this case while a or b is possible for the bromo and iodo ketones. Actually, as k_2 becomes larger and larger, mechanisms a and b merge and are essentially the same.

Finally, the complete loss of deuterium at the α carbon in all of the interruption experiments shows that the hydrogen on the halogen-carrying carbon is much more acidic than the ones on the α' carbon. This is as expected since the electronegative halogen should increase the acidity of the proton.

Registry No.—Ia, 2516-50-9; Ib, 1452-34-2; Ic, 2516-55-4; IIa, 13976-58-4; IIb, 13976-59-5; IIc, 13976-60-8; IId, 13976-61-9.

Citrus Bitter Principles. VII.[1] Rutaevin

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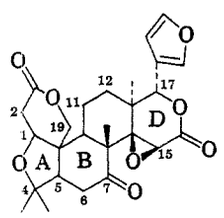
Received April 10, 1967

Chemical and spectroscopic evidence is presented which shows that rutaevin, a limonoid isolated from *Evodia* and *Calodendrum* species, is formulated as 6-ketoepilimonol (2).

Limonoids are a series of degraded C_{26} triterpenes which have been isolated from various plants belonging to the families Rutaceae[3,4] and Meliaceae.[4] The most extensively studied extractive of this type in the Rutaceae is limonin (1).[5] It is the purpose of this article to present evidence that rutaevin, a further member of this series of bitter principles, should be formulated as 6-ketoepilimonol (2).



1

Rutaevin was apparently first isolated by Fujita, *et al.*,[6] from the dried fruit of *Evodia rutaecarpa* Benth and Hook. Fujita and Akatsuka[7] later showed that rutaevin was nonidentical with limonin and co-occurs with limonin (1)[8] and limonin diosphenol (6).[8,9] A further study[10] on the extractives of *E. rutaecarpa* reported the isolation of three limonoids whose physical properties corresponded to 1, rutaevin, and limonin diosphenol (6) and showed that rutaevin is converted to 6 with base. A previous communication[3] from this laboratory described the isolation of rutaevin from *Evodia hupenhensis*. It has now been found that seeds of Cape Chestnut, *Calodendrum capense* (L.f.) Thumb. (Rutaceae),[11] a native of South Africa, are a good source of rutaevin and also contain 1 and 6. The isolation of rutaevin from *Calodendrum* is a much more practical matter than from *E. rutaecarpa*. In the latter, rutaevin is sometimes difficult to free from ultraviolet-adsorping impurities.

Rutaevin, analyzed for $C_{26}H_{30}O_9$, illustrated physical properties that were generally similar to those of 1 and was identical with material isolated from *E. rutaecarpa*, It gave a positive Ehrlich's test, indicating the presence of a furan ring.[12,13] This was further confirmed by the ultraviolet spectrum. The infrared spectrum showed bands assigned to a hydroxyl group, three different carbonyl groups, and a β-substituted furan ring. Rutaevin formed a monoacetate, a monobenzoate, and an oxime. The nmr spectra of rutaevin and its acetate (Table I) showed many features in common with those of 1.[14] Thus, resonances were present for a β-substituted furan ring, H-17, an epoxy H-15, and a C-19 methylene group. The spectra showed three normal C-methyl resonances and one very broad resonance displaced relatively far upfield. The broadness, upfield position, and inconclusive integrations of this resonance lead initially to its assignment as a cyclopropyl methylene.[3] However, the relative stability of rutaevin to strong acids and the failure to observe deuterium incorporation in one of the C-methyl groups upon conversion of rutaevin to limonin diosphenol with NaOD–D_2O made the cyclopropyl grouping unlikely. A 100-Mc nmr spectrum of rutaevin showed that this resonance was clearly due to a C-methyl group. Thus, rutaevin contains four C-methyl groups and must be closely related to 1. The nmr spectrum of rutaevin further showed a poorly resolved triplet corresponding to H-1 in 1 and a one-proton singlet which shifted downfield in rutaevin acetate (3) and benzoate (4). Thus, rutaevin is a secondary alcohol.

