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WRITTEN BY

APPROVED BY

DISTRIBUTION:

Dr. H. Wakeham
Mr. F. E. Resnik
Dr. T. S. Osdene
Mr. R. N. Thomsr
Dr. R. Fagan
Dr. P. A. Eichc
Dr. W. Gannon

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ABSTRACT

Accomplishments this year have been in the fields of nicotine chemistry and flavor-release compounds. Anabasine and 2-,3-, and 4-nornicotine have been prepared, and the groundwork has been laid for synthesis of 2-,3-,and 4-myosmine. Initial work has been started on preparation of compounds with either altered or fixed nitrogen-nitrogen bond distances. Several 5'-substituted nicotines have been made, including 5'-cyanonicotine.

Work on menthol-releasing polymers has been completed. Several aldehyde-releasing compounds have been prepared via Reformatsky reactions, and alkoxy esters are also being investigated.

I. INTRODUCTION AND OBJECTIVES

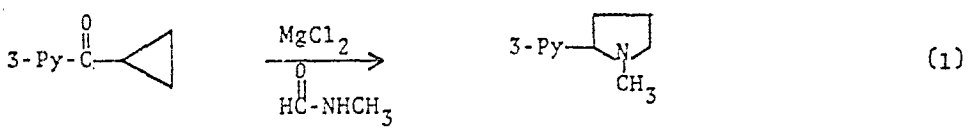
The major objectives of this project are twofold. The first is the synthesis of compounds which can serve as candidates for flavor-release in tobacco. Such compounds can be designed for release primarily in mainstream smoke (taste) or sidestream smoke (aroma) or both. Our second objective is the synthesis of either natural constituents of tobacco or analogues of its constituents. The purpose of such synthetic work is not only to provide pure samples of tobacco compounds for pharmacological testing and comparison with isolated samples, but more importantly to explore structure-activity relationships of pharmacologically active tobacco constituents and, when applicable, to elucidate some of the complex nonenzymatic organic chemistry occurring in tobacco during curing and aging.

II. RESULTS

A. Synthesis of Minor Tobacco Alkaloids

1. d,ℓ-Nicotine and d,ℓ-Nornicotine

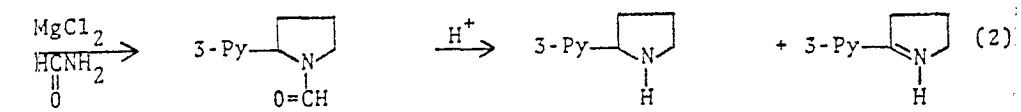
The preparation of d,ℓ-nicotine was undertaken to provide samples for pharmacological testing. In that synthetic routes to the minor alkaloids, as well as nicotine analogues, generally give racemates, racemic nicotine, rather than natural ℓ-nicotine, would serve as a better standard. Synthesis of d,ℓ-nicotine as well as the preparation of the three isomeric d,ℓ-nornicotines, is based upon the rearrangement of cyclopropyl pyridyl ketones. Breuer[1] reported that treatment of pyridyl cyclopropyl ketone (1) with magnesium chloride and N-methylformamide gave d,ℓ-nicotine (2) in a 30% yield (Equation 1). This reaction was initially extended to the synthesis of 3-nornicotine (3) by



(1)

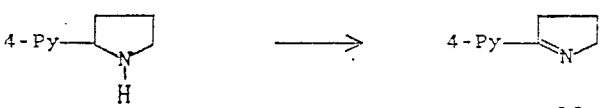
1 2

substituting formamide for N-methylformamide and hydrolysing the intermediate N-formylnicotine (4) (Equation 2). The yield of 3, after isolation, was 50%, although the product was later



