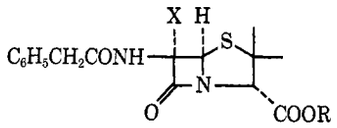
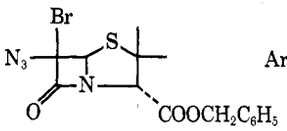
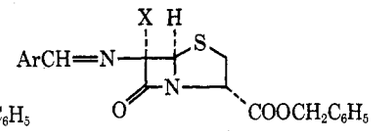


1, R = Na
2, R = $CH_2C_6H_5$
1,2a X = OH
b X = OCH_3
c X = OCHO
d X = $OCH_2C_6H_5$
e X = H



3



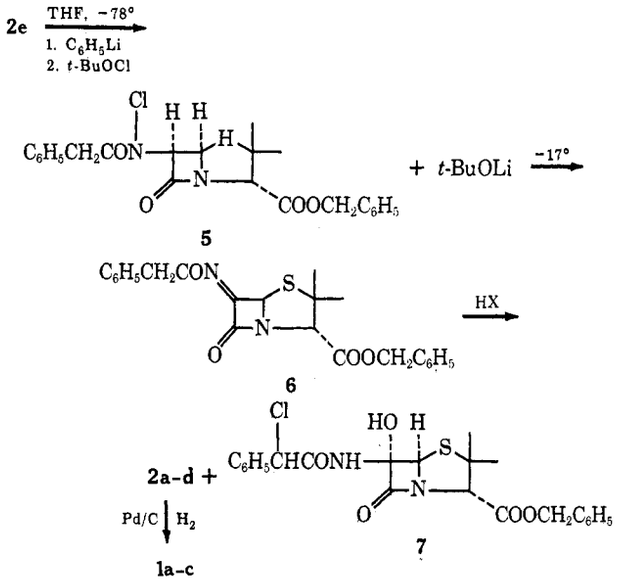
4

have been prepared in which X is alkyl,[4] hydroxyalkyl,[4] Br,[1] and (by exchange with Br) OCH_3,[1] F,[5] N_3,[5] and NC.[5]

When X is a good leaving group, however, the yields of N-acylated penicillins **2** are sometimes poor because X is easily lost during reduction of the azide or hydrolysis of the Schiff base.[1,3,4] Since electronegative 6 substituents become stabilized once the amino group is acylated, a method was sought for their introduction into the intact penicillin G benzyl ester molecule (**2e**).

This was achieved by the method depicted in the Scheme I. Treatment of **2e** (0.25 mmol) in 5 ml of

SCHEME I



THF with PhLi (0.25 mmol) at −78° under N_2 afforded the *N*-lithio derivative, which was chlorinated to **5** at −78° with 35λ *tert*-butyl hypochlorite (0.29 mmol). The by-product, lithium *tert*-butoxide, effected dehydrohalogenation of **5** during warming to −17°, producing *N*-acylimine **6**, benzyl 6-(*N*-phenylacetyl)iminopenicillanate, the key intermediate.[6] Conjugation of the azomethine linkage with the exocyclic carbonyl was expected to confer electrophilic nature on C-6, and attack on the planar site from the less hindered α direction was anticipated.

Addition of 1 ml of methanol at −17° afforded, after chromatography on silica gel with 4:1 $CHCl_3$–EtOAc, 6α-methoxypenicillin G benzyl ester (**2b**), identical with an authentic sample[3] and different from its 6 epimer. Similarly, with water there was obtained the 6α-hydroxy derivative **2a**: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.47 (s, 5-H); mass spectrum *m/e* 440, 250. With triethylammonium formate the 6α-formyloxy compound **2c** was obtained: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.55 (s, 5-H); mass spectrum *m/e* 468, 250. Compounds **2a** and **2c** are assigned the 6α configuration by analogy with **2b**.

Low yields of **2a**, and sometimes **2c**, were always obtained, no matter which reagent was added to **6**; evidently the reactivity of **6** toward water is exceptionally great. Presumably **2c** arises from decomposition of *tert*-butyl hypochlorite to acetone, which undergoes the haloform reaction to give formate ion or its equivalent. A major by-product always formed is assigned the structure **7** on the basis of its ir, nmr, and mass spectra. Another minor by-product often seen by nmr was once isolated in low yield and identified as the 6α-benzyloxy derivative **2d**, identical with an authentic sample.[7] This can only come from addition to **6** of benzyl alcohol formed by base attack on the benzyl ester.

