Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; OCH_3, 10.12. Found: C, 78.60; H, 11.16; OCH_3, 10.19.

Anodic Reaction of Isostevic Acid (III).—To a solution of 284 mg. of isostevic acid in 17 ml. of methanol was added 75 mg. of metallic sodium. The solution was electrolyzed at 100 mamperes and 10 volts for 4.5 hr. During the electrolysis methanol was added periodically to maintain the original volume. The solution temperature was maintained at 25° by use of an evaporating acetone bath. On completion of electrolysis, the solvent was removed under reduced pressure. To the residue was added 35 ml. of ether and the resulting mixture was washed four times with 5-ml. portions of sodium hydroxide (5%) and then with water. The ether solution was dried over sodium sulfate and evaporated to give 254 mg. of a neutral product which was chromatographed on 7.5 g. of grade III alumina. Elution with petroleum ether (b.p. 30–60°) gave 151 mg. of an oil which was distilled at 0.6–0.8 $\times 10^{-4}$ mm. The colorless oil gave positive Zeisel and tetranitromethane tests and showed an infrared band at 1065–1100 $cm.^{-1}$ (methoxyl). Vapor phase chromatographic analysis indicated two major components, 65% 4-normethoxyisostevane (IV) and 25% 4-nor-Δ^4-isostevene (V). Two minor components (10%) were removed by the subsequent step. Repeated column chromatography failed to separate the two major components.

4-Nor-Δ^4-isostevene.—To a solution of 214 mg. of a mixture of 4-normethoxyisostevene and 4-nor-Δ^4-isostevane (obtained from the electrolysis experiment) in 20 ml. of glacial acetic acid was added 12 ml. of 1% aqueous hydrobromic acid solution. The mixture was refluxed in an oil bath (120–130°) for 1 hr. and then allowed to stand overnight at room temperature. After addition of 50 ml. of water, the mixture was extracted four times with 20-ml. portions of ether. The combined ether extracts were washed several times with 5-ml. portions of sodium hydroxide (5%), followed by water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave 172 mg. of pale yellow oil which was chromatographed on grade III alumina (5 g.). Elution with petroleum ether (b.p. 30–60°) gave 132 mg. of colorless oil (positive tetranitromethane test). Distillation at 5.3–5.8 $\times 10^{-4}$ mm. gave a clear, colorless oil; $[\alpha]^{20}D$ $-118° \pm 1.0$ (*c*, 1.15, $CHCl_3$). Vapor phase chromatographic analysis indicated one major component (98%).

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.14; H, 11.64.

4-Norisostevane (VI).—To a solution of 158 mg. of 4-nor-Δ^4-isostevene in 6 ml. of glacial acetic acid and 8 ml. of ethyl acetate was added 73 mg. of platinum oxide. The mixture was hydrogenated for 5.5 hr. at room temperature and under pressure of 20 p.s.i., using the Parr apparatus. Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure gave 156 mg. of pale yellow oil (negative tetranitromethane test). The product was chromatographed on grade III alumina (4.5 g.). Elution with petroleum ether (b.p. 30–60°) gave 133 mg. (83.5%) of colorless oil. The product was distilled at 0.2–0.3 $\times 10^{-4}$ mm. Vapor phase chromatographic analysis indicated one major component (95%), two trace components (5%). $[\alpha]^{20}D$ $-17.5 \pm 1.0°$ (*c*, 0.916, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.70; H, 12.42.

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The Synthesis of Some Heterocyclic Compounds Derived from Guanidines

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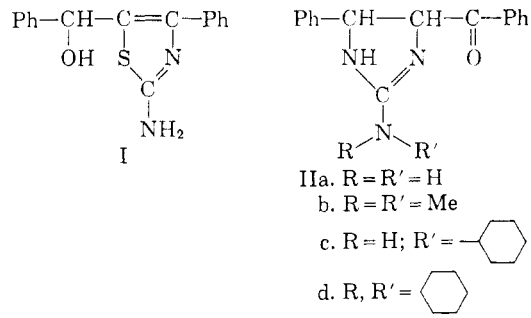
Earlier workers[2] have shown that thiourea reacts with 1-benzoyl-2-phenylethylene oxide to give 2-amino-4α hydroxybenzyl-5-phenylthiazole (I). Because of the structural similarity between thiourea and guanidine, it was of interest to examine the reaction of the latter and some of its homologs with 1-benzoyl-2-phenylethylene oxide. A series of compounds thus was prepared to which the general structure II was assigned.



