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Sesquiterpene Lactones of *Tithonia diversifolia*. Stereochemistry of the Tagitinins and Related Compounds[1]

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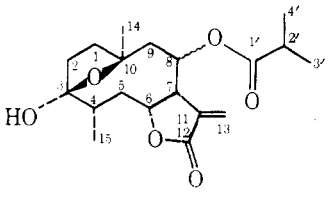
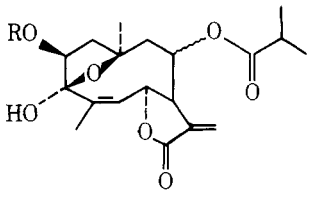
The sesquiterpene lactones tagitinins A, C, and F and tirotundin and the flavone hispidulin were isolated from Indian *Tithonia diversifolia* (Hemsl.) A. Gray. Complete stereochemical expressions are presented for these compounds as well as for tagitinin B and E, and the configuration at C-8 of zexbrevin, zexbrevin B, orizabin, ciliarin, calaxin, tifruticin, deoxytifruticin, viguiestin, and deacetylviguiestin is assigned.

Isolation of six sesquiterpene lactones, tagitinins A–F, from the antileukemic alcoholic extract of what was referred to as *Tithonia tagitiflora* Desf. [sic] has been reported recently.[2,3] We have isolated several of these compounds from an Indian collection of *Tithonia diversifolia* (Hemsl.) A. Gray which we believe represents the actual source of the lactones obtained by Pal and co-workers.[4] Our results which together with our previous work on tirotundin[6,7] and woodhousin[8,9] provide complete stereochemical expressions for the tagitinins and several related substances are described in the present report.

Tagitinin D was identical with tirotundin which we had isolated earlier[6] from *T. rotundifolia;* the name tagitinin D



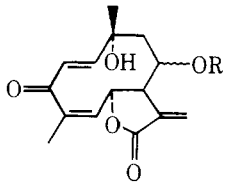
1a, H-8α, tirotundin
b, H-8β



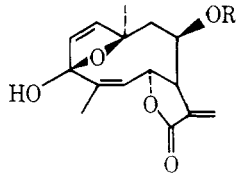
2a, R = H, H-8α, tagitinin D
b, R = Ac, H-8α, woodhousin
c, R = Ac, H-8β

should therefore be abandoned. The stereochemistry **1b** assigned originally[6] to tirotundin was recently[7] altered to **1a** as the result of an X-ray analysis.

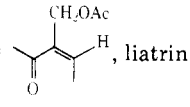
Tagitinin B had properties which suggested[3] that it was a deacetyl derivative of woodhousin;[8] hence formulas **2** (R = H) and **3** (R = H, stereochemistry at C-8 not specified) were assigned to it and to tagitinin C with which it had been correlated.[3] Since the C-8 stereochemistry of woodhousin has recently been revised from **2c** to **2b** as the result of an X-ray analysis,[9] tagitinin B and tagitinin C will have to be reformulated as **2a** and **3a,** respectively. This removes at least one element of confusion emanating from the work of Pal et al. who stated[3] that hydrogenation of tagitinin F (assigned[3] formula **4a** because of its similarity to liatrin, **4b**) furnished the



3a, R = *i*-Bu, H-8α, tagitinin C
b, R = Ang, H-8α
c, R = Ang, H-8β

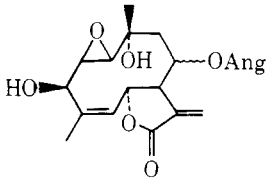


4a, R = *i*-Bu, tagitinin F

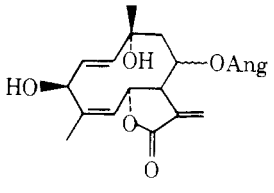


b, R = , liatrin

same hexahydro derivative as hydrogenation of **3a,** a result manifestly impossible if the stereochemistry at C-8 were different.[11] ^{13}C NMR spectra of tirotundin, woodhousin, and tagitinin C are listed in Table I for comparison.[12] Because of the close correspondence in chemical shifts and coupling constants between tagitinin C and dehydrodeoxytifruticin[6,13] and for other reasons cited earlier,[7,9] we conclude that the C-8 stereochemistry of dehydrodesoxytifruticin, and therefore also that of its congeners tifruticin and deoxytifruticin from *T. fruticosa,*[6] must be inverted from **3c** to **3b, 5b** to **5a,** and **6b** to **6a,** respectively.