Hydrogenolysis[8] of **2a** with an equal weight of 10% Pd/C and equimolar $NaHCO_3$ in 4:1 MeOH–H_2O for 1 hr at 40 psi afforded 6α-hydroxypenicillin G (**1a**): nmr (δ, D_2O) 1.35 (s), 1.46 (s) (*gem*-dimethyl), 3.65 (s, $C_6H_5CH_2CO$), 4.23 (s, 3-H), 4.67 (s, HDO), 5.33 (s, 5-H), 7.25 (s, C_6H_5); mass spectrum of Me ester (from CH_2N_2) *m/e* 364. In similar fashion[8] was obtained 6α-formyloxypenicillin G (**1c**): nmr (δ, D_2O) 4.11 (s, 3-H), 4.55 (s, HDO), 5.35 (s, 5-H); mass spectrum of Me ester *m/e* 392. The antimicrobial activities of **1a** and **1c** were markedly lower than that of **1b**.

Acknowledgment.—We are grateful to Dr. L. Cama for many helpful discussions during the course of this work.

(5) Unpublished results from these laboratories.

(6) With triethylamine as base, and (presumably) at ambient temperature, the sulfur atom is chlorinated and the thiazolidine ring opened: J. C. Sheehan in "Molecular Modification in Drug Design," American Chemical Society, Washington, D. C., 1964, p 22.

(7) Prepared by Mr. W. J. Leanza by the method of ref 3.

(8) These experiments were performed by Miss N. Schelechow.

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Improved Routes to Methyl 4-Methylimidazole-2-carboxylate and Methyl 5-Methyl-1,2,4-triazole-3-carboxylate[1]

Summary: Triethyloxonium tetrafluoroborate and methyl fluorosulfate alkylate the sulfur atom of ethyl 2-thiooxamate. The alkylation products (**2a** and **2b**) contain nucleophilic nitrogen atoms and good leaving

(1) Full experimental details will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-1437.

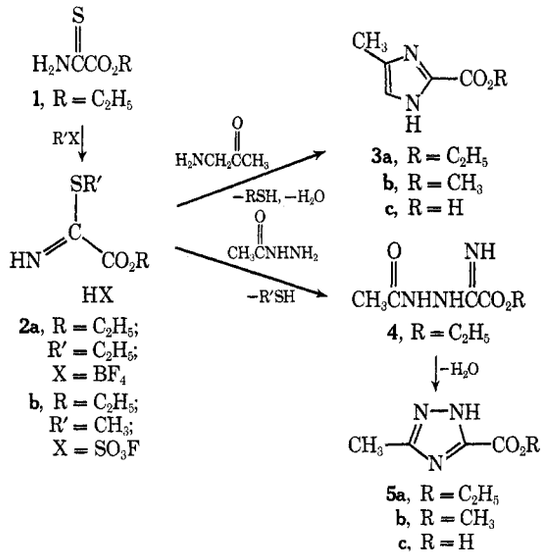
groups, and are thus useful precursors for heterocyclic carboxylates. For example, reaction of **2a** with aminoacetone provided ethyl 4-methylimidazole-2-carboxylate directly, and reaction of **2a** with acethydrazide gave **4** which was cyclodehydrated to ethyl 5-methyl-1,2,4-triazole-3-carboxylate.

Sir: The identification of methyl 4-methylpyrrole-2-carboxylate as a volatile component of the trail pheromone of the leaf-cutting ant, *Atta texana* (Buckley),[2a] prompted us to examine a number of structurally related pyrroles[2b] and similarly constituted pyrazoles, imidazoles, and triazoles.

