rities are present, have indistinct boiling points.[1,3] The higher esters tend to form high-boiling ester interchange products as the major impurities. These by-products do not present purification problems, but they have reduced yields by as much as 30%. They are, apparently, formed during distillation and can be minimized by keeping the distillation temperatures below 100° by use of reduced pressure. For example, parallel runs of ethyl β-hydroxyheptanoate yielded 50% hydroxy ester and 25% pot residue when distilled at 118–120° (6.0 mm) and 75% hydroxy ester with less than 5% residue at 85–88° (0.5 mm).

The Reformatsky reaction is extremely vigorous[1] and, even under the most controlled conditions, can get out of hand. To avoid a hazardous situation and the loss of expensive reagents, we employ the apparatus shown in Figure 1. This system has virtues in its simple construction and ready adaptability to large-scale reactions. If the reaction becomes so violent that the contents of the reactor are expelled, the effluent is effectively contained in the receptacle H. This can be poured back into the flask A and the reaction can be continued with negligible reduction of yield provided the effluent is kept dry during spillage and transfer. The apparatus may be modified conveniently to accommodate lower boiling aldehydes by replacement of condenser E with a Dry Ice condenser.

The hydroxy esters we prepared are summarized in Table I. The yields given represent isolated materials of 98% or better glpc purity. The modified procedures we recommend are described fully in the two examples given below. Method A is used for aldehydes of four carbons or higher; method B is used for propionaldehyde and acetaldehyde.

Experimental Section

Materials.—Ethyl bromoacetate (Eastman) was used without purification, provided it was colorless. Colored material was discarded or distilled. The aldehydes were obtained from various sources and were the highest grade available. They were distilled under reduced pressure, dried over $MgSO_4$,[9] and used as soon as possible. Certified zinc metal dust (assay 98.8%; Fisher Scientific Co.) was activated by washing, successively, with 20% hydrochloric acid, water until neutral, acetone, and anhydrous ether. It was thoroughly air dried and used immediately.

Method A. Ethyl β-Hydroxyoctanoate.[2]—To the apparatus pictured in Figure 1 was charged 250–300 g (3.8–4.6 g-atoms) of activated zinc dust and 750 ml of dry benzene. The suspension was stirred rapidly and heated to vigorous reflux. The heat was removed and a mixture of 517 g (3.1 mol) of ethyl bromoacetate and 300 g (2.9 mol) of hexanal was added, dropwise, at a rate consistent with maintaining the reaction temperature at 80–85°.[10] The addition required 1.5–2 hr. The reaction mixture was cooled in a Dry Ice–isopropyl alcohol bath and stirred vigorously while 600 ml of 50% sulfuric acid was added dropwise. The temperature of the reaction mixture was kept below 35° during the addition. The layers were separated and the organic phase was washed twice with 1-l. portions of water[11] and dried. Distillation under reduced pressure afforded 285–470 g (50–80%) of colorless ester, bp 85–88° (0.5 mm).

(9) Water may be formed, from dehydration of aldol contaminants, during distillation and pass over with the aldehyde. This can be removed, either by drying in solution or by passing the distilled aldehyde rapidly through a cake of $MgSO_4$ on a suction filter.

(10) Some care is required in starting the reaction. It is important that the benzene be *refluxing vigorously* when the initial addition of aldehyde and EBA is made. A slight surge in the reflux rate is indicative of reaction. Once started, the reaction is easy to maintain.

(11) It is best to make sure that the reaction mixture is neutral after the water wash. If not, the benzene layer may be washed with a little 5% potassium carbonate and, finally, with water. Delaying the base wash until this point, or, if possible, omitting it altogether, reduces chances of emulsions forming and facilitates the separation of layers.

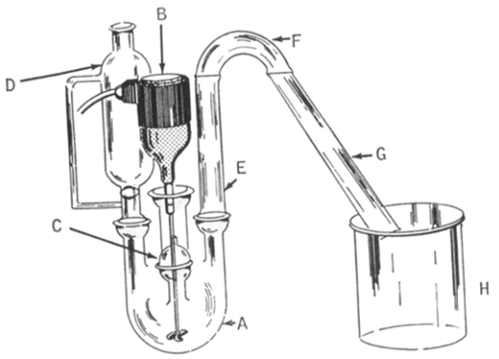

Figure 1.—Apparatus for large-scale Reformatsky reactions. A, 2-l., four-neck flask; B, electric or air-driven stirrer; C, thermometer for reading reaction temperature; D, 500-ml pressure-equalizing dropping funnel; E, Liebig condenser (may be replaced by Dry Ice condenser for lower aldehydes); F, curved adapter; G, Liebig condenser; H, 2-l. beaker.

