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Further Studies on the Interaction between Anthralin Salicylic Acid and Zinc Oxide in Pastes

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Summary. The interaction of ZnO, salicylic acid, and anthralin in various forms of paste and in hexane solution was studied, as well as the interaction of pastes with various solid surfaces.

In zinc oxide paste (P.Z.O.) anthralin is rapidly converted into therapeutically inactive compounds. The deterioration of anthralin paste is initiated on the surface of ZnO or, in the presence of water, also on other—chemically rather inert—surfaces.

The deteriorating effect of ZnO can be greatly reduced by the addition of salicylic acid, but none of the attempts to eliminate the deteriorating effect of other surfaces (skin, lint, glass wool etc.) were successfull.

It is shown that the protective effect of small amounts of salicylic acid is achieved by deactivation of the surface of ZnO, due to the formation of surface zinc salicylate.

A zinc oxide paste containing salicylic acid, an Amylum paste, and Lactacyd pH 2 were found to be good vehicles for anthralin in the clinical treatment of psoriasis vulgaris.

Zusammenfassung. Die Wechselwirkung von Zinkoxyd, Salicylsäure und Anthralin in verschiedenen Pastenzubereitungen wie auch in Hexanlösung wurde untersucht. Gleichfalls wurde das Verhalten von Pasten in Gegenwart verschiedener fester Oberflächen bestimmt.

In Gegenwart von Zinkpaste wird Anthralin schnell in therapeutisch inaktive Substanzen überführt. Der Wirkungsabfall von Anthralinpaste wird an der Oberfläche von Zinkoxyd, in wäßrigem Milieu auch in Gegenwart anderer, chemisch eher inerten Oberflächen ausgelöst. Durch Zugabe von Salicylsäure kann die zinkoxydbedingte Wirkungsabnahme weitgehend verhindert werden. Es gelang jedoch nicht, den Einfluß anderer Oberflächensubstanzen (Haut, Verbandsgaze, Glaswolle usw.) zu eliminieren.

Die Untersuchungen zeigen, daß der konservierende Effekt kleiner Salicylsäuremengen durch eine Inaktivierung der Zinkoxydoberfläche hervorgerufen wird, wobei Zinksalicylat entsteht. Als gutes Vehikel für die Anthralin-Behandlung der Psoriasis vulgaris erwies sich eine Zinkpaste, die Salicylsäure, eine Amylum-Paste sowie Lactacyd pH 2 enthielt.

Introduction

A previous paper [4] dealt with some aspects of the chemical againg of anthralin-zinc oxide pastes prepared with and without addition of salicylic acid as well as their therapeutical effects in psoriasis vulgaris.

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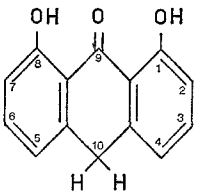
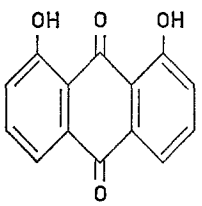
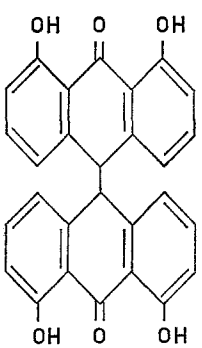
The molecular structure of anthralin (1,8-dihydroxy-9-anthron) is:

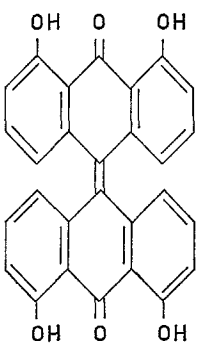


and its therapeutical effect is known to be inherently related to the presence of an OH group in at least one of two positions, 1 or 8, [10,5] and two unsubstituted H atoms in position 10. Anthralin is very easily oxidized to the therapeutically inactive 1,8-dihydroxy-9-antrachinon (danthron, chrysazin, Istizin®)



or oxidatively dimerized [5,2] into dianthrons such as:





Besides these compounds, intensely coloured dyes are also formed whose insoluble nature indicates that either cross-linking or further polymerization has taken place [1].

