bactericidal action of rifampin in the present studies (Fig. 6c). However, when tetracycline or chloramphenicol was added before rifampin, the combined action of tetracycline (curve H in Fig. 6a) or chloramphenicol (curve H in Fig. 6b) with rifampin was dramatically less than that of rifampin alone (curve E).

The postulate that penicillin, kanamycin, or possibly other bactericidal agents will not be active on organisms in the stationary growth state (30) or in the early lag phase affected by bacteriostatic agents cannot be generalized automatically to bacteriostatically affected organisms from balanced cultures and in the logarithmic generation phase. The physiology of resting bacteria may be completely different than that of organisms whose generation is inhibited by bacteriostatic agents in the logarithmic generation phase. It appears that microbial kinetics affected by bactericidal agents alone and in combination with bacteriostatic and other bactericidal drugs need reevaluation using balanced cultures at lower inoculum sizes.

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Pattern of Phenylbutazone Degradation

D. V. C. AWANG▲, A. VINCENT, and F. MATSUI

Abstract □ Phenylbutazone and phenylbutazone–antacid formulations were examined by TLC for the presence of decomposition products. A procedure was developed for minimizing on-plate oxidation of phenylbutazone during TLC analysis, and preparative TLC was utilized for isolation of the major products of decomposition. Unequivocal identification of the major products of degradation was made by NMR and mass spectrometric determination of isolated material. Official phenylbutazone tablets underwent only trace oxidation whereas phenylbutazone–antacid preparations gave evidence of significant levels of oxidation and hydrolysis products. An accelerated decomposition study of the bulk drug and its products of degradation was also conducted.

Keyphrases □ Phenylbutazone and phenylbutazone–antacid formulations—isolation and identification of degradation products □ TLC—isolation, degradation products in phenylbutazone and phenylbutazone–antacid formulations

Two publications have appeared dealing with an evaluation of the integrity of phenylbutazone formulations: Beckstead *et al.* (1) examined both *official* and *alka*[1] preparations in the form of tablets and capsules, while Pawelczyk and Wachowiak (2) were concerned with aqueous injection solutions of sodium phenylbutazone and suppositories.

The former publication outlined an assay procedure for phenylbutazone employing acid–base extraction and determination by UV spectrophotometry. It also described a TLC system to facilitate identification and

[1] The term "alka" was used to designate preparations containing aluminum hydroxide and magnesium oxide or carbonate.

semiquantitative estimation of decomposition products. Pawelczyk and Wachowiak (2) employed column chromatography and preparative TLC for isolation of decomposition products, identification being made by comparison with standards mainly on the basis of melting point and R_f values. A qualitative assessment and rationale of the pattern of phenylbutazone decomposition were presented for the two types of formulation examined.

In view of the extensive use of phenylbutazone as an antiarthritic and analgesic, coupled with its alleged numerous attendant side effects (4), the claim that appreciable deterioration was observed in the majority of its alka formulations warranted a closer examination of the chemistry of the drug and its degradation products. It was felt that the results of such a study would allow a more reliable assessment of the integrity of these formulations. In addition, careful examination of the literature raised some doubts as to the rigor of the published methods of characterization of the decomposition products.

Sixty-six samples of phenylbutazone tablets (representing 35 manufacturers) and 15 samples of phenylbutazone–antacid formulations, in the form of capsules and tablets (representing four manufacturers), were subjected to careful examination. In addition, the degradation of phenylbutazone bulk drug was observed under conditions of accelerated hydrolytic and oxidative decomposition, and the transformations of the derived carboxylic acids were examined under pyrolytic conditions.

Identification of phenylbutazone and its decomposition products was generally made by TLC comparison with standard reference samples. Short wavelength UV light and various spray reagents were utilized for detection. In the case of the major decomposition products, preparative TLC was utilized for isolating sufficient quantities of material from decomposed formulations to allow confirmation of identity by NMR spectroscopy and/or mass spectrometry.

EXPERIMENTAL[2]

Samples of the reference compounds were used as obtained[3], with periodic checks by TLC being made to ascertain their integrity. All compounds were found to be stable when stored in tightly closed dark bottles under normal laboratory conditions.

TLC[4]—*Preparation of Layers*—Five plates (20 × 20 cm. glass) of about 250-μ layer thickness were obtained by application of a slurry, prepared by mixing 20 g. each of silica gel GF_{254}[5] and MN-kieselguhr[6] with 95 ml. of McIlvaine buffer (pH 6), using standard layer-spreading equipment. Two hundred milliliters of buffer is produced by mixing 74 ml. of 0.1 *M* citric acid[7] and 126 ml. of 0.2 *M* disodium phosphate[7].

