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Report for the period Dec. 15 - Jan. 1, (1942-43)

NDRC B-228; University of California

Los Angeles, California

(Dated Jan. 7, 1943)

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In the future, reports of the work done on this contract will cover the period from the first to the last days of each month, rather than the period starting from the 15th of each month. Since it is necessary to start writing these reports well before the 16th if they are to be received by the 15th, they cannot actually cover the period ending on the 15th. Consequently, the present report covers only the last half of December, 1942.

Present Organization. We are still engaged in two main lines of study: (1) the synthesis of intermediates to be used by Professor Calvin in the preparation of new chelates, and (2) an examination of the chemical aspects of the deterioration of Salcomine in use.

Intermediates.

I Salcomine Analogues. We have prepared samples of the following compounds for testing by Professor Calvin:

(a) 6-methylsalicylaldehyde. Prepared by the Reimer-Tiemann reaction on m-cresol, separated from the 4-methyl compound formed at the same time by separation of the two anils followed by hydrolysis; preparation and recrystallization of the phenylhydrazone of the 6-methyl compound; and finally hydrolysis of the purified phenylhydrazone of the

latter.

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BY Don & Ann ADC DATE 4/1/96
AT 7150 Seward ADD 5/1/96

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(b) 4-methylsalicylaldehyde.-- Formed along with the 6-methyl compound and separated from it by separation of the two anils followed by hydrolysis of the pure 4-methylsalicylaldehyde anil.

(c) 2,4-dimethyl-5-formyl-6-hydroxypyridine.-- A small sample of this has been prepared in the course of working out the steps of the synthesis, all of which go very smoothly. The method of synthesis should be applicable to a variety of compounds of this type. Plans for synthesizing analogues of this compound will be held up until we find out whether any particularly interesting properties are shown by the chelates to be prepared from it.

The synthesis of a pyrimidine hydroxyaldehyde has progressed very satisfactorily up to a point one step removed from the final product. The last reaction has not yet been carried out. It was reported last month that the preparation of the starting material for the series of reactions used in this synthesis (ethyl 2-methyl-4hydroxypyrimidine-5-carboxylate) was unsatisfactory. A repetition of this preparation raised the yield to 86% (literature 60%).

The conversion of the carbethoxy group to the formyl group in the syntheses carried out in the pyridine and pyrimidine series is brought about by the use of the MacFayden-Stevens method and involves the steps: ester → hydrazide → benzenesulfonhydrazide → aldehyde.

A sample of 4-hydroxy-6-ethylsalicylaldehyde has been prepared but difficulty is being experienced in carrying out some of the steps in this series. Plans at present

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include the preparation of a larger amount of the ethyl-compound, the n-propyl- and the isopropyl- compounds. It will be recalled that the methyl compound in this series showed considerable promise.

In view of the interesting results recently reported by Dr. Calvin on the chelate prepared from 3-fluorosalicylaldehyde, we are examining methods of introducing fluorine into the aromatic nucleus in the hope of finding a method which may be more practicable for large-scale use than the diazonium salt \rightarrow barofluoride \rightarrow fluoro- series so far found most generally useful.

Efforts will also be made to find a practical synthesis for 3-cyanosalicylaldehyde.

II. Polyamines

(a) The synthesis of tris-aminomethylmethane has been completed, but a smaller amount of final product was obtained than was anticipated. It was originally planned to convert one of the three primary amino groups in this molecule into the methylamino group, but too little material was obtained to permit this additional step. Enough of the triamine should be available to permit its testing with several aldehydes.

(b) The syntheses of the triamines of the general structure $\triangleleft \text{NH}_2(\text{CH}_2)_x \text{N} \text{CH}_2 \text{NHCH}_3 \right\rangle$ ($x=2$ and 3) along the lines discussed last month are progressing according to plan, but slowly.

Studies on deteriorated Salcomine.- Examination of Salcomine samples deteriorated in oil-suspensions has been concluded since Mr. Stevenson advised us that future plans no longer include studies on liquid-suspension operation. Results

so far obtained have shown conclusively that the nature of deterioration in oil suspension differs markedly and fundamentally from that obtaining in packed reactors. Consequently, conclusions drawn from studies on one of these two types of material bear little relationship to those obtained in examination of the other.