5a, H-8α, tifruticin
b, H-8β



6a, H-8α, deoxytifruticin
b, H-8β

Formula **7** with a trans-lactone function but without specification of stereochemistry at C-1, C-4, and C-8 was proposed[3] for tagitinin A because of its similarity to tirotundin and its chemical behavior. We have established its stereochemistry at all centers in the following manner.

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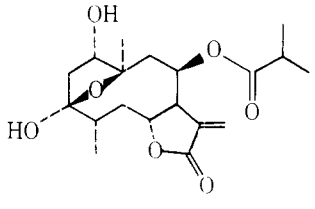
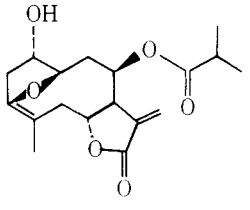
Table I. ^{13}C NMR Spectra of *Tithonia diversifolia* Constituents and Related Compounds[a]

	1b[b]	2b	3a[c]	7	14
C-1	38.9 t	42.72 t[d]	160.49 d	78.46 d	213.45
C-2	42.2 t	76.68 d	129.57 d	46.94 t	47.03 t
C-3	108.8	108.69	196.85	105.69	104.04
C-4	43.4 d	136.46	138.84	44.38 d	44.97 d
C-5	38.0 t[d]	132.44 d	137.14 d	37.81 t	37.75 t
C-6	81.3 d	80.41 d	76.05 d[d]	81.86 d	80.42 d
C-7	47.9 d	50.24 d	47.05 d	47.84 d	47.80 d
C-8	69.8 d	71.57 d	74.11 d[d]	69.90 d	68.33 d
C-9	38.4 t[d]	41.85 t[d]	48.37 t	34.65 t	36.44 d
C-10	80.0	83.52	71.91	81.69	81.84
C-11	137.2	137.70	136.11	137.01	136.37
C-12	169.4	169.10	169.75	169.75	169.12
C-13	121.4 t	122.93 t	124.43 t	121.73 t	122.04 t
C-14	26.9 q	21.77 q[d]	28.88 q	24.96 q	22.21 q
C-15	19.19[d]	21.61 q[d]	19.65 q[d]	19.18 q[d]	18.95 q[d]
C-1′	176.1	176.10	176.18	176.45	175.75
C-2′	34.1 d	34.11 d	34.06 d	34.11 d	33.91 d
C-3′	18.6 q[d]	19.14 q[d]	18.80 q[d]	18.76 q[d]	18.60 q[d]
C-4′	18.7 q[d]	18.75 q[d]	18.64 q[d]	18.42 q[d]	18.32 q[d]

[a] Run in $CDCl_3$ at 67.9 MHz on a Bruker HX-270 instrument. [b] Some assignments revised from those given in ref 6.[12] [c] Assignment of multiplets confirmed by single-frequency off-resonance decoupling except where indicated. [d] Assignments may be interchanged.

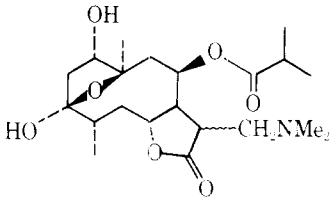


7, tagitinin A

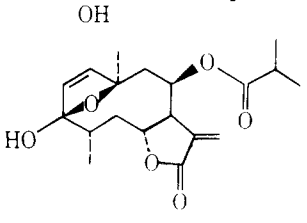


8

An attempt to remove the C-1 hydroxyl group of tagitinin A by heating with tosyl chloride–pyridine resulted in formation of **8**. However, exposure of the dimethylamine adduct **9** to acetic anhydride–pyridine produced a mixture of **10** and **11**, possibly because the cyclic hemiacetal in this compound

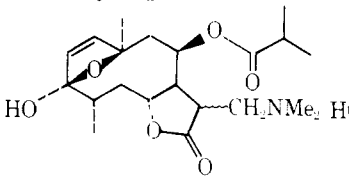


9

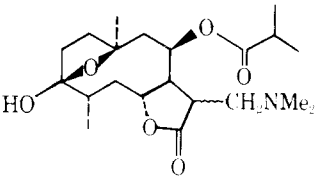


10

was in equilibrium with the open formula containing an unmasked β-hydroxy ketone (IR spectrum). The major product **11** was hydrogenated to **12** which on consecutive treatment