Solvent System—The following was used: cyclohexane (saturated with McIlvaine buffer, pH 6)–chloroform–methanol (60:30:5), all reagent grade. Five milliliters of acetic acid was added to 95 ml. of a mixture of these solvents in the same ratio (buffer excluded) when developing plates coated with silica gel only.

Detecting Agents—The following were used: (*a*) short wavelength UV light, and (*b*) 0.5% w/v potassium dichromate (analytical reagent) in 20% v/v sulfuric acid (ACS), followed by concentrated sulfuric acid.

Standards—The standard solution of phenylbutazone was prepared by dissolving 20 mg. of the bulk drug in 1 ml. of ethyl acetate (analytical reagent). Standard solutions of the decomposition products were prepared by dissolution of 2 mg. of sample in 10 ml. of the same solvent.

Detection of On-Plate Air Oxidation—Ten 20-μl. samples of the standard solution of phenylbutazone were spotted at 15-min. intervals on a single silica gel TLC plate prepared as described previously (1). The procedure was repeated, each plate being developed immediately after application of the final spot[8]. The experiment was repeated on silica gel–kieselguhr plates buffered at pH 6, prepared as already outlined.

Preparation of Sample from Formulation—An amount of powdered tablet or contents of capsule equivalent to 100 mg. of phenylbutazone was placed in a 25-ml. culture tube, 2 ml. of 0.1 *N* sodium hydroxide was added, and the mixture was swirled to a wet powder mass. Then 5 drops of concentrated hydrochloric acid and 10 ml. of ethyl acetate (analytical reagent) were added; the tube was rotated[9] for 15 min. and then centrifuged. The supernate was applied to the chromatoplate.

Procedure for Assessment of Decomposition in Formulations—A preliminary screening of each formulation was conducted by spotting 10 μl. of the standard phenylbutazone solution against a mixture made up of 5 μl. (representing 1% of the label claim for phenylbutazone) of each standard solution of decomposition product. Only those decomposition products present in amounts greater than 1% were subjected to further evaluation.

Decomposition products present in excess of 1% (as determined by the preliminary screening) were assessed on separate chromatoplates by spotting 10 μl. of sample solution against 5-, 10-, 15-, and 20-μl. applications (corresponding to 1, 2, 3, and 4%, respectively, of the label claim for phenylbutazone) of the particular decomposition product.

On all plates, 5 μl. of the standard phenylbutazone solution was applied as the initial and final spots on the chromatoplate. The extent of on-plate oxidation was then reflected in the difference in amount of oxidation product observed in these two samples; for decomposed formulations, only amounts of oxidation product greater than what was seen in the first-applied standard were considered to be indicative of the existence of oxidation products prior to application to the chromatoplate.

Alkaline Hydrolysis of Phenylbutazone—Phenylbutazone, 1.00 g. (0.003 mole), was dissolved in 12 ml. of 10% sodium hydroxide (0.030 mole), and the solution was refluxed[10] for 24 hr. At this point, reflux was halted and the reaction flask was allowed to cool to room temperature. The condenser, in which was deposited a considerable amount of sublimate[11], was washed out with chloroform and the solvent was evaporated under reduced pressure. A yellow solid, 154 mg., was thus obtained; TLC and spectral analysis indicated that this was almost pure hydrazobenzene contaminated

[2] NMR spectra were obtained with a Varian A-60A spectrophotometer, and mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 L spectrophotometer.

[3] Geigy Pharmaceuticals, Basel, Switzerland.

[4] The TLC procedures for preliminary identification, as well as semiquantitative assessment of the components of formulations and degraded bulk drug, are similar to those employed by Beckstead *et al.* (1). Most modifications were introduced to minimize oxidation on the TLC plate, the only degradative process that occurs to any detectable degree during analysis.

[5] Merck.

[6] Macherey, Nagel and Co.

