Ketimines. VIII. Infrared Spectra of Ketimines

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The literature includes much work on the absorption band due to the =N— group but in most instances this group is part of a ring. Randall[1] has published the spectra of a few oximes, imido ethers, thiazolidines, imidazolines, oxazolones and pyridines. His assignments for the C=N maximum range from 5.89–6.50 μ. In addition to these assigned maxima, Randall obtained the spectra of several guanidines and/or their salts, 1-phenyl-3-methylpyrazolone-5 and creatinine. From his spectra we have made assignments for the C=N ranging from 5.95–6.29 μ (Table I).

TABLE I

Compound	Wave length in μ for C=N band
Guanidine acetate	6.00
Aminoguanidine bicarbonate	5.95
Aminoguanidine sulfate	6.05
Guanidine carbonate	6.00
Guanidine thiocyanate	6.03
Methylguanidine hydrochloride	6.00
Methylguanidine sulfate	6.08
Triphenylguanidine	6.11
sym-Diphenylguanidine	6.10
1-Phenyl-3-methylpyrazolone-5	6.24
Creatinine	6.29

Lieber, *et al.*,[2] have published the spectra of 38 guanidine derivatives and assigned values from 5.8–6.15 μ for the C=N group.

In connection with a long range program of preparation and characterization of ketimines in this Laboratory it was desired to establish whether the imino group in these compounds showed characteristic absorption in the range obtained for the compounds investigated by other authors. During this study Fuson[3] published the absorption maxima for N-benzoylduryl phenyl ketimine (6.14 μ), N-methylduryl phenyl ketimine methiodide (6.14 μ) and N-methylduryl *p*-*t*-butylphenyl ketimine (6.11 μ).

A secondary aim of this investigation was to check the possibility of an ene–amine tautomerism in compounds containing hydrogen alpha to the imino group. This tautomeric equilibrium has been hypothesized by Moureau and Mignonac[4] and Weissberger and Glass[5] to explain certain reaction products of imines. In none of our spectra was there evidence of the band due to the olefinic linkage. However, the location of the imine maximum is found so near that expected for the olefin that, due to the probability of overlapping, no conclusion could be drawn as to eneaminization. Imines and the corresponding ketones are given in Table II.

Five dialkyl ketimines were studied, showing strong bands assigned to the imino group in the region from 6.08–6.10 μ. Also, the N–H band occurred from 3.09 to 3.12 μ. One aryl alkyl ketimine, in which the alkyl group was tertiary, absorbed at 6.18 μ.

TABLE II

Ketimine	=N—H	C=N	C=O in corresponding ketone
Bis-(*p*-chlorophenyl)	3.08	6.05	5.82
ω-Cyclohexylethyl *s*-butyl	3.09	6.09	..
ω-Cyclohexylamyl *s*-butyl	3.09	6.09	5.83
Diphenyl	3.09	6.24	..
o-Tolyl *s*-butyl	3.09	6.14	5.92
Phenyl *t*-butyl	3.10	6.18	..
o-Tolyl *i*-amyl	3.10	6.13	5.92
o-Tolyl *n*-propyl	3.10	6.14	5.93
Ethyl *n*-butyl	3.10	6.08	5.83
Di-*n*-propyl	3.10	6.08	..
ω-Cyclohexylpropyl *s*-butyl	3.10	6.10	..
α-Naphthyl phenyl	3.10	6.24	6.02
o-Tolyl ethyl	3.12	6.13	5.91
o-Tolyl *n*-butyl	3.12	6.14	5.92
o-Tolyl *i*-butyl	3.12	6.15	5.93

It is possible that this value might be more nearly that of the imine band and the lower values of 6.13–6.14 due to overlap with the olefin band from the eneamine form—the latter form being impossible with the tertiary group. However, the band assigned to the imine group is, in every case, quite sharp and shows no indication of being a doublet.

As was expected, the increase of wave length of absorption when the imine group is conjugated with a single aromatic nucleus, was greatly enhanced in diaryl ketimines. Diphenyl ketimine and α-naphthyl phenyl ketimine show strong bands at 6.24 μ. It was also expected that the presence on the aromatic nucleus of a "deactivating" group, such as the halogen, would decrease the extent of conjugation, and that absorption would occur at a shorter wave length than in other aryl ketimines. Bis-(*p*-chlorophenyl) ketimine absorbed at 6.05 μ.