None of these compounds have been reported previously in the literature. They are crystalline solids of high melting point and are best purified by recrystallization from aqueous acetic acid. Dissolution in mineral acid followed by dilution with water causes separation of the free base. All compounds in this series are formed in high yield (lowest 81%) in ethanolic solution, separation of the solid product occurring within a few minutes. The parent 2-amino-4-benzoyl-5-phenylimidazoline-2 (IIa) furnishes diacetyl, monoacetyl, and monopropionyl derivatives, although the more heavily substituted analogs are less reactive, but readily yield crystalline picrates. Failure of IIb, c, and d to furnish acetyl derivatives may be due to hydrolysis during the work-up procedure, particularly if acetylation of ring nitrogen atoms is involved.

Possible alternative structures for these compounds may be ruled out from the chemical and physical evidence. Each compound displays a stretching frequency in the carbonyl region which probably excludes structures such as 2-amino (or alkylamino)4α-hydroxybenzyl-5-phenylimidazole. However, the carbonyl function does not form the

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(2) C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson, and W. E. Savige, *J. Chem. Soc.*, 2573 (1949).

usual ketonic derivatives, possibly due to steric hindrance. If ring opening, postulated as the initial step in the formation of the substances, had taken place to give β-hydroxy compounds as the intermediate (*i.e.*, the hydroxy group is β to one phenyl ring), then ring closure by elimination of water between an amino and carbonyl function would yield dihydropyrimidines which, in the present case, ought to undergo very ready, even spontaneous, dehydration to the fully aromatic pyrimidine. Furthermore, at least two of the compounds yielded benzaldehyde on treatment with alkaline permanganate: this behavior cannot be interpreted readily on the basis of a six-membered ring formulation.

It should be noted that the analytical results obtained for these compounds would fit almost as well molecular formulas having two hydrogen atoms less than the empirical formulas which have been assigned. This would almost certainly mean that the compounds synthesised were true aromatics, whether five- or six-membered. It is known[3] that 2-aminoimidazoles and 2-aminopyrimidines are particularly resistant to acetylation, yet the compound obtained from the reaction of guanidine with the epoxide is easily acylated. The preparation of all compounds is unaffected if carried out in a stream of nitrogen; hence, it seems unlikely that any oxidation process is involved in their formation. Furthermore, the carbonyl oxygen functions give no evidence of phenolic behavior (toward diazomethane) typical of ketopyrimidines.

The diacetyl derivative of IIa is thought to be the exocyclic diacetylamino compound since one of the carbonyl frequencies (1778 cm.$^{-1}$) is far too high for a normal secondary or tertiary amide. The possible alternative formulation as 2-acetylamino-4 α acetoxybenzylidene-5-phenylimidazoline-2 cannot be ruled out, although no other member of the series yields an enolic acetate. The presence of a very high carbonyl frequency (1786 cm.$^{-1}$) in a diacetyl derivative of α-naphthylamine[4] recently has been observed. Alkaline hydrolysis of the diacetyl derivative of IIa gives the monoacetyl derivative which can in turn be converted to the free base by acid hydrolysis. Treatment of IIa with propionic anhydride yields only the monopropionyl derivative.

Guanidinium cations (in the form of their salts) do not react with 1-benzoyl-2-phenylethylene oxide to give any crystalline product, starting materials only being recovered in high yield. The contrasting behavior of guanidinium cations and the free bases toward the epoxide suggests that nucleophilic attack on the ethylene oxide is a necessary step in the formation of the imidazolines. It is clear that the initial step of ring opening gives an unstable intermediate alcohol in which the hydroxyl group can be either α or β to one phenyl ring. In the case of the former, cyclization by loss of water can lead only to a five-membered ring, whereas with the latter either an imidazoline or dihydropyrimidine can be formed. In parallel cases[5,6] of amine attack on α aryl- β carbonyl epoxides, it has been shown that it is the carbon atom in the position beta to the phenyl ring which is preferentially attacked by the amine (*i.e.*, the hydroxyl group is α to the phenyl ring). However, recent work by the author[7] has demonstrated unequivocally that attack by guanidine on ethyl phenylglycidate takes place exclusively at the carbon atom alpha to the ring since the isolable and stable intermediate from this reaction can be cyclized to a known pyrimidine.

Experimental[8]

2-Amino-4-benzoyl-5-phenylimidazoline-2. (IIa).—To 1-benzoyl-2-phenylethylene oxide (4 g.)[9] was added a solution of guanidine (2 g.) in ethanol (4 cc.). The mixture was heated under reflux, the epoxide dissolving and the solution turning dark red. After 1 min. a yellowish solid began to precipitate. Heating under reflux was continued for 20 min., the reaction mixture cooled to 0°, and the solid filtered and washed with water. The solid was recrystallized from aqueous acetic acid to give colorless plates (4.3 g., 86%) m.p. > 300°.