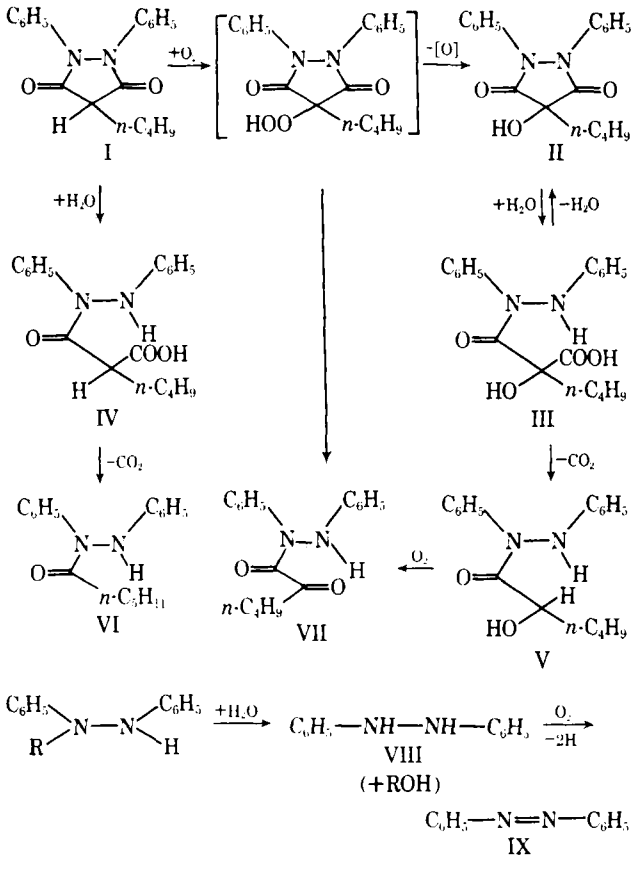
[7] Analar.

[8] There was unmistakably a direct relationship between the duration of residence of the phenylbutazone sample on the unbuffered silica gel plate and the amount of contaminant observed. Only trace contamination could be perceived in samples run on buffered silica gel–kieselguhr plates. Semiquantitative assessment indicated that 2–3% hydroxyphenylbutazone was formed after 1 hr. exposure to the atmosphere on unbuffered silica gel plates.

[9] Multipurpose rotator, model 150 V, Scientific Industries, Springfield, Mass.

[10] A duplicate experiment was conducted simultaneously, and this reaction was sampled hourly (aliquots of approximately 0.25-ml. volume). At the end of 6 hr. of refluxing, both reactions were sampled to check their agreement. There was no apparent difference in the appearance of chromatograms of parallel samples, and all indicated only a slight degree of hydrolysis of I to IV (Scheme I). Five milliliters of the solution from the duplicate experiment was neutralized with 0.1 *N* hydrochloric acid, extracted with chloroform, and dried over anhydrous sodium sulfate. The off-white solid obtained upon evaporation of solvent from the dried filtrate was semiquantitatively analyzed and shown to be phenylbutazone containing less than 4% of IV.

[11] This sublimate was essentially white, but flecks of orange, undoubtedly due to azobenzene, could be easily perceived.



Scheme I

with a trace of azobenzene. The white solid floating on the surface of the solution in the cooled reaction flask was filtered off using suction, washed with water, and allowed to dry in the open air; the yield of essentially pure hydrazobenzene was 385 mg. The filtrate was worked up in the manner described in *Footnote 10* and yielded 82 mg. of phenylbutazone contaminated with less than 4% of the hydrolysis product IV[12]. The merest trace of a contaminant of R_f corresponding to VI also could be detected. The total weight of hydrazobenzene, coupled with the amount of phenylbutazone recovered, corresponded to close to 90% hydrolysis of phenylbutazone.

RESULTS AND DISCUSSION

Preliminary—The likely products of decomposition of phenylbutazone (1,2-diphenyl-4-*n*-butylpyrazolidine-3,5-dione, I) under the relatively mild conditions of normal storage can be predicted from an assessment of the characteristic chemistry of its structural components. Scheme I outlines the salient features and a detailed analysis follows.

Air oxidation at the tertiary C-4 position could be expected to be particularly facile in view of the potential stabilizing effect of two α-carbonyl groups on development of radical or anionic character at that site. Such oxidation[13], probably *via* an unstable hydroperoxide intermediate (5)[14], would give rise to 1,2-diphenyl-4-*n*-butyl-4-hydroxypyrazolidine-3,5-dione (II). This compound has been identified as the major product of phenylbutazone degradation in suppositories (2).

Hydrolysis of II with cleavage of one C—N amide bond would lead to formation of *n*-butyltartronic acid mono-(*N*,*N*′-diphenyl)-hydrazide (III). Indeed, Compound II is so readily hydrolyzed that it cannot normally[15] be detected in the product of phenylbutazone oxidation in alkaline hydroxylic solution (7–11). The survival of II in suppositories (2) was undoubtedly related to the hydrophobic nature of the bases with which phenylbutazone was compounded in the formulations examined. Similar hydrolysis of I would lead to *n*-butylmalonic acid mono-(*N*,*N*′-diphenyl)hydrazide (IV); not surprisingly, the latter compound has been observed to be the major product of phenylbutazone degradation in aqueous solutions of its sodium salt (2, 3).