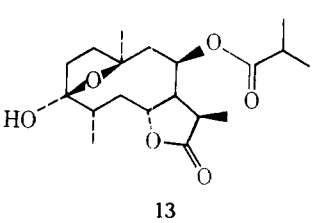


11

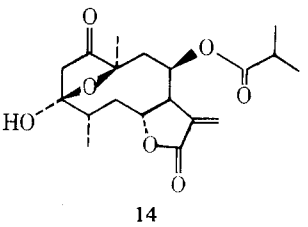


12

with methyl iodide and $NaHCO_3$[14] afforded tirotundin (**1a**). Similarly hydrogenation of **10** (4,5-dihydrotagitinin F) yielded a substance, **13**,[15] identical in all respects with material obtained by hydrogenation of tirotundin. This established the stereochemistry of tagitinin A at C-3, C-4, C-6, C-7, C-8, and C-10. The stereochemistry of **7** at C-1 was established by Horeau's method;[16,17] reaction with excess (±)-α-phenylbutyric anhydride gave (−)-α-phenylbutyric acid in 41.8% optical yield. Hence the configuration at C-1 is *S*; i.e., the hydroxyl group is α since the absolute stereochemistry of tirotundin is known (H-7 α).[6,7,18]



13



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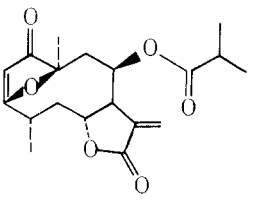

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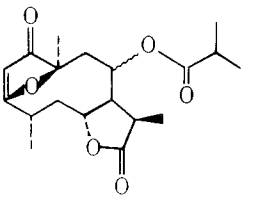
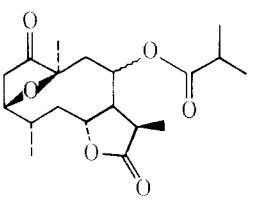
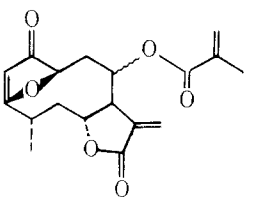


16a, H-8α
b, H-8β



17a, H-8α
b, H-8β



18a, H-8α, zexbrevin
b, H-8β

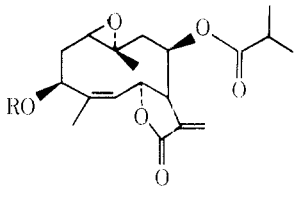
Oxidation of tagitinin A (**7**) with Jones reagent furnished **14** which underwent dehydration (tosyl chloride–pyridine) to an α,β-unsaturated ketone, **15**. The latter was hydrogenated to **16** and **17**. To our surprise the properties of **16a** and **17a** (melting points, NMR signals, and IR bands) tallied exactly with those of the purported C-8 epimers tetrahydro- and hexahydrozexbrevin **16b** and **17b**.[19] Although we were unable to secure authentic samples of these substances for direct comparison, it would appear that the C-8 stereochemistry of zexbrevin must be inverted from **18b** to **18a**. This also applies to orizabin, calaxin, ciliarin, and zexbrevin B[20] which have been correlated with zexbrevin.[22]

In addition, we consider tagitinin E for which the structure of a 1,10-epoxy-*cis*-4,5-germacrenolide with the lactone ring closed to C-8 and an isobutyrate ester attached to C-6 was proposed.[3] Although we did not isolate this substance, analysis of the published data[3] led to the deduction that tagitinin E

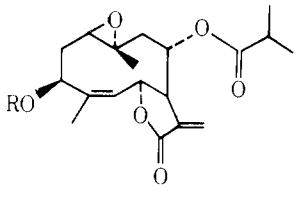
Table II. 270-MHz ^{1}H NMR Spectra[a]

	3a	7	14[c]	20a
H-1	6.94 d (17)	4.23 m		2.81 dd (10, ~5)
H-2a	6.26 d (17)	2.44 m	[g]	2.46 dt (15, ~5)
H-2b		2.1 m[d]	[g]	1.8 m (15, 10, ~3)
H-4		2.1 m[d]	[g]	4.50 br
H-5a	5.88 d, br (10)	2.1 m[d]	2.22 m[h]	5.31 d, br (11, 1.5)
H-5b		2.1 m[d]		
H-6	5.42 d, br (10)	4.55 ddd[e]	4.55 m	6.62 dd (12, 2)
H-7	3.55 m	3.99 m	4.13 m	2.85 br
H-8	5.33 m	5.59 ddd[f]	5.57 m	5.19 br[k]
H-9a	~2.4	1.81 dd (13, 8)	1.94 m[h]	2.72 dd (16, 5)
H-9b	~2	1.95 dd (13, 5)		1.35 d, br (16, 3)
H-13	6.36 d (2)	6.25 d(3.5)	6.28 d (3.5)	6.37 d (2)
H-13b	5.81 d (2)	5.53 d (3)	5.57 d (3.5)	5.76 d (2)
H-14[b]	1.56	1.43 br	1.44	1.14
H-15[b]	1.97 br	1.11 d (6.5)	1.16 d (7)	1.81 d (1.5)
H-2′	2.44 m	2.44 m	2.43 m	2.5 m
H-3′[b]	1.10 d (7)	1.07 d (7)	1.07 d (7)	1.12 d (7)
H-4′[b]	1.08 d (7)	1.04 d (7)	1.05 d (7)	