Anal. Calcd. for $C_{16}H_{15}N_3O \cdot {}^1/_2\ H_2O$: C, 70.1; H, 5.9; N, 15.3. Found: C, 70.1; H, 5.7; N, 14.9. Infrared spectrum: 3380, 3300, 2885, 1705, 1662, 1590, 1500, 1336, 1315, 1300, 1283, 1250, 1158, 1085.

Diacetyl Derivative.—IIa (2.0 g.) was refluxed with a 1:1 ratio by volume of acetic anhydride–acetic acid (6 cc.) for 2 hr. and cooled to 0°. The crystalline solid (1.7 g.) was filtered and recrystallized from ethanol as plates of m.p. 200–201° dec.

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.7; H, 5.5; N, 21.0; —CO CH_3, 24.6. Found: C, 68.9; H, 5.5; N, 12.1; —CO CH_3, 23.7. Infrared spectrum: 3290, 2875, 1778, 1716, 1654, 1618, 1606, 1504, 1462, 1452, 1398, 1316, 1275, 1238, 1162, 1110.

Monoacetyl Derivative.—The diacetyl derivative (1.0 g.) was dissolved in ethanol (20 cc.) at 40° containing potassium hydroxide (0.3 g.). After 1-hr. standing at 40°, the solution was cooled at 0° and held at this temperature for 2 days. The solid (0.4 g.) which separated, was recrystallized from aqueous acetic acid to furnish plates of m.p. > 300° which gave a depression on admixture with an authentic sample of IIa.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.3; H, 5.5; N, 13.7; —CO CH_3, 14.0. Found: C, 70.2; H, 5.6; N, 13.8; —CO CH_3, 13.3.

Hydrolysis of Monoacetyl Derivative.—When the monoacetyl derivative of IIa was heated under reflux with 30% sulfuric acid for 1 hr., cooled, and the solution made basic with sodium carbonate, 2-amino-4-benzoyl-5-phenylimidazoline-2 was regenerated which gave no depression of m.p. on admixture with an authentic sample of IIa.

Monopropionyl Derivative.—IIa (1.5 g.) was heated under reflux for 2 hr. with a 1:1 mixture by volume of propionic anhydride–propionic acid (6 cc.). Propionic acid was distilled and on cooling the flask filled with colorless

(3) B. Lythgoe, *Quart. Rev.* (London), **3**, 181 (1949).
(4) J. E. Banfield, *J. Chem. Soc.*, 2098 (1961).
(5) V. F. Martynov and G. Ol'man, *Zh. Obsch. Khim.*, **28**, 592 (1958).
(6) V. P. Martynov and G. Ol'man, *ibid.*, **27**, 1881 (1957).
(7) J. E. Banfield and D. S. McGuinness, unpublished results.
(8) All melting points are uncorrected.
(9) E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921).

solid (1.4 g.). This was recrystallized from propionic acids as rods of m.p. 274–275°.

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.0; H, 6.1; N, 13.1. Found: C, 70.4; H, 5.9; N, 13.4.

Oxidation of IIa.—To a suspension of 2-amino-4-benzoyl-5-phenylimidazoline-2 (5.0 g.) in 10% sodium carbonate solution (120 cc.) was added potassium permanganate (2.2 g.) and the mixture heated under reflux for 30 min. The mixture was steam distilled to give a few drops of a heavy oil smelling strongly of bitter almonds. Treatment of the oil with 2,4-dinitrophenylhydrazine reagent gave an orange 2,4-dinitrophenylhydrazone of m.p. 236–237°, undepressed on admixture with an authentic sample of benzaldehyde 2,4-dinitrophenylhydrazone.

2-Dimethylamino-4-benzoyl-5-phenylimidazoline-2. (IIb) was prepared by the same general method as IIa from 1-benzoyl-2-phenylethylene oxide (10 g.) and N,N-dimethylguanidine (4.5 g.) in ethanol (120 cc.). The solid (10.5 g. 81%) was recrystallized from ethanol as colorless needles of m.p. 284–285°. The analytical sample was purified by sublimation.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.7; H, 6.5; N, 14.3. Found: C, 73.9; H, 6.5; N, 14.4. Infrared Spectrum for II (b): 3180, 2887, 1670, 1636, 1502, 1461, 1412, 1328, 1303, 1232, 1198, 1088, 1056.

Treatment of II (b) with picric acid gave the picrate as yellow needles of m.p. 207–209°, purified by recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{22}N_6O_8$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.4; H, 4.3; N, 16.2.

2-Cyclohexylamino-4-benzoyl-5-phenylimidazoline-2 IIc was prepared as for IIa using 1-benzoyl-2-phenylethylene oxide (5 g.) and a solution of cyclohexylguanidine (3 g.) in ethanol (60 cc.). The solid (6.7 g., 82%) was purified by recrystallization from aqueous acetic acid to give colorless needles of m.p. 291–292°.

