melting points of the others agreed with that previously reported.[5] These ten compounds exhibited similar infrareds with characteristic peaks (KBr) at 3210–3250, 1610–1630, 1585–1608, and 1560–1575 cm^{-1} which are consistent with structure V. Examination of the nmr of several of these compounds indicated that these were indeed in the enamine form rather than the ketimine form as reported by earlier workers.[5,6] The enamine N–H and only six protons on the five-membered ring were observed. This assignment of the enamine structure V to these amides is consistent with the recent enamine assignment made to the related esters VI.[7]

Hydrolysis of seven of these compounds gave near quantitative yields of the keto amides I only one of which (Table I) had not been previously reported.[5] In addition, use of 3-methyl-4-fluoroaniline led only to the formation of I with no bis adduct being obtained. These eight keto amides exhibited consistent infrared spectra (KBr): 3025–3100, 1700–1720, 1600–1648 (two peaks or peak and shoulder), and 1563–1592 cm^{-1}.

This route to aza steroids is not being pursued further.

Experimental Section[8]

2-Keto-N-(5′-isoquinolyl)cyclopentanecarboxyamide Methiodide (II).—A mixture of 2.54 g (0.01 mole) of 2-keto-N-(5′-isoquinolyl)cyclopentanecarboxyamide[4] (Ib) in 30 ml of methanol containing 10 ml of methyl iodide was refluxed for 2 hr. The solutions was concentrated to a volume of 10 ml and cooled. The light orange plates that separated were filtered, washed with ether, and dried to give 3.56 g (90%) of the crude product. A small portion was recrystallized from water, mp 206–207.5°.

Anal. Calcd for $C_{16}H_{17}N_2O_2I$: C, 48.50; H, 4.33; N, 7.07; I, 32.03. Found: C, 48.24; H, 4.31; N, 6.98; I, 32.11.

12-Keto-1,2,3,4,11,12,15,16-octahydro-3-methyl-3,11-diazacyclopenta[*a*]phenanthrene (IV).—A solution of 3.96 g (0.01 mole) of 2-keto-N-(5′-isoquinolyl)cyclopentanecarboxyamide methiodide (II) in 30 ml of ethanol and 20 ml of water was shaken under 3 to 4 atm of hydrogen in the presence of 0.1 g of platinum oxide. After the uptake of hydrogen had ceased, the solution was filtered and the filtrate concentrated. The residue was taken up in water and treated with a concentrated potassium carbonate solution. The aqueous alkaline solution was extracted thoroughly with benzene. The benzene extracts were dried over anhydrous sodium sulfate and concentrated to give 1.63 g (60%) of the intermediate reduced amide as a light brown oil.

The intermediate reduced amide was added to 15 g of polyphosphoric acid at 100°. After 15 min, the reaction mixture was poured onto ice. The aqueous acidic solution was treated with dilute sodium hydroxide until alkaline and extracted with benzene. The benzene extracts were dried over anhydrous sodium sulfate and concentrated to give 0.29 g (19.7%) of the desired product as a light yellow solid. A portion was recrystallized from a mixture of ethanol–water, mp 197–200°.

Anal. Calcd for $C_{16}H_{18}N_2O \cdot 0.5H_2O$: C, 72.97; H, 7.27; N, 10.64. Found: C, 73.20; H, 7.42; N, 10.78.

A portion of the same analytical sample was dried *in vacuo* at 100°.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13. Found: C, 75.66; H, 7.09.

2-Keto-N-(5′-quinolyl)cyclopentanecarboxyamide (Id).—To 11.0 g (0.07 mole) of ethyl 2-ketocyclopentanecarboxylate heated to 150° was added 10.0 g (0.069 mole) of 5-aminoquinoline over a 5-min period. After the addition was complete, the temperature was increased to 170–180° for 4 min. The mixture was cooled and triturated with ether; the solid that separated was filtered, giving 5.46 g (31%) of the desired product which gave a semicarbazone mp 204.5–206°.

Anal. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.50. Found: C, 61.56; H, 5.61; N, 22.30.