[a] Run in $CDCl_3$ on Bruker HX-270 instrument. Shifts in ppm downfield from Me_4Si. Coupling constants (Hz) in parentheses. [b] Intensity three protons. [c] Spectrum not spin-decoupled. [d] In four proton multiplet. [e] $J_{5a,6}$ = 9 Hz, $J_{5b,6}$ = 3 Hz, $J_{6,7}$ = 7 Hz. [f] $J_{7,8}$ = 1.5 Hz, $J_{8,9a}$ = 8 Hz, $J_{8,9b}$ = 5 Hz. [g] In envelope. [h] Two protons. [i] H-3 ($W_{1/2}$ = 9 Hz). [j] $W_{1/2}$ = 6 Hz. [k] $W_{1/2}$ = 9 Hz.



19a, R = H, tagitinin E
b, R = Ac



20a, R = H, deacetylviguiestin
b, R = Ac, viguiestin

must be reformulated as a heliangolide **19a.** In arriving at this conclusion, we noted that the values reported for $J_{7,13a}$ and $J_{7,13b}$ are diagnostic for heliangolides[21] and therefore invalidate the other arguments used for structure assignment. H-6 is abnormally deshielded (reported value 6.64 ppm) by the oxirane, as is characteristic of 1(10)-epoxyheliangolides with a trans-lactone closed to C-6 (reported $J_{5,6}$ = 1 Hz; $J_{6,7}$ = 2.2 Hz),[26] but it experiences the diamagnetic shift (~0.5 ppm) on acetylation to **19b** characteristic[27] of heliangolides carrying a β-orientated ($J_{2,3}$ = 4.4 and 2.2 Hz) hydroxyl group on C-3. Examination of an authentic sample of tagitinin E[29] demonstrated the correctness of our argument; the 4,5 double bond was cis, irradiation at the frequency of the C-4 methyl producing a 15.5% enhancement in the strength of the H-5 signal. The new assignments are given in Table II; the small half-height width of the H-8 signal and the values for $J_{8,9}$ establish that tagitinin E possesses a β-orientated ester side chain on C-8 like the other constituents of *Tithonia* species. The positive sign of the lactone Cotton effect[3] is in agreement with that of other heliangolides containing a trans-fused lactone ring closed to C-6.[30]

Deacetylviguiestin, mp 212–214 °C, from *Viguiera stenoloba* with identical stereochemistry at C-1, C-3, C-6, C-7, and C-10, but of uncertain stereochemistry at C-8,[31] is therefore the C-8 epimer of tagitinin E, or **20a.** Viguiestin[31] is **20b.**

Experimental Section

Isolation of *T. diversifolia* Constituents. Above-ground parts of *T. diversifolia* (Hemsl.) A. Gray, 2 kg, collected in the Bokaghat area, Sibsagar district, Assam, on Dec 15, 1977, were extracted with methanol and worked up in the usual fashion.[33] The crude gum, 20 g, was chromatographed over silica gel (600 g) packed in benzene, 200 mL fractions being collected in the following order: 1–10 (Bz), 11–20 (Bz–$CHCl_3$, 4:1), 21–30 (Bz–$CHCl_3$, 2:1), 31–40 (Bz–$CHCl_3$, 1:1), 41–50 (Bz–$CHCl_3$, 1:2), 51–60 (Bz–$CHCl_3$, 1:4), 61–70 ($CHCl_3$), 71–80 ($CHCl_3$–MeOH, 99:1), 81–90 ($CHCl_3$–MeOH, 19:1), 91–100 ($CHCl_3$–MeOH, 9:1).