Decarboxylation of III and IV appears a likely further degradative pathway in view of the well-known facilitation of decarboxylation of carboxylic acids by a β-keto group (12). Loss of carbon dioxide from III and IV would then lead to formation of *N*-(α-hydroxycaproyl)hydrazobenzene (V) and *N*-caproylhydrazobenzene (VI), respectively.

Oxidation of IV to III and dehydrogenation of V to *N*-(α-ketocaproyl)hydrazobenzene (VII) also appear feasible.

Hydrolytic cleavage of the second C—N amide bond in all of the ring-opened hydrazobenzene derivatives would result in formation of hydrazobenzene (VIII), which is readily oxidized to azobenzene (IX).

Interpretation of Results—Application of the procedure recommended for TLC identification of phenylbutazone decomposition products (1) revealed some inconsistencies in the published data as well as shortcomings which could vitiate both qualitative and semiquantitative assessments of deteriorated formulations.

Table I lists the R_f values relative to that of phenylbutazone (I) (assigned a value of 1) calculated for the decomposition products considered in the present study. For comparison, corresponding "relative" R_f values calculated from the published (1) data[16] are also listed. The glaring discrepancy in the values for Compound V is somewhat enigmatic. In our experience, the R_f values for Compounds II and V are so similar under the TLC conditions employed that they can only be differentiated on the basis of their reaction to oxidizing spray reagents: the open-chain, more readily oxidizable hydrazo compounds such as V give rise to much more intense and rapid color development than Compounds I and II, where tertiary aromatic nitrogen atoms are involved in a closed-ring system. Upon treatment with 0.5% potassium dichromate in 20% (v/v) sulfuric acid, Compounds III, IV, V, and VI give almost instantaneously violet-colored spots, while VII affords a yellow to pink coloration. Compounds I and II show up as yellow to orange spots only upon the succeeding application of concentrated sulfuric acid, which also intensifies the other spots.

Hydrazobenzene (VIII) gives R_f values identical with those of phenylbutazone (I) under all conditions employed in the present study. Compound VIII is easily detected in mixtures with I, however, since it gives an instantaneous yellow-brown coloration with the dichromate–sulfuric acid spray reagent. Compound VIII was not detected in any formulation examined but was produced when I was refluxed in aqueous sodium hydroxide. The fact that VIII was not observed in decomposed aqueous injection solutions of

Table I—Relative R_f Values for Phenylbutazone Derivatives

Compound	R_f Silica Gel GF—Earlier Study	R_f Silica Gel GF—Present Study	R_f Silica Gel GF–Kieselguhr (1:1)
II	0.51	0.55	0.66
III	0.27	0.25	0.12
IV	0.37	0.39	0.30
V	0.72[a]	0.55	0.66
VI	0.80	0.75	0.91
VII	—	0.70	0.85

[a] It seems probable that Compound VII, which was not considered in the earlier study, was mistaken for V.

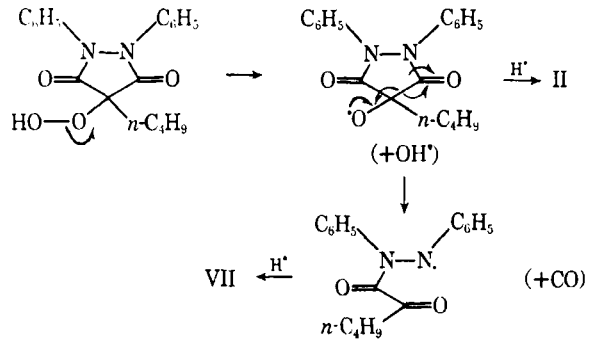
[12] No attempt was made to isolate *n*-butylmalonic acid, but its presence was indicated when a TLC plate was developed in iodine vapor.

[13] This process is probably the major cause of difficulties encountered in attempts at TLC and paper chromatographic assays of substances of the pyrazolone class (6).

[14] Hydrazobenzene catalysis, which takes place in alkaline ethanolic solution (7), is obviously not involved in the mechanism of solid-state or near-neutral air oxidation. No azobenzene, which would be formed in concomitant oxidation, was observed in those instances of appreciable C-4 oxidation in capsules or tablets or on TLC plates.

[15] Awe and Kienert (8) reported recovery of a 10% yield of II from such an oxidation, but we have not been able to duplicate this. Likewise, Veibel *et al.* (7) have not been successful in detecting II upon repetition of the procedure of Sokolova and Magidson (9) which was claimed to allow its isolation.

[16] These relative R_f values are much less variable than absolute R_f values.