These dyes are also responsible for the unpleasant discoloration of the patients' skin and linen. The chemical structure of these compounds is still unknown.

In the study reported here an attempt was made to elucidate further the interaction between anthralin, ZnO, and salicylic acid; and in addition some modifications of the originally described pastes were tested.

Materials

Anthralin (1,8-dihydroxy-9-anthron), Brocades, Ned. Ph. Ed. VI (= dithranol).
Danthron (1,8-dihydroxy-9-antrachinon) p.a. Fluka.
Dianthron (1,8-1′,8′-tetrahydroxy-10,10′-bianthronyl) generously supplied by Prof. Dr. H. Schaltegger, Bern.
Hexane, Brocades, boiling range 65—69° C.
ZnO, Brocades, Ned. Ph. Ed. VI, p.a. Merck.
TiO_2, Brocades, Ned. Ph. Ed. VI.
Salicylic Acid, Brocades, Ned. Ph. Ed. VI.
Zinc salicylate, Brocades, Ned. Ph. Ed. VI.
Petroletherum, boiling range 40—60° C, Brocades, Ned. Ph. Ed. VI.
Ethyl formiate, p.a. Fluka.
Formic acid, p.a. Fluka.
TLC aluminium sheets Silica Gel F_{254} (fast running, layer thickness 0.25 mm, Merck.
Following vehicles were used:
Pasta Zinci Oleosa (P.Z.O.): oleum sesami 10%, zinci oxydum 22.5%, amylum 22.5%, vaselinum flavum ad 100%.
Pasta Titani Oleosa (P.T.O.): oleum sesami 10%, titanium dioxide 22.5%, amylum 22.5%, vaselinum flavum ad 100%.
Amylum paste: oleum sesami 10%, amylum 45%, vaselium flavum ad 100%.
Lactacyd pH 2®: a cream containing lactic acid and buffer (lactoserum), pH 2.
Commercial pastes (Stiefel):
Stie-Lasan 2®: Anthralin 0.2% in a paste with 0.4% salicyclic acid.
Stie-Lasan 4®: Anthralin 0.4% in a paste with 0.6% salicylic acid.
Stie-Lasan Pomade®: Anthralin 0.4% in a base composed of cetyl alcohol, liquid paraffin, sodium lauryl sulphate, and soft paraffin, with 0.4% w/w salicylic acid.

Methods

1. Interaction between Anthralin, Salicylic Acid and ZnO in Hexane

To anthralin solutions in hexane (0.001—0.05%), ZnO or salicylic acid was added. The mixture was shaken at room temperature and after a certain interval ZnO was separated from the solution by filtration or centrifugation. The supernatant fluid was then analysed by UV spectroscopy and thin layer (TL) chromatography.

The absorption maximum of anthralin was found to lie at 354 nm, that of salicylic acid at 315 nm, that of danthron at 428 nm, and that of dianthron at 365 nm. The mixture showed no shift of the absorption maxima of these compounds individually apparently no mutual interaction took place. The TL chromatography was performed on TLC aluminium sheets, the running fluid containing 90 ml petrolether, 9 ml ethyl formiate, and 1.5 ml formic acid. Routinely, 10 µl of the sample was applied and the R_f values compared with the standards.

2. Extraction of the Pastes

A 10-g sample of a paste containing 0.1% anthralin was extracted by boiling in 150 ml hexane for 6 h. The composition of the extracts was determined by UV spectroscopy and TL chromatography.

As the blank for UV spectroscopy, the extract of a 10-g sample paste base (without anthralin) was used. For the control (standard), 10 mg anthralin was added to 10 g paste base and the mixture extracted for 6 h in hexane; no signs of anthralin oxidation were found in these control experiments.