Although limonin gives a slight test with 2,3,5-triphenyltetrazolium chloride, rutaevin gives a strong positive test with this reagent,[15] indicating the presence of an α-ketol group. As has been observed previously,[10] treatment of rutaevin with base gave limonin diosphenol (6). This reaction indicates that both the

(1) Part VI: D. L. Dreyer, *J. Org. Chem.*, **31**, 2279 (1966).

(2) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) D. L. Dreyer, *Phytochemistry*, **5**, 367 (1966).

(4) G. P. Moss, *Planta Med. Suppl.*, 86 (1966).

(5) D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 255 (1961).

(6) A. Fujita, N. Nozoe, and T. Shimoda, *J. Pharm. Soc. Japan*, **55**, 474 (1935).

(7) A. Fujita and M. Akatsuka, *ibid.*, **69**, 322 (1949); *Chem. Abstr.*, **44**, 1954 (1950).

(8) S. Maeda, *J. Pharm. Soc. Japan*, **55**, 531 (1935); *Chem. Abstr.*, **29**, 5831 (1935); M. Li and H. Huang, *Yao Hsueh Hsueh Pao*, **13**, 265 (1966); *Chem. Abstr.*, **65**, 3922 (1966).

(9) Y. Hirose, *Chem. Pharm. Bull. Tokyo*, **11**, 535 (1963).

(10) J. H. Chu, *Sci. Record* (China), **4**, 279 (1951); *Chem. Abstr.*, **46**, 11589 (1952).

(11) J. M. Watt and M. G. Breyer-Bradwijk, "The Medical and Poisonous Plants of Southern and Eastern Africa," 2nd ed, E. & S. Livingstone Ltd., Edinburgh, Scotland, 1962, p 912.

(12) T. Reichstein, *Helv. Chim. Acta*, **15**, 1110 (1932).

(13) D. L. Dreyer, *J. Org. Chem.*, **30**, 749 (1965).

(14) D. L. Dreyer, *Tetrahedron*, **21**, 75 (1965).

(15) R. A. Fairbridge, K. J. Willis, and R. G. Booth, *Biochem. J.*, **49**, 423 (1951).

TABLE I

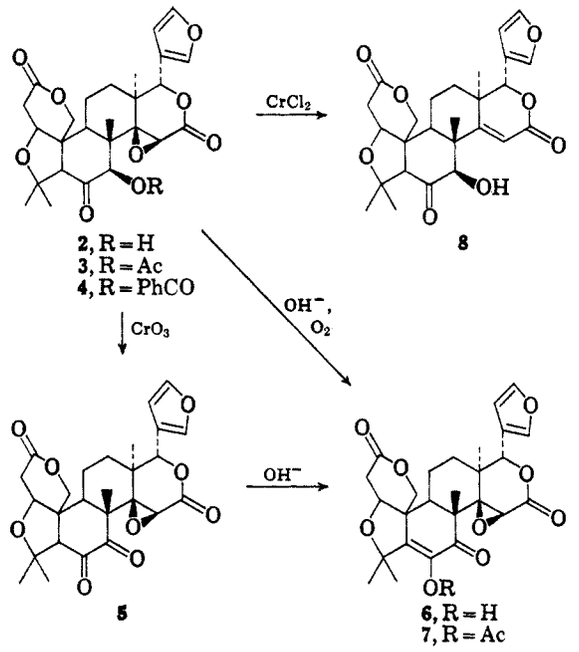
NMR SPECTRA (δ) OF RUTAEVIN DERIVATIVES[a]

