Solid State Stability of Some Crystalline Vitamin A Compounds

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Theoretical and experimental studies relating the relative stability of solid vitamin A derivatives to their melting points have shown that, in general, resistance toward degradation increases with fusion temperature. This is attributed to the part that crystal lattice energy plays in stabilizing these compounds, and is supported by the fact that the solution stabilities of the derivatives appear to be generally comparable. Of the several compounds studied, vitamin A benzhydrazone and vitamin A succinate triphenylguanidine salt exhibited the greatest stability.

THE PRESENT investigation has been concerned with the experimental examination of the relationship between fusion temperature and the rate of chemical degradation of certain susceptible solid drugs. Although it has been known that the stability of many solids is closely related to their melting points, rational application of this condition to stabilization of drugs has not been generally recognized by pharmaceutical investigators, and therefore has been quite limited. Specifically, several vitamin A derivatives of widely differing melting points have been prepared and their relative stability evaluated. The compounds studied in detail included vitamin A acetate, vitamin A benzhydrazone, vitamin A nicotinate, vitamin A phthalimido-N-acetate, vitamin A succinate triphenylguanidine salt, and vitamin A 3,4,5-trimethoxybenzoate.

The stability of organic compounds to degradation in the solid state is intimately related to the strength of the crystal lattice. Since the forces between molecules in a crystal are small compared with the energy required to break bonds, liquefaction normally occurs before degradation begins. As a general rule, reactions proceed at a much faster rate in liquids and in solution than in solids; consequently the melting point of a compound is a very important factor in determining stability.

The surfaces of higher melting crystals are a strong barrier to penetration of external agents responsible for degradation of chemicals in the dry state. The resistance of a crystalline compound to fusion can therefore be taken as a crude, but useful, index of its general stability.

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Past Work on Degradation of Solids.—Most studies on reactions which occur in the solid state have dealt with inorganic solids and, in particular, with oxidation taking place at the surface of metals. Nearly all organic compounds, including drugs, are apparently essentially stable within their crystalline structure. Degradation, when it is observed, usually occurs in the surface film phase. Bawn (1) points out that decomposition of solid explosives, for example, is usually accompanied by the formation of a liquid phase at temperatures below the normal melting point of the pure solid. As a consequence, there is a rapid increase in the reaction rate. In the absence of melting, the formation of product molecules is assumed to induce a strain in the crystal which produces cracks and thus forms fresh surfaces on which decomposition can occur. Degradation of explosives usually leads to the formation of gaseous products. The rate of the process can therefore be most conveniently followed by measuring the pressure developed in a constant volume system. A sigmoid shaped pressure-time curve is often obtained experimentally.

Wobbe and Noyes (2) studied the solid state decomposition of anhydrous oxalic acid into gaseous formic acid and carbon dioxide at temperatures just below its melting point. The reaction was again shown to occur largely on the surface of the crystals. When small amounts of solid were used, the reaction could be better represented by a zero-order than by a first-order equation. For large amounts of solid, the constants were always high, however.

Garrett (3), studying the solid state decomposition of aspirin anhydride, found that the degree of degradation could be qualitatively correlated with the amount of liquefaction in the samples at the various temperatures studied.

Micronization, drying, and avoidance of contact with alkali increased the thermal instability of the anhydride. The unusual observation that small crystals were more stable than larger ones was explained by the fact that the large crystals were probably solvates or contained trapped solvents.

Past Work on the Stability of Vitamin A.—Details of the early work on the stability of vitamin A, particularly in the form of oily concentrates, have been described elsewhere (4–6) and will not be discussed extensively here. Certain aspects of this work are, however, pertinent to the present investigation.