Surprisingly, there appear to be no general methods for preparing either imidazole-2-carboxylic acid or 1,2,4-triazole-3-carboxylic acid derivatives. Ethyl 4- (or 5-) methyl-2-imidazolecarboxylate **3a** has been prepared by a Radziszewski synthesis involving the condensation of cinnamaldehyde with pyruvaldehyde and ammonia, followed by barium permanganate degradation of the resulting 2-styryl-4- (or 5-) methylimidazole to the carboxylic acid **3c**, and esterification of **3c** to **3a** with EtOH–HCl at 110°.[3] The yields were not reported, but the Radziszewski method is known to afford complex mixtures frequently and poor yields of the desired imidazoles.[4] 5-Methyl-1,2,4-triazole-3-carboxylic acid was recently reported,[5] but again the carboxyl function was generated by a permanganate oxidation, in this case by the selective oxidation of one of the methyl groups of 3,5-dimethyl-1,2,4-triazole. We here report new syntheses of 4-methylimidazole carboxylates **3a** and **3b** and 5-methyltriazole carboxylates **5a** and **5b** from a common precursor, **2**.

Ethyl 2-thiooxamate (**1**)[6] was alkylated[7] with triethyloxonium tetrafluoroborate in CH_2Cl_2 to provide **2a** as a pale yellow oil which we were unable to crystallize and therefore did not characterize.[8] Treatment of **2a** with aminoacetone hydrochloride[9] (1 equiv) and NaOAc (2 equiv) in HOAc at 90–100° provided the imidazole carboxylate **3a** in a single step (77% from **1**), mp 115–116°; its nitrate had mp 125.5–126° (lit.[3] mp 124°). The reaction proceeded equally well in Me_2CO with aqueous Na_2CO_3. Transesterification with $NaOCH_3$–CH_3OH gave the desired methyl ester **3b** (30%, mp 143–145°) (Scheme I).

SCHEME I



Reaction of **2a** with acethydrazide in CH_2Cl_2 containing Et_3N provided **4** in 77% yield (from **1**), mp 196.5–197.5°. Cyclization of **4** to **5a** was effected by heating **4** at 210–215° for 15 min (44%, mp 185–185.5°). Transesterification with $NaOCH_3$–CH_3OH gave the methyl ester **5b** (48%, mp 231°).

The thiooxamate **1** could also be alkylated with methyl fluorosulfate to give **2b**, and **2b** was converted to both **3a** and **4** under conditions similar to those described for the reactions of **2a**. Although the yields were slightly lower in these cases, the possibility of optimizing conditions and the ready availability of methyl fluorosulfate could make this reagent the alkylating agent of choice in some cases. Similarly, since the yields in the transesterification reactions were rather low, other esters of 2-thiooxamic acid might profitably be employed as starting materials.

Since our goal was simply the preparation of **3b** and **5b**, we have not further investigated the scope of these reactions, but it appears that each should be readily adaptable to the preparation of other members of each ring system wherein the methyl group could be replaced by a variety of other substituents. Furthermore, **2** should be a useful starting material for a number of other heterocyclic carboxylates.

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(2) (a) J. H. Tumlinson, J. C. Moser, R. M. Silverstein, R. G. Brownlee, and J. M. Ruth, *Nature (London)*, **234**, 348 (1971); (b) P. E. Sonnet and J. C. Moser, *J. Agr. Food Chem.*, **20**,1191 (1972).

(3) W. John, *Chem. Ber.*, **68B**, 2283 (1935).

(4) K. Hofmann "Imidazole and Its Derivative," Vol. 6, in the series in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1953, pp 33–38.

(5) T. N. Vereshchagina and V. A. Lopyrev, *Khim. Geteotsikl., Soedin.*, 1695 (1970); *cf. Chem. Abstr.*, **74**, 99951y (1971).

(6) W. R. Boon, *J. Chem. Soc.*, 601 (1945). We found that the use of pyridine as the solvent for the addition of H_2S to ethyl cyanoformate greatly facilitated the reaction and **1** was thus obtained in essentially quantitative yield.

(7) Ethyl 2-thiooxamate (**1**) was rather resistant to alkylation and did not react with methyl iodide in refluxing acetone (15 min); with MeI in refluxing CH_3CN the color rapidly darkened, the odor of methyl mercaptan was evident, and no pure product was obtained.

(8) Except for **2a** and **2b** the structures of all new compounds were confirmed by analytical as well as spectral data.

(9) *Org. Syn.*, **45**, 1 (1965).