All spectra were obtained with the Perkin–Elmer Model 12C, single beam instrument with NaCl optics, using NaCl cells. The compounds used were prepared in this Laboratory as reported in previous papers in this series.[6]

(1) H. Randall, *et al.*, "Infrared Determination of Organic Structures," D. Van Nostrand, Inc., New York, N. Y., 1949.

(2) E. Lieber, D. Levering and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(3) R. C. Fuson, *et al.*, THIS JOURNAL, **75**, 5321 (1953).

(4) C. Moureu and G. Mignonac, *Compt. rend.*, **158**, 1395 (1914).

(5) A. Weissberger and D. Glass, THIS JOURNAL, **64**, 1724 (1942).

(6) P. L. Pickard, *et al.*, *ibid.*, **72**, 876, 5017 (1950); **73**, 42 (1951); **74**, 4607 (1952); **75**, 5899 (1953).

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Steroids. LVIII.[1] Synthesis of Allopregnane-3β,6β,21-triol-20-one Triacetate

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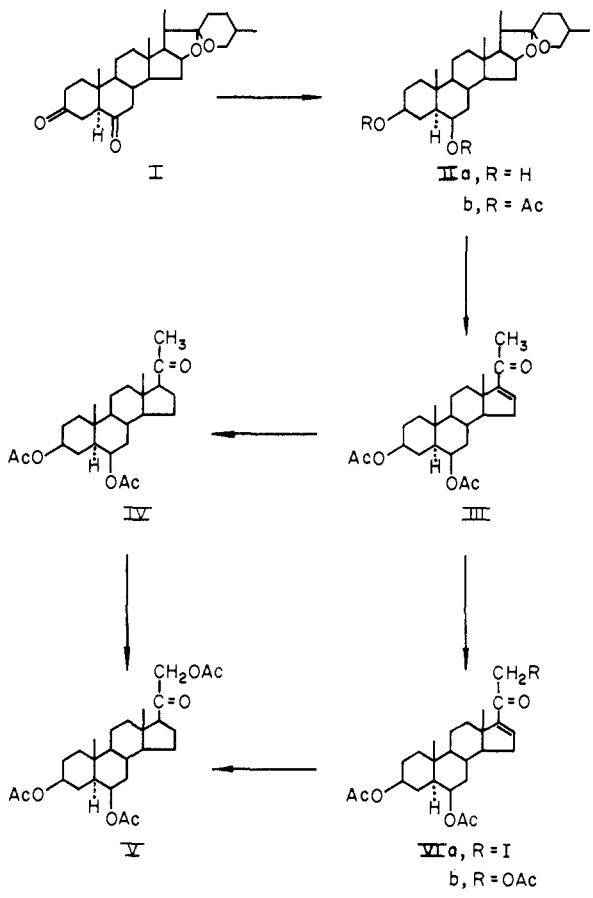
For certain biological studies we required the triacetate V of allopregnane-3β,6β,21-triol-20-one, an isomer of Reichstein's substance R with the 11β-hydroxy group transposed to C-6. The Δ^4-unsaturated compound corresponding to V has been described,[2] but its hydrogenation does not

(1) Paper LVII, G. Rosenkranz, M. Velasco and F. Sondheimer, THIS JOURNAL, **76**, 5024 (1954).

(2) O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951).

lead to the required saturated triacetate since hydrogenolysis of the allylic acetoxy groupings predominates.[2] In this paper we describe a synthesis of V from 22a,5α-spirostane-3,6-dione (chlorogenone) (I), a compound readily prepared from diosgenin by successive chromium trioxide oxidation and zinc reduction.[3]



