pure phenol **6**: prisms; mp 277–278; ultraviolet maxima (95% ethanol) at 256, 264, and 333 mμ (ε 16,700, 18,200, 26,400); and infrared absorption (Nujol) at 3160, 1668, 1601, 1570, 1500, and 1460 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.99. Found: C, 70.71; H, 6.93.

Acetate 7.—A mixture of phenol **6** (60 mg, 0.21 mmole), pyridine (15 ml), and acetic anhydride (25 ml) was stirred for 8 hr at room temperature. Excess reagent was removed *in vacuo* and the residue chromatographed on a 6:5 mixture of silica gel G and Hyflo Super-Cel (0.25% methanol–chloroform). The yellowish crystals (58 mg, 84%) were sublimed at 100° (0.005 mm) to yield the acetate **7**. Recrystallization from chloroform–hexane gave colorless needles: mp 144–145°; $[\alpha]^{25}D$ +3.1° (*c* 2.77, chloroform); ultraviolet maxima (95% ethanol) at 250 and 315 mμ (ε 17,760, 29,000); and infrared absorption ($CHCl_3$) at 1760, 1710, 1630, and 1600 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.86; H, 6.66.

Ozonolysis of Acetate 7.—The acetate **7** (720 mg, 2.3 mmoles) was ozonolyzed in 100 ml of methylene chloride at 15° for 12 hr. Volatile components from the reaction mixture were collected by passing the effluent gases through a Dry Ice–acetone trap. Additional methylene chloride was added periodically to the reaction vessel to keep the volume of the reaction mixture at *ca.* 100 ml. The liquid in the trap and the reaction mixture were then combined and treated with 10% sodium hydroxide (30 ml). Methylene chloride was removed *in vacuo* and the reaction mixture was further treated with ethanol (45 ml) and hydrogen peroxide (7 ml of 30%) for 0.5 hr at room temperature followed by 0.5 hr at reflux. The reaction mixture was extracted with chloroform and then neutralized with dilute hydrochloric acid.

Steam distillation of the reaction mixture yielded (+)-(*S*)-2-methylbutanoic acid (**8**) (40 mg, 17%) identified by the vpc retention time of the acid and its methyl ester and by conversion to (+)-(*S*)-2-methylbutanoic amide (**9**). The acid was found to be dextrorotary, but the exact rotation could not be determined. Continuous chloroform extraction of the aqueous phase yielded, after chromatography of the extract, glutaric acid (21 mg, 16%), mp 92–93° characterized by comparison with an authentic sample.

(+)-(*S*)-2-methylbutanoic Amide (9).—To (+)-(*S*)-2-methylbutanoic acid (43 mg, 0.42 mmole), obtained from the ozonolysis of acetate **7**, was added 1 equiv of oxalyl chloride. The mixture was heated to 45° for 2 hr. A small amount of ether was added and gaseous ammonia was passed through the solution for 1 hr. The ether mixture was filtered and evaporated to dryness. Recrystallization from benzene–ether–ethanol (5:5:1) yielded (+)-(*S*)-2-methylbutanoic amide (**9**) as colorless plates: mp 109–110°; $[\alpha]^{25}D$ +14.2° (*c* 0.244, chloroform); $M^{25}D$ +14.3 (lit.[5] mp 109.9–110.3°; $[\alpha]^{25}D$ +22.5; $M^{25}D$ +22.7).

Kuhn–Roth Oxidation of Phenol 6.—Kuhn–Roth oxidations were carried out according to the procedure of Wiesenberger.[15] The phenol **6** (52 mg, 0.18 mmole) was treated with 4 *N* chromic acid (4 ml) and water (4 ml). Steam distillation was immediately begun with addition of 2 ml of water for each 2 ml of distillate. The distillate was titrated against phenolphthalein with 0.05 *N* NaOH (0.17 mequiv of acid found). This distillate was reduced to a volume of 3 ml and acidified (pH < 1) with concentrated sulfuric acid. Extraction with five 10-ml portions of ether and vpc separation of the products (4 ft × 0.25 in., 4% phosphoric acid, 20% diethylene glycol succinate on Chrom W (60–80 mesh) at 110°) yielded acetic acid (5%), propionic acid (5%), and (+)-(*S*)-2-methylbutanoic acid (**8**) (11 mg, 90%), $[\alpha]^{25}D$ +19.2° (lit.[5] $[\alpha]^{25}D$ +19.3°). The (+)-(*S*)-2-methylbutanoic acid (**8**) was characterized by conversion into (+)-(*S*)-2-methylbutanoic amide (**9**), $[\alpha]^{25}D$ +22.4° (*c* 0.32, chloroform) (lit.[5] $[\alpha]^{25}D$ +22.5°).