(2)

found to be contaminated slightly (~ 5%) with the corresponding myosmine (5). The nornicotine (3) could be methylated in high yield (~ 95%) to give 2. The reaction shown in Equation 2 has since been applied to 4-pyridyl (6) and 2-pyridyl (7) cyclopropyl ketones to give 2-nornicotine (8) and 4-nornicotine (9). Compound 9 was contaminated with a significant amount (~ 30%) of the corresponding 4-myosmine (10). The two compounds were separated by preparative thin-layer chromatography. It was found, however, that 9 slowly is converted to 10 on standing in the dark under argon (Equation 3). This interesting transformation is



9 → 10 (3)

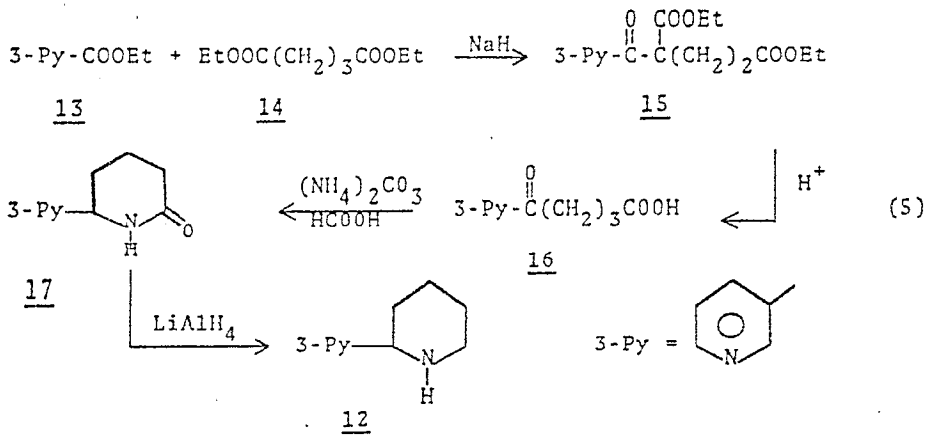
now under study. Also under study are several routes using the three pyridyl cyclopropyl ketones (1, 6, and 7) as starting materials for the three isomeric myosmines[2] (5, 10, and 11) (Equation 4).

(4)

1 R=3-Py	5 R=3-Py
6 R=4-Py	10 R=4-Py
7 R=2-Py	11 R=2-Py

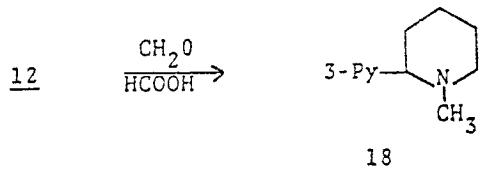
2. d,ℓ-Anabasine

The successful synthesis of d,ℓ-anabasine (12) has been carried out during this year. Although several literature routes exist for the preparation of anabasine[3,4], none of these has previously been optimized. The synthetic procedure ultimately chosen, a combination of literature routes, gives anabasine in reasonable yield from ethyl nicotinate (13) (Equation 5).



(5)

Methylation of 12 gave N-methylanabasine (18) with no complications (Equation 6).

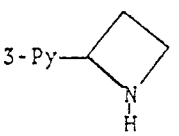


(6)

B. Synthesis of Nicotine Analogues

1. Pyridyl Azetidines

The successful synthesis of 2-(3-pyridyl)-azetidine (19) and 1-methyl-2-(3-pyridyl)-azetidine (20) has been completed and a completion report was issued.[5] In addition the



