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THE VOLATILE CONSTITUENTS OF COFFEE—III[1]

THE STRUCTURES OF TWO HETEROCYCLIC COMPOUNDS AND THE SYNTHESIS OF TETRAHYDROFURANONES

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Abstract—This paper describes the elucidation of the structures of two volatile constituents of roasted coffee by means of spectroscopic techniques. A convenient synthetic procedure for tetrahydrofuranones and tetrahydrothiophenones is also described.

IN PREVIOUS communications from this Laboratory,[1] which described the isolation of an "aroma complex" from roasted coffee and the elucidation of the structures of some of its components, it was pointed out that the instability and complexity of the mixture and the very low concentration of many of its constituents cause some difficulty in the analysis of the aromatic fraction of coffee.

In this paper will be described the elucidation of the structures of two of these minor components—compounds A and B—which were isolated in pure form by repeated vapor-liquid chromatography of the "aroma complex". The concentrations of A and B in the roasted coffee employed, a commercial blend, were approximately 3×10^{-5} and $1 \times 10^{-5}\%$ respectively; the quantities available were of the order of the milligram. The VPC retention times of the two compounds are given in Table 1 and their IR spectra in Figs. 1 and 2.

The structure of compound A. The wavelength of the carbonyl stretching absorption of this compound—5·65 μ in carbon tetrachloride—was rather puzzling, especially in view of the fact that the substance appeared to be relatively low-boiling. Compound A emerged, in fact, from a non-polar VPC column well ahead of the simplest 5-membered lactone, 6-membered γ,δ-unsaturated lactone, 5-membered unsaturated anhydride and *p*-bridged ketone, which are four of the five more common types of substances that can be expected to show carbonyl absorption at approximately this wavelength.[3–7]

The other possibility, that compound A was a vinyl ester, could also be excluded,

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[1] Parts I and II of this series: [a] M. A. Gianturco, A. S. Giammarino and R. G. Pitcher, *Tetrahedron* **19**, 2051 (1963); [b] M. A. Gianturco and P. Friedel, *ibid.* **19**, 2039 (1963).

[2] To whom inquiries concerning this paper should be addressed.

[3] L. J. Bellamy, *The Infrared Spectra of Complex Molecules.* Methuen, London (1958).

[4] F. Korte, K. H. Büchel and L. Göhring, *Angew. Chem.* **71**, 523 (1959).

[5] W. G. Dauben and W. E. Williams, *J. Org. Chem.* **24**, 1595 (1959).

[6] C. F. H. Allen, *Chem. Rev.* **62**, 653 (1962).

[7] Five-membered unsaturated anhydrides actually show, as other anhydrides, two absorption bands in the carbonyl region; for instance, maleic anhydride absorbs at 5·65 and 5·45 μ. However, the band at shorter wavelength in the spectra of 5-membered unsaturated anhydrides can be so much less intense than the other as to go unobserved, unless the spectra are determined on neat samples or on rather concentrated solutions.[3] This is not always feasible in flavor work, due to the paucity of the material available.

TABLE I. VPC RETENTION TIMES OF COMPOUNDS A, B AND REFERENCE SUBSTANCES[a]

Compound	$R_T{}^A$	$R_T{}^b$	$R_T{}^c$	R_T
A	10·0	7·7	—	—
B	—	—	24·7	47·7
Toluene	8·6	4·7	—	—
Acetophenone	—	—	13·6	28·3
2-Undecanone	—	—	47·3	64·5

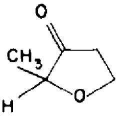
[a] For VPC conditions, see Experimental.

since no bands appear in its spectrum that could be attributed to the stretching of a carbon-carbon double bond[8] or to vibrations of the C—O—R linkages of an ester.

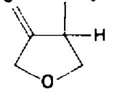
Microtests tending to establish the nature of the carbonyl group of compound A revealed, instead, that it responded to typical carbonyl reagents, such as 2,4-dinitrophenylhydrazine. However, neither aliphatic nor alicyclic ketones absorb ordinarily at 5·65 μ. The same and other reasons, such as the absence of the typical C—H stretching absorption of formyl groups, seemed to exclude the possibility that the substance were aldehydic in nature. Finally, since the origin of compound A rendered unlikely the presence in the molecule of electron-attracting groups (Cl, NO_2, etc.) capable of causing an hypsochromic shift of the carbonyl stretching absorption from the "normal" values, it was concluded that compound A should contain a keto-carbonylic function modified by some unusual effect.

At this point, the mass spectrum indicated the molecular weight to be 100 and the measurement of the intensities of the peaks at M + 1 and M + 2 led to the molecular formula $C_5H_8O_2$, which requires two points of unsaturation.[9] Since the position of the carbonyl stretching absorption in the IR was not compatible with a diketonic structure[10] and no hydroxyl group was indicated by the spectrum of Fig. 1, the second oxygen atom of the molecule could only be ascribed to an ether function, a supposition corroborated by the strong absorption at 9·35 μ. Lacking indications of the presence of a carbon-carbon double bond, the second point of unsaturation required by the molecular formula could then be attributed to a ring.

