The starting material generally used was a mixture of 46.7% *cis*- and 53.3% *trans*-2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene. One run was stopped when approximately 70% had reacted. The recovered butene contained 98% of the *cis* isomer and 2% of the *trans*.

A series of similar runs was made with varying amounts of SO_3 and water in the sulfuric acid to study the effect of varied concentrations of sulfur trioxide on the oxidation. The results are summarized in Table II.

To test the possible use of other acidic solvents, runs were made as described above but using acetic anhydride, acetic acid, trifluoroacetic acid, and phosphoric acid containing phosphorus pentoxide as solvents. In phosphoric acid there was only slight reaction, and the recovered starting material had a yellow color. However, neither PFBA nor chlorine could be positively identified. In runs using acetic anhydride, acetic acid, and trifluoroacetic acid, oxidation was very slow. PFBA was not detected in any of these runs, but the recovered butene from the acetic acid and trifluoroacetic acid runs was richer in the *cis* isomer than was the starting material.

A distillate, b.p. 62–71°, obtained from the run using trifluoroacetic acid was a mixture of chromyl chloride in trifluoroacetic acid.

Chromic Acid Oxidation of Hexafluoro-2-butyne, 1,1,1,4,4,4-Hexafluoro-2-butene, and Perfluoro-2-butene.—The fluorinated compound was bubbled through a stirred mixture of 44–50 g. (0.44 to 0.50 mole) of chromium trioxide in 400–500 g. of fuming sulfuric acid at 60–70°. The products were collected in Dry Ice–acetone cooled traps and then distilled or analyzed by gas chromatography. The results are shown in Table I.

Perchlorate Oxidation of 2,3-Dichloro-1,1,1,4,4,4-hexafluoro-2-butene.—Potassium perchlorate (40 g., 0.29 mole) was added in four portions to 600 g. of fuming sulfuric acid at 60–65° while also adding 61 g. (0.26 mole) of 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene. Yellow liquid collected in Dry Ice–acetone cooled traps and the kettle material became orange. Distillation of the material from the traps gave 2 g., 7%, of PFBA, and dilution of the kettle material gave 13 g., 15%, of the cyclic sulfate.

A smaller run in which the kettle was heated at 75–95° yielded 35.6% of PFBA, isolated as 2,3-bis(trifluoromethyl)quinoxaline, and a very small amount of cyclic sulfate.

Chlorate Oxidation of 2,3-Dichloro-1,1,1,4,4,4-hexafluoro-2-butene.—To 500 g. of fuming sulfuric acid at 25–50° were added 13.5 g. (0.11 mole) of potassium chlorate and 25 g. (0.11 mole) of 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene in three portions each. After standing over the weekend the mixture was heated to 96° with a slow nitrogen purge, and the products were collected in a Dry Ice–acetone cooled trap. Distillation gave 1.5 g. (0.01 mole), 5%, of trifluoroacetyl chloride and 0.5 g. (0.003 mole), 3%, of PFBA. No cyclic sulfate was isolated.

2,3-Bis(trifluoromethyl)quinoxaline.—Addition of PFBA to excess *o*-phenylenediamine at 0° caused an exothermic reaction. Recrystallization from an ethanol–water mixture gave white crystals, m.p. 117–118°. The same product was obtained from PFBA hydrate or 2,3-dichloro-1,1,1,4,4,4-hexafluorobutane-2,3-diol cyclic sulfate with *o*-phenylenediamine by heating in water.

Anal. Calcd. for $C_{10}H_4F_6N_2$: C, 45.1; H, 1.60; N, 10.52. Found: C, 44.93, 44.87; H, 1.59, 1.56; N, 10.32.

Steroids. XX.[1] Some 2-Aza- and 3-Aza-5α-cholestanes[2-5]

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The synthesis of 2-aza- and 3-azasteroids for biological evaluation was of interest to us as an extension of the work on azasteroids.[8-12] Hara[13] had prepared 2-aza- and 3-azacholanes by a Beckmann rearrangement of methyl 2-oximino-A-nor-5β-cholanate and was able to separate the lactams formed by chromatography. Shoppee[14] reported the preparation of 3-aza-A-homo-5α-cholestan-4-one by the Beckmann rearrangement of 5α-cholestan-3-one oxime. Later, after preparing this lactam by a more rigorous route, he recognized that the original product was a mixture and stated ". . . it now appears that this reputed compound is an inseparable mixture, or a molecular compound, of the 3-aza-A-homo-5α-cholestan-4-one and the isomeric Beckmann rearrangement product 4-aza-A-homo-5α-cholestan-3-one."[15] Although Hara and Shoppee employed the Beckmann rearrangement in the preparation of azasteroids, our experience indicates that the Schmidt reaction conducted in polyphosphoric acid usually gives superior yields and fewer purification problems.[12,16]

The reaction of A-nor-5α-cholestan-2-one (I) with hydrazoic acid in polyphosphoric acid gave a mixture of lactams (III), 2-aza-5α-cholestan-3-one (IIIa) and 3-aza-5α-cholestan-2-one (IIIb), in 77% yield. The Beckmann rearrangement of A-nor-5α-cholestan-2-one oxime (II) in polyphosphoric acid gave the same mixture, but in lower yield (30%). The product appeared to exist as a uniform, homogeneous material, m.p. 220–221°, after purification. Attempts to separate these isomers from this mixture were unsuccessful, but their presence was established by the preparation and separation of some derivatives.