3. Interaction of Anthralin with Various Solid Surfaces

To a piece of lint we applied 0.1% anthralin in P.Z.O., 0.1% anthralin and 0.2% salicylic acid in P.Z.O., 0.1% anthralin in Amylum paste, or 0.1% anthralin in Lactacyd pH 2. When tested, the pastes were less than 14 days old. The lint was placed in closed petri dishes (two for each paste). In one of each pair of petri dishes the lint was dampered with physiological saline to imitate the conditions on the perspiring skin surface. The petri dishes were then placed in the dark.

Results

Interaction of Anthralin, ZnO and Salicylic Acid in a Hexane Solution

a) Interaction of Anthralin and Salicylic Acid

The anthralin concentration in the 0.05% hexane solution decreased less than 2% in 48 h. UV spectra of the solution of anthralin and salicylic acid in hexane showed no indications of mutual interaction. After having been in contact for 3 h in the solution, the dissolved components were recrystallized. The solid phase was then mixed with KBr and used for obtaining infrared (IR) spectra. The spectra too showed no indications of mutual interaction.

b) Interaction of ZnO and Salicylic Acid

After addition of 20 mg salicylic acid to 20 ml hexane, this saturated solution was brought into contact with 2 g ZnO. This led to a rapid disappearance of the salicylic acid from the solution, as can be seen from Fig. 1.

After the reaction with salicylic acid, the ZnO was washed out 6 times with hexane to desorb any weakly physically bound salicylic acid, and after pelleting with KBr, IR spectra were obtained for comparison with the IR spectra of salicylic acid, zinc salicylate and ZnO.

The IR spectra of zinc salicylate and salicylic acid differ little, the main difference occurring in the band with a maximum around 1650 cm^{-1}, which has a pronounced structure for salicylic acid, but for zinc salicylate takes the form of a broad envelope with the maximum shifted to 1600 cm^{-1}. In addition, the band with the maximum at 1380 cm^{-1} has a much higher intensity in zinc salicylate (for this compound comparable with that of the band at 1600 cm^{-1}) than in salicylic acid. The spectrum with the broad peak at 1600 cm^{-1} and a relatively intensive peak at 1380 cm^{-1}, obtained from the washed ZnO with firmly adsorbed salicylic acid, resembles the zinc salicylate spectrum more than the salicylic acid

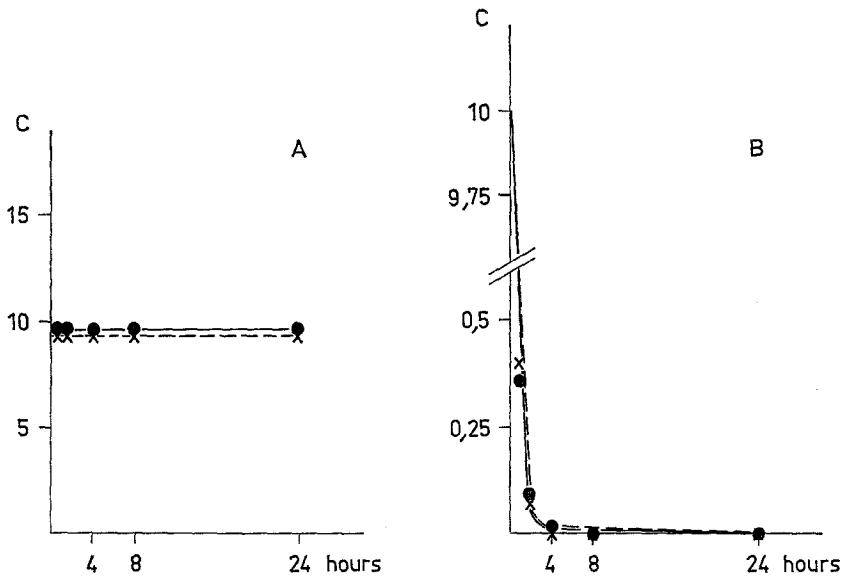


Fig. 1. Time course of the salicylic acid concentration in a hexane solution (20 ml). *A* no adsorbent added; *B* 2 g ZnO added. Solid line: only 20 mg salicylic acid added. Dotted line: anthralin (0.05%) and 20 mg salicylic acid added. *C* concentration of salicylic acid in arbitrary units

spectrum. This indicates that zinc salicylate was formed after the adsorption of salicylic acid on the ZnO.