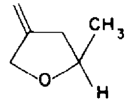
Eliminated the structures of 3- and 4-oxacyclohexanone, whose carbonyl absorption would be expected to occur very close to that observed for cyclohexanones, the only structures possible for compound A remained those of the three isomeric methyltetrahydrofuranones, I, II and III.



I



II



III

This postulation found support in the fact that the unsubstituted tetrahydrofuranone, easily obtained from the commercially available 3-hydroxytetrahydrofuran, was indeed found to show absorption at 5·65 μ. Apparently, the added strain resulting

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[8] The absorption corresponding to this vibration is quite intense in the spectra of vinyl esters.

[9] For a discussion of mol wt determinations by mass spectrometry, see Chap. 8 in Ref. 20.

[10] α- and γ-diketones, as well as non-enolized β-diketones, absorb in the IR as normal ketones. Enolized β-diketones show very "abnormal" and easily recognizable absorption.[3]

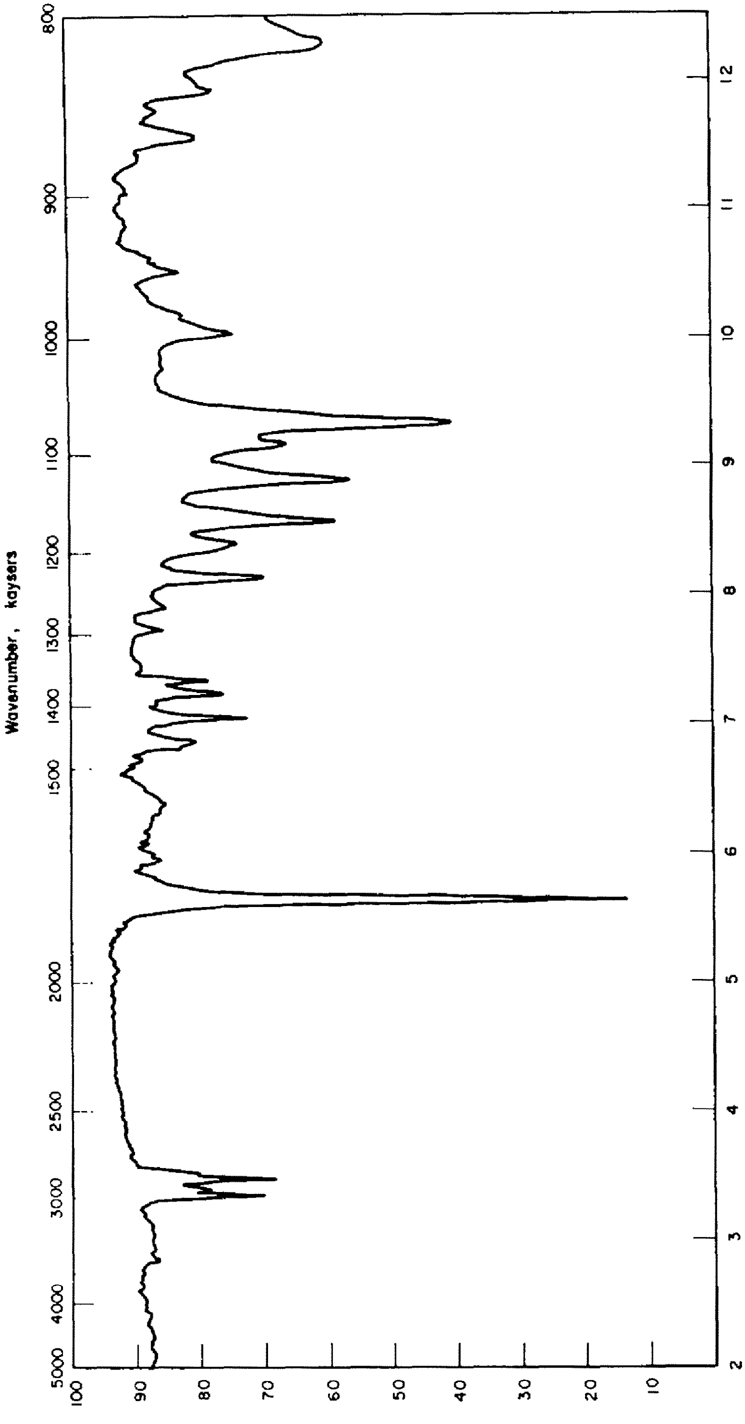


FIG. 1. IR spectrum (CCl_4) of compound A.