For many years after its isolation from fish liver sources no crystalline derivatives of vitamin A were available. It was not until 1935 that Hamano (7) succeeded in crystallizing the first derivative of the vitamin, vitamin A β-naphthoate. Vitamin A alcohol itself was not obtained in the form of solvent-free crystals until 1942. In 1942, Baxter and Robeson (8) prepared crystalline vitamin A acetate, vitamin A palmitate, and divitamin A succinate; and they studied the relative stability of these compounds in the solid state. Thin layers of the crystals were exposed to air at 5° in darkness. The percentage decomposition at various times was determined by the percentage decrease in the extinction coefficient. Vitamin A β-naphthoate was included in the stability study. The apparent order of stability of the compounds studied was: vitamin A acetate, vitamin A β-naphthoate, vitamin A palmitate, vitamin A succinate. The greater stability of vitamin A acetate was attributed to its crystal size. Apparently other factors were involved, however, for the authors could not explain with this hypothesis the exceptional stability of vitamin A β-naphthoate.

In recent years studies on the solid state stability of vitamin A and its compounds have been largely concerned with the effectiveness of various antioxidants. Some work has also been done on the preparation of protein complexes (9, 10), inclusion compounds (11, 12), and coatings (13–15). Few new crystalline derivatives of vitamin A have been reported.

The mechanism by which crystalline vitamin A compounds degrade has not yet been completely elucidated. This degradation is probably similar to the changes which occur in the drying of oils and in the polymerization of similar conjugated polyolefinic molecules. Two related types of reactions probably are involved: (*a*) free radical catalyzed autoxidative polymerization occurring at the surface of the crystal, and to as great a depth in the liquid film covering the crystal as oxygen can penetrate, and, less likely, (*b*) polymerization involving carbon-carbon linkages beyond the depth of penetration of oxygen.

Reinstein (16) has studied the degradation of vitamin A alcohol, vitamin A acetate, and vitamin A palmitate at 25° and 90° in heptane and ethanol, in the presence and in the absence of air. In the presence of air, the two esters degraded at similar rates, while the alcohol form decomposed approximately three times faster than the esters. The order of the reaction with respect to vitamin A was 1.3 to 1.5, indicating that very concentrated solutions lose vitamin A at a much faster rate than dilute solutions. When air was excluded, the rate of degradation was barely detectable, indicating that the degradation of vitamin A in heptane was essentially oxygen initiated.

EXPERIMENTAL PROCEDURE

Reagents.—Crystallize vitamin A alcohol was obtained by base-catalyzed hydrolysis of vitamin A acetate (Hoffmann-LaRoche). Benzhydrazide, potassium phthalimide, 1,2,3-triphenylguanidine, and dichloromethane were used as obtained (Eastman Organic Chemicals Co.). Chloroacetyl chloride and methyl formate (Eastman Organic Chemicals) were redistilled. Skellysolve A, Skellysolve B, and petroleum ether were used without purification. Manganese dioxide was obtained from General Metallic Oxides Co. All other solvents and chemicals were reagent grade.

Apparatus.—All ultraviolet spectra were determined in chloroform on a Cary recording spectrophotometer model 11MS. Infrared spectra were determined using a Beckman model IR-5 double-beam infrared spectrophotometer. Melting points were determined in capillary tubes, using a 3-inch immersion thermometer.

Analyses.—The microanalyses were performed by Dr. Stephen M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

Synthesis of Compounds

Vitamin A Benzhydrazone.—This compound precipitated when a solution of benzhydrazide in methanol was added to vitamin A aldehyde. The vitamin A aldehyde was prepared from vitamin A alcohol by oxidation with manganese dioxide, a method first used by Ball, *et al.* (17).

Activated manganese dioxide (28 Gm.) was added to a solution of 4 Gm. vitamin A alcohol in 40 ml. petroleum ether. The solution was agitated from time to time for 20 hours at room temperature. The ether solution was filtered off and evaporated to a yellow oil. Benzhydrazide (1.9 Gm.) dissolved in 50 ml. methanol was added to the vitamin A aldehyde. After a few minutes crystals formed in the solution. The crystals were filtered off, washed with petroleum ether, and recrystallized from methanol, m. p. 181–182°.

Anal.—Calcd. for $C_{27}H_{34}N_2O$: C, 80.5; H, 8.5; N, 7.0. Found: C, 78.9; H, 8.7; N, 7.1.