Fractions 24–36 were mixtures of several components which could not be separated by repeated column chromatography. Tirotundin (**1a**) was eventually separated from one of these fractions by preparative TLC, cutting a band which had the same R_f as authentic material: yield 0.1 g, mp 142 °C after recrystallization from ethyl acetate, no depression on admixture of authentic material. NMR and mass spectra were identical. The revised ^{13}C NMR spectrum is given in Table I. Tagitinin F was also present in fractions 24–36 and was separated in small amount by repeated preparative TLC (Bz–EtOAc, 9:1). Melting point and IR, NMR, and mass spectra were identical with those of authentic material.

Fractions 40–49 were a mixture of two components (TLC) and were combined. The yield was 1.5 g of gummy material which was dissolved in $CHCl_3$ and allowed to stand overnight, after which time 0.25 g of a pale yellow flavonoid, mp 278 °C dec, had separated. This was identified as hispidulin (6-methoxy-4′,5,7-trihydroxyflavone,[34] lit. mp variously reported as 291–292[34] and 274–276 °C[35]) by its mass spectrum (*m/e* 300 M^+), NMR spectrum, methylation to salvigenin (mp and mmp 186 °C), and conversion to the triacetate, mp 168–170 °C (lit.[34,35] mp 168–170 °C). The NMR spectrum was superimposable on that of authentic material. Evaporation of the mother liquor provided tagitinin C (**3a**) as a gum, yield 0.65 g, which was further purified by preparative TLC (Bz–EtOAc, 4:1) and identified by comparison of its IR (see also Table II) and mass spectra with those in the literature.[3] The ^{13}C NMR spectrum is listed in Table I; assignments of multiplets were made by single-frequency off-resonance decoupling.

Fractions 64–75 exhibited one major spot only and were combined. Crystallization from $CHCl_3$–petroleum ether (bp 60–80 °C) yielded 2.5 g of tagitinin A (**7**), mp 168–170 °C, with IR and mass spectra as reported.[3] The ^{13}C and ^{1}H NMR spectra are listed in Table I and in Table II.

A solution of 359.4 mg (1.15×10^{-3} mol) of α-phenylbutyric anhydride and 120 mg of **7** in 2 mL of pyridine was allowed to stand at room temperature for 48 h. Excess anhydride was destroyed by adding H_2O and allowing the solution to stand for 12 h. The solution was extracted with ether, and the ether extract was washed with H_2O, three 10-mL portions of 5% $NaHCO_3$, and again several times with H_2O. The combined aqueous extracts were washed with $CHCl_3$, acidified with 1 N H_2SO_4, and extracted with $CHCl_3$. The washed and dried $CHCl_3$ extract was evaporated; this afforded 136.4 mg of α-phenylbutyric acid (pure on TLC) which had $[\alpha]_D$ −6.55° (benzene) and corresponded to an optical yield of 41.8%.

Preparation of 8. A solution of 30 mg of **7** in 0.5 mL of dry pyridine was allowed to stand with 0.1 g of tosyl chloride for 1 h, poured into ice water, and extracted with $CHCl_3$. The washed and dried extract was evaporated, purified by preparative TLC (Bz–EtOAc 4:1), and recrystallized from EtOAc: yield 20 mg of **8**; mp 120 °C; IR bands at 3450, 1765, 1730, 1650, 1150, 1000 and 970 cm^{-1}; NMR signals (ppm)

at 6.30 (z) and 5.60 (d, 2, H-13a and H-13b), 5.45 (m, H-8), 4.30 (m, H-6), 4.05 (dd, H-1), 1.75 (br, H-15), 1.45 (H-14), and 1.10 (d, 7, H-3′ and H-4′); MS peaks (low resolution) at *m/e* 350 (M^+), 332 ($M^+ - H_2O$), 261 ($M^+ - H_2O - C_4H_7O$), 243, 215, 122, 71 (base peak, C_4H_7O).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.03; H, 7.38.

Conversion of Tagitinin A to Tirotundin and Dihydrotirotundin. To a solution of 0.1 g of **7** in $CHCl_3$ kept at 0 °C was added 0.5 mL of dimethylamine solution. The mixture was kept at 0–5 °C for 3 h, diluted with $CHCl_3$, washed with water, dried, and evaporated. Recrystallization of the residue from $CHCl_3$–petroleum ether afforded **9**: yield 0.09 g; mp 181 °C; IR bands at 3400, 1760, 1725, 1150, and 990 cm^{-1}; NMR signals (ppm) at 5.40 (m, H-8), 4.40 (H-6), 4.20 (dd, H-1), 2.30 (N-methyls), 1.40 (H-14), 1.20 (br, H-15) superimposed on 1.20 (d, 7, H-3′ and H-4′); MS peaks (low resolution) at *m/e* 413 (M^+), 389 ($M^+ - H_2O$), 377 ($M^+ - 2H_2O$), 342 ($M^+ - C_4H_7O$), 326 ($M - C_4H_7O_2$), 298, 254, 212, 71, 58 (base peak).