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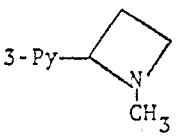
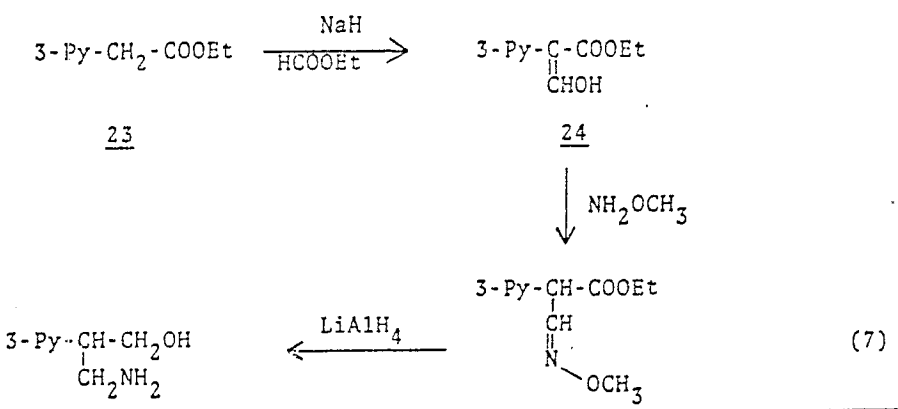


20

synthesis of 3-(3-pyridyl)-azetidine (21) is in progress and has been successfully carried to the penultimate step, namely 1-tosyl-3-(3-pyridyl)-azetidine (22). The synthetic scheme, shown in Equation 7, is more general than the scheme used for the preparation of 19, due to the development of a new procedure for the preparation of the amino alcohol 26. As a consequence it can easily be applied to the synthesis of other pyridyl azetidines.



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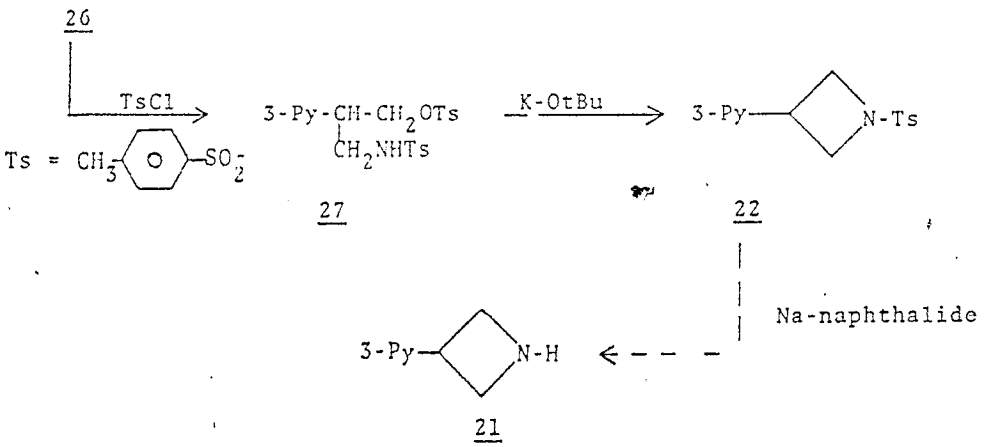
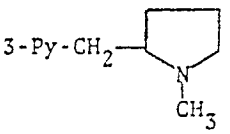


2. Nicotine Analogues with Altered Nitrogen-Nitrogen Bond Distance

a. Picolylpyrrolidines

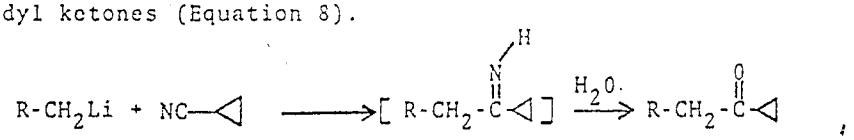
A projected synthesis of picolylpyrrolidines, such as 28 is of interest in that the methylene group placed



28

between the pyridine and pyrrolidine rings alters the nitrogen-nitrogen bond distance. It is of interest to determine pharmacological differences between this type of compound and nicotine itself. The route chosen for the preparation of 28, as well as the isomeric 2- and 4-picolylpyrrolidines, is via the rearrangement of the corresponding picolyl cyclopropyl ketones. Therefore, in preparation for these syntheses the

three isomeric cyclopropyl picolyl ketones have been synthesized using reactions analogous to those used to make the cyclopropyl pyridyl ketones (Equation 8).



