tate, washed with 5% hydrochloric acid, water, saturated sodium bicarbonate, dried, and evaporated to yield 650 mg. of oil which crystallized when triturated with acetone-ether. After recrystallization from acetone, the resultant diacetate (IIa) melted at 255–259°.

*Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; acetyl, 18.95. Found: C, 67.75; H, 7.40; acetyl, 19.61. $\lambda_{max}^{Nujol}$ 2.88, 5.72, 5.79, 5.85, 5.94, 6.09, 6.18$\mu$. $[\alpha]_D^{24}$ +92° ± 2° ($CHCl_3$); $M_D$ = +408°. $[\alpha]_D^{23}$ +71° ± 2° (dioxane); $M_D$ +315°.

*1,4-Pregnadiene-17α,20α,21-triol-3,11-dione* (IIb). To 150 mg. of IIa dissolved in 5 ml. of methanol was added 2 ml. of water containing 150 mg. of potassium bicarbonate. The reaction mixture was allowed to reflux for 2 hr., evaporated to a small volume under reduced pressure, and extracted several times with ethyl acetate. After distillation of the ethyl acetate there was obtained 100 mg. of crystals which were recrystallized from methanol to yield 70 mg. of IIb with a double melting point, 225–227° and 238–240°. Another recrystallization from methanol gave 46 mg. of analytically pure material, m.p. 225–227°, 240–242°.

*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.03; H, 7.82. $\lambda_{max}^{MeOH}$ 239 m$\mu$, E 14,900. $\lambda_{max}^{Nujol}$ 3.0, 5.88, 6.01, 6.15, 6.21$\mu$. $[\alpha]_D^{23}$ +132° ± 2° (dioxane); $M_D$ +477°.

$\Delta M_D$ (diacetate) $-_A M_D$ (free alcohol) = +315° − (+477°) or $\Delta M_D$ = −162°. Since the $\Delta M_D$ is negative, the configuration at $C_{20}$ is $\alpha$.[15]

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## Disubstituted Tetrazoles as Analogs of Esters[1]

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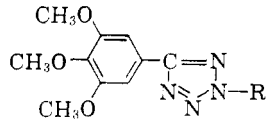
Following the elucidation of the structure of reserpine[4] and its confirmation by unequivocal synthesis,[5] efforts to determine the active portion of the molecule took a variety of courses. Of particular interest to us was the report that dialkylaminoalkyl 3,4,5 - trimethoxybenzoates exhibited certain features of the reserpine activity.[6]

In view of the acidic character of 5-substituted tetrazoles,[7] it was of interest to prepare a number of derivatives of 5-(3′,4′,5′-trimethoxyphenyl)-tetrazole (I) in which the ring was alkylated with dialkylaminoalkyl groups (II–IV). The possibility that the disubstituted tetrazoles might bear some similarity to the comparable esters, at least in the pharmacological responses evoked, was attractive.



I. R = H
II. R = —$(CH_2)_2N(C_2H_5)_2$
III. R = —$(CH_2)_3N(CH_3)_2$
IV. R = —$(CH_2)_3N(C_2H_5)_2$

Using the general procedure for preparation of 5-aryltetrazoles involving interaction of nitriles with sodium azide and acetic acid in boiling *n*-butyl alcohol,[8] 3,4,5-trimethoxybenzonitrile was converted into I in 93% yield. A general procedure involving interaction of nitriles with lithium or ammonium azides in dimethylformamide[9] which permitted shorter reaction periods was described after conclusion of this work. Ring alkylation was accomplished by interaction of I with appropriate dialkylaminoalkyl halides in aqueous acetone in the presence of sodium hydroxide. Studies on alkylation of 5-aryltetrazoles with a number of alkylating agents have shown that the 2,5-disubstituted derivatives are the major products,[10,11] although treatment of 5-phenyltetrazole with methyl iodide and sodium hydroxide in aqueous acetone gave appreciable amounts of the 1,5-disubstituted product.[10] Pharmacological screening of compounds II–IV is under way in the Schering Corp. research laboratories.

### EXPERIMENTAL[12]

*3,4,5-Trimethoxybenzonitrile* was prepared from the acid by conversion successively to the acid chloride and amide,[13] followed by dehydration of the latter with sodium metabisulfite and phosphorus oxychloride, m.p. 93–94.5°, previously reported[14] m.p. 95°.

*5-(3′,4′,5′-Trimethoxyphenyl)tetrazole* (I). A mixture of 29.8 g. of 3,4,5-trimethoxybenzonitrile, 14.9 g. of sodium azide and 13.8 g. of glacial acetic acid in 100 ml. of *n*-butyl alcohol was boiled under reflux for 4 days when further 5 g. of sodium azide and 10 g. of glacial acetic acid were added; refluxing was continued for 2 days. The mixture was diluted with 250 ml. of water and distilled to remove *n*-butyl alcohol. The residual aqueous solution was cooled, acidified with hydrochloric acid (Caution: hydrazoic acid liberated), and the precipitated product filtered off. The product was recrystallized from aqueous isopropyl alcohol, yield 33.9 g. (93%), m.p. 199–200°.

*Anal.* Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.8; H, 5.1; N, 23.7. Found: C, 51.1; H, 5.2; N, 23.6.

*2-(Diethylaminoethyl)-5-(3′,4′,5′-trimethoxyphenyl)tetrazole* (II) *hydrochloride.* A suspension of 11.8 g. of I and 8.6 g.