22a,5α-Spirostane-3,6-dione (I) has been reduced by Marker, *et al.*, with sodium and alcohol[3a] to chlorogenin, whereas catalytic hydrogenation[3a] had given an isomer named "β"-chlorogenin. By analogy with similar experiments in the cholestane series, chlorogenin was assigned the 3β,6α-diol and "β"-chlorogenin the 3β,6β-diol IIa structure. We have found the catalytic hydrogenation of I to be an unsatisfactory route to the diol IIa. Reduction with lithium aluminum hydride or sodium borohydride proceeded more smoothly and also yielded the 3β,6β-diol IIa, as evidenced by comparison of the product and of its diacetate IIb with samples prepared by catalytic hydrogenation. The 6β-hydroxy structure[4] for the "β"-chlorogenin thus obtained was confirmed by the fact that the negative M_D contribution (−33)[5] of the 6-hydroxy group in the compound is in excellent agreement with that (−36)[6] found for the 6β-hydroxy group in cholestane-3β,6β-diol. On the other hand the *positive* M_D contribution (+71)[5,7] of the 6-hydroxy function of chlorogenin clearly shows it to be of the α-configuration.[7a]

The next step, the side chain degradation of 22a,5α-spirostane-3β,6β-diol diacetate (IIb) to Δ[16]-allopregnene-3β,6β-diol-20-one diacetate (III), has been described previously by Marker and coworkers.[8] This transformation is, however, reported briefly in the Experimental section, since the product exhibits different physical properties from those recorded.[8] Catalytic hydrogenation of III over a palladium–charcoal catalyst led to allopregnane-3β,6β-diol-20-one diacetate (IV), which differed from the known 3β,6α-[2,7a] and 3α,6α-isomers.[9] The required allopregnane-3β,6β,21-triol-20-one triacetate (V) was prepared from the diacetate IV through acetoxylation at C-21 with lead tetraacetate. An alternative route from III to V involved enol acetylation at C-20 and treatment with N-iodosuccinimide[10] to the 21-iodo compound VIa, potassium acetate displacement to the unsaturated triacetate VIb, and hydrogenation of the Δ[16]-double bond.

Experimental[11]

22a,5α-Spirostane-3β,6β-diol ("β"-Chlorogenin) (IIa).—A solution of 100 g. of 22a,5α-spirostane-3,6-dione (chlorogenone) (I)[3] in 1.5 l. of dry tetrahydrofuran was added gradually to 15 g. of lithium aluminum hydride in 500 cc. of tetrahydrofuran. The mixture was refluxed for 30 minutes and ethyl acetate was then slowly added until reaction ceased. Addition of dilute hydrochloric acid and much water yielded a precipitate which after crystallization from chloroform–ethyl acetate furnished 58.5 g. (58%) of the 3β,6β-diol IIa with m.p. 243–248°. A further purified specimen showed m.p. 249–251°, $[\alpha]_D$ −78°, M_D −337, ν_{max} free hydroxyl band only. The spectrum was identical with a specimen of IIa prepared[3a] by catalytic hydrogenation of I, but differed from that of authentic chlorogenin.

Very similar results were obtained when the reduction was carried out with sodium borohydride in ethanol overnight at room temperature. It is probable that some of the 3β,6α-diol (chlorogenin) is also formed on reduction with either hydride, but no attempt at its isolation was made.

The diacetate IIb was obtained in nearly quantitative yield under the usual conditions (acetic anhydride, pyridine, steam-bath, 1 hour), and after crystallization from methanol exhibited m.p. 169–170°, $[\alpha]_D$ −86°, ν_{max} 1718 cm.$^{-1}$ and no free hydroxyl band. There was no depression in m.p. on admixture with a sample prepared by acetylation

(3) (a) R. E. Marker, E. M. Jones and D. L. Turner, THIS JOURNAL, **62**, 2537 (1940); (b) R. E. Marker, E. M. Jones, D. L. Turner and E. Rohrmann, *ibid.*, **62**, 3006 (1940).

(4) *Cf.* C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1790, 3361, 3374 (1952).

(5) 22a,5α-Spirostan-3β-ol (tigogenin), the 6-desoxy derivative, shows M_D −304 (G. Rosenkranz, J. Romo and J. Berlin, *J. Org. Chem.*, **16**, 290 (1951)).

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 216, no. 29.

(7) Chlorogenin: $[\alpha]_D$ −54°, M_D −233 (determined in these laboratories). The M_D contribution of the 6α-hydroxy function in cholestane-3β,6α-diol is given as +61 (reference 6).

(7a) Added in proof: I. I. Salamon and K. Dobriner (*J. Biol. Chem.*, **207**, 323 (1954)) have now published a similar argument for assigning configurations to chlorogenin and "β"-chlorogenin.