Vitamin A Nicotinate.—This ester was prepared by alcoholysis from Vitamin A alcohol and methyl nicotinate in Skellysolve B, with sodium methoxide as catalyst.

Crystalline vitamin A alcohol (18 Gm.) and crystalline methyl nicotinate (10 Gm.) were dissolved in 200 ml. Skellysolve B. Sodium methoxide (0.1 Gm.) was added and the mixture was heated at 60° for 2 hours. Skellysolve B was collected as it distilled in a Barrett trap, and fresh solvent was added to the reaction vessel as required. The flask was protected from light and moisture, and nitrogen was bubbled into the solution throughout the reaction. After the heating period the solution was extracted several times with water until the washings were neutral to litmus. The Skellysolve layer was dried over sodium sulfate, filtered, and refrigerated at 0°. Crystals formed in the solution overnight. The yield of vitamin A nicotinate was 8.5 Gm. An additional 4 Gm. of nicotinate was obtained from the mother liquor after concentration. Vitamin A nicotinate was recrystallized from methyl formate, m.p. 93–94°.

Anal.—Calcd. for $C_{26}H_{33}NO_2$: C, 79.7; H, 8.5; N, 3.6. Found: C, 77.1; H, 8.2; N, 3.8.

Vitamin A Phthalimido-N-acetate.—Vitamin A chloroacetate and potassium phthalimide afforded this compound in dimethylformamide.

Vitamin A chloroacetate was prepared by a modification of the procedure of Baxter and Robeson (8) for preparing esters of vitamin A from acid chlorides. Chloroacetyl chloride (4 Gm.) dissolved in 50 ml. dichloromethane was added dropwise from a dropping funnel into a solution of vitamin A alcohol (10 Gm.) in 100 ml. dichloromethane and 30 ml. pyridine. Nitrogen was bubbled into the solution throughout the reaction, and the mixture was kept at 0–5°. After the acid chloride was added, the solution was stored in the dark at room temperature for 2 hours. A saturated aqueous solution of oxalic acid was added and the solution was extracted with petroleum ether. After several washings with oxalic acid solution the ether layer was washed with water until neutral to litmus, then dried over sodium sulfate. The solvent was removed under reduced pressure and nitrogen, and potassium phthalimide (3 Gm.) dissolved in 50 ml. dimethylformamide was added. The solution was stored in the dark at room temperature for 12 hours. Water (100 ml.) was added, and the solution was extracted with ethyl ether. The ether layer was washed several times with water, then with 5% sodium hydroxide solution, and finally with water again, until neutral to litmus. The ether solution was dried over sodium sulfate, filtered, and refrigerated at 0°. Vitamin A phthalimido-N-acetate crystallized from the ether solution was filtered off and recrystallized from anhydrous ethyl ether, m.p. 111–112°.

Anal.—Calcd. for $C_{30}H_{35}NO_4$: C, 76.1; H, 7.5; N, 3.0. Found: C, 75.8; H, 7.6; N, 3.4.

Vitamin A Succinate Triphenylguanidine Salt.—Vitamin A succinate half ester was prepared by heating vitamin A alcohol and succinic anhydride in pyridine. 1,2,3-Triphenylguanidine was added to the ester in saturated ether solution and the salt precipitated.

Vitamin A alcohol (11.5 Gm.) and succinic anhydride (4.0 Gm.) were dissolved in 50 ml. pyridine in a flask protected from light. The solution was heated at 75° for 1 hour. Nitrogen was bubbled through the solution throughout the reaction while the mixture was cooled to room temperature. The pyridine solution was transferred to a low-actinic separator and 50 ml. petroleum ether was added. The ether solution was extracted four times with 75-ml. portions of saturated aqueous oxalic acid solution, then washed with distilled water until washings were neutral to litmus.