Method B. Ethyl β-Hydroxybutyrate.[12]—The apparatus shown in Figure 1 was modified to the extent that a Dry Ice condenser was substituted for the condenser E. The reaction was carried out on the same scale and in the same way as described above, using acetaldehyde in place of hexanal. The volatilized unreacted aldehyde was condensed and returned to the reactor continuously. The reaction mixture was hydrolyzed as in method A and washed twice with 500 ml of water. The water washings were extracted twice with 500 ml of chloroform. The combined chloroform and benzene solutions were dried over magnesium sulfate and distilled. The main fraction, bp 58–60° (2.0 mm), weighed 255–283 g (67–74%).

Registry No.—EBA, 105-36-2.

Acknowledgments.—The authors wish to thank Mr. C. W. Drastura for suggesting some of the essential features of the reactor design. In addition, the technical assistance of Mr. F. M. Cornman and Mr. R. C. Hanna is gratefully acknowledged.

(12) See footnote *b*, Table I.

Solvent Shift Studies on Pseudoguaianolides of the Helenalin Series[1,2]

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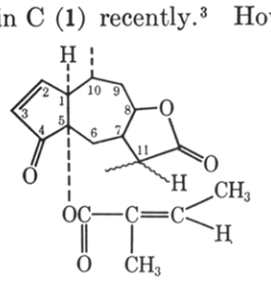
Received April 11, 1969

The pseudoguaianolide brevilin A was formulated as angeloylmexicanin C (**1**) recently.[3] However, in view



1, H-11 β
2, H-11 α

(1) Constituents of *Helenium* Species. XXIV. Previous paper: W. Herz, P. S. Subramaniam, and N. Dennis, *J. Org. Chem.*, **34**, 2915 (1969).

(2) Supported in part by grants from the National Science Foundation (GP-6362) and the National Institutes of Health (GM-05814).

(3) W. Herz, C. M. Gast, and P. S. Subramaniam, *J. Org. Chem.*, **33**, 2780 (1968).

TABLE I

SOLVENT SHIFTS OF METHYL GROUPS[a]

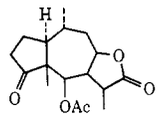
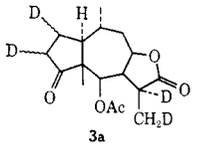
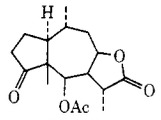
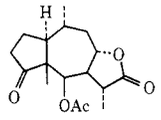
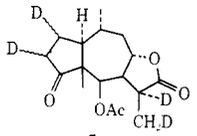
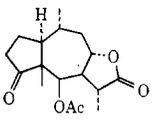
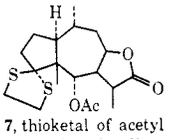
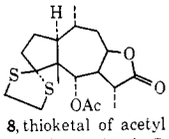
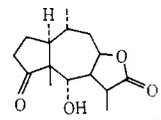
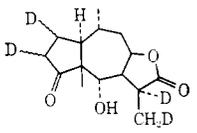
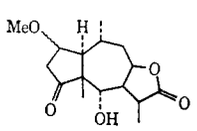
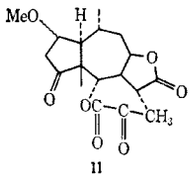
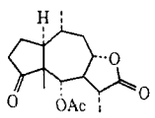
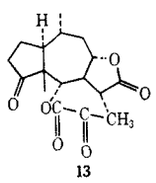
Compound	C-11 Me			C-10 Me			C-5 Me			Ref
	$CDCl_3$	C_6H_6	Δ	$CDCl_3$	C_6D_6	Δ	$CDCl_3$	C_6D_6	Δ	
 3, tetrahydrobalduilin	1.11	1.09	+0.02	1.15	0.76	+0.39	0.90	0.60	+0.30	*b*
 3a				1.13[c]	0.74	+0.39	0.88	0.58	+0.30	*b*
 4, tetrahydrobalduilin A	1.36	0.92	+0.44	1.16	0.64	+0.52	0.90	0.61	+0.29	*b*
 5, tetrahydrolinifolin	1.23	1.10	0.13	1.10	0.65	+0.45	0.91	0.53	+0.38	*d*
 5a				1.07[c]	0.62	+0.45	0.88	0.50	+0.38	*d*
 6, dihydroisotenulin	1.20	1.25	−0.05	1.06	0.92	+0.14	1.02	0.67	+0.35	*e*
 7, thioketal of acetyl tetrahydrohelenalin	1.45	1.45	0.00	1.00	0.73	+0.27	1.10	1.06	+0.04	*f*
 8, thioketal of acetyl dihydromexicanin C	1.29	1.23	+0.06	1.03	0.60	+0.43	1.17	1.04	+0.13	*g*
 9, tetrahydrohelenalin	1.29	1.16	+0.13	1.08	0.74	+0.34	0.76	0.63	+0.13	*h*
 9a				1.06[c]	0.75	+0.31	0.80	0.65	+0.15	*h*
 10	1.43	1.40	+0.04	1.10	0.90	+0.20	1.04	1.16	−0.12	*i*