Registry No.—**1**, 1162-65-8; **2**, 1389-06-6; **3**, 1165-39-5; **4**, 7241-98-7; **5**, 13133-70-5; **6**, 13133-71-6; **7**, 13133-72-7; **8**, 1730-91-2; **9**, 13133-74-9.

Acknowledgment.—We are indebted to the National Cancer Institute for financial support.

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Stereochemistry of the Alkaloid Gitingensine

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The steroidal alkaloid gitingensine was isolated from the leaves of *Kibatalia gitingensis* Woods[1] in low yields and structure **1a** was proposed for this compound, without assignment of configuration. Moreover, it was shown[1] that N-methylgitingensine (**1b**), although isomeric with, was different from paravallarine (**2**).[2] This difference seemed to be due to the configuration at C-3 and/or at C-20 in gitingensine (**1a**).

It has been shown recently[3] that primary and secondary amines react readily with dimedone to form condensation compounds. These substances possess a vinylogous amide group exhibiting strong ultraviolet absorption in the 280-mμ region. When in an asymmetric surrounding, this chromophore is optically active, as in the case of similar derivatives in the amino acid series.[4] Moreover, the sign of the Cotton effect reflects the configuration of the asymmetric center adjacent to the chromophore.

In order to assign the configuration to the primary amine in gitingensine (**1a**), its dimedone condensation derivative (**3**) was prepared and submitted to optical rotatory dispersion (RD) and circular dichroism (CD) examination.[5] As shown in Figure 1, the Cotton effect[5] associated with the vinylogous amide group of compound **3** at *ca.* 280 mμ is strongly positive (a = +214, $[\theta]_{288}$ +13,400).

As reference compounds, the adduct of 3β-amino-5α-pregnane (**4a**) and its 3α isomer (**4b**) were then prepared. Although their specific rotations at the sodium D line are very similar (see Experimental Section), compound **4a** of absolute configuration (3*S*), and presenting a stereochemistry at C-3 opposite that of **4b** (3*R*), exhibits a negative Cotton effect (a = −70) and (**4b**, a = +62) a positive one. This shows that inversion of the configuration of the 3-amino grouping gives rise to opposite Cotton effects for the dimedone condensation compounds. Since gitingensine (**1a**) and its dimedone derivative (**3**) present a double bond at C-5, the condensation compound of 3β-amino-20β-hydroxypregn-5-ene (**5**) was prepared for comparison purposes in order to make sure that the Δ^5 double bond does not invert the sign of the Cotton effect associated with the (3*S*) configuration. The sign of the rotatory dispersion curve of the condensation product (**5**, a = −183) is the same as in **4a**, but the molecular

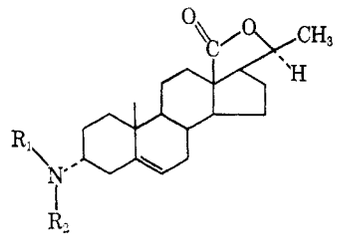
(1) G. Aguilar-Santos, *Philippine J. Sci.*, **94**, 217 (1965).

(2) (a) J. Le Men, *Bull. Soc. Chim. France*, 860 (1960); (b) R. Goutarel "Les Alcaloides Stéroidiques des Apocynacées, Hermann, Ed., Paris, 1964, pp 39, 86.

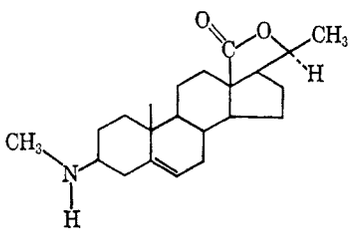
(3) (a) P. Crabbé, B. Halpern, and E. Santos, *Bull. Soc. Chim. France*, 1446 (1966); (b) P. Crabbé, *Vietnamica Chim. Acta*, 1 (1966); (c) E. Santos, Ph.D. Thesis, Universidad Nacional Autonoma de México, Mexico City, 1967.