Compd	Solvent	α-Furan	β-Furan	H-17	H-19	H-7	H-1	H-15	H-5	H-2	C-Methyls			
Rutaevin (2)	CF_3COOH	7.44 (1)	6.40 (1)	5.67	4.54 4.45	4.72	4.72	4.25	3.28	3.07[c]	1.50	1.47	1.37	0.82
6-Ketolimonin (5)	CF_3COOH	7.44 (1)	6.39 (1)	5.64	4.74[b] 4.70		4.60	3.82	3.52	3.10[c]	1.45	1.27	1.23	1.15
Limonin (1)	CH_3COOH	7.42 (1)	6.37 (1)	5.70	5.13 4.74 (13)		4.60	4.28			1.45	1.33	1.30	1.30
Limonol	CF_3COOH	7.50 (1)	6.43 (1)	5.85	4.84	3.87	4.62	4.22			1.45	1.40	1.32	1.03
Epilimonol	CF_3COOH	7.44 (1)	6.35 (1)	5.70	4.80	4.27 (5)	4.52	4.67			1.45	1.38	1.32	1.20
Deoxyrutaevin (8)	CF_3COOH	7.59 7.50	6.52 (1)	5.32	4.55 4.54	4.54	4.79	6.75	3.40	3.09[c]	1.55	1.47	1.44	1.32
Deoxyepilimonol	CF_3COOH	7.55	6.49	5.26	4.82	4.26	4.80	7.12			1.41	1.35	1.35	1.30
Deoxylimonin	CF_3COOH	7.53 7.47	6.47 (1)	5.25	4.99		4.60	7.03			1.58	1.48	1.35	1.35
Rutaevin oxime	$CDCl_3$–DMSO-d_6	7.44 (1)	6.40 (1)	5.65	4.65[b] 4.60	[e]	4.37	[e]	[e]	3.60[c]	1.45	1.38	1.25	0.65
Rutaevin acetate (3)	$CDCl_3$	7.44 (1)	6.40 (1)	5.65	4.27[b] 4.24	5.52	4.40	3.84	3.07	2.79[c]	1.40	1.32	1.27	0.78
Rutaevin benzoate (4)	$CDCl_3$	7.40 (1)	6.39 (1)	5.70	4.24[d]	5.42	4.39[c]	3.77	3.08	2.77[c]	1.37	1.37	1.37	0.88
Limonin diosphenol (6)	CF_3COOH	7.52 (1)	6.47 (1)	5.75	4.97		4.64	4.40		3.28[d]	1.75	1.67	1.27	1.20

[a] Data collected at 60 Mc, coupling constants in parentheses in cps. The areas of peaks were consistent with the assignments. [b] AB doublet, weak outside peaks indistinguishable in the noise. [c] Unresolved. [d] Broad. [e] Three singlets at δ 4.22, 4.20, and 3.95 are assigned to H-7, H-15, and H-5 in no certain order.

hydroxyl and keto groups of rutaevin must be located in the B-ring at the 6 and 7 positions. Rutaevin was recovered unchanged after standing overnight in pyridine. Chromic acid oxidation of rutaevin gave a yellow α-diketone which is formulated as 6-ketolimonin (**5**). Treatment of the α-diketone (**5**) with hot sodium hydroxide converted it to limonin diosphenol (**6**). Treatment of **5** with acetic anhydride–pyridine gave limonin diosphenol acetate (**7**) (Scheme I). Oxidation of rutaevin with bismuth trioxide, a specific reagent for oxidizing α-hydroxy ketones to α-diketones,[16] gave limonin diosphenol (**6**). These reactions suggest that the base-catalyzed conversion of rutaevin to limonin diosphenol is caused by air oxidation. The conversion of α-ketols to diosphenols under basic conditions by oxygen or air oxidation is a well-documented reaction.[17,18] Reduction of rutaevin with chromous chloride, a specific reagent for α-epoxycarbonyl compounds,[19] gave deoxyrutaevin (**8**). Deoxyrutaevin (**8**) still showed a hydroxyl band in its infrared spectrum. Rutaevin and its noncrystalline tosylate were both recovered unchanged from zinc dust in refluxing glacial acetic acid or acetic anhydride for 16 hr.