Anal. Calcd. for $C_{22}H_{25}N_3O$: C, 76.0; N, 7.2; N, 12.1. Found: C, 75.5; H, 7.2; N, 12.3.

Treatment with picric acid yielded the picrate as yellow needles of m.p. 214–216°, purified for analysis by recrystallization from ethanol.

Anal. Calcd. for $C_{28}H_{28}N_6O_8$: C, 58.3; H, 4.9; N, 14.6. Found: C, 58.1; H, 4.9; N, 14.5.

2-N-Piperidino-4-benzoyl-5-phenylimidazoline-2 IId was prepared from 1-amidinopiperidine (3 g.) in ethanol (30 cc.) and 1-benzoyl-2-phenylethylene oxide (7 g.) by the usual method. The solid (8.7 g., 95%) was recrystallized from aqueous acetic acid as colorless plates of m.p. > 300°.

Anal. Calcd. for $C_{21}H_{23}N_3O$: C, 73.7; H, 7.0; N, 12.3. Found: C, 73.9; H, 6.9; N, 12.4. Infrared spectrum: 3320, 3140, 3080, 1668, 1595, 1502, 1461, 1435, 1356, 1340, 1325, 1300, 1215, 1204, 1165.

Oxidation of IId.—A suspension of IId (6.5 g.) in 10% sodium carbonate solution (100 cc.) was refluxed with potassium permanganate (2 g.) for 30 min. then steam distilled to give a few drops of benzaldehyde, identified by its odor and the formation of a 2,4-dinitrophenylhydrazone of m.p. 235–237°, which gave no depression on admixture with an authentic sample.

Attempted Acylation of IIb, c, and d.—One gram of each of IIb, c, and d was refluxed individually for 6 hr. with a 1:1 ratio by volume of acetic acid–acetic anhydride (10 cc.), cooled, and poured into ice–water. In all cases only starting material was recovered, identified by m.p. and mixed m.p.

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Cleavage of Steroidal Digitonides in Dimethyl Sulfoxide

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In connection with another problem under investigation in this laboratory, it became desirable to develop a procedure for cleavage of steroidal digitonides and recovery of the sterol directly by extraction. We now wish to report the following rapid and convenient method.

Dimethyl sulfoxide, in which cholesterol and cholestanol are sparingly soluble, exhibits remarkable solvent power for digitonin and brings about complete dissociation of digitonides at steam-bath temperature. When the solution is allowed to come to room temperature, the sterol precipitates and is extracted with hexane. Recovery of the sterol is nearly quantitative, and the saponin, which remains in the dimethyl sulfoxide layer, may be obtained in good yield by evaporation of the solution to dryness.

Heretofore, pyridine has been the preferred solvent for cleavage of digitonides according to the method originally introduced by Schoenheimer and Dam,[1] and later modified by Bergmann.[2] This method has proved to be reliable, but is often tedious and time consuming.

The use of dimethyl sulfoxide has the distinct advantage of convenience and speed in the isolation of digitonin precipitable sterols. The method also gives excellent results in the decomposition of cholesterol complexes with tomatine and holothurin.[3]

Experimental[4]

Cleavage of Digitonides.—The general procedure is illustrated by the following example. A mixture of dimethyl sulfoxide[5] (20 ml.) and cholesteryl digitonide (1.006 g.) was heated on the steam bath for 15 min.[6] and the resulting solution allowed to come to room temperature, whereupon cholesterol precipitated. The mixture was transferred to a separatory funnel and extracted with 70 ml. of *n*-hexane. The dimethyl sulfoxide layer was extracted further with four 30-ml. portions of *n*-hexane and the combined hydrocarbon layers were allowed to stand for 20 min. over sodium sulfate (15 g.), filtered, and evaporated to dryness. The residue was dried to constant weight (100°/1 mm.) giving cholesterol (0.227 g., 94% recovery) melting at 147–148.5° (m.m.p., infrared spectrum). Evaporation of the dimethyl

(1) R. Schoenheimer and H. Dam, *Z. Physiol.*, **215**, 59 (1933).

(2) W. Bergmann, *J. Biol. Chem.*, **132**, 471 (1940).

(3) J. D. Chanley, R. Ledeen, J. Wax, R. F. Nigrelli, and H. Sobotka, *J. Am. Chem. Soc.*, **81**, 5180 (1959).

(4) The skillful technical assistance of Mr. Steven Frank is gratefully acknowledged.

(5) Supplier: Crown Zellerbach, Chemical Products Div., Camas, Wash.

(6) In more recent experiments the heating period has been reduced to five minutes with equally good results.