For comparison also spectra of ZnO (pressed with KBr) were recorded. This record revealed apart from the usual spectrum of surface OH groups only monotonous (no maxima) absorption in the region were maxima of salicylic acid and zinc salicylate appeared.

In our experiments, 20 mg salicylic acid proved sufficient to inhibit the inactivation of anthralin by 2 g ZnO. Such a remarkable small amount of salicylic acid could do this if the zinc salicylate were able to cover the surface of a proportionally large amount of ZnO crystals. To find out whether this small amount salicylic acid could completely cover the ZnO, we measured the specific surface of the latter by means of the physical adsorption of N_2. This was found to be 3.5 m^2/g. To estimate the number of adsorption sites (probably Zn ions) on 1 g ZnO, the crystallographic structure of ZnO must be taken into consideration. Although it is not known exactly which crystallographic planes of ZnO form the surface the {1100} planes are the most likely ones [12]. They contain 6×10^{14} Zn ions/cm^2. It therefore seems safe estimate to put the maximum number of adsorption sites at 10^{15} sites/cm^2, as also suggested by Stone [9]. In 100 g paste containing 22.5 g ZnO the total number of adsorption sites

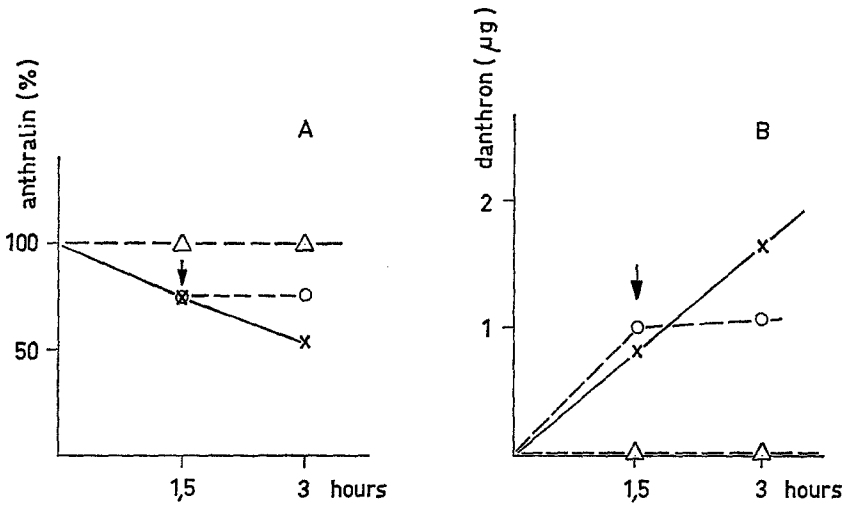


Fig. 2 A and B. Time course of A anthralin and B danthron concentration in the hexane solution (20 ml) after the addition of: 0.2 g ZnO (×), 0.2 g ZnO and 20 mg salicylic acid (△), or 0.2 g ZnO added at the start, 20 mg salicylic acid added at the point shown by the arrow (○). (Original anthralin concentration 0.01%)

would then be 8×10^{20} (the surface of 22.5 g ZnO amounting to $3.5 \times 22.5 = 79\ m^2 = 7.9 \times 10^5\ cm^2$, which means $7.9 \times 10^5 \times 10^{15} = 7.9 \times 10^{20}$ adsorption sites).

The amount of salicylic acid in the paste, i.e. 0.2 g salicylic acid/100 g paste = 1.45 mMoles, 1 mM contains 6×10^{20} molecules (Avogadro number); 1.45 mM is then $1.45 \times 6 \times 10^{20}$ molecules = 8.7×10^{20} molecules, is thus sufficient for the complete covering of all adsorption sites.

c) Interaction of Anthralin, Salicylic Acid and ZnO

When ZnO (0.2 g) is added to a solution of anthralin (0.001—0.05%) in hexane, the concentration of anthralin decreases rapidly. Virtually all of the anthralin is converted into danthron, dianthrons, and insoluble products which could not be analyzed because they remain on the ZnO surface. Fig. 2 shows an example of the rapid oxidation of anthralin under the above mentioned conditions.