Anal. Calcd for $C_{21}H_{35}NO_7$: C, 61.00; H, 8.53. Found: C, 61.08; H, 8.61.

A solution of 0.1 g of **9** in 1 mL of pyridine and 0.5 mL of acetic anhydride was heated at 100 °C for 3 h, poured into ice water, and extracted with $CHCl_3$. The residue from the washed and dried extract was purified by preparative TLC (Bz–EtOAc, 2:1). The less polar component **10** was recrystallized from EtOAc: yield 10 mg; mp 130 °C; IR bands at 3400, 1750, 1725, 1250, 1145, 1000, and 950 cm^{-1}; NMR signals at 6.10 (d, 3.5, H-13a), 5.90 (H-1 and H-2), 5.50 (d, 3, H-13), 5.40 (m, H-8), 4.30 (m, H-6), 1.50 (H-14), 1.10 (d, 7, H-15), 1.05 (d, 7, H-3′ and H-4′); MS peaks (low resolution) at *m/e* 350 (M^+), 332 ($M^+ - H_2O$), 279 ($M^+ - C_4H_7O$), 261, 243, 215, 165, 151, 147, 137, 122, 71 (base peak).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.06; H, 7.23.

The more polar product **11** was recrystallized from $CHCl_3$–petroleum ether: mp 145 °C; yield 50 mg; IR bands at 3400, 1750, 1725, 1145, and 990 cm^{-1}; NMR signals (ppm) at 6.10 (H-1 and H-2), 5.45 (m, H-8), 4.05 (m, H-6), 2.40 (N-methyl), 1.45 (H-14), 1.20 (d, 7, H-15), 1.10 (d, 7, H-3′ and H-4′); MS peaks (low resolution) at *m/e* 395 (M^+), 377 ($M^+ - H_2O$), 324 ($M^+ - C_4H_7O$), 308, 142, 71, 58 (base peak).

Anal. Calcd for $C_{21}H_{33}O_6N$: C, 63.78; H, 8.41. Found: C, 63.56; H, 8.35.

A solution of **11** (40 mg) in 30 mL of MeOH was hydrogenated for 30 min over 50 mg of 10% Pd–C at atmospheric pressure. Filtration followed by evaporation and recrystallization of the residue from EtOAc yielded 30 mg of **12**: mp 176 °C; IR bands at 3400, 1760, 1725, 1130, 1025, and 1000 cm^{-1}; NMR signals (ppm) at 5.40 (m, H-8), 4.50 (m, H-6), 2.40 (*N*-methyl), 1.45 (H-14), 1.20 (d, 7, H-15), 115 (d, 7, H-3′ and H-4′); MS peaks at *m/e* 397 (M^+), 3.82 ($M^+ - CH_3$), 379 ($M^+ - H_2O$), 327 ($M^+ - C_4H_7O$), 310, 71, 58 (base peak).

Anal. Calcd for $C_{21}H_{35}NO_6$: C, 63.45; H, 8.87. Found: C, 63.31; H, 8.63.

A mixture of 30 mg of **11** and 0.5 mL of CH_3I was kept overnight at room temperature, diluted with $CHCl_3$, washed with 10% $NaHCO_3$ and water, dried, and evaporated. The residue **1a** crystallized spontaneously, mp 140–141 °C. It was identical with authentic tirotundin in all respects.

A solution of 10 mg of **10** in 25 mL of MeOH was hydrogenated with 10% Pd–C as described for **11**. The usual workup provided 10 mg of dihydrotirotundin (**13**): mp and mmp with material prepared as described below 130–131 °C, IR, NMR, and MS identical.

A solution of 15 mg of **1a** in 25 mL of methanol was hydrogenated as described above. The usual workup provided 15 mg of **13**: mp 130–132 °C; IR bands at 3400, 1760, 1725, 1710, 1200, and 920 cm^{-1}; NMR signals (ppm) at 5.20 (m, H-8), 4.60 (m, H-6), 1.30 (H-14), 1.05 (d, 7, H-13, H-15, H-3′, and H-4′); MS peaks at *m/e* 354 (M^+), 336 ($M^+ - H_2O$), 266 ($M^+ - C_4H_8O_2$), 248, 167, 141, 124, 109, 99 (base peak), 71.