We have received samples of Salcomine from test runs performed with "Thermek" and "flat case" reactors at A.D. Little, Inc. These samples are labelled L-1 and L-2:

L-1: Described in letter from F.S. Bacon, Dec. 16, 1942
shallow bed; 1350 cycles, total O₂ produced = 27.6 lbs. per lb. of powder; % of orig. sat. at 1350 cycles = 25%

L-2: Described in letter from F.S. Bacon, Dec. 16, 1942
Deep bed; total O₂ produced = 23.6 lbs per lb. of powder;
800 cycles; % of orig. sat. = 54%

These have been submitted to the basic tests for activity, aldehyde content, and elementary analysis. We are now studying them in greater detail by means of the technique of solvent extraction. Some of these results are reported below.

Extension of the method of examination of deteriorated samples by means of exhaustive extraction with suitable solvents leads us to believe that the method will prove a very useful one. The procedure we are using involves a) a separation of the original sample into an "extractable" fraction and a non-extractable residue. The "extractable"

fraction consists of crystalline "red isomer" and a variable amount of soluble material which, upon evaporation of the solvent, is obtained as a tarry, amorphous substance.

- b) Examination of the non-extractable residue with solvents other than the one first used.
- c) Examination of the various fractions (extracts, mother-liquor-soluble residues and non-extractable residues) by analyses for aldehyde, ethylenediamine and cobalt content.

A typical study is described, using sample A-67 as an example; some of these results have been reported earlier in an incomplete form:

Five grams of A-67 was extracted (Soxhlet) with dry benzene for 32 hours. The residue in the thimble (I) weighed 3.82 g. (76%). The benzene extract was cooled and filtered; 0.88g (17%) of crystalline red isomer (II) was obtained. Evaporation of the filtrate gave 0.52 g (10%) of brown, amorphous solid (III).

A portion of 0.83 g. of the red isomer (II) was extracted with 75 cc. of benzene containing 5 cc of dry pyridine. The crystallizate in the extract weighed 0.87 g. and after activation at 170°-25mm. showed an activity of 3.8%. The red isomer can be activated in a variety of ways. It gives 100% recoverable aldehyde on hydrolysis. It will henceforth be treated as chemically intact Salcomine.

The non-extractable residue (I) and the material (III) from the mother-liquor were analyzed for aldehyde content:

I = 55.9% recoverable aldehyde; 10.9% residue

III = 66.8

Aldehyde balance.-

I	.76	x	55.9	=	43
II	.17	x	100	=	17
III	.10	x	66.8	=	<u>6</u>
					66% (61% found on original sample)

Residue (from hydrolysis) balance.-

I	0.76	x	10.9	=	8.3
II	0.17	x	0.0	=	0
III	0.10	x	17.6	=	<u>1.8</u>
					10.1 (18% found on original sample)

The somewhat higher percentage of aldehyde recovery from each fraction separately and the somewhat lower residue means that more efficient hydrolysis is possible on the separate fractions and thus that a small amount of recoverable aldehyde must be present in the 18% residue found in the original sample. The difference is small and not significant. The important conclusion is that the extraction procedure does not give rise to further amounts of non-hydrolyzable (polymeric) residue.s.

A conclusion to be drawn from these results is that
 a) either the aldehyde present in a given sample is not all in the form of chemically-intact Salcomine (either active or inactive), or b) some of the aldehyde so present is not accessible to the action of the solvent. This choice can be made certain, we feel, by the application of one other

analytical approach: the determination of recoverable ethylene diamine. We have done a considerable amount of work on this determination and now feel that the simplest of the many possible procedures will give us the needed information. This involves the precipitation of the diamine dibenzoate from the aqueous solution obtained after acid hydrolysis of the sample. It was pointed out in an earlier report that the precipitation of the diamine is incomplete in the presence of cobalt, even in a strongly alkaline medium. However, it appears that a close approximation to the figures we need can be obtained by a series of empirical results obtained on samples whose diamine content can be estimated on other bases. For instance, it is a safe assumption that red isomer contains 100% of the amount calculated for the theoretical composition of Salcomine. Salicylaldehyde ethylenediamine serves as another standard. Some experiments have been carried out along these lines, and are as follows.

Procedure.- The acid-hydrolyzed sample is steam-distilled to remove salicylaldehyde. The aqueous solution remaining is filtered from insoluble residue and made strongly alkaline with sodium hydroxide. The precipitated cobalt hydroxide is filtered off (through filter-aid) and to the filtrate is added an excess (several times the required amount) of benzoyl chloride. After shaking and allowing the mixture to stand until the benzoyl chloride is decomposed the precipitated diamine dibenzoate is collected, dried and weighed.

recovery: % of calculated amount

Salicylaldehyde ethylene-	
diimine	91
Red isomer	87
L-2	47
G-1	52
L-1	49

Red isomer contains	100%	recoverable aldehyde			
L-2 contains	78.6%	recoverable aldehyde;	activity	2.0%	
G-1	"	70.2%	"	"	0.9%
L-1	"	72.3%	"	"	1.0%

These figures indicate strongly that some of the recoverable aldehyde in L-1, L-2 and G-1 is not bound in the form of chemically intact Salcomine, and are further support for the still provisional assumption that a certain amount of the chemical attack on the complex is directed at the diamine moiety.