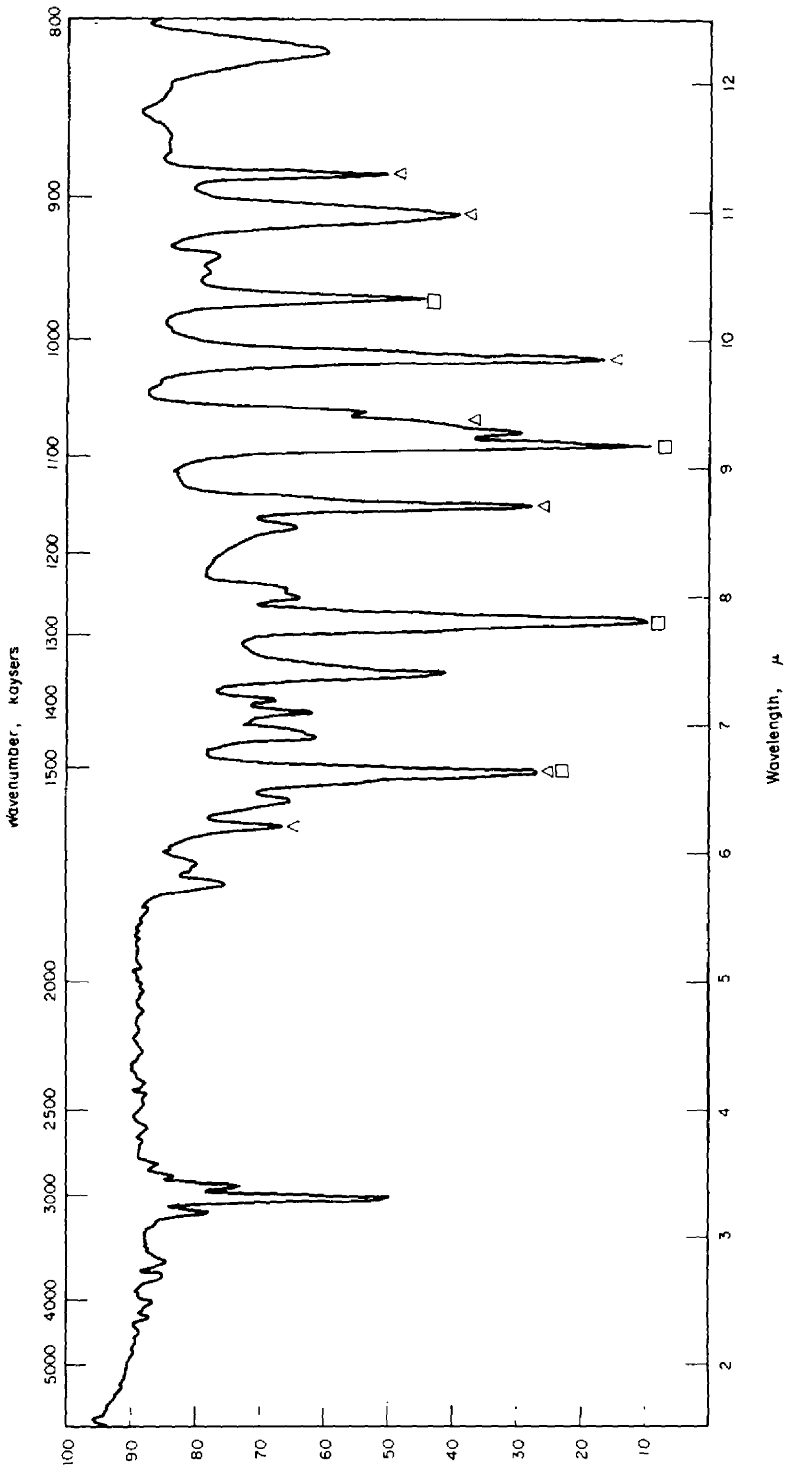
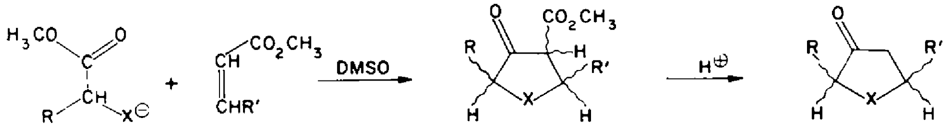


Fig. 2. IR spectrum ($CHCl_3$) of compound B.

by substitution of the 3-CH_2 group of cyclopentanones by an oxygen atom causes the observed shift to shorter wavelengths; however, an inductive effect may also be operative.

While the paucity of the material available did not permit the determination of the NMR spectrum or of the number of exchangeable hydrogen atoms by deuterium exchange, the low relative intensity of the M-15 peak in the mass spectrum of compound A seemed to suggest that structure III should be eliminated. This was expected, in fact, to expel a methyl group with considerable ease.[11] Finally, compound A was found to be identical (R_T's, IR and mass spectrum) with synthetic 2-methyltetrahydrofuran-3-one (I).