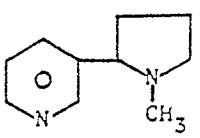
(8)

29 R = 3-Py
31 R = 2-Py
33 R = 4-Py

30 R = 3-Py
32 R = 2-Py
34 R = 4-Py

b. Bridged Nicotines

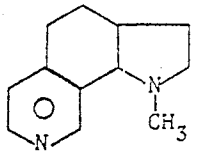
A second proposed approach to altering the nitrogen-nitrogen bond distance is based on the preparation of bridged nicotine derivatives. Since the pyridine and pyrrolidine rings of nicotine (2) are free to rotate with respect to one



2

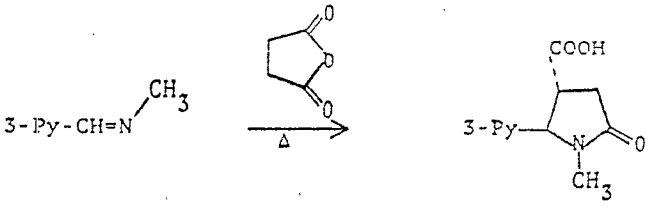
another, the nitrogen-nitrogen bond distance in nicotine can vary considerably depending on the conformation of the two rings. It is a reasonable assumption that the two rings adopt a single conformation, however, in order to complex or interact with an active site in an organism. By preparing bridged nicotines and testing them for pharmacological activity, information can be gained as to the nitrogen-nitrogen bond distance necessary for nicotine to interact with the appropriate substrate.

One bridged nicotine now under study is compound 35. The proposed synthesis of this compound is



35

complex and has been discussed in another report.[6] The synthesis of 35 has been initiated by the synthesis of 3'-carboxycotinine (36) via a known reaction[7] (Equation 9).



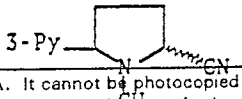
(9)

37 36

3. Nicotine Analogues with Substituents in the Pyrrolidine Ring

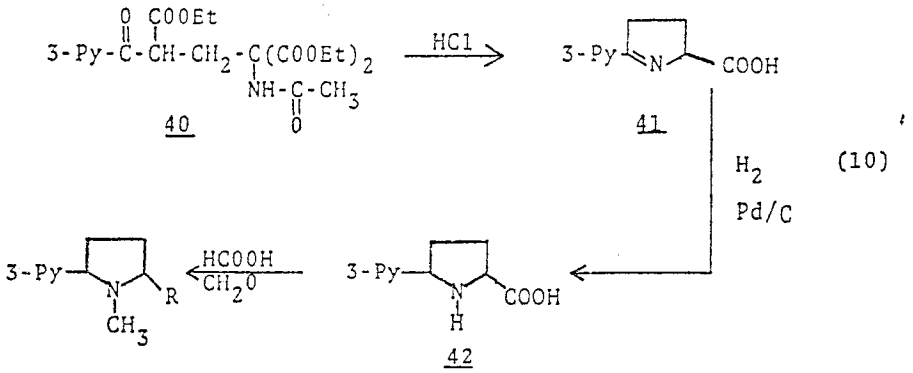
a. 5'-Substituted Nicotines

A program was initiated some time ago with the ultimate goal of synthesizing 5'-cyanonicotine (38). The original approach to the problem, described in the previous Annual Report[8], utilized 5'-carboxamidonicotine (39) as the potential precursor (Equation 10). All attempts directed to the conversion of 39



38

to 38 have failed. However, this procedure has provided samples



40 41 42 (10)

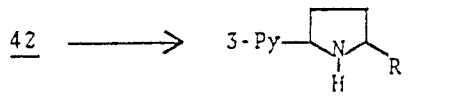
39 R = $CONH_2$

43 R = COOH

44 R = $COOCH_3$

45 R = CH_2OH

of 5'-carboxynicotine (43), 5'-carbomethoxynicotine (44), 5'-carboxamidonicotine (39), as well as 5'-hydroxymethylnicotine (45) obtained by reduction of 44. In addition, when esterification and amidation, or reduction, are carried out on 42, the analogously substituted nornicotines are obtained (Equation 11).