Scheme II

sodium phenylbutazone (2), which contained its oxidation product azobenzene (IX)[17], is probably due to the rate of oxidation of VIII being greater than its rate of formation under normal storage conditions. A mixture of I and VIII was separated by preparative TLC from the product of a hydrolysis experiment and was characterized by comparison with authentic material using NMR spectroscopy.

It has been confirmed that air oxidation of phenylbutazone is a remarkably facile process (see earlier discussion) which readily occurs on the TLC plate unless special precautions are taken to obviate it. Two products of on-plate oxidation were observed. The major product was indicated to be 4-hydroxyphenylbutazone (II) by comparison of its R_f value and its reaction to spray reagents with those of an authentic sample. In addition, enough material was isolated by preparative TLC of partially oxidized phenylbutazone to allow its identity to be confirmed by mass spectrometry. The minor product of oxidation was not present in sufficient quantity to allow convenient isolation (and thereby unequivocal identification), but it was almost certainly *N*-(α-ketocaproyl)hydrazobenzene (VII). Its R_f value and reaction to various spray reagents were identical with those of an authentic sample. The complete absence of carboxylic acids III and IV in the oxidized product renders unlikely the involvement of hydrolysis and decarboxylation in the sequence leading to VII (Scheme I); also, Compounds IV and V do not suffer any observable on-plate oxidation. The most plausible mechanism of formation of VII appears to be that outlined in Scheme II.

The formation of II and VII by on-plate oxidation was effectively suppressed by utilizing a 1:1 mixture of kieselguhr–silica gel (instead of silica gel alone) and by impregnating the TLC support with McIlvaine buffer (pH 6).

The absence of II in formulations, concomitant with the presence of trace amounts of VII and appreciable quantities of III and IV (Table II), is consistent with facile hydrolysis of II, formed by air oxidation of the formulations examined. Observation of III in formulations that showed no evidence of IV also attests to the fact that the rate of hydrolysis of II is considerably greater than that of I.

No products of decarboxylation were observed in the formulations examined, but slight formation of *N*-caproylhydrazobenzene (VI) was observed after prolonged refluxing of phenylbutazone in aqueous sodium hydroxide. As noted earlier, there was attendant formation of hydrazobenzene (as well as trace quantities of azobenzene), a result of more extensive hydrolysis. Evidently, the rate of hydrolysis of IV is comparable with its rate of formation.

An interesting situation, probably reflective of the complexity of conformation and association involved in the case of the two carboxylic acids III and IV, concerns their behavior under thermolytic and mass spectrometric conditions. Whereas pyrolysis of solid IV gives an almost quantitative yield of the product of *decarboxylation*, VI, similar pyrolysis of III is a most efficient method of preparation of the product of *dehydration*, II[18] (10). On the other hand,

[17] This compound shows up as a bright-yellow spot having an R_f value greater than that of I, and it was undoubtedly mistakenly designated as "hydroazobenzene" by Beckstead *et al.* (1).

[18] This result is particularly surprising since incorporation of electron-withdrawing groups normally facilitates decarboxylation (12). The preference for dehydration is so overwhelming that refluxing of a suspension of III in water resulted in the exclusive formation of II. No indication of V was detected when the dichromate–sulfuric acid spray was applied. The sodium salt of III, when subjected to the same conditions, showed no sign of degradation.

Table II—Assessment of Impurities in Phenylbutazone–Antacid[a] Formulations by TLC

Formulation	Percent Decomposition Product III	IV	VII
Capsule			
1	1	1	—
2	1.5	1.5	Trace
3	2	2.5	Trace
4	1	>0.5<1	—
5	0.5	0.5	—
6	1.0	0.5	—
7	<0.5	0.5	—
Tablet			
8	>1<1.5	1	—
9	0.5	0.5	—
10	<0.5	—	—
11	<0.5	—	—
12	<0.5	—	—
13	<0.5	—	—
14	0.5	0.5	—
15	<0.5	0.5	—

[a] Only two of the 66 samples of phenylbutazone tablets showed more than trace amounts of any impurity. The major contaminant in both cases constituted less than 0.5% impurity and appeared to be Compound II on the basis of R_f value and reaction to spray reagents.

the mass spectrum of IV was identical with that of I, the highest mass peak appearing at *m/e* 308 (M − 18) and indicating facile loss of water from the parent molecule of IV. However, no peak corresponding to its molecular ion or to loss of water, carbon dioxide, or both from its parent molecule could be perceived in the mass spectrum of III, the highest mass peak being found at *m/e* 205[19].

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[19] The remarkable differences observed in the thermal degradative behavior of Compounds III and IV in the solid and liquid states, as well as under varying conditions of temperature and concentration in different solvents, will be reported and interpreted (as will be their mass spectral fragmentation) in a forthcoming article.