Reaction of 8-Aminoquinoline and Ethyl 2-Ketocyclopentanecarboxylate.—In a similar manner these two compounds gave 2-keto-N-(8′-quinolyl)cyclopentanecarboxyamide (Ia), mp 100–102° (lit.[4] mp 100–102°), and a small amount of bis condensation product[9] (V): mp 218–219° from ethanol; nmr ($CDCl_3$) τ −2.20 (enamine NH), 0.22 (amide NH), 7.93 (splitting 6.5 cps, cyclopentene 4-CH_2).

Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.80; H, 5.28; N, 14.72. Found: C, 75.55; H, 5.38; N, 14.85.

Reaction of Simple Aromatic Amines with Ethyl 2-Ketocyclopentanecarboxylate.—Ethyl 2-ketocyclopentanecarboxylate (6 g) was heated to 150° and 3 g of the aniline was added. The temperature was raised to 180° and kept there for 24 hr. After cooling the product crystallized in 20–70% yield. New compounds are included in Table I. The infrared data is included in the discussion. The nmr ($CDCl_3$) data follow: *p*-chloroaniline product, τ −0.45 (enamine NH), 8.07 (cyclopentene 4-CH_2); 2-methyl-4-fluoroaniline product, 0.08 (enamine NH), 2.22 (amide NH), 7.97 (cyclopentene 4-CH_2) (in DMSO-d_6 the NH were at −0.13 and 1.83); *p*-fluoroaniline product, −0.28 (enamine NH), 2.03 (amide NH).

A mixture of 2 g of the above products (V), 250 ml of 80% methanol, and 10 ml of 5% hydrochloric acid was stirred at room temperature for 48 hr to give a near quantitative yield of I. The infrared data is included in the discussion. The nmr ($CDCl_3$) data follow: *p*-chloroaniline product, τ 1.27 (amide NH), 6.87 (t) (CH on cyclopentane ring attached to carbonyl); *p*-fluoroaniline product, 1.18 (amide NH), 6.83 (t) (CH on cyclopentane ring attached to carbonyl).

Registry No.—Ethyl 2-ketocyclopentanecarboxylate, 611-10-9; Id, 14901-52-1; I (Ar = *p*-FC_6H_4–), 14796-10-2; I (Ar = 3-CH_3-4-FC_6H_3–), 14796-15-7; II, 14796-16-8; IV, 14796-17-9; V (Ar = *o*-FC_6H_4–), 14796-18-0; V (Ar = *p*-FC_6H_4–), 14901-53-2; V (Ar = 2,3-$(CH_3)_2C_6H_3$–), 14789-52-7; V (Ar = 2-CH_3-4-FC_6H_3–), 14789-53-8.

(5) R. J. Brown, F. W. S. Carver, and B. L. Hollingsworth, *J. Chem. Soc.*, 4295 (1961).

(6) R. Mayer, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Forst, Ed., Academic Press Inc., New York, N. Y., 1963.

(7) F. C. Pennington and W. D. Kehret, *J. Org. Chem.*, **32**, 2034 (1967).

(8) Analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points are corrected.

(9) This compound was first prepared at the University of Miami by S. Roth and F. D. Popp.

Nor Steroids. VII. Ring Contraction of 2α-Bromo-5α-cholestan-3β-ol

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Although halohydrins are known to undergo rearrangement in the presence of metal ions[1,2] including ring contraction in the case of cyclic compounds,[3] the reaction has not been used for the preparation of ring nor steroids. Steroidal α-halo ketones, particularly bromo ketones, are readily available and can be reduced to the halohydrins. In addition, the point of carbonium ion generation can be controlled by using, for example, silver salts, which then will determine the course of the subsequent rearrangement. In this manner

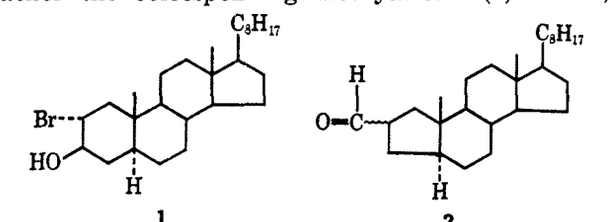
(1) M. Tiffeneau, *Ann. Chim.*, [8] **10**, 322 (1907).