(11)

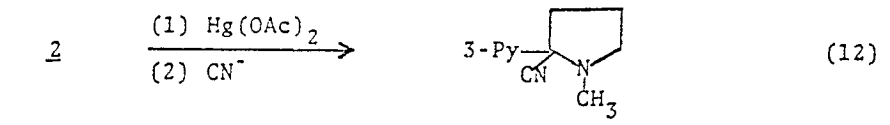
46 R = $COOCH_3$

47 R = $CONH_2$

48 R = CH_2OH

All of these intermediates have the cis configuration as has been shown by comparison of nmr spectra to analogous compounds.[7,9] Compounds 39 and 42-48 can be expected to yield valuable information concerning the effect of election density at the pyrrolidine ring on the pharmacological activity of nicotine analogues.

A second approach to 5'-cyanonicotine was based on a literature report of its synthesis[10] by treatment of nicotine with mercuric acetate and cyanide. When the reaction was repeated in this laboratory a low yield (∿ 4%) of a cyanonicotine was obtained which gave the same spectral data as the published compound. We have shown, however, that the compound obtained is 2'-cyanonicotine (49), possibly contaminated with about 10% of the 5'-isomer. (Equation 12)

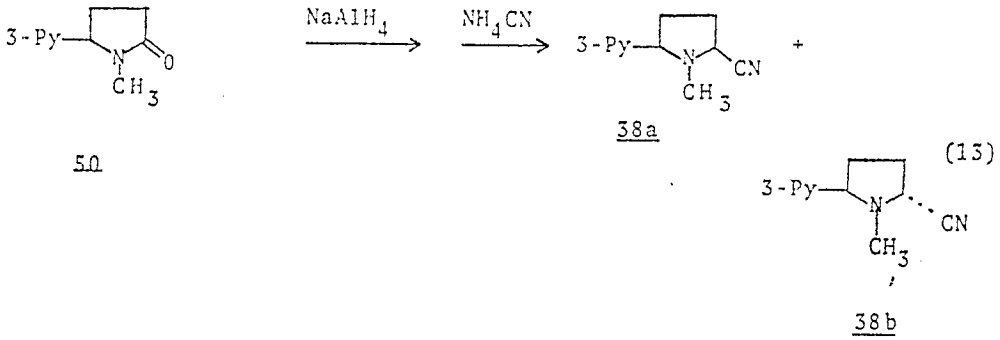


(12)

49

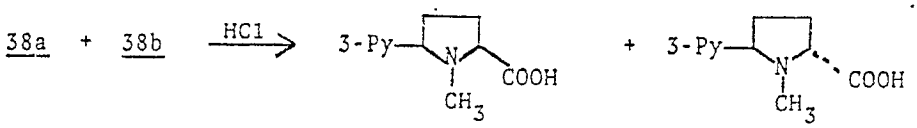
Evidence for this structural assignment was obtained principally from ^{1}H- and ^{13}C-nmr.

Recently 5'-cyanonicotine has been obtained in one step from cotinine (50) (Equation 13). This synthesis gives both cis and trans isomers. Structure proof of the nitriles



50 38a 38b (13)

in addition to routine spectral analysis, was carried out by hydrolysis of the mixture of 38a and 38b to the acids which could be separated by fractional crystallization (Equation 14)



43a 43b (14)

Acid 43a was identical to that prepared by the route described earlier (Equation 10). The preparation of 5'-cyanonicotine allows for the synthesis of a large series of 5'-substituted compounds in both cis and trans forms.

b. 3'-Substituted Nicotines

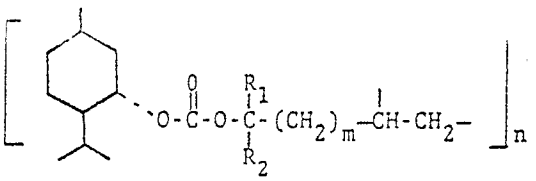
Compound 36, already prepared, will be utilized to prepare a series of 3'-substituted nicotines for comparison with 5'-substituted nicotines.