(4) P. Crabbé and B. Halpern, *Chem. Ind.* (London), 346 (1965).

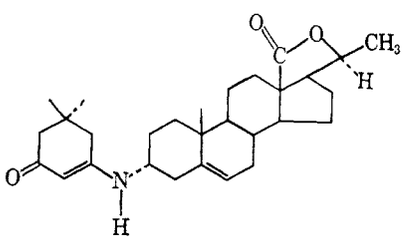
(5) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965.



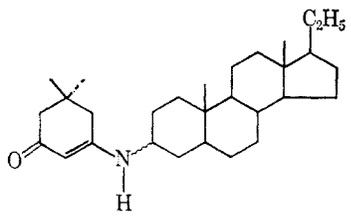
1a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = CH_3$



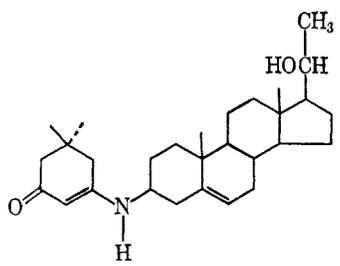
2



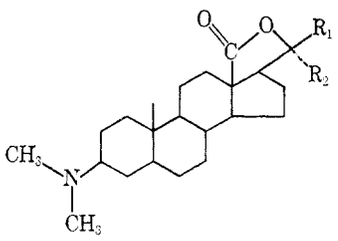
3



4a, 3α-H, 3β-dimedonyl
b, 3α-dimedonyl, 3β-H



5



6a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$

amplitude of the rotatory dispersion curve of compound **5** is considerably higher than in **4a**. Since the Cotton effect exhibited by the adduct (**3**) in the 280-mμ region is positive, as in most optically active amines presenting the (*R*) configuration[3] (see Figure 1), the 3α configuration, *i.e.*, the (3*R*) stereochemistry, could be assigned to the primary amine in compounds **1a** and **3**.

The (3*R*) configuration in gitingensine was supported by nuclear magnetic resonance (nmr) evidence. The difference in the chemical shift between axial and equatorial protons in six-membered rings is well documented.[6] Usually such axial ring protons absorb at higher field than do their equatorial counterparts. In compounds **3** and **4b**, the resonance of the proton at C-3 is at *ca.* 210–230 cps, in agreement with their equatorial configuration. Conversely, in steroids **4a** and **5**, the signal of the proton at C-3 appears around 180–205 cps, corresponding to the axial configuration.[6]

Attention was then focused on the stereochemistry of the methyl group at C-20. Samples of N-methyldihydro-5α-paravallarine (**6a**) and N-methyldihydro-5α-20-isoparavallarine (**6b**) were obtained.[7] These alkaloids differ only by their stereochemistry at C-20. The former presents the 20β-methyl configuration (20*S*), the latter the 20α-methyl (20*R*). Since the $n-\pi^*$ transition of a lactone (or ester) grouping in the 200–230-mμ region is optically active when in an asymmetric surrounding,[8] compounds **6a** and **6b** were examined by optical methods. The 20β-methyl compound (**6a**) exhibits a positive Cotton effect in the 220-mμ region, whereas its isomer (**6b**) presents a negative molecular ellipticity in the same wavelength range. When gitingensine (**1a**) or its dimedone condensation derivative (**3**) was submitted to the same measurements, a positive Cotton effect was observed at *ca.* 217 mμ ([θ] +7185) (see Figure 1), thus establishing the stereochemistry at C-20 as 20β (20*S*). Hence the absolute configuration of gitingensine (**1a**) can be defined as (3*R*) and (20*S*). N-Methylgitingensine (**1b**) differs from paravallarine (**2**) only by the stereochemistry of the amino group at C-3. Gitingensine (**1a**) can also be considered as bis(demethyl)kibataline, since kibataline (**1c**) is known to possess a 3α-N,N-dimethylamino grouping.[9]