SCHEME I



The problem of the structure determination of rutaevin is now reduced to distinguishing between a 6-hydroxylimonin or a 6-ketolimonol system. The ORD curves of both 6-keto and 7-keto A/B *trans*-steroids exhibit negative Cotton effects. Each can normally be distinguished in a system since there is a significant difference in their amplitudes.[20] This difference cannot be relied upon in the present case since subtle structural and conformational effects may greatly alter the relative amplitudes in limonoids compared to steroids. If rutaevin is 6-hydroxylimonin, the hydroxyl group must be axial so that H-6 will have a small coupling constant with H-5.[21] However, an axial α-hydroxyl group would cause the Cotton effect of the ORD curve to exhibit a substantial positive shift compared with that of limonin.[13] Such is not the case (Experimental Section). Accordingly a 6-keto-7-hydroxyl system is favored. Closer inspection of the nmr spectra of rutaevin and its derivatives reveals a one-proton singlet in the range δ 3.0–3.5 assignable to H-5. The lack of a positive shift to the ultraviolet maxima,[22] ORD, and CD Cotton effect[23] is inconsistent with an axial α-hydroxyl group in rutaevin. An equatorial hydroxyl group in rutaevin is also consistent

(16) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(17) D. H. R. Barton and J. F. Eastham, *ibid.*, 424 (1953); D. Lavie and Y. Shvo, *J. Am. Chem. Soc.*, **81**, 3058 (1959); R. L. Clarke, *ibid.*, **82**, 4629 (1960); P. N. Rao and L. R. Axelrod, *ibid.*, **82**, 2830 (1960); K. Susaki, *Chem. Pharm. Bull. Japan*, **9**, 684 (1961); S. M. Kupchan, S. McLean, G. W. A. Milne, and P. Slade, *J. Org. Chem.*, **27**, 147 (1962).

(18) Although rutaevin is easily converted to limonin diosphenol (**6**) by air oxidation, it is unlikely that the natural occurrence of **6** is an artifact since tlc indicated the presence of limonin diosphenol in freshly prepared crude plant extracts. Rutaevin is only slightly bitter.

(19) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954). One example of chromous chloride reduction of an isolated epoxy group has been reported: C. W. L. Bevan, A. H. Rees, and D. A. H. Taylor, *J. Chem. Soc.*, 983 (1963).

(20) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, p 37.

(21) Such a situation is found in limonilic acid which has an axial 6 ether bridge. H-6 in limonilic acid is a singlet.[14]

(22) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(23) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and Ch. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

with its inertness toward reduction with zinc.[24] Rutaevin is thus 6-ketoepilimonol (2).

As has been pointed out previously,[14] the upfield C-methyl resonance in limonoids must be due to the methyl at C-8. Its broadness in **2** appears due to the two axial protons at the 7 and 9 positions.[25] The mass spectra of rutaevin and limonin both failed to show a molecular ion (see Experimental Section). Deoxyrutaevin (**8**) showed a weak M−1 peak and facile loss of furan aldehyde (M−96).[26]

Reduction of limonin (**1**) with hydriodic acid under controlled conditions gives deoxylimonin.[5] Rutaevin was recovered unchanged from the same conditions. Limonin is converted to citrolin[27] under more vigorous conditions—red phosphorous in refluxing hydriodic and glacial acetic acids. The crude produet obtained when rutaevin was subjected to these conditions gave a negative Ehrlich's test and was not investigated further.

It seems likely that rutaevin is identical with dictamnolide,[28] a limonoid occurring in *Dictamnus albus* L. (Rutaceae). The physical properties reported for dictamnolide, its apparent nonidentity with limonin,[28] and its conversion to an acidic material having physical constants consistent with those of limonin diosphenol all suggest that dictamnolide is identical with rutaevin.

