UNCLASSIFIED

AD NUMBER

AD045717

CLASSIFICATION CHANGES

TO: unclassified

FROM: secret

LIMITATION CHANGES

TO:
   Approved for public release, distribution unlimited

FROM:
   Controlling DoD Organization: Army
   Chemical Corps, Army Chemical Center, MD.

AUTHORITY

Edgewood Arsenal, 5 Feb 1955; Edgewood Arsenal ltr, 6 Oct 1972

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Task 3. Analogs of Tetrahydrocannabinol for Chemical Corps Procurement Agency

Contract No. DA 18-IOS-CML-1564
Progress Report from December, 1952 thru January, 1953

Best Available Copy
SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA
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Bi-Monthly Report No. 3

on

TASK 3

for

Chemical Corps Procurement Agency

under

Contract No. DA18-108-CML-4564

Period Covered: December, 1952 through January, 1953

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Summary

The preparation of one of the most active tetrahydrocannabinol analogs mentioned by Adams (Formula I, \( R = 1\text{-methyloctyl} \)) has been completed except for the final distillation. The preparation of the second of Adams' compounds (\( R = 1,2\text{-dimethylheptyl} \)) has been delayed because of delay in the arrival of an intermediate.

Concurrently with the above work, various synthetic methods have been tried for the preparation of intermediates which could lead to nitrogen and sulfur analogs of tetrahydrocannabinol. A proposed synthesis has been outlined and several steps have been completed on a small scale.

Analogs of Tetrahydrocannabinol

Changes in Alkyl Groups

The structure of tetrahydrocannabinol (I, \( R = n\text{-C}_{5}H_{11} \)) is given again for reference.

\[
\begin{array}{c}
\text{CH}_{3} \\
\downarrow \\
\text{C} \\
\downarrow \\
\text{CH}_{2} \\
\downarrow \\
\text{CH}_{3}
\end{array}
\begin{array}{c}
\text{CH}_{3} \\
\downarrow \\
\text{C} \\
\downarrow \\
\text{CH}_{2} \\
\downarrow \\
\text{CH}_{3}
\end{array}
\begin{array}{c}
9 \\
10 \\
7 \\
6 \\
5 \\
4
\end{array}
\begin{array}{c}
\text{HO} \\
\downarrow \\
1 \\
2 \\
3 \\
R
\end{array}
\begin{array}{c}
\text{I}
\end{array}
\]

The steps leading to Adams' two most active tetrahydrocannabinol analogs were described in a previous report. The synthesis of one of these compounds, 1-hydroxy-3-secondary nonyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (I, \( R = 1\text{-methylloctyl} \)) has been completed except for the final distillation.

The preparation of the second of Adams' compounds in which the alkyl group (\( R \) in Formula I) is 1,2-dimethylheptyl has been carried through to the 3,5-dimethoxyphenyl-2-heptyl ketone. This synthesis has been delayed by difficulty in obtaining an intermediate.

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Nitrogen and Sulfur Analogs

The method outlined in the previous report\(^a\) for the preparation of N and S analogs has required some changes since one of the steps involved a reaction between a cadmium alkyl and an aromatic acid halide containing a nitro group. The literature\(^b\) does not state that nitro groups interfere with such a reaction; however, it has been our experience that the reaction between dibutyl cadmium and 3,5-dinitrobenzoyl chloride leads to a tar. It will therefore be necessary to prepare our aromatic ketone via the amide and butyl magnesium bromide. The fact that nitro groups interfere with this reaction also means that they will have to be replaced.

A satisfactory method involving reduction with ammonium sulfide has been found for converting 3,5-dinitrobenzoic acid to 3-amino-5-nitrobenzoic acid so it will not be necessary to go through the methyl ester as previously indicated. The method which is now being proposed for the preparation of N and S analogs involves the following steps:

\[\text{NH}_{4}\text{OH} \rightarrow \text{COOH} \rightarrow \text{COOH} \rightarrow \text{COOH}\]

\[(\text{CH}_3\text{O})_2\text{SO} \rightarrow \text{COOH} \rightarrow \text{COOH} \rightarrow \text{COOH}\]

\[\text{PCl}_3 \rightarrow \text{COCl} \rightarrow \text{CONH}_2 \rightarrow \text{C}_4\text{H}_5\text{MgBr} \rightarrow \text{COOH}\]

\[\text{Zn-Hg} \rightarrow \text{C}_9\text{H}_11 \rightarrow \text{Br} \rightarrow \text{HCl} \rightarrow \text{Na} \rightarrow \text{Br} \rightarrow \text{H}_2\text{N} \rightarrow \text{Br} \rightarrow \text{HS} \rightarrow \text{OCH}_3\]

---

The last two compounds can probably be condensed with ethyl 5-methyl-
cyclohexanone-2-carboxylate to give respectively the desired N and S
intermediates. The methoxy group will then have to be cleaved and the
resulting product reacted with excess methyl magnesium iodide.

In the above synthesis, 3-methoxy-5-nitrobenzoic acid and 3-
bromo-5-nitrobenzoic acid have been prepared. Besides preparing 3-bromo-
5-nitrobenzoic acid via the amino compound, it has also been prepared
by the direct bromination of m-nitrobenzoic acid. This requires pressure
equipment and twenty hours heating at 160°C to get a 50% conversion.

Several other methods for the preparation of suitable inter-
mediates have been explored. Gilman and Kyle\(^{a)}\) indicate that when o-
haloanisoles are treated with sodamide in liquid ammonia one obtains m-
amino anisole. It was hoped that this rearrangement to the meta position
would also occur when an alkyl group is present on the ring as shown
below:

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{Br}
\end{array} \xrightarrow{\text{NaNH}_2} \begin{array}{c}
\text{H}_2\text{N} \\
\text{OCH}_3
\end{array}
\]

For a trial run m-methylanisole was brominated in carbon tetra-
chloride and the distilled product reacted with sodamide in liquid ammonia
according to the reference cited above. The recovered amine was shown to
be an aromatic amine by diazotization and reaction with \(\beta\)-naphthol. Its
acetyl derivative contained the required amount of nitrogen; however, its
melting point was lower than the expected 3-acetamino-5-methoxy toluene
or any of its isomers. It is possible that the amination reaction produced
more than one isomer and they were not easily purified by recrystallization.

Considerable attention was also given to the use of butyl phenyl
ketone as a starting material. Trial runs were made with acetophenone.
m-Nitroacetophenone was easily prepared and reduced to m-amino acetophenone.
Attempts to introduce a second nitro group into m-nitroacetophenone or to
nitrate m-amino acetophenone were unsuccessful. The sulfonation of m-
nitroacetophenone was not promising.

It is planned soon to try another approach to this problem which
will involve the replacement of one hydroxyl group in 3,5-dihydroxy n-amyl
benzene with the amino group. Such a reaction is known to proceed with
resorcinol when it is heated to 200°C with ammonium hydroxide. The result-
ing compound with appropriate modification could then be used for the

condensation step with ethyl 5-methylcyclohexanone-2-carboxylate to give a nitrogen or sulfur analog of tetrahydrocannabinol. The 3,5-dihydroxy n-amylbenzene can be prepared from benzoic acid via the steps outlined in a previous report.a)

a) Winkler, D. E., Progress Report 2 (1952.)