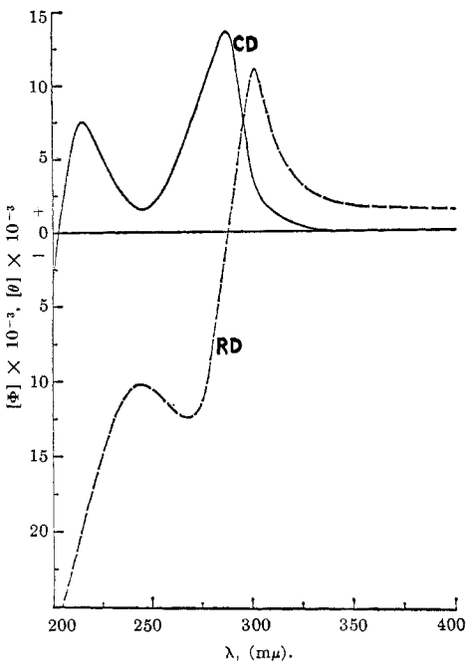


Figure 1.—Optical rotatory dispersion (RD) and circular dichroism (CD) curves of the dimedone condensation product (**3**) of gitingensine (**1a**).

(6) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 47, 77.

(7) We are grateful to Professor J. Le Men, Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, France, for a sample of these substances.

(8) *Inter alia:* (a) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211, 7229 (1965); (b) H. Wolf, *Tetrahedron Letters*, No. 16, 1075 (1965); No. 42, 5151 (1966).

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Experimental Section[10]

Dimedone Condensation Product (3) of Gitingensine.—The hydrochloride of gitingensine (**1a**)[1] (250 mg) was treated with 5% sodium bicarbonate solution. The free base was extracted with methylene chloride; the organic solution was washed, dried, filtered, and concentrated *in vacuo*. The dry material was dissolved in 100 ml of anhydrous benzene and 100 mg of dimedone was added. The reaction mixture was gently refluxed for 24 hr, water being eliminated with a Stark separation funnel. The solution was then evaporated to dryness under vacuum and the residue was separated on preparative thin layer chromatoplate on silica gel. The crude product obtained was dissolved in ether and a stream of dry hydrogen chloride was passed through the solution. The crystalline hydrochloride (185 mg) was purified by further crystallization from methylene chloride–acetone to afford the hydrochloride of (**3**), mp 245–260°. Mild base hydrolysis with sodium bicarbonate provided the dimedonyl condensation product (**3**) of gitingensine, exhibiting mp 252–253°; $[\alpha]_D$ + 59°; RD (*c* 0.058, methanol), $[\Phi]_{600}$ +285°, $[\Phi]_{350}$ +1706°, $[\Phi]_{302}$ +9344°, $[\Phi]_{290}$ ±0°, $[\Phi]_{274}$ −12059°, $[\Phi]_{244}$ −10239°, $[\Phi]_{208}$ −23038°; CD (*c* 0.058, ethanol), $[\theta]_{288}$ +13400, $[\theta]_{217}$ +7185; $\lambda_{max}^{dioxane}$ 293 mμ (log ε 4.52); $\nu_{max}^{CHCl_3}$ 3500, 1750, 1580, and 1520 cm^{-1}; nmr, 63.1 (*gem*-dimethyl), 66.1 (19-H), 78.5, 84.7 (21-H, doublet), 129.4 (allylic CH_2 and CH_2CO), ~210–230 (3 β-H), ~265–295 (NH and 20-H), 306 (vinylic H of dimedonyl group), ~324 cps (vinylic 6-H); mass spectrum, M^+ = 451.6, 421.6 (M − $2CH_3$), 311, 140. *Anal.* Calcd for $C_{29}H_{41}O_3N$ (mol wt 451.63): C, 77.12; H, 9.15; N, 3.10. Found: C, 76.66; H, 9.18; N, 3.53.