Experimental Section

Isolation of Rutaevin (2).—Nuts from *Calodendrum capense* Thumb., collected in Elysian Park, Los Angeles, Calif., were ground and defatted with hexane. The defatted material was extracted with acetone. Solvent was removed from the acetone extracts and the residue taken up in a large volume of hot chloroform. Concentration of the chloroform solution and cautious addition of ethanol gave a crop of rutaevin, mp 285–291°. Further concentration and addition of more alcohol gave further crops of less pure rutaevin, contaminated with limonin. Rutaevin was recrystallized from chloroform–ethanol or acetonitrile–ethanol to give an analytical sample, mp 301–305° dec. Samples with this melting point were difficult to obtain. Rutaevin gave R_f on tlc[13] 0.8 that of limonin; ν 3470 (hydroxyl), 1772, 1746, 1714 (carbonyl), 1504, 882 cm^{-1} (β-substituted furan) (Nujol); $\lambda_{max}^{CH_3CN}$ 205 mμ (ϵ 9000), 281 (40); ORD in acetonitrile (*c* 0.213) at 25°, $[\alpha]_{600}$ −141°, $[\alpha]_{316}$ −1150°, $[\alpha]_{286}$ −211°, $[\alpha]_{248}$ −2900°, $[\alpha]_{227}$ 0° (last reading); CD (dioxane), 25°; $[\theta]_{350}$ 0, $[\theta]_{300}$ −1850, $[\theta]_{272}$ 0, $[\theta]_{232}$ −7260.

Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.18; H, 6.22. Found: C, 64.7; H, 6.19.

Solvent was removed from the rutaevin mother liquors and the residue chromatographed on acid-washed alumina. The content of the fractions was monitored by tlc as described previously.[13] Those fractions containing limonin as indicated by tlc were combined and solvent was removed. The residue was crystallized from chloroform–ethanol to give limonin, identical in all respects with limonin isolated from various *Citrus* species.

Rutaevin showed major mass spectrum peaks at *m/e* 95 (100), 105 (46), 107 (14), 108 (14), 109 (16), 115 (16), 117 (14), 119 (27), 121 (27), 128 (24), 129 (22), 133 (22), 135 (24), 303 (24), 305 (14), 345 (60), 346 (22), 347 (22), 361 (22), 363 (22), 469 (14).

Limonin showed major mass spectrum peaks at *m/e* 95 (35), 106 (12), 107 (12), 108 (23), 109 (9), 119 (7), 121 (10), 135 (18), 136 (13), 137 (6), 147 (6), 329 (6), 331 (6), 347 (100), 348 (33), 413 (6).

Rutaevin Acetate (3).—A solution of rutaevin in pyridine–acetic anhydride was allowed to stand overnight at room temperature. The mixture was then decomposed with water and extracted with chloroform. The chloroform extracts were washed with dilute hydrochloric acid, 5% sodium carbonate, and dried. Removal of solvent and crystallization of the residue from ethanol gave a crop of material melting broadly at *ca.* 250°. Tlc indicated this material to be a mixture from which no pure product could be obtained. Further crops from the mother liquors gave the acetate: mp 186–191°; ν 1759, 1752 (carbonyl), 1507, 879 cm^{-1} (β-substituted furan) (Nujol); ORD in acetonitrile (*c* 0.085) at 25°, $[\alpha]_{600}$ −115°, $[\alpha]_{317}$ −1080°, $[\alpha]_{315}$ −1070°, $[\alpha]_{310}$ −1095°, $[\alpha]_{300}$ −850° (sh), $[\alpha]_{291}$ −565° (sh), $[\alpha]_{283}$ −470°, $[\alpha]_{247}$ −2190°, $[\alpha]_{220}$ +377° (last reading).

Anal. Calcd for $C_{28}H_{32}O_{10}$: C, 63.62; H, 6.10. Found: C, 63.2; H, 6.06.

Rutaevin benzoate (4) was prepared from rutaevin and benzoyl chloride in pyridine in the same manner as the acetate: mp 285–288° (chloroform–ether); ν 1780, 1748, 1732 (carbonyl), 1605 (aromatic), 1508, 883 cm^{-1} (β-substituted furan) (Nujol).

Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.11; H, 5.80. Found: C, 66.8; H, 5.78.

Rutaevin Oxime.—A solution of equal weights of rutaevin and hydroxylamine hydrochloride in 1:1 pyridine–absolute ethanol was refluxed for 4 hr. Solvent was then removed on a rotatory evaporator and water added to the residue. The product was collected and recrystallized from methanol–water: mp 266–271° dec; ν 3422 (hydroxyl), 1752 (carbonyl), 1508, 882 cm^{-1} (β-substituted furan).

Anal. Calcd for $C_{26}H_{31}NO_9$: C, 62.46; H, 6.23; N, 2.79. Found: C, 62.9; H, 6.30; N, 3.02.

Limonin Diosphenol (6).—A solution of 300 mg of rutaevin in dioxane was prepared by warming. Aqueous 5% sodium hydroxide was added and the solution allowed to stand 1 hr at room temperature. The product was collected after acidification and recrystallized from 95% ethanol to give 180 mg of **6**, mp 291–298°. The product was identical in all respects with an authentic sample of limonin diosphenol.[5] Extraction of a chloroform solution of rutaevin in a separatory funnel with 5% aqueous sodium hydroxide, acidification of the base extracts, and working up the acidic material also gave limonin diosphenol.

A solution of rutaevin in glacial acetic acid and excess bismuth trioxide was refluxed for 1 hr. Excess water was added and the mixture extracted with chloroform. The chloroform extracts were washed with 5% sodium bicarbonate and dried. Removal of solvent gave limonin diosphenol, mp 279–287°, from ethanol. Limonin diosphenol showed major mass spectrum peaks at *m/e* 91 (24), 93 (12), 95 (58), 97 (9), 105 (12), 107 (9), 109 (15), 119 (9), 121 (15), 135 (15), 167 (15), 178 (9), 206 (27), 329 (9), 343 (9), 345 (9), 347 (15), 361 (100), 362 (24), 469 (90), 470 (27), 484 (9).

6-Ketolimonin (5).—Jones reagent[29] was added dropwise to a stirred solution of 100 mg of rutaevin in acetone. After standing 20 min at room temperature, a large volume of water was added and the mixture extracted with chloroform. The chloroform extracts were washed with 5% sodium bicarbonate and dried. Concentration of the chloroform solution gave 40 mg of a lemon yellow product, mp 304–308° when recrystallized from chloroform–ethanol. A further 20 mg was obtained from the mother liquors: ν 1768, 1739, 1707 (carbonyl), 1502, 882 cm^{-1} (β-substituted furan (Nujol); $\lambda_{max}^{CH_3CN}$ 207 mμ (ϵ 5900), 278 (320), 398 (21) mμ.

Anal. Calcd for $C_{26}H_{28}O_9$: C, 64.45; H, 5.83. Found: C, 64.0, 64.7; H, 6.02, 6.11.

Limonin Diosphenol (6).—The yellow 6-ketolimonin (30 mg) was warmed on a steam bath with 5% sodium hydroxide in 50% ethanol. The diketone quickly went into solution. After 20 min the solution was cooled, acidified, and concentrated. The product crystallized on cooling and standing and was collected by filtration, mp 289–290° dec. The infrared spectrum was identical with that of an authentic sample of limonin diosphenol.[5]

Limonin Diosphenol Acetate (7).—A solution of the yellow 6-ketolimonin in acetic anhydride pyridine was warmed on a steam bath for 3 hr. The solution was then decomposed with a large volume of water and extracted with chloroform. After drying, solvent was removed from the chloroform extracts and the residue recrystallized from methanol, mp 308–313° dec.

(24) R. S. Rosenfeld and T. F. Gallagher, *J. Am. Chem. Soc.*, **77**, 4367 (1955); J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(25) C. W. Shoppee, E. P. Johnson, R. E. Lack, J. S. Shannon, and S. Sternhell, *Tetrahedron Suppl.*, **8**, 421 (1966), and references cited therein.