Five per cent sodium hydroxide (40 ml.) was added in 10-ml. portions with shaking. The ether layer contained unreacted vitamin A alcohol and was discarded, while the aqueous layer contained the sodium salt of vitamin A succinate. This was washed four times with 50-ml. portions of petroleum ether, which were discarded. The aqueous layer was acidified with saturated oxalic acid solution, and the vitamin A succinate was taken up with 50 ml. petroleum ether. The ether layer was washed again with 50-ml. portions of distilled water until neutral. It was then dried over anhydrous sodium sulfate and filtered. The ether solution was evaporated to a yellow oil by distillation from a 40° water bath under reduced pressure and nitrogen. The product obtained (13 Gm.) had an ester peak in the infrared at 5.81 μ. There was no alcohol peak.

Triphenylguanidine (4 Gm.) dissolved in 125 ml. anhydrous ether was added to 5 Gm. vitamin A succinate dissolved in 25 ml. ethyl ether. A white precipitate formed within 2 minutes at room temperature. After 15 minutes the precipitate was filtered off, washed several times with anhydrous ether, then dried in a vacuum desiccator, m.p. 140–140.5°. Vitamin A succinate triphenylguanidine salt was recrystallized from methyl formate without change in melting point.

Anal.—Calcd. for $C_{43}H_{51}N_3O_4$: C, 76.6; H, 7.6; N, 6.2. Found: C, 75.9; H, 8.0; N, 6.2.

Vitamin A 3,4,5-Trimethoxybenzoate.—This ester was prepared in the same way as vitamin A nicotinate, i. e., by alcoholysis from vitamin A alcohol and methyl-3,4,5-trimethoxybenzoate in Skellysolve B, with sodium methoxide as catalyst.

When crystals of vitamin A 3,4,5-trimethoxybenzoate were obtained from the Skellysolve B solution from which they were crystallized, they were washed with Skellysolve A, then recrystallized from Skellysolve B, m.p. 85–86°.

Anal.—Calcd. for $C_{30}H_{40}O_5$: C, 75.0; H, 8.4. Found: C, 75.0; H, 8.2.

Stability Studies

Solid State Studies.—Samples of 3×10^{-5} moles of each crystalline vitamin A compound were weighed into 1-dr. vials. The vials, open to air, were placed in a thermostated oven at 50 ± 1°. At intervals, sample vials were withdrawn and their contents transferred quantitatively into 100-ml. volumetric flasks. Samples of vitamin A nicotinate, phthalimido-N-acetate, succinate triphenylguanidine salt, 3,4,5-trimethoxybenzoate, and acetate were scanned in the ultraviolet region from 400 to approximately 280 mμ. All these compounds exhibited a peak at 333 mμ in chloroform, the only readily available solvent in which all the derivatives

were soluble. Vitamin A benzhydrazone solutions were scanned in the visible region, from 500 to 350 mμ. The vitamin A benzhydrazone peak was at 398 mμ. As degradation proceeded, the decrease in height of the respective peaks was noted.

Solution Studies.—Samples of each vitamin A compound were dissolved in chloroform, and aliquots containing 4×10^{-4} moles/L. were pipetted into 100-ml. volumetric flasks. The flasks were stored open to air in a dark cabinet. Periodically samples were removed, the proper dilution made, and the samples analyzed in the same way as in the case of the solid state studies.

RESULTS AND DISCUSSION

For the purpose of the present investigation the synthesis of a large number of derivatives was attempted. These derivatives are listed in Table I. Because of the extreme susceptibility of vitamin A to isomerization, polymerization, dehydration, and other chemical changes, these attempts led, in many instances, to reaction products contaminated with side products. Many of the derivatives successfully prepared were hygroscopic and, therefore, unsuitable for the planned studies. Stability investigations were limited to those compounds, marked with a superscript *a* in Table I, which were recoverable as sharply melting, nonhygroscopic crystals.

Relative Stability of the Derivatives in the Solid State

Results of studies on the relative stabilities of several vitamin A derivatives in the solid state are shown in Fig. 1. The data collected were based on spectrophotometric determinations of the absorption peak in the ultraviolet of separate solid samples kept for varying periods of time at 50°. Since there was a loss of less than 33% of the vitamin during the period of study, it is presumed that the data provide a fair representation of the stabilities of these derivatives.