2-Methyltetrahydrofuran-3-one was prepared by decarboxylative hydrolysis of 2-methyl-4-carbomethoxytetrahydrofuran-3-one (IVb). The latter was obtained by reacting the anion of methyl lactate with methyl acrylate in dimethyl sulfoxide at room temperature.



X = 0; R=R'=H	IVa	V
X = 0; R=CH_3; R'=H	IVb	I
X = 0; R=H; R'=CH_3	IVc	III
X = S; R=R'=H	IVd	VI

This almost instantaneous reaction ran so smoothly that it was subsequently adapted to the synthesis of other compounds necessary in this Laboratory; tetrahydrofuran-3-one (V, from glycolate and acrylate), 2-methyltetrahydrofuran-4-one (III, from glycolate and crotonate) and tetrahydrothiophen-3-one (VI, from thioglycolate and acrylate). 3-Methyltetrahydrofuran-4-one (II) was obtained by decarboxylative hydrolysis of 3-methyl-3-carbomethoxytetrahydrofuran-4-one (VII), which was prepared by alkylation of IVa in dimethyl sulfoxide.

The preparation of V (in low yield), by oxidation of 3-hydroxytetrahydrofuran, has already been reported;[13] compound VI has also been previously prepared from the product of the Dieckmann condensation of the appropriate thia-diester.[14] Thus, the ones described above represent only alternate, and probably more convenient, procedures for the synthesis of V and VI.

Compounds I, II and III, instead, have not been adequately described in the literature. Their synthesis has been recently reported[15] (acid-catalyzed ring closure

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[11] This postulation was based upon the fact that the mass spectra of some 2-alkyl-substituted tetrahydrofurans, as well as those of γ-alkyl-substituted γ-lactones, are reported to show a prominent M-R peak, corresponding to the loss of the group R from the molecular ion.[12] When compounds I, II and III became available, it was instead found that the intensity of the M-15 peak is low in the spectra of *all three* isomers $\left(\frac{\text{M-15}}{\text{M}} \times 100 < 10\right)$. Obviously, some other fragmentation pattern is so prevalent in the case of tetrahydrofuranones that no generalization seems possible in this instance concerning the relationship between the position of an alkyl substituent and the intensity of the M-R peak.

[12] For some examples, see: K. Biemann, *Mass Spectrometry* pp. 97, 127. McGraw-Hill, New York, N.Y. (1962).

[13] H. Wynberg, *J. Amer. Chem. Soc.*, **80**, 364 (1958).

[14] R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **66**, 849 (1944).

[15] H. Wynberg, *Angew. Chem.* 453 (1963).

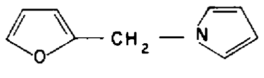
of the appropriate β-alkoxydiazoketones), but experimental details have not been given, nor have the physical properties of the compounds been indicated. Furthermore, the yields reported appear to be low (5, 41 and 30%, respectively, for the last step in the preparation of I, II and III).[16] The synthesis from the appropriate α-hydroxy- and α,β-unsaturated esters seems to represent a more convenient procedure for the preparation of the three compounds; moreover, it should be generally applicable to the preparation of tetrahydrofuranones substituted at one, two or all three ring-positions.

The structure of compound B. Inspection of the IR spectrum of this substance (Fig. 2) did not reveal the presence of any functional group in the molecule and only suggested, at first, that the material should be mostly aromatic in nature. This was indicated by the position of the carbon-hydrogen stretching absorption (mostly below 3·33 μ), by the bands of good intensity between 6·2 and 6·7 μ and by the sharpness of several other bands.[3]

However, a closer inspection of the spectrum revealed the presence of a group of bands, a "pattern", which is highly characteristic of furanic systems carrying a saturated substituent in the 2-position.[18]

The odd molecular weight of the compound, 147, determined by mass spectroscopy, indicated that the molecule should contain an odd number of nitrogen atoms. Consultation of Beynon's tables[19]—taking into account that the molecule should have at least one atom of oxygen and no fewer than three points of unsaturation (from the furanic ring)—led to the following possible molecular formulas for compound B: $C_7H_5N_3O$, $C_8H_5NO_2$ and C_9H_9NO. This would leave for the molecule corresponding to the second moiety of compound B—the first being a furanic ring—the three possible formulas: $C_3H_3N_3$, C_4H_3NO and C_5H_7N, respectively.

Consideration of the above formulas led to the choice of the methylpyrroles as the most likely partners of the furanic ring in the molecule of compound B. Moreover, the absence of bands that could be attributed to N—H stretching vibrations in the spectrum of Fig. 2 indicated that, if its molecule contained indeed a furanic and a pyrrolic ring, compound B could only have structure VIII.



