others contained trace amounts totaling well under 0.5%.

All six phenylbutazone–aluminum hydroxide formulations examined (encompassing nine samples) contained decomposition products. In some cases the quantities could be described as high. Table V lists the levels of degradation products determined by semiquantitative TLC and compares these with the data found by the analytical method (based on the value of Y from the simultaneous equations). Agreement between the two methods is satisfactory. Where differences arise, these underline the specificity of the analytical method. Samples B, B^b, D, and D^b give lower results by TLC since the values quoted do not include the quantity of decomposition product appearing at R_f 0.35.

The presence of large amounts of decomposition products of phenylbutazone in some alka preparations together with acceptable levels of the drug appears to indicate that the manufacturers of these products include an overage at time of formulation, and that the drug in the formulation is unstable. Alternatively, the bulk drug utilized could have contained significant quantities of degradation products to begin with, or were generated during manufacturing processes. Since normal phenylbutazone formulations (*i.e.*, no alkaline compound ingredients) labeled as conforming to compendial monographs contain no significant amounts of decomposition products, one can assume that the former alternative explains the analyses of the so-called alka formulations.

The proposed method of phenylbutazone analysis has been found to be effective for the accurate analysis of the drug in the presence of decomposition products, other analgesics, antacid agents, steroids, alkaloids, and quaternary alkaloids. It also should be effective in analyzing the medicament when it is present in salt complexes containing *p*-chlorophenylether moieties (26). This procedure should be of value in more precise drug quality control and shelf-life testing.

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Keyphrases

Phenylbutazone tablets—analysis
Acid-base extraction—phenylbutazone
UV spectrophotometry—analysis
TLC—separation, identity
Decomposition products—phenylbutazone analysis