TABLE I (*Continued*)

Compound	C-11 Me			C-10 Me			C-5 Me			Ref
	$CDCl_3$	C_6H_6	Δ	$CDCl_3$	C_6H_6	Δ	$CDCl_3$	C_6D_6	Δ	
 11	1.48	1.35	+0.13	1.12	0.85	+0.27	1.10	1.13	−0.03	*d*
 12, tetrahydrobigelovin	1.18	1.13	+0.05	0.98	0.58	+0.40	1.09	0.59	+0.50	*j*
 13	1.12	1.15	−0.03	1.04	0.60	+0.44	1.10	0.58	+0.52	*k*

[a] Spectra were recorded on a Varian A-60 spectrometer. Positive shifts are upfield shifts in benzene relative to chloroform. Signals are given in parts per million relative to TMS as internal standard. [b] W. Herz, R. B. Mitra, and P. Jayaraman, *J. Amer. Chem. Soc.*, **81**, 6061 (1959). [c] Small differences in chemical shifts are due to errors in calibration of spectrometer when samples were not run simultaneously. [d] Reference 3. [e] B. H. Braun, W. Herz, and K. Rabindran, *J. Amer. Chem. Soc.*, **78**, 4423 (1956). [f] W. Herz and R. B. Mitra, *ibid.*, **80**, 4876 (1958). [g] W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963). [h] R. Adams and W. Herz, *J. Amer. Chem. Soc.*, **71**, 2554 (1949). [i] W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963). [j] B. A. Parker and T. A. Geissman, *J. Org. Chem.*, **27**, 4127 (1962). [k] W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).

of the complex nature of the hydrolysis products and the possibility of epimerization at C-11 during hydrolysis, the less likely structure **2** could not be excluded with certainty.

It has been shown recently that solvent shifts of C-11 methyl groups in eudesmanolides can be used to assign stereochemistry.[4,5] Pseudoequatorial C-11 methyl groups exhibit an upfield (positive) shift of 0.23 ± 0.06 ppm in benzene relative to chloroform solution, pseudoaxial C-11 methyl groups have $\delta_{CDCl_3} - \delta_{C_6D_6}$ values of 0.046 ± 0.06 ppm. Although it appeared unlikely that this method would be applicable to the less rigid guaianolides and pseudoguaianolides, it seemed possible that some generalizations could be reached and that the ambiguity in the structure of brevilin A might be resolved.

In our previous publications we tacitly assumed that in the nmr spectra of saturated pseudoguaianolides, which were generally measured in $CDCl_3$ solution, the C-11 methyl doublet appears at lower field than the C-10 methyl doublet owing to the deshielding effect of the adjacent lactone carbonyl. Before the applicability of the solvent shift method to pseudoguaianolides could be tested, it was necessary to verify the correctness of this assumption and to establish whether it also held in C_6D_6 solution.