(2) V. Pocker, *Chem. Ind.* (London), 322 (1959).

(3) P. D. Bartlett and R. H. Rosenweld, *J. Am. Chem. Soc.*, **56**, 1990 (1934); D. Y. Curtin and S. Schmukler, *ibid.*, **77**, 1105 (1955); D. Y. Curtin and R. J. Harder, *ibid.*, **82**, 2357 (1960); J. G. Traynham and J. Schneller, *ibid.*, **87**, 2398 (1965).

difficulties such as migration of angular methyl groups, encountered in the pinacol rearrangement of 5,6-diols,[4] can be avoided.

The compound chosen for study was 2α-bromo-5α-cholestan-3β-ol (**1**)[5] which was prepared in 70% yield by reduction of 2α-bromo-5α-cholestan-3-one with lithium aluminum tri-*t*-butoxy hydride. In this bromohydrin the equatorial 2α-bromine atom and the 4-carbon atom are *trans* and coplanar. Backside attack of the 4-carbon atom on the incipient carbonium ion at the 2-carbon atom is therefore feasible, and ring contraction should occur to give A-nor-5α-cholestan-2-carboxaldehyde (**2**). In fact, when the bromohydrin was treated with boiling alcoholic silver nitrate solution, the aldehyde was not obtained, but rather the corresponding diethylacetal (**3**) in 63%



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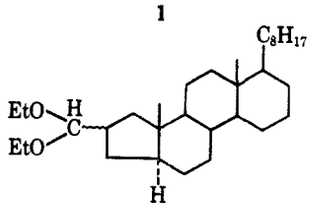

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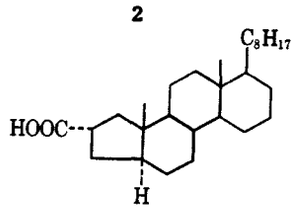

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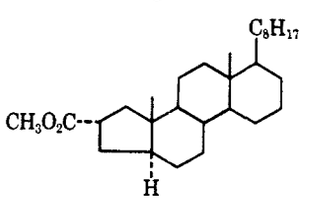

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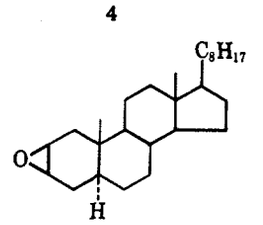

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yield. The nmr spectrum showed a one-proton doublet at 4.17 ppm for the proton on the aldehyde carbon and a quartet (four protons) at 3.51 ppm for the methylene groups of the ethyl groups in the acetal.

Acid hydrolysis of the acetal gave the free aldehyde as a solid which could not be recrystallized, and which was changed to a new, unidentified, substance on chromatography on neutral alumina. However, chromatography on silica gel gave the pure aldehyde whose nmr spectrum showed a doublet at 9.60 ppm for the aldehyde proton. Satisfactory analytical data could not be obtained for the aldehyde, which appeared to decompose on standing. However, the 2,4-dinitrophenylhydrazine derivative did give satisfactory analytical results.

It was suggested[6] that 2β,3β-oxidocholestane might be an intermediate in the rearrangement reaction. The oxido compound was prepared and when treated with nonacidified alcoholic silver nitrate gave no reaction. However, treatment with alcoholic silver nitrate containing 1 equiv of nitric acid gave a mixture of starting material and what appeared to be cholestane-2,3-diol 3-nitrate ester. The mass spectrum of the mixture showed a parent peak at *m/e* 449 (nitrate ester) and major peaks at 432 (nitrate ester minus hydroxyl group) and 386 (parent peak of the oxide). The absence of peaks at *m/e* 458 and 103 confirmed the fact that no A-norcholestane-2-carboxaldehyde diethyl acetal was present in the product mixture. Also, the lack of any carbonyl absorption in the infrared spectrum of the product mixture indicated the absence of A-norcholestane-2-carboxaldehyde itself. It thus appears that the oxide is not an intermediate in the rearrangement reaction under the conditions used.

Jones oxidation[7] of the crude aldehyde gave a solid carboxylic acid whose infrared spectrum was nearly identical with that of an authentic sample of A-norcholestane-2α-carboxylic acid (**4**).[8] The mass spectra of the two samples were also nearly identical. However, attempted recrystallization of the crude acid was unsuccessful, suggesting that the material was a mixture of two isomers.