No serious attempt was made to control the size of the crystals employed in these studies. The compounds, listed in order of decreasing crystal size were: vitamin A nicotinate, vitamin A acetate, vitamin A 3,4,5-trimethoxybenzoate, vitamin A phthalimido-N-acetate, vitamin A benzhydrazone, and vitamin A succinate triphenylguanidine salt. No marked correlation is apparent between crystal size and stability for these compounds, as shown in Fig. 1.

In the discussion of possible mechanisms of degradation of vitamin A it was postulated that degradation probably occurs almost exclusively in a liquid film at the surface of the crystal. A difference in reactivity of substances in the solid and liquid state is to be expected since there is a difference in internal energy between the two states equal to the latent heat of fusion (1). The relative amount of material in the liquid state may be expected in these instances to determine, in some large measure, the rate of degradation. The fraction of material in the liquid state is related to the melting point of the pure crystalline solid by the following equation

$$\ln x_l = \frac{-L_f}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right)$$

Table I.—Synthesized Derivatives

Vitamin A Compound	Melting Point, °C. Crystalline	Melting Point, °C. Amorphous
Divitamin A fumarate[b]	...	...
Divitamin A diglycol carbonate[b]	...	...
Divitamin A pyromellitate[b]	...	...
Vitamin A benzhydrazone[a]	181–182	...
Vitamin A *p*-phenylenediamine, Schiff's base	155–156	...
Vitamin A succinate half ester[c]	...	...
Calcium salt	...	225
Magnesium salt	...	225
Procaine salt[d]	...	...
Ethylenediamine salt[d]	...	98–99
Triphenylguanidine salt[a]	140–140.5	...
1,4-Butanediamine salt[b]	...	...
Guanidine salt[b]	...	...
1,2-Propanediamine salt[b]	...	...
Thiamine salt[b]	...	...
Gramine salt[d]	...	130–132
N,N′-Dibenzylethylenediamine salt[b]	...	...
Tris-(hydroxymethyl)-aminomethane salt[b]	...	...
p-Xylyldiamine salt[d]	...	...
Arginine salt[d]	...	...
Glycine ethyl ester salt[d]	...	...
Glycine amide salt[b]	...	...
Vitamin A phthalate half ester[c]	...	...
Calcium salt	...	225
Ethylenediamine salt[d]	...	150
Hydrazine salt[d]	...	134
Triphenylguanidine salt[b]	...	...
Procaine salt[d]	...	82
1,2-Propanediamine salt[b]	...	...
Thiamine salt[b]	...	...
p-Xylyldiamine salt	...	122
N,N′-Dibenzylamine salt	...	...
Glycine amide salt[d]	...	117
Vitamin A chloroacetate	...	...
Vitamin A phthalimido-N-acetate[a]	111–112	...
Vitamin A dimethylglycinate	...	...
Tartrate salt	...	70–71
Gentisic acid salt	...	66–67
Maleic acid salt	...	94–95
Gallic acid salt	...	...
Vitamin A oxamido urethane	...	114
Vitamin A nicotinate[a]	93–94	...
Vitamin A isonicotinate[c]	...	...
Vitamin A 3,4,5-trimethoxybenzoate[a]	85–86	
Vitamin A *p*-aminobenzoate[c]	...	...

[a] Compounds used in this study. [b] Not obtained. [c] Obtained as an oil. [d] Hygroscopic.

where x_l is the mole fraction of the solvent, here the liquid phase, L_f is the molar heat of fusion, R is the gas constant, and T_m is the melting point of the pure solid.

It would appear for these systems then, that the relative rates of degradation of series of similar solid derivatives measured at any temperature, T, would be such that the logarithm of the rates would be, to a first approximation, a linear function of the reciprocal of their melting points. This would assume, of course, that the heat of fusion changes relatively slowly compared with $(T_m - T)$. That this general relation does, in fact, hold for the present situation is evident from Fig. 2.