VIII

This postulation found support in a comparison of Fig. 2 with the spectra of 2-methylfuran (Fig. 3) and N-methylpyrrole (Fig. 4).

A substance described, with no proof of structure, as N-furfuryl-2-pyrrole (VIII) has been reported by Reichstein.[21] This product was obtained by dry distillation of

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[16] What appears to be somewhat impure III, on the basis of the analytical data presented, has also been recently prepared by a multistep procedure, to prove the identity of this compound with a product of the pyrolysis of a cardenolide.[17]

[17] R. F. Curtis, C. M. Massal and J. Weatherstone, *J. Chem. Soc.* 4225 (1962).

[18] A. R. Katritzky and J. M. Lagowsky, *J. Chem. Soc.* 657 (1959).

[19] These tables[20] list all the most plausible combinations of C, H, N and O which are possible for any mol wt from 12 to 250.

[20] J. H. Beynon, *Mass Spectroscopy and Its Application to Organic Chemistry.* Elsevier, New York, N.Y. (1960).

[21] T. Reichstein, *Helv. Chim. Acta* **13**, 349 (1930).

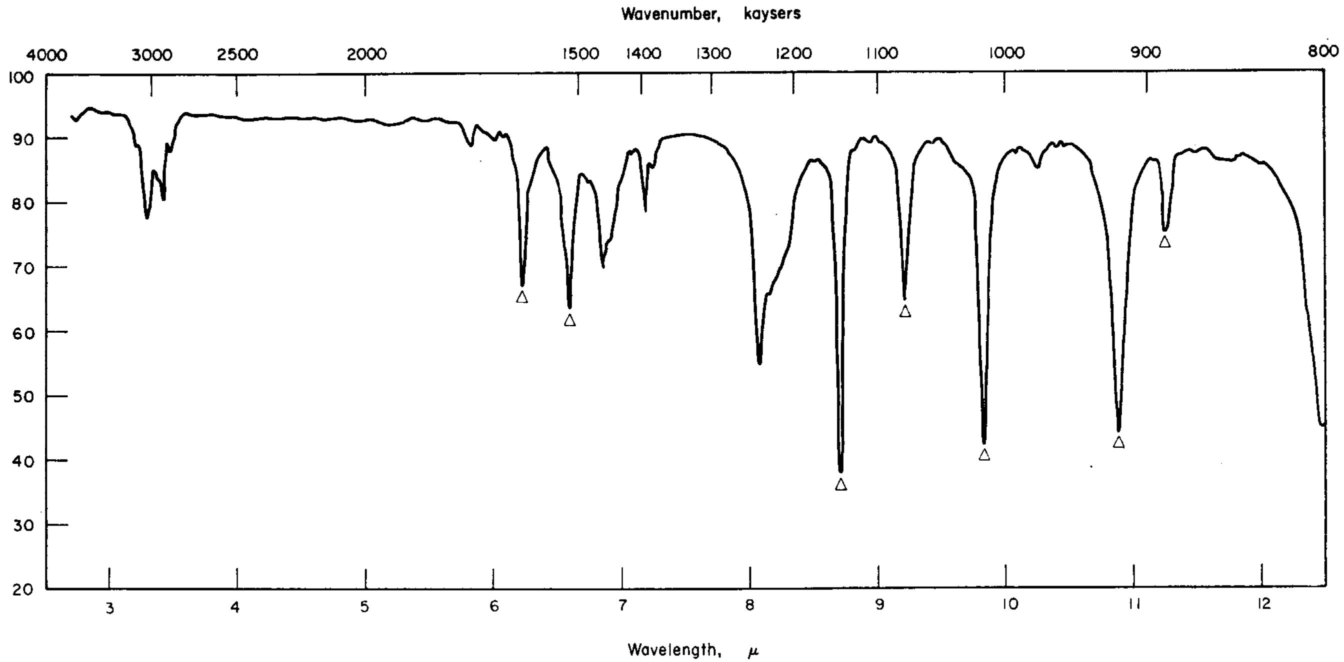

FIG. 3. IR spectrum ($CHCl_3$) of 2-methylfuran.