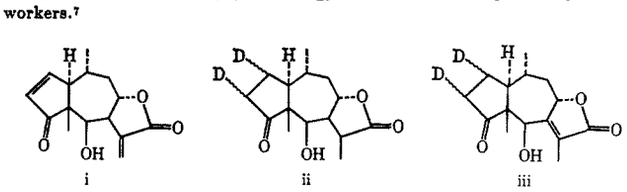
Table I lists chemical shifts of methyl groups in three C-11 epimeric pairs of pseudoguaianolides whose structure is known with certainty (**3**–**8**) and those of selected other compounds including a derivative of brevilin A (**11**). A comparison of the nmr spectra of **3**, **5**, and **9** with those of the tetradeuterio derivatives **3a**, **5a**, and **9a**[6] which lack the C-11 methyl signal shows that the assumption is on the whole correct and that it certainly holds in C_6D_6 solution. The existence of an unexpected and surprisingly large solvent shift to higher field of the C-10 methyl resonance which is invariably much greater than the solvent shift of the C-11 methyl signal proved the wisdom of utilizing the deuterated compounds for identifying the signals and provides another means for distinguishing between the groups responsible for the two doublets. Even if the methyl doublets are practically superimposed in $CDCl_3$ as in the case of tetrahydrobalduilin (**3**), an assignment of a given signal to C-10 or C-11 methyl can be made on the basis of the solvent shift, and it seems safe to extend the generalization to those compounds whose 11,13-dideuterio derivatives were not accessible (**4**, **7**, **8**, **10**, **11**, **12**, and **13**).

It can be seen from Table I that the solvent shift of the C-11 methyl signal in pseudoguaianolides related to helenalin is in general quite small, regardless of whether the lactone is *cis* or *trans* and the methyl group α or β, although **4** constitutes a notable exception. We conclude therefore that application of the solvent shift method to determination of C-11 stereochemistry in individual pseudoguaianolides is not warranted. This

(4) C. R. Narayanan and N. K. Venkatasubramaniam, *Tetrahedron Lett.*, 5865 (1966); *J. Org. Chem.*, **33**, 3156 (1968).

(5) W. Herz, P. S. Subramaniam, and T. A. Geissman, *ibid.*, **33**, 3743 (1968).

(6) These compounds were prepared from **3**, **5**, and **9** by hydrogenation in a deuterium atmosphere. Unfrtunoately, hydrogenation of mexicanin I (i) to the tetradeuterio derivative ii (11-epidesacetyldihydroisotenulin) could not be achieved, but resulted instead in the formation of the 2,3-dideuterioisomexicanin I (iii) in analogy with the results reported by earlier workers.[7]



i ii iii

(7) E. Dominguez and J. Romo, *Tetrahedron*, **19**, 1415 (1963).

is perhaps not particularly surprising when the greater conformational mobility of bicyclo[5.3.0]decanes is taken into account. Moreover, all the compounds listed in Table I contain carbonyl groups other than the lactone carbonyl in the C-7 side chain which must affect the nature of the collision complex.

One other item of interest can be gleaned from the present study. The expected large positive solvent shift associated with a quasiaxial methyl group[8] is not displayed by those compounds having the stereochemistry of helenalin (lactone ring *cis*, C-6 hydroxyl α), *i.e.* **7**, **8**, **9**, **10**, and **13**.[9] In the other two *cis* lactones (C-6 hydroxyl β; **3**, **4**) the C-5 methyl solvent shift is appreciable (0.30 ppm) as it is in the *trans* lactone series, with C-6 hydroxyl β (0.35 ppm). In the two *trans* lactones with C-6 hydroxyl α (**11**, **12**) the solvent shift reaches the very high value of 0.51 ppm. This information may be useful diagnostically in the analysis of other closely related compounds.[10]

Experimental Section

Compounds listed in Table I were available from our sample collection or prepared by the cited literature method. The extent of deuterium incorporation in samples **3a**, **5a**, and **9a** and in 2,3-dideuterioisomexicanin I was evident from the proton count in the nmr spectrum and was checked by mass spectrometry.

(8) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, pp 163–165.