C. Flavor-Release Compounds

1. Menthol-Release Polymers

A number of menthol release polymers have been prepared

this year, primarily in order to extend the patent coverage on poly(ℓ-menthyl 1,1-dimethylallyl carbonate) discussed last year.[8] These compounds are poly(ℓ-menthyl 1-ethyl-1-methyl-4-pentenyl carbonate) (51), poly(ℓ-menthyl 1,1-dimethyl-3-butenyl carbonate) (52) and poly(ℓ-menthyl 1,1-dimethyl-10-undecenyl carbonate) (53). All three compounds released



51 $R_1 = CH_3$, $R_2 = C_2H_5$, m = 2

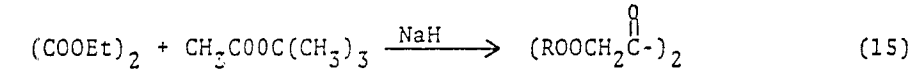
52 $R_1 = CH_3$, $R_2 = CH_3$, m = 1

53 $R_1 = CH_3$, $R_2 = CH_3$, m = 8

menthol on heating.

2. Biacetyl-Release Compounds

Several approaches have been explored for the purpose of obtaining a compound which will release biacetyl (54) when heated. The first approach utilized the preparation of a diester of 3,4-dioxoadipic acid (55) from the reaction of diethyl oxalate (56) with t-butyl acetate (57). (Equation 15). Compound 55 would be expected to yield biacetyl (54) on heating



56 57 55 R = Et or $C(CH_3)_3$ (15)

(Equation 16). The odor of 54 was detected when 55 was

$$\underline{55} \xrightarrow{\Delta} (CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-})_2 \qquad (16)$$

54

pyrolyzed, but no quantitative data have been obtained at this time. An analogous approach was based on the synthesis of a monobasic, rather than a dibasic, ester. Ethyl 3,4-dioxovalerate (58) was prepared, but the yield was extremely low. This

$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}COOEt$$

58

approach was therefore abandoned. An alternative type of biacetyl-release substance is 3,3-diethoxybutan-2-one (59), prepared by the acid-catalyzed reaction of biacetyl with ethyl orthoformate. A product was obtained from this reaction, but it has not been fully characterized. Despite the promising results obtained, no further time was devoted to this problem, due to projects of higher priority.

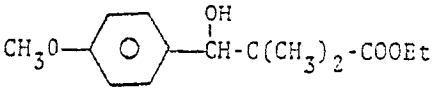
$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{OC_2H_5}{\overset{|}{C}}\text{-}CH_3 \quad (OC_2H_5)$$

59

3. Aldehydic Type Flavor-Release Compounds

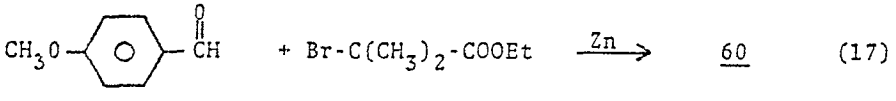
a. Compounds Prepared from Reformatsky Reactions

During this year, the Development Department has expressed great interest in testing CR-1214; i.e., ethyl 2,2-dimethyl-3-hydroxy-3-(4-methoxyphenyl)-propionate (60), a cherry



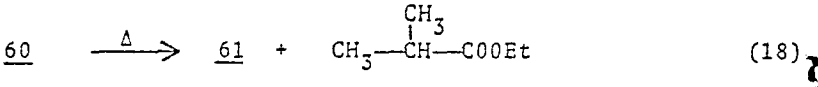
60

release substance. Compound 60, prepared via a Reformatsky reaction between anisaldehyde (61) and ethyl bromoisobutyrate (62) (Equation 17), releases both anisaldehyde (61) and ethyl isobutyrate