(8) R. E. Marker, D. L. Turner and E. L. Wittbecker, THIS JOURNAL, **64**, 809 (1942).

(9) S. Liebermann, K. Dobriner, B. R. Hill, L. F. Fieser and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948); S. Liebermann, D. K. Fukushima and K. Dobriner, *ibid.*, **182**, 299 (1949).

(10) *Cf.* C. Djerassi and C. Lenk, THIS JOURNAL, **76**, 1722 (1954). We would like to thank these authors for informing us of this method prior to publication.

(11) Melting points are uncorrected. Rotations were measured (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. Infrared spectra were determined in chloroform solution with a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. We are grateful to Mrs. P. Lopez for these measurements, to Mrs. A. Gonzalez for the microanalyses, and to Miss C. Amendolla for technical assistance.

of the catalytic hydrogenation product of Ia (m.p. 166–168°; Marker, *et al.*,[3a] give m.p. 120°) and the infrared spectra were identical. The diacetate differed from chlorogenin diacetate (m.p. 155–156°) as evidenced by a depression in m.p. on admixture and differences in the infrared spectra.

Δ^{16}-Allopregnene-3β,6β-diol-20-one Diacetate (III).—A mixture of 10 g. of the diacetate IIb and 50 cc. of acetic anhydride was heated in an autoclave at 185–190° for 8 hours, poured into water, extracted with ether, washed well with sodium carbonate solution, dried and evaporated. The resulting oily "furosten" was oxidized with chromium trioxide and the resulting "diosone" subjected to saponification as described previously.[12] Chromatographic purification on alumina and crystallization from ether–pentane afforded 5.11 g. (63%) of the allopregnene derivative III with m.p. 164–165°, $[\alpha]_D$ −18°, λ_{max} 238 mμ, log ϵ 4.03, ν_{max} 1718 and 1660 cm.$^{-1}$ (reported[8] m.p. 233–235°).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.38; H, 8.58.

Allopregnane-3β,6β-diol-20-one Diacetate (IV).—The Δ^{16}-compound III (1.20 g.) dissolved in 100 cc. of ethyl acetate was hydrogenated over 0.4 g. of 5% palladium–charcoal at atmospheric pressure and room temperature. After 2 hours, the catalyst and solvent were removed and the residue was crystallized from ether–pentane. The resulting allopregnane-3β,6β-diol-20-one diacetate (0.96 g.) showed m.p. 175–177°, $[\alpha]_D$ +18°, no appreciable absorption in the ultraviolet, ν_{max} 1718 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.45; H, 8.89.

$\Delta^{16,20}$-Allopregnadiene-3β,6β,20-triol Triacetate (Enol Acetate of III).—A solution of 8.0 g. of the Δ^{16}-derivative III and 1.5 g. of *p*-toluenesulfonic acid in 180 cc. of isopropenyl acetate was slowly distilled during the course of 10 hours (120 cc. of distillate collected). Addition of water, followed by extraction with ether, washing with sodium carbonate, drying and evaporation left a residue which on crystallization from ether–pentane yielded 7.1 g. (81%) of the enol acetate with m.p. 169–172°. The analytical sample showed m.p. 179–181°, $[\alpha]_D$ +36°, λ_{max} 238 mμ, log ϵ 4.18, ν_{max} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.98; H, 8.53.

Δ^{16}-Allopregnene-3β,6β,21-triol-20-one Triacetate (VIb).—The above enol acetate (6.9 g.) was heated with 6.9 g. of N-iodosuccinimide in 40 cc. of dioxane at 80° for 2 hours. Addition of water, extraction with ether (ether layer washed with sodium thiosulfate and water) and crystallization from methanol afforded 6.7 g. of the iodoketone VIa with m.p. *ca.* 200° (dec., varies with rate of heating), λ_{max} 250 mμ, log ϵ 3.94, ν_{max} 1718 and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}O_5I$: C, 55.33; H, 6.51. Found: C, 55.01; H, 6.60.