(26) For a similar case, see W. R. Chan, D. R. Taylor, and R. T. Aplin, *Chem. Commun.*, 576 (1966).

(27) T. A. Giessman and V. Tulagin, *J. Org. Chem.*, **11**, 760 (1946).

(28) T. Kaku and H. Ri, *J. Pharm. Soc. Japan*, **55**, 219 (1935); *Chem. Abstr.*, **31**, 6642 (1937).

(29) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

The infrared spectrum was identical with that of an authentic sample.[5]

Deoxyrutaevin (8).—To a solution of 200 mg of rutaevin in 40 ml of 1:1 acetic acid–dioxane was added an excess aqueous chromous chloride solution under inert atmosphere. The mixture was allowed to stand overnight at room temperature. A large volume of water was added and the mixture extracted with chloroform. The chloroform extracts were dried and concentrated to give 100 mg of deoxyrutaevin. A second impure crop of 25 mg was obtained after further concentration and was recrystallized from chloroform–ethanol, mp 286–293 dec. Deoxyrutaevin showed major mass spectrum peaks at *m/e* 95 (20), 133 (13), 148 (20), 316 (100), 317 (15), 358 (8), 374 (40), 375 (8), 455 (4), 469 (2); ν 3417 (hydroxyl), 1761, 1717, 1693 (carbonyl), 1503, 882 cm^{-1} (β-substituted furan) (Nujol); ORD in dioxane (*c* 0.9) at 25°, $[\alpha]_{600}$ −89°, $[\alpha]_{310}$ −635°, $[\alpha]_{277}$ +667°, $[\alpha]_{250}$ −1820°, $[\alpha]_{245}$ −1560° (last reading).

Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 66.3; H, 6.36.

Registry No.—**2**, 13942-86-4; **3**, 13942-87-5; **4**, 13942-88-6; **5**, 13942-89-7; **6**, 989-95-7; **7**, 991-07-1; **8**, 14120-03-7.

Acknowledgment.—The author is indebted to L. M. White for the analytical data, to Dr. D. J. Bertelli for the 100-Mc nmr spectrum, and to Drs. R. M. Horowitz and W. E. Thiessen for helpful discussions.

1,11-Iminoestrones.[1] I. Synthesis and Proof of Structure

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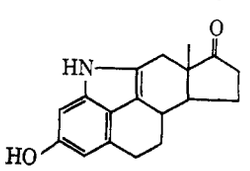
Received May 9, 1967

1-Aminoestrone 3-methyl ether (**10b**) has been synthesized (five steps, 40% yield) from 4-nitroestrone using diazo coupling in the key step. 1-Azidoestrone 3-methyl ether (**13**), prepared from **10b**, on pyrolysis underwent a nitrene insertion reaction to give 1,11α-iminoestrone 3-methyl ether (**14**) in 73% yield. The structure of the latter was supported by nmr and mass spectral analyses. Dehydrogenation of **14** with palladium on charcoal gave, in 90% yield, 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**) which, on fusion with pyridine hydrochloride, gave 3-hydroxy-1,11-iminoestra-1,3,5(10),9(11)-tetraen-17-one (**1**).

In our program on the synthesis of modified estrogens,[2] the preparation of some 1-substituted derivatives was considered worthwhile since few of these compounds have been reported.[3] In particular, an appealing aspect of this problem was the possibility of forming a nitrogen bridge[4] between the C-1 and C-11 positions *via* a nitrene[5] insertion reaction. The resulting indoline (**14**) should then be easily converted to **1** an interesting heterocyclic steroid which would incorporate the structural features of estrone with those of a highly substituted indole.