61 62 (17)

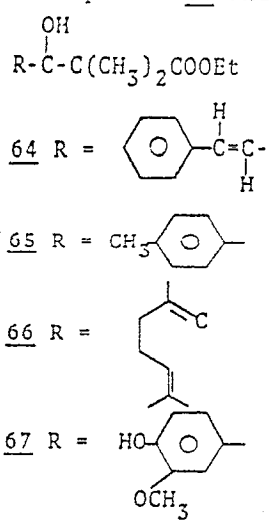
(63) on pyrolysis (Equation 18). Both 61 and 63 impart



63 (18)

a noticeable fragrance to sidestream smoke, but little flavor to the mainstream smoke of a cigarette, as desired. In addition to preparing large amounts of 60 for Development during this year, to other potential flavor-release substances have been

synthesized utilizing Reformatsky reactions; namely, ethyl 2,2-dimethyl-3-hydroxy-5-phenyl-trans-4-pentenoate (64) (cinnamon), ethyl 2,2-dimethyl-3-hydroxy-3-(4-methylphenyl)-propionate (65) (cherry-almond), ethyl 2,2,5,9-tetramethyl-3-hydroxy-4,8-decadienoate (66), (lemon) and ethyl 2,2-dimethyl-3-hydroxy-3-(3-methoxy-4-hydroxyphenyl)-propionate (67) (vanilla). Compounds 64 and 65 have been submitted to



Development for evaluation; 64 was dropped and 65 is still under study. Compound 66 dehydrated on distillation to give a mixture of four trienes. It was assumed that it would dehydrate on cigarettes as well and was not explored further. Compound 67 is not yet analytically pure due primarily to the added complication introduced by the hydroxyl on the benzene ring which must be blocked before the Reformatsky reaction can be run. Both tetrahydropyranyl and acetyl have been utilized

as blocking groups.

b. Compounds Prepared by the Williamson Ether Synthesis

One disadvantage of Reformatsky-type flavor-release substances is the restriction of the system to aromatic aldehydes. As previously noted, compound 66 undergoes dehydration, rather than fragmentation to give citral, an aliphatic aldehyde, when heated. Under study at present are β-alkoxy- or aryloxyesters, which in theory, can fragment to give the desired aldehyde, but cannot dehydrate. The initial test of this system has utilized benzyl 2-benzyloxyacetate (68), one of two products obtained from the reaction of benzyl alcohol (69) with ethyl bromoacetate (70) (Equation 19). The ester

$$\underset{\underline{69}}{C_6H_5CH_2OH} + \underset{\underline{70}}{BrCH_2COOEt} \longrightarrow \underset{\underline{68}}{C_6H_5CH_2OCH_2COOCH_2C_6H_5} + \underset{\underline{71}}{C_6H_5CH_2OCH_2COOEt} \qquad (19)$$

68 has been shown to release benzaldehyde on pyrolysis using a g.c. pyrolysis instrument. Maximum benzaldehyde formation occurred between 500-600°C. No benzaldehyde could be observed at 850°. Apparently either the compound is sufficiently volatile so that it distills at 850° before any pyrolysis can take place or it is undergoing more extensive pyrolysis at the higher temperature. The former problem could be obviated by incorporating the benzyloxy group into a polymer.