The acidic material was esterified with methanolic hydrogen chloride and from the product a pure crystalline sample of methyl A-norcholestane-2α-carboxylate (**5**) was obtained, its melting point almost identical with that of authentic material.[9]

The mother liquors gave more crystalline material which proved to be a mixture of the α- and β-methyl esters, as shown by the presence of two C-19 methyl peaks in the nmr spectrum, one at τ 9.35 for the α isomer and one at 9.20 for the β isomer (both in benzene). The peak areas indicated that the mixture contained 54% of the α ester and 46% of the β ester. These assignments are based on the work of Cava, Weintraub, and Glamkowski[9] who obtained the same two esters from a different source.

Although it is difficult to state with certainty at which point the second isomer appeared, the acetal appeared to be a single isomer. Isomerization could occur *via* the enol during the acid hydrolysis of the acetal, or in the Jones oxidation step, which also involved the aldehyde and strong acid. However, the crude 2,4-dinitrophenylhydrazone, prepared from crude aldehyde, showed only one spot on tlc on alumina, indicating that both the acetal and the aldehyde consisted of a single isomer. It seems most likely therefore that the isomerization occurred in the Jones oxidation step.

Experimental Section[10]

2α-Bromo-5α-cholestan-3β-ol (1).—The bromohydrin was obtained in 70% yield by reduction of 2.0 g (4.3 mmoles) of the bromo ketone with 4.0 g of lithium aluminum tri-*t*-butoxy hydride according to the procedure of Fajkos[5] and had mp 105–107° (lit. mp 112–113°).

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 325.

(5) J. Fajkos, *Chem. Listy*, **52**, 2134 (1958); *Chem. Abstr.*, **53**, 5344 (1959).

(6) Private communication from Dr. H. J. Ringold.

(7) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. Weedon, *J. Chem. Soc.*, 39 (1946).

(8) B. A. Olsen, Ph.D. Thesis, Brown University, Providence, R. I., 1964.

(9) M. P. Cava, P. M. Weintraub, and E. J. Glamkowski, *J. Org. Chem.*, **31**, 2015 (1966).

(10) Melting points are corrected and were obtained with a Hershberg apparatus and Anshutz thermometers. The analytical samples were recrystallized to constant melting point. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. The infrared spectra were obtained with a Perkin-Elmer Model 337 spectrometer. The nmr spectra were determined with a Varian HA-60A spectrometer using 10% solutions in carbon tetrachloride unless stated otherwise. The peaks' positions are reported in parts per million relative to TMS as an internal standard. The mass spectra were obtained with a Hitachi-Perkin-Elmer RMU6D. The ORD curve was obtained with a Cary 60 spectrometer. The nmr, mass, and ORD spectrometers were purchased with funds granted by the National Science Foundation and grateful acknowledgment is made of these grants.

Reaction of the Bromohydrin with Silver Nitrate.—A mixture of 1.0 g (2.1 mmoles) of the bromohydrin and 80 ml of a 2% solution of silver nitrate in absolute ethanol was boiled under reflux for 30 min and then allowed to cool to room temperature. The liquid phase was decanted and the silver bromide residue was rinsed several times with small portions of ether, which were then added to the alcohol. More ether was then added to bring the total ether volume to 125 ml and then the organic layer was washed with 500 ml of water in portions. The combined water wash was washed with a small volume of ether, which was added to the organic layer. This was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from 150 ml of absolute methanol to give 610 mg (63%) of white crystals, mp 49–50°. Tlc on Eastman Chromatogram sheets with 1:1 benzene–pentane gave two spots after development with a solution of 2,4-dinitrophenylhydrazine in ethanol containing hydrochloric acid. The major spot had R_f 0.65 and the minor spot R_f 0.15, possibly due to some nitrate ester as indicated by a small peak at 1645 cm^{-1} in the infrared spectrum. Four recrystallizations from methanol gave the analytical sample of the acetal **3**: mp 52.5–53.5°; R_f 0.65; $\nu_{max}^{CCl_4}$ 2950, 1480, 1385, 1128, 1062, and 1012 cm^{-1}; nmr, methyl peaks at 0.66, 0.69, 0.83, 0.92 and 1.15 ppm, a four-proton quartet at 3.51, and a one-proton doublet at 4.17 ppm. The mass spectrum exhibited a molecular ion peak at m/e 458 (only under high amplification), and major peaks at 103 (diethyl acetal side chain), 414 (steroid nucleus minus an ethoxy radical), and 29 (ethyl ion).