When 0.1% salicylic acid is present from the onset of the interaction between the anthralin solution and ZnO, there is almost no oxidation of anthralin. When salicylic acid is added after a certain period of interaction ($1^1/_2$ h), oxidation ceases almost entirely. Fig. 2 also shows the time course of the danthron concentration.

When salicylic acid was added to the mixture of ZnO and anthralin in hexane at the moment when practically all of the anthralin had dis-

appeared from the solution and the ZnO had a pinkish-violet colour, the added salicylic acid displaced from the surface danthron and dianthron into the solution. The presence of desorbed compounds was demonstrated by both the UV spectra and the results of TL chromatography.

Unlike salicylic acid, the addition of zinc salicylate to the suspension of ZnO in the anthralin solution did not stop the deterioration of the anthralin.

d) Interaction of Anthralin Conversion Products with ZnO

Since, as shown above, in a suspension of ZnO in hexane anthralin is almost entirely converted into danthron and dianthron, the interactions of these compounds with ZnO were also studied. When 0.1 g ZnO was added to 10 ml of the 0.01% solution of danthron in hexane, danthron was quickly adsorbed and no other conversion products appeared in the solution. After the adsorption of danthron the ZnO became light pink, and never violet, as after the reaction with anthralin. When the pink ZnO was flushed several times with 10 ml hexane and then brought into a fresh hexane solution (10 ml) to which 50 mg of salicylic acid had been added, not only danthron but also dianthron was found in the solution.

In a similar experiment the adsorption of dianthron on ZnO was followed. After this adsorption or after displacement of adsorbed particles back into the solution by addition of salicylic acid, no other compound except dianthron was detected.

When danthron and dianthron were brought into contact with ZnO simultaneously both compounds were adsorbed, which means that neither of them can completely prevent the adsorption of the other. In this case, too, the colour of ZnO after adsorption was light pink (never violet).

e) Substitution of TiO_2 for ZnO

In some experiments, which were otherwise performed as described above, ZnO was replaced by TiO_2. TiO_2 is known to be much less reducible than ZnO and also less reactive to acids. Anthralin proved also to be oxidized in the presence of TiO_2, but more slowly, and the degree of dimerization was lower as well. Per weight unit, TiO_2 adsorbed less salicylic acid, but the latter nevertheless slowed down the conversion of anthralin in a way similar to the effect of ZnO.

Chemical Deterioration of Various Anthralin Pastes

Compounds soluble in hexane were extracted from various pastes by 6 h of extraction in boiling hexane. Control experiments have shown (see under Methods) that anthralin itself is not oxidized by this extraction. Extraction was repeatedly performed on different samples of the

Table 1. Percentage of anthralin recovered from hexane extracts of various vehicles containing 0.1% anthralin

Time (months)	P.Z.O.	P.Z.O. + 0.2% sal. acid.	Amylum paste	Lactacyd pH 2
0	100	100	100	100
1	20	80	90	100
2	0	80	90	100
3	0	75	87	95
4	0	80	93	90
5	0	60	85	85

same batch at 14-day intervals in the course of 5 months, and the hexane extracts were analyzed by UV spectra and TL chromatography. The anthralin content of various pastes declined with time, as can be seen from Table 1.

These results are in accordance with the colour changes observed on inspection of the pastes. Without addition of salicylic acid, after only 1 day the P.Z.O. paste containing 0.1% anthralin is a deep pink which quickly turns to violet. The paste prepared with salicylic acid shows much less colour change, but even where salicylic acid is added to anthralin in P.Z.O. it remains important not to use a paste older than 4 months (see Table 1). This means that anthralin pastes, even those containing salicylic acid, are only suitable for prescription use.