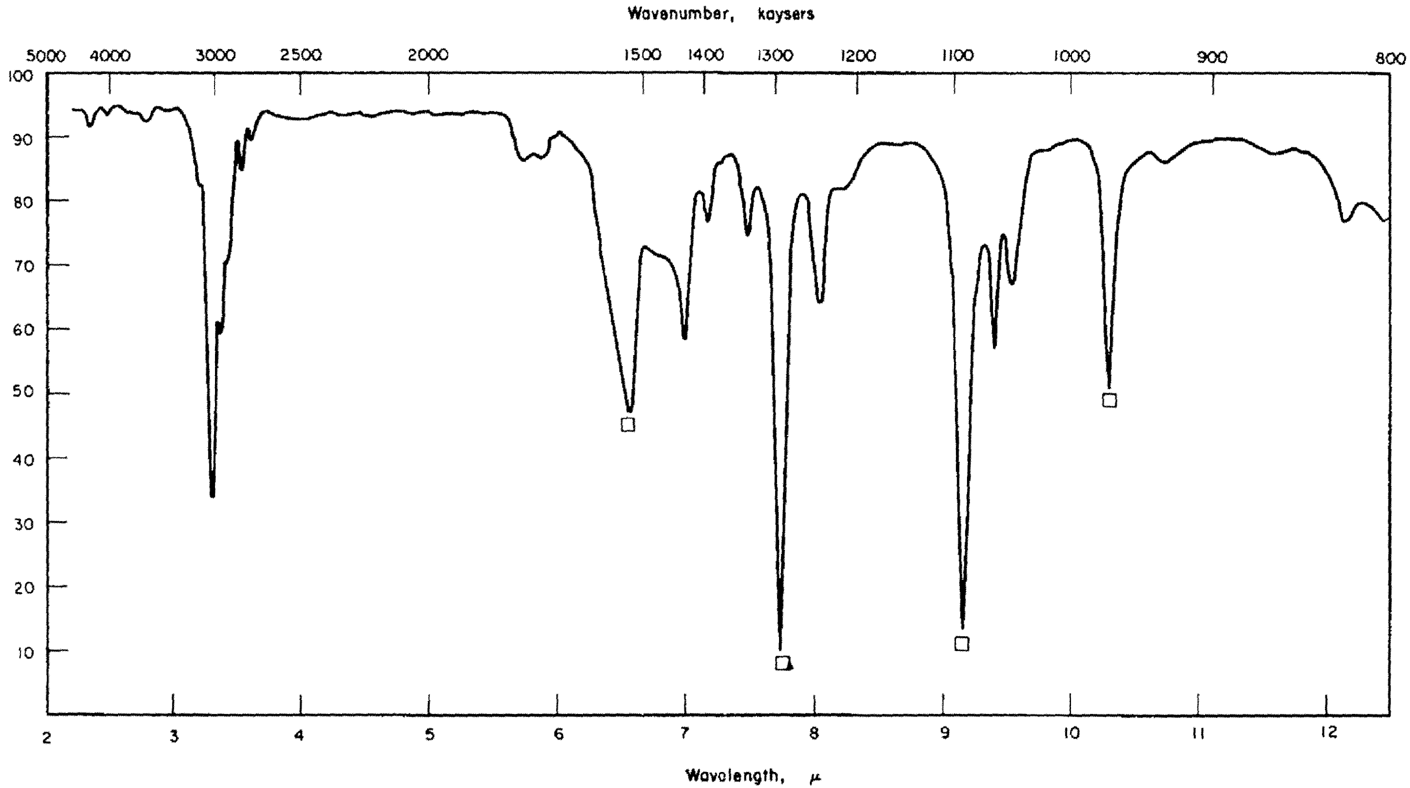

FIG. 4. IR spectrum ($CHCl_3$) of N-methylpyrrole.

saccharic acid in presence of furfuryl amine, a synthesis that could not be considered unequivocal. However, the elemental analysis and the NMR spectrum of that component of the synthetic mixture which had retention time, IR and mass spectra identical with those of compound B are in good agreement with the structure assigned to the synthetic material[21] and, consequently, to compound B. The NMR spectrum at 60 megacycles of a solution of the synthetic material in deutero-chloroform (TMS as internal standard) contained: (a) a quartet for one proton centered at $\delta = 7{\cdot}38$ ppm (alpha-hydrogen of the furanic ring); (b) a triplet for two protons centered at $\delta = 6{\cdot}70$ ppm (alpha-hydrogens of the pyrrolic ring); (c) very complex absorption for four protons between 6·1 and 6·4 ppm, attributed to the beta-hydrogens of the furanic and pyrrolic rings; and (d) a singlet for two protons at $\delta = 4{\cdot}97$ ppm, which is ascribed to the methylene group.[22]

EXPERIMENTAL[25]

Vapor-liquid chromatography was carried out on 2 m × 0·25″ packed columns in the following conditions: (a) $[R_T^a]$: silicone gum (20% on acid-washed chromosorb W), 75°, 100 ml He/min; (b) $[R_T^b]$: didecyl phthalate (Perkin-Elmer column A), 125°, 110 ml He/min; (c) $[R_T^c]$: silicon gum (20% on acid-washed chromosorb W), 125°, 70 ml He/min; (d) $[R_T^d]$: didecyl phthalate (Perkin-Elmer column A), 150°, 65 ml He/min

The IR spectra were determined with an ultramicrocell in the previously described conditions.[1]

Materials. Compounds A and B were obtained by repeated VPC of the "aroma complex" of coffee.[26] Their retention times on a polar and a non-polar column are given in Table 1, with the corresponding values of easily available standards. The IR spectra of A and B are given in Figs. 1 and 2, respectively.