Dimedone Condensation Product (4b) of 3α-Amino-5α-pregnane.—A solution of 400 mg of 3α-amino-5α-pregnane,[11] 210 mg of dimedone, and 30 mg of *p*-toluenesulfonic acid in 100 ml of anhydrous benzene was heated under reflux for 24 hr, eliminating the water with a Stark separating funnel. After cooling, the benzene layer was washed with 5% sodium bicarbonate–water solution until neutral. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was chromatographed on alumina. Elution with benzene–chloroform (3:7) afforded 450 mg of compound, which was recrystallized in acetone, providing 40 mg of the 3β isomer (**4a**), mp 291–292° (see below).

The mother liquors of these crystals were dissolved in methylene chloride and a stream of dry hydrogen chloride was passed through the solution. The hydrochloride of **4b** which precipitated was crystallized from methanol and then treated with a 5% sodium bicarbonate solution. The free base was extracted with chloroform, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness. The crystalline material was recrystallized from methanol–water to furnish the analytical sample of **4b**: mp 227–228°; $[\alpha]_D$ +44°; RD (*c* 0.004, dioxane), $[\Phi]_{600}$ +187°, $[\Phi]_{320}$ +788°, $[\Phi]_{300}$ +830°, $[\Phi]_{284}$ +3527°, $[\Phi]_{270}$ ±0°, $[\Phi]_{254}$ −2697°, $[\Phi]_{236}$ −3181°, $[\Phi]_{222}$ −4011°, $[\Phi]_{218}$ −2351°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.43); $\nu_{max}^{CHCl_3}$ 3500 and 1540 cm^{-1}; nmr, 34 (18-H), 49.6 (19-H), 64.6 (*gem*-dimethyl), ~132 (CH_2CO), ~222 (3β-H), 307.9 cps (vinylic H of dimedonyl group). *Anal.* Calcd for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; O, 3.76; N, 3.29. Found: C, 81.70; H, 11.13; O, 3.76; N, 3.20.

Dimedone Condensation Product (4a) of 3β-Amino-5α-pregnane.—A solution containing 200 mg of 3β-amino-5α-pregnane,[12] 100 mg of dimedone, and 20 mg of *p*-toluenesulfonic acid in 100 ml of benzene was refluxed under the conditions described above for the preparation of **4b**. After the usual extraction procedure, the crude material was chromatographed on neutral alumina. Elution with benzene–chloroform (3:2) afforded 130 mg of the crystalline condensation product (**4a**) which, after recrystallization from methylene chloride–hexane, exhibited mp 291–292°; $[\alpha]_D$ +35°; RD (*c* 0.0005, dioxane), $[\Phi]_{600}$ +151°, $[\Phi]_{350}$ −815°, $[\Phi]_{301}$ −2506°, $[\Phi]_{296}$ −3842°, $[\Phi]_{284}$ −1503°, $[\Phi]_{274}$ ±0°, $[\Phi]_{256}$ +3174°, $[\Phi]_{226}$ ±0°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.44); $\nu_{max}^{CHCl_3}$ 3400, 1580, and 1520 cm^{-1}; nmr, 33.8 (18-H), 48.9 (19-H), 63.8 (*gem*-dimethyl), 130 (CH_2CO), 180–204 (3α-H), ~283 (NH), 309.6 cps (vinylic H of dimedonyl group). *Anal.* Calcd for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; O, 3.76; N, 3.29. Found: C, 81.84; H, 11.01; O, 3.74; N, 3.39.

Dimedone Condensation Product (5) of 3β-Amino-20β-hydroxypregn-5-ene.—Holafillamine hydrochloride[13] (300 mg) in 25 ml of methanol was treated with 600 mg of sodium borohydride. At the end of the reaction, water was added and the compound extracted with chloroform. The organic layer was washed, dried, filtered, and evaporated *in vacuo*. The crude extract (265 mg), devoid of absorption in the carbonyl region, was dissolved in 70 ml of benzene. After addition of 117 mg of dimedone and 50 mg of *p*-toluenesulfonic acid, the reaction mixture was treated as described above. The dimedonyl derivative, isolated as its hydrochloride (*vide supra*), was treated with a water solution of 5% sodium bicarbonate. The precipitate which formed was filtered, dried (280 mg), and recrystallized from acetone–hexane solution to provide the analytical sample of **5** with the following properties: mp 294–296°; $[\alpha]_D$ +82°; RD (*c* 0.0005, dioxane), $[\Phi]_{600}$ −353°, $[\Phi]_{350}$ −2032°, $[\Phi]_{293}$ −6626°, $[\Phi]_{288}$ −14799°, $[\Phi]_{270}$ ±0°, $[\Phi]_{260}$ +3534, $[\Phi]_{242}$ ±0°, $[\Phi]_{231}$ −884°, $[\Phi]_{224}$ ±0°, $[\Phi]_{212}$ +12370°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.43); $\nu_{max}^{CHCl_3}$ 3600, 1580, and 1520 cm^{-1}; nmr, 47 (18-H), 61 (19-H), 63 (*gem*-dimethyl), 61.72 (21-H), ~132 (CH_2CO), 170–195 (3α-H), 308.5 (vinylic H of dimedonyl group), 324.5 cps (C-6H). *Anal.* Calcd for $C_{29}H_{45}O_2N$: C, 79.22; H, 10.32; O, 7.28; N, 3.19. Found: C, 79.07; H, 10.25; O, 7.35; N, 3.33.