(1) Based on part of the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.
(2) White Laboratories Fellow, 1956–58.
(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.
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of diethylaminoethyl chloride hydrochloride in 80 ml. of acetone was treated with a solution of 8.4 g. of sodium hydroxide in 7.5 ml. of water. The mixture was heated under reflux for 3 hr. with continuous stirring, then diluted with 50 ml. of water and extracted with benzene. After removal of the solvent from the benzene solution the residual liquid was taken up in 250 ml. of ether. Dry hydrogen chloride was passed into the ethereal solution until precipitation of the crude hydrochloride was complete, yield 15.4 g. (83%). Recrystallization from isopropyl alcohol gave the pure hydrochloride, m.p. 147–148°.

*Anal.* Calcd. for $C_{16}H_{26}ClN_5O_3$: C, 51.7; H, 7.1; Cl, 9.5; N, 18.8. Found: C, 51.7; H, 7.0; Cl, 9.5; N, 19.1.

*2-(3'-Dimethylaminopropyl)-5-(3',4',5'-trimethoxyphenyl)-tetrazole* (III) *hydrochloride* was obtained in essentially the same way from I and 3-dimethylaminopropyl chloride hydrochloride, yield 50%, m.p. 162.5–163.5°.

*Anal.* Calcd. for $C_{15}H_{24}ClN_5O_3$: C, 50.3; H, 6.8; Cl, 9.9; N, 19.6. Found: C, 50.2; H, 6.9; Cl, 10.0; N, 19.4.

*2-(3'-Diethylaminopropyl)-5-(3',4',5'-trimethoxyphenyl)-tetrazole* (IV) *hydrochloride* was prepared similarly from I and 3-diethylaminopropyl chloride hydrochloride, yield 74%, m.p. 160–161°.

*Anal.* Calcd. for $C_{17}H_{28}ClN_5O_3$: C, 52.9; H, 7.3; Cl, 9.2; N, 18.2. Found: C, 52.9; H, 7.3; Cl, 9.4; N, 18.3.

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## C1-C2 Acetyl Migration on Methylation of the Anomeric 1,3,4,6-Tetra-*O*-acetyl-D-glucopyranoses

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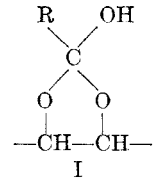
A need for the hitherto undescribed anomers of 2-*O*-methyltetra-*O*-acetyl-D-glucopyranose has prompted us to attempt their preparation by the direct methylation of the anomeric 1,3,4,6-tetra-*O*-acetyl-D-glucopyranoses with Purdies' reagent. When 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose was methylated with methyl iodide and silver oxide a quantitative yield of a clear sirup resulted, from which crystalline methyl tetra-*O*-acetyl-β-D-glucopyranoside could be isolated in a state of high purity in 81% yield. When 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose was similarly methylated, the same acetylated methyl β-D-glucopyranoside was obtained crystalline in a yield of 51%. The identity of each reaction product was established by elemental analysis, optical rotation, melting point, mixed melting point, and comparison of its infrared absorption spectrum with that of an authentic sample of methyl tetra-*O*-acetyl-β-D-glucopyranoside.

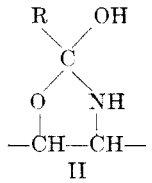
The facile migration of acyl groups in partially acylated polyhydroxylic compounds under mildly alkaline conditions is well known and has been the subject of numerous reports in the literature. Originally discovered and correctly interpreted in 1920 by E. Fischer[1] among partially acylated glycerol esters, acyl migration was apparently first noted in the carbohydrate series by Ohle[2] in 1924, who observed the conversion of 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose into the 6-*O*-benzoyl isomer under the influence of traces of alkali. Since this observation, subsequent investigators have noted migrations of acyl groups involving each carbon except $C_6$ of the hexose chain as the site of migration origin. Examples of known acyl migrations in the carbohydrate series as well as the conditions producing them are summarized in Table I.

Table I illustrates the variety of positions in the partially acylated aldose chain between which acyl migrations have been demonstrated to occur. In table I it is clear that the present acetyl migrations from $C_1$ to $C_2$ during methylation of the anomeric 1,3,4,6-tetra-*O*-acetyl-D-glucopyranoses with Purdies reagent (No. 1) represent acyl migrations of a type not hitherto observed, previous $C_1$-$C_2$ migrations having involved only aroyl groups in the ribofuranose (No. 2), glucopyranose (No. 3), and mannitol (No. 4) series under quite different reaction conditions. The present $C_1$-$C_2$ acetyl migration confirms in a sense the prediction, based on other considerations, by Lemieux[3] that 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose should possess a tendency to rearrange into the 2,3,4,6-tetra-*O*-acetyl isomer. It is interesting to note that the previously stated generalization[4] that acyl migrations invariably proceed *away* from $C_1$ and *towards* $C_6$ appears to be substantiated in most of the examples in Table I. Only in Nos. 7,8,9 and possibly 14 do the acyl migrations proceed in an opposite sense, *i.e.*, towards $C_1$.

In 1920 E. Fischer[1] suggested intuitively that the mechanism of acyl migration in partially acylated polyhydroxylic systems involved 1,2-ortho acid ester intermediates such as I. This concept was later expanded to include cyclic ortho acid ester intermediates spanning more than merely adjacent carbon atoms to account for acyl migrations over the longer carbon chain systems in the pyranose



I



II

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