Anal. Calcd for $C_{31}H_{54}O_2$: C, 81.15; H, 12.08. Found: C, 80.89; C, 12.18.

A-Nor-5α-cholestane-2-carboxaldehyde (2).—A crude, noncrystallized sample of the acetal, obtained from the reaction as above of 1.0 g of bromohydrin was dissolved in a mixture of 80 ml of acetone and 15 ml of 10% hydrochloric acid and the solution was boiled under reflux for 1 hr, then cooled, and poured into 100 ml of water. The resulting mixture was extracted once with 100 ml and once with about 25 ml of ether and the combined extract was washed with three 100-ml portions of water, and then dried over anhydrous sodium sulfate. The ether was evaporated to yield a solid, nearly white product which could not be recrystallized. Chromatography on neutral alumina (Fluka AG Buchs SG) gave a new unidentified compound: mp 134.5–136°; $\nu_{max}^{CCl_4}$ 3620, 3525, 2930, 1720, 1470, 1380, 1173, and 1037 cm^{-1}; nmr (10% CCl_4), 3.28 (doublet), and 2.30 (singlet) ppm.

However, chromatography of 200 mg of the crude aldehyde on 8 g of silica gel (Baker Analyzed Reagent) and elution with 25-ml portions of 1:1 benzene–hexane gave 173.5 mg of A-norcholestan-2-carboxaldehyde from the second fraction: mp 70–71°; $\nu_{max}^{CCl_4}$ 2945, 2715, and 1735 cm^{-1}; nmr (10% CCl_4), 0.65 (singlet), 0.81 (singlet), 0.90 (singlet), and 9.60 (doublet, aldehyde proton) ppm; ORD (C 0.08, hexane 20°), $[\phi]_{400}$ −65°, $[\phi]_{326}$ −3,854°, $[\phi]_{317}$ −3,586°, $[\phi]_{272}$ +9,962°, $[\phi]_{245}$ 9,438°.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.86; H, 11.99. Found: C, 82.08; H, 11.90.

The aldehyde appeared to decompose slowly on standing which accounts for the analytical results.

The 2,4-dinitrophenylhydrazine derivative was prepared by adding a solution of 542 mg of crude aldehyde to a solution of 400 mg of 2,4-dinitrophenylhydrazine in 2 ml of concentrated sulfuric acid, 3 ml of water, and 10 ml of ethanol. The reaction was allowed to proceed for 1 hr and was then cooled in ice for 1 hr. The resulting precipitate was recrystallized from a mixture of 25 ml of ethanol and 8 ml of ethyl acetate to yield 559 mg (75%) of product, mp 118.7–121° dec. Tlc on alumina with 1:1 benzene–pentane gave only one spot. Four more recrystallizations from the same solvent gave the analytical sample, mp 137–139°.

Anal. Calcd for $C_{33}H_{50}N_4O_4$: C, 69.93; H, 8.89; N, 9.89. Found: C, 70.10; H, 8.86; N, 10.01.

2β,3β-Oxidocholestane (6).—The compound was prepared from 2α-bromo-3β-hydroxy-5α-cholestane by the method of Alt and Barton[11] and had mp 86–88° (MeOH); infrared bands appeared at ν_{max}^{Nujol} 3650, 812, and 805 cm^{-1}. A mass spectrum showed the parent peak (strong) at m/e 386.

Reaction of the Oxide with Silver Nitrate.—A solution of 20 mg (0.05 mmole) of 2β,3β-oxidocholestane in 3 ml of a 2% solution of silver nitrate in ethyl alcohol was boiled under reflux on a steam bath for 20 min. No precipitate formed during the heating period. The solution was filtered into a separatory funnel, diluted with 12 ml of ether, and washed twice with distilled water. The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure to yield 20.1 mg of damp solid. The infrared spectrum of this crude material (dried) showed no carbonyl stretching. A mass spectrum of the sample was nearly identical with that of the starting material and showed no increase in intensity of the m/e 103 (diethyl acetal side chain) peak relative to the background.