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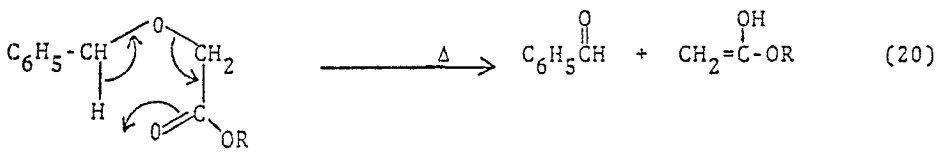
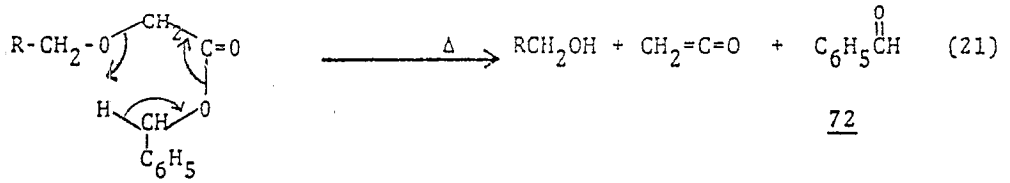
It should be noted that ester 68 could pyrolytically deliver benzaldehyde (72) from either the benzyl ether moiety (Equation 20) or the benzyl ester moiety (Equation 21). If a major portion of the benzaldehyde is



68 72 (20)



68 72 (21)

indeed derived from Equation 21, then the entire concept of aryloxyethers as flavor-release compounds is doubtful. This question can be resolved by a product study of the pyrolysis of the ethyl ester which will be investigated shortly.

III. TESTING RESULTS

A large number of compounds have been submitted to Amchem Products, Inc., for evaluation as to agricultural use. At the present time 2- and 4-picolyl cyclopropyl ketones (32 and 34) have shown promising results as plant freeze-protectants and have been placed in a secondary screening program.

Samples of 2-(3-pyridyl)-azetidine (19) and 1-methyl-2-(3-pyridyl)-azetidine (20) were evaluated pharmacologically, along with ℓ-nicotine, by Woodard Research Corporation. Both azetidines displayed rather interesting properties. Although the LD_{50} value for the 1-methylazetidine (20) was approximately equal to that of ℓ-nicotine while compound 19 was forty times less toxic, fundamental differences between the azetidines and nicotine were observed in a neurological examination of their effect on cats. Administration of ℓ-nicotine showed no effect other than an increase in heart rate. Both azetidines, however, in equivalent dosages, showed the immediate onset of central nervous system depression, including decreased heart rate, increased respiratory rate, excess salivation, and motor ataxia. In addition, 1-methyl-2-(3-pyridyl)-azetidine (20) was approximately three times more effective in increasing blood pressure in dogs than was ℓ-nicotine. These results are yet difficult to interpret, and further testing is warranted.

IV. FUTURE PLANS

Plans and projections for next year have been discussed in detail in an earlier report.[6] Briefly, we plan to extend the

work already summarized in this report. In addition we plan to complete the syntheses of the minor tobacco alkaloids, such as myosmine and anatabine; begin work on other substituted pyrrolidines; and investigate linking flavor compounds to natural polymers.

V. PATENTS AND PUBLICATIONS

A. "The Synthesis of Carbon-14 Labeled Tobacco Constituents II The Synthesis of d,ℓ-Nicotine (2'-^{14}C)," R. A. Comes, M. T. Core, M. D. Edmonds, W. B. Edwards, III, and R. W. Jenkins, Jr., J. Label. Compounds, 9, 253-9 (1973).

B. "The Synthesis of Pyridyl and Picolyl Cyclopropyl Ketones," W. B. Edwards and H. V. Secor, to be submitted to J. Org. Chem.

C. "Synthesis of Pyridyl Azetidines," W. B. Edwards and H. V. Secor, in preparation.

D. "Mass Spectra of Two 5'-Substituted Nicotine Derivatives," J. F. DeBardeleben and D. F. Glenn, to be submitted to Org. Mass Spectrum.

E. Invention Record: "2-(3-Pyridyl)-Azetidines."

F. Patent Application: "Menthol-Release Compounds."

VI. REFERENCES

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6. Memo from E. B. Sanders to W. F. Gannon, Nov. 16, 1973.

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10. P. J. Murphy, J. Biol. Chem., 248, 1796 (1973).

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