1

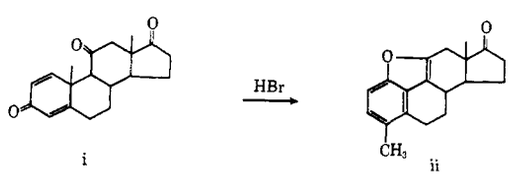
The projected synthesis of **1** required the development of a method for gaining access to the C-1 position of estrone and specifically for the preparation of 1-aminoestrone 3-methyl ether (**10b**). To accomplish this by an electrophilic substitution reaction required that the estrone molecule should first be substituted with a group that would overcome the *ortho* orienting effect of the C-3 hydroxyl or methoxyl group and direct substitution to C-1. Another factor which we thought would impede reaction at C-1 was steric hindrance by the 11-methylene group.[6,7] However,

(1) For a preliminary announcement of this work, see E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 2943 (1964).

(2) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64, 214 (1964); S. Gordon, E. W. Cantrall, W. P. Cekleniak, H. J. Albers, S. Mauer, S. M. Stolar, and S. Bernstein, *Steroids*, **4**, 267 (1964); and R. B. Conrow E. W. Cantrall, and S. Bernstein, *ibid.*, **9**, 307 (1967).

(3) For the preparation of various 1-substituted estrone 3-methyl ethers and references to previously reported 1-substituted 1,3,5(10)-estratrienes, see E. W. Cantrall, R. B. Conrow, and S. Bernstein *J. Org. Chem.*, in press.

(4) Related bridged compounds having an oxygen atom between these positions have been described in the C-19 and C-21 series: C. Tamm and G. Volpp, U. S. Patent 3,057,860 (Oct 9, 1962); J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailovic, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, **44**, 186 (1961); K. Heuser, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 352 (1963); Ch. Meystre, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 2844 (1963); L. Canonica, G. Jommi, F. Pelizzoni, and C. Scolastico, *Gazz. Chim. Ital.*, **95**, 138 (1965); and G. Jommi, P. Manitto, and C. Scolastico, *ibid.*, **95**, 151 (1965). The corresponding oxygen derivative (ii) of estrone has been reported in the patent literature [F. B. Colton, U. S. Patent 2,923,709 (Feb 2, 1960)] as arising from the aromatization of androsta-1,4-diene-3,11,17-trione (i).

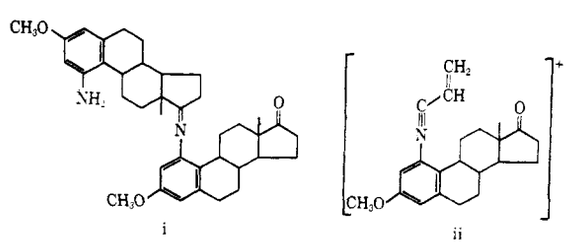


i ii

(5) For recent reviews on the chemistry of nitrenes, see L. Horner and A. Christmann, *Angew. Chem.*, **75**, 707 (1963); *Angew. Chem. Intern. Ed. Engl.*, **2**, 599 (1963); and R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

(6) In a nmr study, appreciable van der Waals interaction between the C-4 and C-5 protons of ring-A-aromatic octahydrophenanthrenes has been demonstrated by W. Nagata, T. Terasawa, and K. Troi, *J. Am. Chem. Soc.*, **86**, 3746 (1964). However, experimental evidence indicates that this steric hindrance is not as great as one would predict from an inspection of molecular models.

(7) In one reductive cleavage performed at 55–85° for 25 min, there was isolated in 20% yield a compound (mp 250–260°) with structure i. Evidence



i ii

for i was the presence of an imino band at 1670 cm^{-1} in the infrared spectrum. Also, hydrolysis of the product with 10% hydrochloric acid–methanol gave the 1-amino compound **10b**. Conclusive evidence for the structure of i was obtained by high-resolution mass spectrometry. Thus, the molecular ion M^+ was found to be 580.3649 (calcd for $C_{38}H_{46}NO_3$: 580.3662). The base peak (II) occurred at *m/e* 336 which is consistent with the predicted fragmentation of the imino structure i.