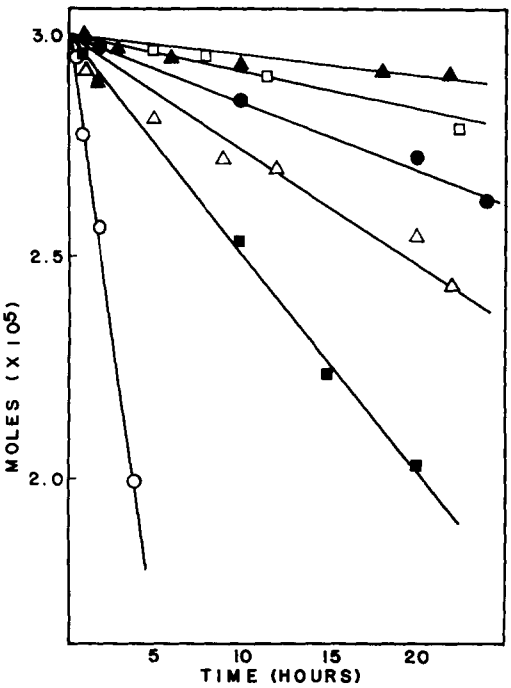

Fig. 1.—Solid state degradation of vitamin A compounds at 50°. ▲ Vitamin A benzhydrazone, m.p. 181–182°; □ vitamin A succinate triphenylguanidine salt, m.p. 140–140.5°; ●, vitamin A 3,4,5-trimethoxybenzoate, m.p. 85–86°; △ vitamin A nicotinate, m.p. 93–94°; ■ vitamin A phthalimido-N-acetate, m.p. 111–112°; ○ vitamin A acetate, m.p. 57–58°.

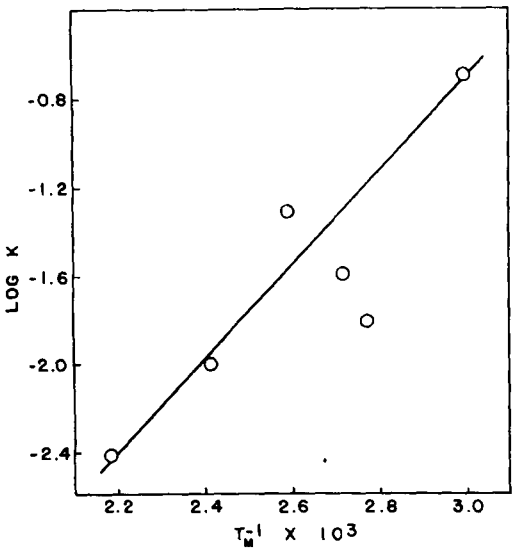

Fig. 2.—Relationship between zero-order rate constant and melting point for vitamin A derivatives.

From the slope of the line in this plot, an approximate mean value of 10 Kcal./mole is obtained for the compounds employed in this study. The heats of fusion of these vitamin A derivatives have not been determined experimentally, but they can be expected to be in the range of 10–18 Kcal./mole by comparison with similar compounds. This is in reasonable agreement with the mean value indicated by the slope and, therefore, supports the general line of reasoning presented above.

All points obviously cannot be expected to fall consistently on the average line in plots such as that shown in Fig. 2. Indeed, the effects of such uncontrolled factors as particle size, relative purity, and presence of catalytic species would also strongly influence the relative rates of degradation. The nature of the derivatives certainly must have some effect. It would appear, for example, that the greater stability of vitamin A 3,4,5-trimethoxybenzoate may be related to the fact that the acyl portion of the molecule may impart some free radical scavenging property to the whole molecule. This is suggested by the behavior of the ester in solution. The incorporation of even a mild antioxidant into the vitamin A molecule should increase its stability considerably.

None of the derivatives tested showed an appreciable induction period before degradation. Induction periods are often observed in reactions which proceed by free radical mechanisms. In such systems, nucleation is often a slow process, and some time elapses before foci of initiation reactions are developed. Many free radical processes show no induction period however, due to the reactivity of the molecules, involved.

Relative Stability of the Derivatives in Solution

The solution stabilities of the several vitamin A derivatives would not be expected to differ appreciably, particularly if the dissimilar portions of the molecule do not participate significantly in any free radical reactions. This is borne out in the data presented in Fig. 3.