Reaction of the Oxide with Silver Nitrate and Dilute Nitric Acid.—The procedure was essentially that of the previous reaction except that 1 ml of 0.05 *M* nitric acid in ethyl alcohol was added to the mixture containing 20 mg (0.05 mmole) of 2β,3β-oxidocholestane. No precipitate formed during the heating period. The same work-up yielded 19.5 mg of white crystalline solid. The infrared spectrum (CCl_4 solution) showed no carbonyl stretching, but exhibited peaks at 3650, 1645, 1270, 1090, and 1010 cm^{-1}. The mass spectrum showed strong peaks at m/e 449 (molecular weight of 2,3-cholestanediol-3-nitrate ester), 432 (nitrate ester minus a hydroxyl group), and 386 (oxide). No increase in the intensity of the m/e 103 peak (relative to background) was observed.

A-Nor-5α-cholestane-2-carboxylic Acid (4).—To a solution of 243 mg (0.60 mmole) of the crude aldehyde in 10 ml of acetone was added 7 drops of Jones oxidation[7] solution and the resulting mixture was allowed to stand at room temperature until the precipitation of green chromate salts ceased (about 10 min). The mixture was then filtered and the filtrate diluted with 80 ml of water and extracted twice with ether. The ether extract was washed three times with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a white, solid residue. The infrared and mass spectra of this solid were nearly identical with those of an authentic sample of A-nor-5α-cholestane-2α-carboxylic acid. The nmr spectrum (5% solution in CCl_4) showed peaks at 0.66 (C-18 methyl), 0.71 (C-19 methyl), and 2.82 ppm (br).

Methyl A-Nor-5α-cholestane-2α-carboxylate (5).—A solution of 100 mg (0.20 mmole) of crude A-nor acid in 50 ml of 10% methanolic hydrogen chloride was allowed to stand at room temperature for 45 hr. At the end of this time the precipitate was collected to yield 26.6 mg of methyl A-nor-5α-cholestane-2α-carboxylate: mp 95–97° (lit.[12] mp 97.5–98°); $\nu_{max}^{CCl_4}$ 2940, 1735, 1165, and 1035 cm^{-1}; nmr (3% in CCl_4 0.67 (C-18); 0.70 (C-19), 2.84 (broad, proton on C-2), and 3.62 ppm (methyl protons of ester group, singlet).

The filtrate was allowed to stand at 0° for 24 hr and then the precipitate was collected to give 51.4 mg of crystalline material melting over a broad range up to 75°. The infrared spectrum was nearly identical with that of methyl A-nor-5α-cholestane-2α-carboxylate. However, the nmr spectrum, determined in 5% benzene solution showed two C-19 methyl resonances at τ 9.20 (2β ester) and 9.35 (2α ester) and the relative areas indicated that the mixture contained 54% of the 2α and 46% of the β ester. These assignments are based on the results of Cava, Weintraub, and Glamkowski,[9] who obtained the same two esters from a different source.

Registry No.—**1**, 3903-52-4; **2**, 14789-57-2; 2,4-dinitrophenylhydrazone of **2**, 14789-58-3; **3**, 14789-62-9; **4**, 2312-00-7; **5**, 2312-02-9; **6**, 2789-50-6.

(11) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(12) B. B. Smith and H. R. Nace, *J. Am. Chem. Soc.*, **76**, 6119 (1954).

The Reactions of α-Nitro Ketones with Mineral Acids

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Received July 7, 1967

Though considerable work has been reported[1] on the preparation of hydroxamic and carboxylic acids

(1) (a) V. Meyer and C. Wurster, *Ber.*, **6**, 1168 (1873); (b) E. Bamberger and E. Rust, *ibid.*, **35**, 45 (1902); (c) S. B. Lippincott and H. B. Hass, *Ind. Eng. Chem.*, **31**, 118 (1939).