3-*Carbomethoxytetrahydrofuran*-4-*one* (IVa). 4·6 g (0·2 mole) Na was pulverized under toluene and the solvent was replaced with 150 ml ether. To the mixture was added 18 g (0·2 mole) distilled methyl glycolate and stirring was continued until the evolution of hydrogen had ceased. To the dry sodium derivative remaining after distillation of the ether, a solution of 20·7 g (0·24 mole) distilled methyl acrylate in 100 ml dimethyl sulfoxide (DMSO) was added in one lot, while the reaction flask was kept immersed in an ice bath. After 15 min, the cooling bath was removed and the solution stirred for an additional 1/2 hr at room temp, filtered, poured into ice-cold aqueous H_2SO_4 and extracted with ether. Washing of the organic layer with a saturated NaCl solution, drying over Na_2SO_4 and removal of the ether was followed by distillation (red. press.). 3-Carbomethoxytetrahydrofuran-4-one (13·5 g, 46% yield based on the glycolate employed) was obtained as the fraction boiling at 57–58°/0·15 mm, n_D^{19} 1·4562 (Found: C, 50·28; H, 5·79. $C_6H_8O_4$ requires: C, 50·00; H, 5·60%).

2-*Methyl*-3-*carbomethoxytetrahydrofuran*-4-*one*(IVc). To a suspension of 4·8 g (0·2 mole) NaH in 200 ml ether, 18 g (0·2 mole) methyl glycolate was added with good stirring. After the evolution of H_2 had ceased, the solvent was removed (red. press.) and to the residue, 100 ml DMSO followed by 22 g (0·22 mole) methyl crotonate (ice-water cooling) was added. After 15 min, the cooling bath was removed and stirring continued for an additional 1/2 hr. The usual work up (see above) yielded 32 g of an oily residue which, upon distillation, gave 20·5 g (65% yield based on the glycolate

[22] It should be noted that the occurrence in coffee of some unspecified "precursor" of this compound—and of many other substances the presence of not all of which could be verified in this Laboratory—has been indicated in the vague language of the patent literature by Reichstein and Staudinger in 1928.[23] However, these authors—who conducted a masterful investigation of the volatile constituents of coffee during a period of at least a decade—after reporting in 1955 that more detailed publications on the subject were then in preparation,[24] do not seem to have published their results in a scientific journal.

[23] British Patents 246,454 and 260,960.

[24] T. Reichstein, *Perfumery and Essential Oils* **46**, 86 (1955).

[25] Microanalyses by Mr. Joseph Nemeth of the Department of Chemistry and Chemical Engineering of the University of Illinois, Urbana, Illinois.

[26] For the isolation of the "aroma complex", see Ref. 1 in footnote 1.

employed) 2-methyl-3-carbomethoxytetrahydrofuran-4-one, b.p. 51°/0·2 mm, $n_D^{19\cdot5}$ 1·4480 (Found: C, 53·47; H, 6·46. $C_7H_{10}O_4$ requires: C, 53·16; H, 6·37%).

3-*Methyl-3-carbomethoxytetrahydrofuran-4-one* (VII). 14·4 g (0·1 mole) IVa was added dropwise, with external cooling and good stirring, to a solution of 2·3 g Na in 100 ml methanol. The solvent was removed (red. press.) and to the residual white sodium derivative, 100 ml DMSO was added with good stirring; when all the material was in solution, 28·4 g (0·2 mole) MeI was added dropwise. After 1/2 hr stirring at room temp, the solution was neutral and gave no color with $FeCl_3$. Dilution. with water, ether extraction, washing of the organic layer with saturated NaCl solution, drying and removal of the solvent left 13·1 g (82% yield) of an oily residue distilling almost in toto at 51–53°/0·18 mm, $n_D^{19\cdot5}$ 1·4496 (Found: C, 53·07; H, 6·45. $C_7H_{10}O_4$ requires: C, 53·16; H, 6·37%).

2-*Methyl-4-carbomethoxytetrahydrofuran-3-one* (IVb). The preparation of this compound was analogous to that of IVc, but methyl lactate was used instead of glycolate and methyl acrylate instead of crotonate. IVb, obtained in 58% yield (based on the lactate employed), had b.p. 60–62°/0·3 mm, n_D^{17} 1·4494 (Found: C, 52·97; H, 6·42. $C_7H_{10}O_4$ requires: C, 53·16; H, 6·37%).