Anal. Calcd for $C_{19}H_{30}O_6$: mol wt 354.2042. Found: mol wt (MS) 354.2031.

Dehydrotagitinin A (14). To 0.1 g of **7** in 100 mL of AnalaR acetone cooled to 5 °C was added dropwise 0.5 mL of Jones reagent with shaking. After 30 min at 5 °C, excess reagent was destroyed with MeOH. The mixture was diluted with water and extracted with EtOAc. The washed and dried extract was evaporated and purified by preparative TLC (Bz–EtOAc, 2:1) to give **14**: yield 40 mg; mp 196 °C; IR bands at 1750 (vs, γ-lactone and tetrahydrofuranone), 1725, 1130, 1100, 1020, and 980 cm^{-1}; NMR signals in Table II; MS peaks (low resolution) at *m/e* 366 (M^+), 348 ($M^+ - H_2O$), 295 ($M^+ - C_4H_7O$), 278 ($M^+ - C_4H_8O_2$), 260 ($M^+ - H_2O - C_4H_8O_2$), 250, 235, 233, 232, 224, 217, 207, 192, 192, 181, 164, 147, 137, 125, 97, 71 (base peak).

Anal. Calcd for $C_{19}H_{26}O_7$: C, 67.28; H, 7.18. Found: C, 62.35; H, 7.05.

Dehydration of 14. A solution of 25 mg of **14** and 0.1 g of tosyl chloride in 0.5 mL of dry pyridine was heated at 100 °C for 30 min. The solvent was removed by codistillation with toluene, and the residue was purified by preparative TLC (petroleum ether–EtOAc, 2:1) to give **15** as a gum: yield 15 mg; IR bands at 1760, 1740, 1720, 1610, 1025, 990, 865, and 850 cm^{-1}; NMR signals (ppm) at 6.20 (d, 3.2, H-13a), 5.60 (d, 3, H-13b), 5.45 (H-2), 5.05 (m, H-8), 4.45 (m, H-6), 3.20 (m, H-7), 1.30 (H-14), 1.15 (d, 7, H-15), 1.05 (d, 7, H-3′ and H-14′); MS peaks at *m/e* 348 (M^+), 278 ($M^+ - C_4H_6O$), 260 ($M^+ - C_4H_8O_2$), 250, 232, 204, 189, 181, 168, 125 (base peak, $C_7H_9O_2$), 71.

Anal. Calcd for $C_{19}H_{24}O_6$: mol wt 348.1573. Found: mol wt (MS) 348.1562.

Hydrogenation of 15. A solution of 0.40 g of **15** in 25 mL of EtOH was hydrogenated over 50 mg of 10% Pd–C for 15 min. After the usual workup, TLC indicated the presence of two products which were separated by preparative TLC (Bz–EtOAc, 6:1). The more polar product **16a** was recrystallized from EtOAc: yield 15 mg; mp 156 °C, lit.[19] mp for tetrahydrozexbrevin 156–157 °C; IR bands at 1770, 1735, 1705, 1600, 1150, 995, and 950 cm^{-1}; NMR signals (ppm) at 5.58 (H-2), 5.10 (m, H-8), 4.60 (m, H-6), 1.40 (H-14), 1.25 (d, 7, H-15), 1.10 (d, 7, H-13), 1.0 (w, d, 7, H-3′ and H-4′); UV $\lambda_{max}^{(EtOH)}$ 260 nm (ε 12 600). These values correspond to those reported for tetrahydrozexbrevin. The low-resolution MS exhibited diagnostic peaks at *m/e* 350 (M^+), 280 ($M^+ - C_4H_6O$), 262 ($M - C_4H_8O_2$), 237, 219, 192, 181, 168, 125, and 71 (base peak).

Anal. Calcd for $C_{19}H_{24}O_6$: mol wt 350.1729. Found: mol wt (MS) 350.1721.

The less polar product **17a** was recrystallized from MeOH: yield 12 mg; mp 126–128 °C, lit.[19] mp for hexahydrozexbrevin 125–127 °C; IR bands at 1760 (vs, lactone and tetrahydrofuranone), 1730, 1125, 1095, 1010, and 950 cm^{-1}; NMR signals at 5.00 (m, H-8), 4.40 (m, H-6), 3.90 (H-3), 1.25 (H-14), 1.10 (d, 7, H-15, H-3′, and H-4′). These values correspond to those reported for hexahydrozexbrevin. The low-resolution MS exhibited diagnostic peaks at *m/e* 352 (M^+), 324 ($M^+ - H_2O$), 281 ($M^+ - C_4H_7O$), 264 ($M^+ - C_4H_8O_2$), 236, 181, 167, 128, 125, 98, and 71 (base peak).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.35; H, 8.02.