The iodoketone was refluxed with 20 g. of potassium acetate in 200 cc. of acetone for 6 hours, and was then poured into water. Ether extraction and crystallization from ether–pentane furnished 4.8 g. (54% over-all based on III) of the unsaturated triacetate VIb with m.p. 137–138°, λ_{max} 240 mμ, log ϵ 4.20.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.48; H, 8.24.

Allopregnane-3β,6β,21-triol-20-one Triacetate (V). (a) From Allopregnane-3β,6β-diol-20-one Diacetate (IV).—A solution of 0.80 g. of the saturated diacetate IV and 1.5 g. of lead tetraacetate (Arapahoe Chemicals, Boulder, Colo.; *ca.* 90% pure) in 20 cc. of glacial acetic acid was heated on the steam-bath for 6 hours and then left at room temperature overnight. The solution was poured into water, the product was isolated with ether and chromatographed on 30 g. of neutral alumina. Crystallization of the fractions eluted with hexane–benzene from ether–pentane yielded 0.44 g. (48%) of the triacetate V with m.p. 138–140°, $[\alpha]_D$ +25°, ν_{max} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.10; H, 8.12.

(b) From Δ^{16}-Allopregnene-3β,6β,21-triol-20-one Triacetate (VIb).—The unsaturated triacetate VIb (2.0 g.) dissolved in 40 cc. of ethyl acetate was hydrogenated over 0.4 g. of a 5% palladium–charcoal catalyst at room temperature and atmospheric pressure. Crystallization of the product from ether–pentane afforded 1.81 g. (90%) of the saturated triacetate V with m.p. 137–139°, $[\alpha]_D$ +23°, no appreciable absorption in the ultraviolet. Identity with the sample prepared by method (a) was established through mixture m.p. determination and infrared comparison.

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(12) *Cf.* C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

Steroids. LIX.[1] Ring D Rearrangement of 17α,-21-Dihydroxy-20-ketosteroids

BY E. BATRES, G. ROSENKRANZ AND FRANZ SONDHEIMER

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The so-called "D-homo" rearrangement of 17α-hydroxy-20-ketosteroids of the pregnane series (type Ia) to the corresponding 17aα-hydroxy-17aβ-methyl-17-keto-D-homoandrostane derivatives (type IIa) has been effected stereospecifically through heat treatment and through reaction with aluminum alkoxides and with boron trifluoride–acetic acid–acetic anhydride (to yield the 17aα-acetates).[2,3] Moreover this isomerization may be brought about by the action of potassium hydroxide, which however yields the 17a-isomer of IIa as the major product.[3] The D-homo rearrangement has not been carried out previously with compounds of type Ib, possessing the 17α-hydroxy-21-acetoxy-20-keto side chain characteristic of cortisone acetate. We were interested in performing the isomerization with compounds of this series so as to make available reference substances which could be compared with microbiological transformation products.[4]

17α-Hydroxydesoxycorticosterone (Reichstein's substance S) 21-acetate (Ib) was subjected to Oppenauer oxidation conditions (boiling with aluminum isopropoxide and cyclohexanone in toluene). The product, isolated in 46% yield, was assigned the 17aβ-acetoxymethyl-17aα-hydroxy-17-keto-D-homoandrostane structure IIb, since analysis proved it to be isomeric with the starting material, and since similar conditions (aluminum *t*-butoxide in benzene with or without acetone) in the 21-desoxy series had led to the corresponding 17aβ-methyl-17aα-hydroxy-17-keto compounds (type IIa).[2] In agreement with this formulation, the rearranged acetate IIb gave a negative reaction with triphenyltetrazolium chloride,[5] although the saponification product IIc reacted weakly positively.

(1) Steroids. LVIII, J. Romo, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 5169 (1954).

(2) *Inter al.*, P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941); R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).

(3) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

(4) *Cf.* J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952). Added in proof: V. Georgian and N. Kundu [*Chemistry and Industry*, 431 (1954)] have now described the D-homo rearrangement of Substance S Acetate and of cortisone acetate with boron trifluoride–acetic acid–acetic anhydride.

(5) This test in the steroid series has been found so far to be specific for compounds containing the 21-hydroxy-20-keto function either in the free or esterified form (*cf.* A. Zaffaroni, "Recent Progress in Hormone Research," Academic Press, Inc., New York, N. Y., Vol. VIII, 1953, p. 77.