3-*Carbomethoxytetrahydrothiophen-4-one* (IVd). To a solution of 4·6 g (0·2 mole) Na in 100 ml methanol, 21·2 g (0·2 mole) methyl thioglycolate was added. To the white sodium derivative after removal of the solvent (red. press.), 100 ml DMSO was added, followed by dropwise addition of 20·6 g (0·23 mole) methyl acrylate (ice-water cooling). After 15 min stirring, the cooling bath was removed and the solution was stirred for an additional 1/2 hr at room temp. The usual work-up (see preparation of IVa above), followed by distillation yielded 24·8 g (77·3% yield, based on the thioglycolate employed) of essentially pure IVd. A fraction redistilled for analysis had b.p. 74–76°/0·35 mm (lit.[14] 128·5–129·5/20 mm), n_D^{18} 1·5163 (Found: C, 44·82, H, 5·03. Calc. for $C_6H_8O_3S$: C, 44·99; H, 5·03%).

Hydrolysis of IVa, b, c, d *and* VII. The decarboxylative hydrolysis of the five β-ketoesters was effected by 1-hr refluxing in 10% H_2SO_4. The usual work-up (ether extraction, drying over Na_2SO_4, removal of the solvent and distillation) yielded the corresponding ketones (see below) in nearly quantitative yields.

Tetrahydrofuran-3-one (V). B.p. 139-140° (lit.[13] 136-136·5; lit.[27] 139·4-139·8) n_D^{20} 1·4363 (lit.[13] n_D^{21} 1·4352; lit.[27] n_D^{20} 1·4384). 2,4-Dinitrophenylhydrazone, m.p. 155-157° (lit.[13] 155·6–156·2°). Compound V was also prepared, in very low yield, by the procedure of Wynberg.[13]

2-*Methyltetrahydrofuran-4-one* (III). B.p. 140°, n_D^{20} 1·4301 (Found: C, 59·96; H, 8·11. $C_5H_8O_2$ requires: C, 59·98; H, 8·06%). 2,4-Dinitrophenylhydrazone, m.p. 139·5–141° (Lit.[17] 135–136°). (Found: N, 19·68. $C_{11}H_{12}N_4O_5$ requires: N, 19·99%).

3-*Methyltetrahydrofuran-4-one* (II). B.p. 142–143°, n_D^{20} 1·4350. (Found: C, 59·81; H, 8·03. $C_5H_8O_2$ requires: C, 59·98; H, 8·06%). 2,4-Dinitrophenylhydrazone, m.p. 177·5–179° (Found: N, 19·89. $C_{11}H_{12}N_4O_5$ requires: N, 19·99%).

2-*Methyltetrahydrofuran-3-one* (I). B.p. 139°, n_D^{20} 1·4291, $R_T{}^a$: 10·0 min; $R_T{}^b$: 7·7 min. This compound, pure by VPC, repeatedly analyzed somewhat low for carbon (Found: C, 59·59; H, 8·04. $C_5H_8O_2$ requires: C, 59·98; H, 8·06%). 2,4-Dinitrophenylhydrazone, m.p. 179–181° (Found: N, 19·90. $C_{11}H_{12}N_4O_5$ requires: N, 19·99%).

Tetrahydrothiophen-3-one (VI). B.p. 86–87°/25 mm (lit.[28] 86–87/25 mm), n_D^{20} 1·5268 (Found: C, 46·86; H, 5·90. Calc. for C_4H_6OS: C, 47·03; H, 5·92%). 2,4-Dinitrophenylhydrazone, m.p. 175–176·5° (Found: N, 19·64. $C_{10}H_{10}N_4O_4S$ requires: N, 19·85%).

N-Furfuryl-2-pyrrole (VIII). This material was prepared according to the procedure of Reichstein.[21] B.p. 77–79°/1 mm (lit.[21] 76–78°/1 mm). A sample purified by preparative VPC had the following properties: $R_T{}^c$: 24·7 min, $R_T{}^d$ 47·7 min, n_D^{21} 1·5317. (Found: C, 73·16; H, 6·33; N, 9·56. C_9H_9NO requires: C, 73·43; H, 6·17; N, 9·53%).[29]

Acknowledgments—The authors extend their thanks to Dr. Stanley Freeman and to Mr. Henry Bandarovich, International Flavors and Fragrances, Union Beach Research Laboratories, Union Beach, New Jersey, for the mass spectra and to Mr. Eugene Pier, Varian Associates, Palo Alto, California, for the determination of the NMR spectra.

[27] Yu. K. Yur'ev, E. M. Lukima, Yu. M. Polikarpov and V. P. Volkov, *Zh. Obsh. Khim.* **26**, 553 (1956).

[28] H. Wynberg, A. Logothetis and D. Ver Ploeg, *J. Amer. Chem. Soc.* **79**, 1972 (1957).

[29] *Note added in proof:* It has now been found that compound VIII can be obtained more conveniently and in excellent yield by reacting furfuryl amine with 2,5-dimethoxytetrahydrofuran. A detailed procedure will be described in the next paper of this series.