(9) The small negative shift in compounds **10** and **13** may be due to the presence of the methoxyl group at C-2.

(10) NOTE ADDED IN PROOF.—E. H. White, S. Eguchi, and J. N. Marx [*Tetrahedron*, **25**, 2009 (1969)] have recently shown that the solvent shift method for the determination of C-11 methyl stereochemistry gave erroneous results when applied to the guaianolides deacetoxymatricarin[11] and achillin.[12]

(11) H. A. Lindo and M. S. Ragab, *Helv. Chim. Acta*, **50**, 1961 (1967).

(12) J. Smolenski, C. L. Bell, and L. Bauer, *Lloydia*, **30**, 144 (1967).

8-Aza Steroids. VI. 21 Hydroxylation[1]

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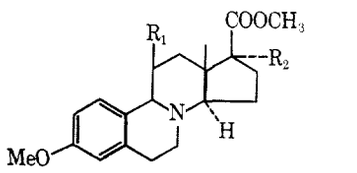
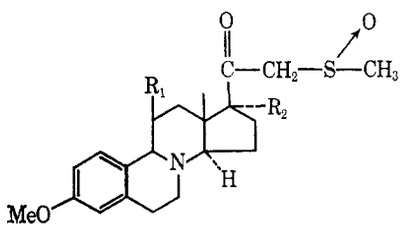
Received March 24, 1969

Russell[2] and coworkers recently described the conversion of esters into α-hydroxy ketones by Pummerer reaction on derived β-keto sulfoxides. We independently studied this reaction sequence in the 8-aza steroid series, and in this Note wish to report its application to the elaboration of the corticoid side chain.

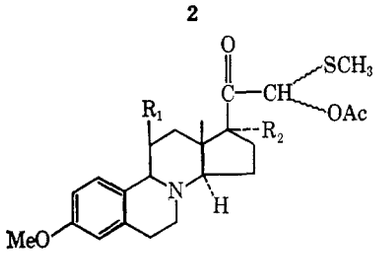
Treatment of esters **1a–1d** with the anion of dimethyl sulfoxide[3] gave β-keto sulfoxides **2a–2d** as epimeric mixtures in yields of 80–100%. When the sulfoxide mixtures were heated in acetic acid for 2 hr at 100°, Pummerer rearrangement to hemimercaptal acetates **3a–3d** took place. These products, also obtained as epimeric mixtures, were formed in crude yields of 70–90%. Since purification of these intermediates proved difficult, the crude products were characterized only by spectral properties and desulfurized directly with Raney nickel. Under these conditions, acetates **4a–4d** were obtained in yields of 50–70% based on sulfoxide **2**.



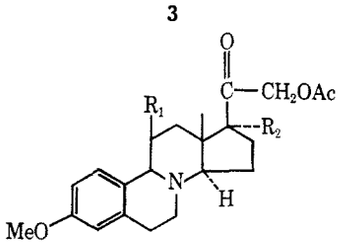
1



2



3



4

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = OH$
c, $R_1 = OH$; $R_2 = H$
d, $R_1 = R_2 = OH$

Structural assignments were based on microanalysis and spectral data. Thus **3** showed two carbonyl peaks in the ir at 1715 (ketone) and 1755 cm^{-1} (acetate). In the nmr, the acetate methyl and S-methyl signals appeared at 2.13 and 2.00 ppm, respectively, while the C-21 proton resonated as a sharp singlet at 5.9 ppm. For **4**, the spectral data were the same as for **3** except for disappearance of the S-methyl signal and appearance of either a two-proton singlet or AB quartet at 4.65 ppm for the C-21 methylene.

For the dihydroxy ("d") series, the starting ester, **1d**, has not been previously reported, and was prepared by the route previously described.[1] Treatment of ester **5a**[4] sequentially with base followed by bromine, silver nitrate, and potassium borohydride gave **5b**, **5c**, and **1d**, respectively, in yields of 90–100%. This sequence

(1) Part V: R. E. Brown, H. V. Hansen, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **33**, 4180 (1968).

(2) (a) H. D. Becker, G. J. Mikol, and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3410 (1963); (b) G. A. Russell, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966); (c) G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966).

(3) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

(4) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Med. Chem.*, **10**, 451 (1967).