For purposes of comparison, a commercial anthralin paste (Stie-Lasan paste) containing salicylic acid was extracted. TL chromatography showed only dianthron and danthron in hexane extracts of Stie-Lasan paste 2. Stie-Lasan paste 4 yielded not only dianthron and danthron but also traces of anthralin. Only Stie-Lasan pomade, which does not contain ZnO, showed anthralin in large amounts, and only traces of dianthron and dantron were found. Unfortunately, exact data on the age of those pastes are not available, but in our opinion the shelf life of these pastes is short.

Interaction of Anthralin Pastes with Various Solid Surfaces and the Influence of Moisture

The present experiments revealed that the oxidation of anthralin is dependent on interaction with the surface of ZnO. Furthermore, the results show that the deteriorating influence of ZnO on anthralin can be counteracted by the addition of salicylic acid to the system. In clinical use, the pastes come into contact with various other surfaces, i.e. of the

skin and cloth, which might have a catalytic effect on oxidation similar to that of ZnO. For this reason, the interaction between anthralin pastes and some model solid surfaces was investigated.

It was found that once the anthralin in P.Z.O. had turned violet it underwent no further change in either dry or moist surroundings. With respect to the anthralin-salicylic acid-P.Z.O. combination the cream colour of the paste persisted in a dry environment even after a month, but in a moist environment the paste showed a brownish-violet discoloration where it came into contact with moist lint. The part of the paste that was not in direct contact with the lint did not change colour. The anthralin in Amylum paste showed the same phenomenon. It may therefore be concluded that moisture and an adsorbing surface both play an important role in the discoloration and consequently in the deterioration of anthralin.

Additional support for this conclusion was obtained with anthralin powder applied to lint in petri dishes. In a dry environment no changes occurred; the powder remained yellow. In the moist environment a brownish-violet discoloration of the powder and lint appeared where they were in direct contact, the rest of the powder remaining yellow. A glass plate, which has a smooth surface, did not catalyze the oxidation and polymerization even when moist, but on moist glass wool a brown discoloration developed rapidly. Anthralin powder on glass wool or on pieces of lint moistened with hexane showed no discoloration of antralin.

Light also seems to play a role in anthralin deterioration, but during our experiments we got the impression that its effect is only an additional, since the abovementioned reactions also occur in complete darkness.

We tried to determine what substance was responsible for the brown discoloration. For this purpose we subjected the discoloured lint to extraction with various solvents, including benzene, chloroform, a mixture of both, ethyl acetate, toluene, acetone, methanol, ethanol, ether, pyridine, acetic acid, formic acid, HCl in alcohol, and sulfuric acid. It proved impossible to extract the pigment from the lint in this way.

Since the reactions leading to the deterioration of anthralin might have an oxidative character, we attempted to inhibit the reaction with anti-oxidantia. To this end, pieces of lint were impregnated with anti-oxidantia (ascorbic acid, natrium bisulfite, tocopherol, thioureum) before application of the anthralin pastes. This failed to prevent the discoloration, which is in accordance with the results of Melis [7]. The impregnation of lint with salicylic acid did not prevent discoloration by the P.Z.O. paste containing anthralin and salicylic acid under moist conditions.

It is known from the literature [6,8] that anthralin is stable in an acid milieu. We therefore added 0.1% anthralin to a commercially available vehicle of pH 2 (Lactacyd pH 2®). This cream, applied to a

Table 2. Results of the clinical trial

I	II	I > II	I = II	I < II
Anthralin and salicylic acid in P.Z.O.	Anthralin in P.Z.O.	6	0	0
Anthralin in P.Z.O.	Anthralin in P.T.O.	0	9	2
Anthralin and salicylic acid in P.Z.O.	Anthralin and salicylic acid in P.T.O.	0	9	1
Anthralin and salicylic acid in P.Z.O.	Anthralin in Amylum paste	1	6	1
Anthralin in Amylum paste	Anthralin in Lactacyd pH 2	2	6	1

piece of lint, kept in a moist environment, gave no appreciable discoloration of the lint and the cream itself remained yellow, which seemed promising for clinical use.