N-Methyldihydro-5α-paravallarine (6a).[7]—RD (*c* 0.005, dioxane), $[\Phi]_{360}$ ±0°, $[\Phi]_{280}$ −190°, $[\Phi]_{256}$ ±0°, $[\Phi]_{247}$ +210°, $[\Phi]_{240}$ ±0°, $[\Phi]_{215}$ −4500°, and CD (*c* 0.06, dioxane), $[\theta]_{270}$ ±0, $[\theta]_{235}$ +3100 (extremum not reached), were properties shown by **6a**.

N-Methyldihydro-5α-20-isoparavallarine (6b).[7]—RD (*c* 0.005, dioxane), $[\Phi]_{350}$ ±0°, $[\Phi]_{260}$ −520°, $[\Phi]_{233}$, −1830°, $[\Phi]_{210}$ −530°, and CD (*c* 0.04, dioxane), $[\theta]_{260}$ ±0°, $[\theta]_{236}$ −2100 (extremum not reached), were properties shown by **6b**.

Registry No.—**1a**, 13084-70-3: **3**, 13084-71-4; **4a**, 13084-72-5; **4b**, 13084-73-6; **5**, 13084-74-7.

(10) Microanalyses were done by Dr. A. Bernhardt, Mühlheim, Germany. Melting points were determined with a Bausch and Lomb apparatus; they are corrected. Rotations were taken between 16 and 22° with a 1-dm tube at sodium D light. RD curves were taken with an automatic recording JASCO/UV-5 spectropolarimeter. CD curves have been obtained with a ORD-CD JACSO instrument and with a Jouan dichrograph at the University of California and Braunschweig, Germany, through the kind cooperation of Professor J. Cymerman Craig and Dr. H. Wolf. Infrared spectra were taken with a Perkin-Elmer Model 21 NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU. The nmr spectra were recorded at 60 Mcps using 5–8% w/v solutions of substance in chloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, ν, are quoted as cps downfield from the TMS reference (0.0 cps) and are accurate to ±1 cps. We are indebted to Dr. L. Throop, Syntex Research, Palo Alto, Calif., for several RD curves and nmr spectra and to Syntex S.A., Mexico, for a generous gift of steroid used as starting material in this work.

(11) M. M. Janot, Q. Khuong-Huu, X. Lusinchi, and R. Goutarel, *Bull. Soc. Chim. France*, 1669 (1960).

(12) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

(13) M. M. Janot, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. France*, 896 (1959).

Steroids. VII. The Synthesis and Reactions of Some α,β-Unsaturated α′-Oximino-3-keto Steroids[1a]

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The conversion of a number of 3-keto steroids into the corresponding 2,4-bisoximino 3-ketones was described in the previous paper of this series.[1a] We now report the results of the nitrosation of several α,β-unsaturated 3-keto steroids. The products of these reactions were of interest to us as precursors of new types of unsaturated α-diazo ketones.

(1) (a) Part VI of this series: M. P. Cava, E. J. Glamkowski, and P. M. Weintraub, *J. Org. Chem.*, **31**, 2755 (1966). (b) To whom all correspondence should be addressed at the Department of Chemistry, Wayne State University, Detroit, Mich. 48202.