It seems a safe assumption that values for diamine recovery, empirical as they will be, will be of value in examining extraction residues which a) are not further extractable but b) contain 50-60% of aldehyde recoverable on hydrolysis.

The table on the following page gives in summary form results similar to those described above in detail for sample A-67. The most notable conclusion to be drawn these results is that while two samples (e.g., A-67 and A-68) may be of essentially the same activity, they may vary widely in their content of both recoverable aldehyde and extractable red isomer. (It should be noted that the red isomer formed

on extraction is a product of recrystallization and is not necessarily present in the sample; compare X-1, which is nearly pure, active Salcomine but which yields 85% red isomer on extraction with benzene.)

Sample	X-1	G-2	L-2	L-1	A-68	G-1	A-67
1. Activity (110°)	4.41	3.92	2.01	1.00	0.19	0.42	0.13
2. " (170°)	4.57	4.24	--	--	0.67	0.91	0.51
3. % Ald. ⁸	101	96.1	78.6	72.7	69.9	70.2	59.8
4. % res.	0	3.5	4.9	6.2	6.4	8.0	18.0
5. Solv. ¹	Bz-70 ¹⁰	--	Bz-65	Bz-148	Bz-64	--	Bz-32 ⁵
6. % Crystals ²	85	--	22 61	50	46	--	17
7. % Rec.	12	--	29	49	42	--	76
8. % Ald. Crystals	100	--	100	100	100	--	100
9. % res. "	0	--	0	0	0	--	0
10. % solid (M.L.) ⁷	--	--	6	--	--	--	10
11. % Ald. "	--	--	46	47	--	--	66.8
12. % res. "	--	--	36.0	38.0	--	--	17.6
13. % Ald. Res.	82.9	--	50	35.0	39.2	--	55.9
14. % res. Res.	9.8	--	16.7	12.5	12.1	--	10.9
15. Ald. bal. ³	92	--	79	73 ⁹	62	--	66
16. res. bal. ⁴	1	--	7.0	5.6 ⁹	5	--	10.1
17. Diamine Recov.	88 ⁶	--	47	50	--	--	--

Blanks to be filled in by experiments in progress.

1. Figure represent hours extracted

2. Red isomer

3. Ald. bal. = (6x8)+(7x13)+(10x11) compare with 3

4. res. bal. = (6x9)+(7x12)+(10x12) " " 4

6. Assumed the same as "red isomer"

5. complete(?)
7. M.L.=mother-liquor

8. All aldehyde determ. run on deox. samples

9. Does not include M.L. solid

10. Benzene - 70 hours

Studies of L-1 and L-2 are still in progress, but certain results aside from those reported in the table, are of interest. Cobalt analyses on these samples show them to be markedly different.

<u>Sample</u>	<u>% Co</u>	
X-1	18.9	(added for comparison)
L-2	18.7	
L-1	16.8	

Since L-1 is more extensively deteriorated than L-2 (1.0% activity vs. 2.0%) gives a lower aldehyde recovery (73% vs. 79%) and gives less extractable red isomer (50% vs. 61%) it appears that previous ideas concerning one aspect of the deterioration are again supported; namely an increase in the total weight of the sample (introduced oxygen) has occurred, resulting in a lowering of the analytical figures for the other elements.

In the description of the operating conditions which was sent with these samples, nothing was said of the humidity of the entering air. It would be of interest to know whether this was the same for both L-1 and L-2, and what it was (absolute value). It would appear, from previous experience, that L-1 was treated with wetter air than L-2, but perhaps the difference in actual duration of these two runs would be adequate to account for the differences.