Clinical Trials

In a previous paper [4] we concluded that the addition of a low percentage of salicylic acid to an anthralin paste containing ZnO potentiates the antipsoriatic effect considerably by inhibiting the inactivating interaction between anthralin and ZnO. Since, according to de Vries [11], salicylic acid does not react with TiO_2 as it does with ZnO, we decided to test the behaviour of anthralin in a paste containing TiO_2 instead of ZnO. The pastes were investigated by paired comparison, as described in our earlier paper [4].

Anthralin in P.T.O. did not prove to be superior to anthralin in P.Z.O. (Table 2); and the addition of 0.2% salicylic acid to both pastes improved the results equally. This is in accordance with the results of experiments subsequently performed in vitro.

The next step was to determine whether salicylic acid could also be omitted from pastes lacking ZnO or TiO_2. This resulted in the Amylum paste, in which ZnO was replaced by an equal percentage of amylum. We compared this Amylum paste containing 0.1% anthralin with P.Z.O. containing 0.1% anthralin and 0.2% salicylic acid. These pastes showed equal clinical activity (Table 2). An extra advantage of the Amylum paste, especially for out-patients, is that although it has the consistency of a paste, it is greasier and causes less scattering of scales when old layers of the paste are removed from the skin.

Because in the in vitro studies with anthralin pastes on pieces of lint the anthralin in Lactacyd pH 2® gave little discoloration and the combi-

nation showed little chemical aging, this anthralin cream was given a clinical trial in which it was compared with anthralin in Amylum paste. The antipsoriatic effect of both appeared to be equal, but unfortunately the discoloration of skin and linen did not differ essentially.

Discussion

Our in vitro experiments showed that small proportions of salicylic acid prevented the deterioration of anthralin in the presence of ZnO. Zinc salicylate added to the hexane solution or pastes containing both ZnO and anthralin did not influence the reactions at all. This suggests that the surface of the ZnO has to be deactivated by salicylic acid to stop the deterioration reactions due to formation of a surface salicylate. The percentage of salicylic acid that proved empirically to be sufficient for this purpose is too small for a quantitative reaction. However, we could demonstrate that the amount of salicylic acid is sufficient to deactivate the total surface of the amount of ZnO used, i.e. by the formation of the surface zinc salicylate.

Although an acidic environment stabilizes anthralin, the primary effect of salicylic acid in ZnO pastes is not a change in the pH, because other acids do not give the same effect as salicylic acid as was shown by Comaish [3].

Salicylic acid can even stop the conversion of anthralin in the presence of ZnO after the reaction has started (see Fig. 2). This means that the surface of ZnO is not only necessary for initiation of the reaction (e.g. by the production of some radicals), but is a kind of stationary catalyst for the deterioration reaction.

Although, as shown above, salicylic acid displaces adsorbed compounds from the ZnO surface back into fluid phase (hexane), it does not restore the original concentration of anthralin. This proves that the deterioration reactions are irreversible under the conditions of normal use. Anthralin in P.Z.O. loses its therapeutic activity very quickly, owing to its rapid oxidation in the presence of ZnO.

When the active surface of ZnO (or TiO_2) is deactivated by salicylic acid or when the paste does not contain ZnO (or TiO_2) at all, the pastes are much more stable. However, when even these more stable pastes are brought into contact with rough solid surfaces (e.g. lint, skin, glass wool), reactions leading to the deterioration of anthralin again set in. Water seems to catalyze these reactions. We attempted to inactivate the lint surface with salicylic acid, but the usual discoloration due to anthralin deterioration recurred.

In vitro, a cream of pH 2 (acid buffer added) containing 0.1% anthralin appeared to be most stable of all anthralin containing vehicles we

tested, but in clinical use this cream caused the same discoloration of the skin and cloth by anthralin oxidation products as the pastes did.

Thus, by adapting the components we were able to obtain more stable anthralin pastes but did not succeed in preventing the discoloration of skin and linen, which is the most objectionable aspect of anthralin treatment.

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