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Registry No.—**1a**, 56377-67-4; **4a**, 59979-57-5; **8**, 69440-04-6; **9**, 69440-05-7; **10**, 69440-06-8; **11**, 69440-07-9; **12**, 69440-08-0; **13**, 63807-89-6; **15**, 69440-09-1; **16a**, 28644-87-3; **17a**, 28644-88-4; hispidulin, 1447-88-7; saloiginin, 19103-54-9; hispidulin triacetate, 1178-23-0; (+)-α-phenylbutyric anhydride, 40348-94-5; (−)-α-phenylbutyric acid, 938-79-4; **19a**, 59979-58-7; **20a**, 69483-10-9; **20b**, 69440-10-4; orizabin, 34367-14-1.

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Mild Oxidation of Alkyl Halides

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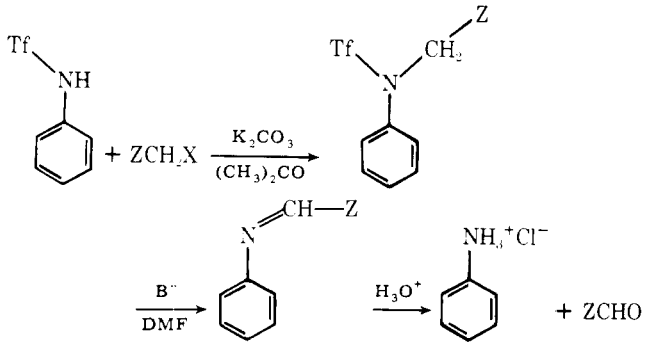
The application of *N*-phenyltrifluoromethanesulfonamide to the oxidation of activated halides (α-halo carbonyl compounds) has been extended and shown to be general. A new reagent, *N*-(4-acetoxyphenyl)trifluoromethanesulfonamide, has been developed for the mild oxidation of unactivated alkyl halides. The reagent was N-alkylated with a number of different alkyl halides. The elements of CF_3SO_2H were then eliminated under mild basic conditions generating imines which were easily hydrolyzed to the corresponding amines and carbonyl compounds. The ease of $CF_3SO_2^-$ elimination was demonstrated to be dependent on intermediate aminoquinone formation.

Although there are a number of techniques currently available for the oxidation of unactivated primary halides to aldehydes, the reaction conditions frequently do not lend themselves to polyfunctional or labile systems. Most of these oxidations employ dimethyl sulfoxide as the oxidant and require temperatures in excess of 100 °C,[2-4] or the presence of strong acids[5-7] or heavy metals.[8-10] We wish to report an oxidation procedure which does not require activated alkyl halides or harsh reaction conditions.

N-Phenyltriflamide is N-alkylated in high yield under very mild conditions with a variety of activated and unactivated electrophiles, including alkyl halides[11-15] (eq 1). These alkylated sulfonamides can be converted to imines by treatment



with base and the imines hydrolyzed under mild acidic conditions to the corresponding aldehydes and amines. However, the conditions required to generate the imine, i.e., to abstract this α proton and eliminate $CF_3SO_2^-$ (Tf), are very harsh. Thus, when Z is *p*-BrC_6H_4CO, potassium carbonate in refluxing acetone is adequate. When Z is C_6H_5, NaH in DMF at 100 °C for 24 h is required, and when Z is $CH_3(CH_2)_2CH_2^-$, elimination is not observed at all.[11]

Because of our interest in the synthesis of 1,2-dicarbonyl compounds, we had the occasion to extend this sequence of reactions to a number of different alkylating agents (Table I). It was determined that activated secondary halides alkylated *N*-phenyltriflamide cleanly and in high yield. Treatment of these intermediates with base under mild conditions followed by acid hydrolysis led to the expected dicarbonyl compounds in good yield. However, as in earlier studies, unless the methylene protons were activated, the conditions necessary for elimination of $CF_3SO_2^-$ were very harsh.

It was clear from these findings that elimination of $CF_3SO_2^-$ required a rather substantial buildup of charge on the methylene carbon, much like the elimination of HF from fluorinated hydrocarbons.[6] This requirement could, of course, be expected to substantially reduce the applicability of an otherwise very useful oxidizing system.

Because of the potential ease of formation of aminoquinones from systems of the type in eq 2 and the driving force

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