Activation attempts .- It is easy to activate the red isomer in a variety of ways, all involving its conversion into a pyridinate which becomes active upon depyridination. If a deteriorated sample were to contain accessible (to a

solvent) active material or red isomer, or if the "coating" around the active material (~~xxx~~ cf. X-ray results) were soluble in a given solvent, it should be possible to activate deteriorated material in situ. So far, all attempts to do this have resulted in failure, in spite of the fact that the Salcomine can be removed by extraction and that crystals of red isomer are often found intermingled with the material in the extraction thimble. Typical experiments are described herewith:

I. 1.00 g. of red isomer was moistened with 2 cc. of pyridine, 50 cc. of isopropyl ether was added, and the mixture was heated under reflux for a few minutes. The solid was collected; it weighed 1.29 g., and after activation at 170° had an activity of 3.14%. II. A sample of A-68 was treated in exactly the same way. Its activity was then 0.96% (original 0.5 - 0.8%) A slight but hardly significant activation was thus brought about.

III 2.0 g. of A-68 was boiled for 4 hours with a mixture of 150 cc. of benzene and 0.8 cc. of pyridine. After recovery and activation at 170°/ 25mm. it showed no increased activity.

IV. 2.23 g. of A-68 was heated with 100 cc. of water and 0.55 ml. of pyridine. After heating at 170°/ 25 mm. it showed an activity of 0.64% (no activation).

It was thought that it might be possible to choose a solvent which would attack the "coating" around the active Salcomine and thus expose active material. It has not been

possible to do this. Extraction of A-68 with alcohol and acetone removed much of the original sample (65% and 54%, respectively) these solvents behaving like benzene in this respect. Continued extraction of A-68 with carbon tetrachloride and isopropyl ether for 28 hours resulted in the removal of only 2% and 7% of the sample weight, respectively. The residual material was inactive. It is of interest to note that the carbon tetrachloride extract contained a definite, but small, amount of free salicylaldehyde (approximately 0.5%).

Activation by heating.- We have observed in the course of activity determinations that a higher activity is found when the sample is deoxygenated at 170° than ~~when the sample is deoxygenated at 170°~~ when it is deoxygenated at 110° (both at 25mm.). The difference between these two activities is greater the more deteriorated the sample. Part of this change is due to an actual loss of some tarry material during the high temperature treatment; this material can be seen collecting in the outlet tubes. Part must also be due to a slight temporary activation at the higher temperature, due either to removal of traces of residual oxygen or to the removal of some of the "coating" which presumably covers the active material. The total gain is not large, and in several experiments an increase in activity after 170° treatment was not preserved in a subsequent measurement after 110° treatment. Two experiments show the magnitude of these effects:

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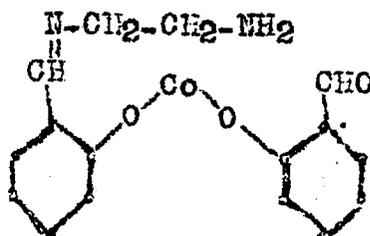
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I. A 4.5 g. sample of A-67 was heated at 170° at the vacuum of an oil-pump (5mm.) for 4 hours. The total loss in weight was approximately 16%. The activity of the residual sample was 0.31%, or within the range of values obtained on the original sample.

II. A 19.93g. sample of G-1 was treated as above for 5 hours. It lost 1.98 g. (9.9%). Some free aldehyde was present in the sublimate. Water collected in the dry-ice trap. The activity of the 17.95 g. of residual material was 1.21%. This is a slight gain over the "170° activity" previously found (1.0, 1.1%) and is preserved on subsequent measurement of "110° activity."

The significance of these observations, and of others made from time to time along the same lines is that activation by heating alone is possible only to very limited degree, and ~~as~~ may not be "activation" in the strict sense. This conclusion is not a new one, but has been pointed out by others in the past. It is of interest to reemphasize it, however, in view of some suggestions recently made in a DuPont report (Oct.1-Dec. 12, 1942). It was proposed there that the action of water was to hydrolyze one of the Schiff's base linkages in the chelate to give the structure,



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and that it should be possible to effect a reactivation by "dehydration". It is likely that if such a hydrolysis were to occur, and if the groups were to remain disposed in the same relative positions they had before hydrolysis, that dehydration to reform the chelate would be very easily brought about. It will be recalled that salicylaldehyde and ethylenediamine react almost instantly to form the Schiff's base in aqueous solution. It is our opinion that if any appreciable amount of deterioration were due to a partial hydrolysis as shown, the reversal of this to reform the chelate would take place with ease and completeness. The fact that heating effects so little reactivation speaks strongly against such an explanation for the deterioration. It is still our view that the action of water ^{is in} ~~is in~~ acting upon the oxygenated complex in such a way that a simultaneous hydrolysis and oxidation, with participation of the bound oxygen, takes place.

Respectfully submitted

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