These results were obtained in chloroform solution at room temperature. Measurements were carried out on solutions of essentially the same molar concentration since polymerization reactions have been shown to be approximately 1.5 order with respect to vitamin A (16). The pertinent measurements were limited to the initial stages of degradation just as they were in the case of the solid state study.

In contrast to its behavior in the solid state, vitamin A acetate appears to exhibit stability in solution comparable to that of other esters. The stabilizing effect of the strong lattice, which is apparently an important factor in determining the relative stability of the compounds in the solid state is, of course, no longer effective in solution. In fact, five of the compounds studied showed almost parallel decomposition rates. This finding appears to support the contention that the stability of compounds in the solid state is directly related to the strength of the crystal lattice.

The unusual stability of vitamin A benzhydrazone in solution is probably a reflection of its different structure. This difference in structure was not important in the solid state studies, where the principal degradative routes are probably autoxidation and polymerization; but in solution it becomes a determining factor in stability.

In solution, two reactions, in addition to autoxidation and polymerization, appear to participate in the degradation of vitamin A compounds. Isomerization of the polyolefin and formation of anhydro-

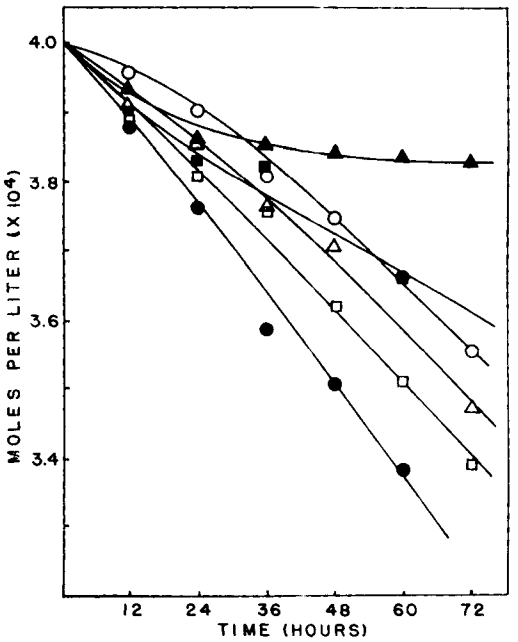

Fig. 3.—Degradation of vitamin A compounds in chloroform at room temperature. ▲ vitamin A benzhydrazone; ■ vitamin A nicotinate; O vitamin A 3,4,5-trimethoxybenzoate; △, vitamin A acetate; □ vitamin A phthalimido-N-acetate; ● vitamin A succinate triphenylguanidine salt.

vitamin A are indicated in the ultraviolet spectra of partially degraded samples. Both reactions are associated with the double bond system of the molecule. Vitamin A benzhydrazone has an additional double bond in conjugation with the double bonds in the vitamin A carbon chain. This additional double bond probably greatly influences the reactivity of the compound to isomerization and anhydrovitamin A formation.

PHARMACEUTICAL SIGNIFICANCE

It is likely, on the basis of present findings, that in a series of vitamin A derivatives, the compound having the highest melting point will be the most stable, all other factors being equal. Stability is not, however, the only criterion employed in selecting a vitamin A derivative for use in solid formulations. Equally important to the manufacturer and user of vitamin A products is the biological activity, or "availability," of the compound. Biological availability of many compounds is determined by the solubility of the substances in water and in fats and oils.

The same equation which was used to describe the influence of the melting point of a compound on its stability in the solid state can be used to correlate solubility with melting point. From this equation it is evident that for compounds having similar molar heats of fusion, those with lower melting points will have the higher solubilities. Thus, if all other factors are equal, compounds with high melting points will have lower solubilities, and hence, frequently lower biological availabilities.

The conclusions reached in this study with regard to vitamin A may also be applied to other unstable compounds. Pharmaceutical chemists have applied their energies toward the goal of increasing the solubility of compounds and of improving their taste by chemical modification. The suggested approach of using chemical alteration to provide derivatives having high melting points and hence, greater stability, should also prove useful in those instances where drug degradation poses a serious problem.

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