Treatment of III with phosphorus pentachloride[17] yielded a mixture of dichloro lactams which were separated into two fractions, m.p. 227–229 and 209–211°, in a 1:1 ratio. The carbonyl absorption in these products was shifted 0.18 μ toward a smaller wave length as for α,α-dichloroamides.[18] The higher melting fraction yielded 4-chloro-2-aza-4-cholesten-3-one (VI) on treatment with collidine establishing that it was 4,4-dichloro-2-aza-5α-cholestan-3-one (IV). The lower melting fraction, 1,1-dichloro-3-aza-5α-cholestan-2-one (V), which is unable to eliminate HCl, was unchanged by this treatment.

N-Methylation of III with methyl iodide in the presence of sodium hydride resulted in the recovery of two crystalline products, fraction I, m.p. 137–138°, and

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[1] For paper XIX, see N. J. Doorenbos and K. A. Kerridge, *J. Heterocyclic Chem.*, in press.

[2] Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963.

[3] This study was supported by Grant CA-04132 from the National Cancer Institute, National Institutes of Health.

[4] Gifts of steroid intermediates from the Cancer Chemotherapy National Service Center, National Institutes of Health, were appreciated.

[5] First prize was awarded to R. E. Havranek for this paper in the Southern District of the 1963 Lundsford–Richardson Awards, sponsored by the Richardson-Merrell Co.

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[7] Noxzema Foundation Fellow, 1958–1960; Dunning Foundation Fellow, 1960; National Institutes of Health Fellow, 1961–1962.

[8] N. J. Doorenbos, C. L. Huang, C. R. Tamorria, and M. T. Wu, *J. Org. Chem.*, **26**, 2546 (1961).

[9] N. J. Doorenbos and C. L. Huang, *ibid.*, **26**, 4548 (1961).

[10] N. J. Doorenbos and C. L. Huang, *ibid.*, **26**, 4106 (1961).

[11] N. J. Doorenbos and H. Singh, *J. Pharm. Sci.*, **50**, 628 (1961).

[12] N. J. Doorenbos and H. Singh, *ibid.*, **51**, 418 (1962).

[13] S. Hara, *Yakugaku Zasshi*, **78**, 1027 (1958); *Chem. Abstr.*, **53**, 3273c (1959).

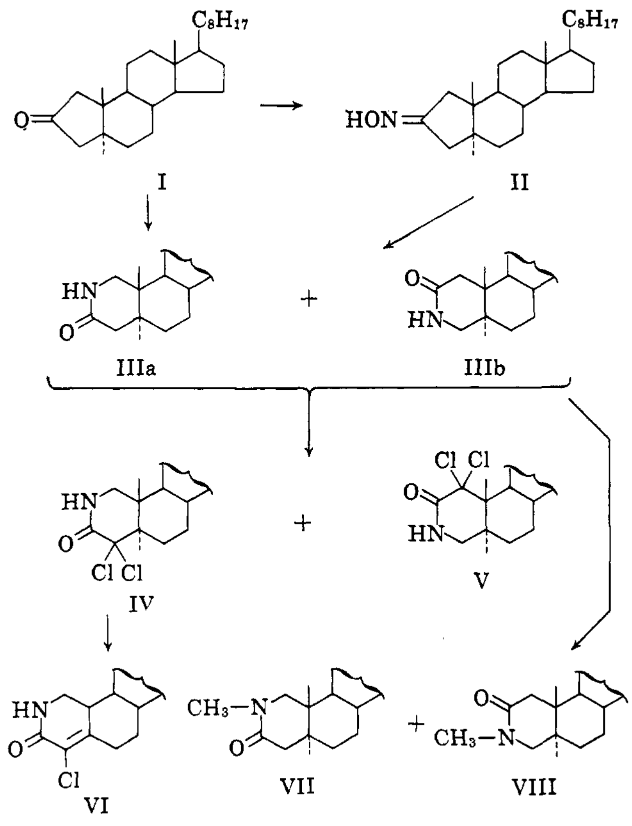
[14] C. W. Shoppee and J. Sly, *J. Chem. Soc.*, 3458 (1958).

[15] C. W. Shoppee, G. Krüger, and R. N. Mirrington, *ibid.*, 1050 (1962).

[16] N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, **26**, 2548 (1961).

[17] W. Francis, J. Thornton, J. Werner, and T. Hopkins, *J. Am. Chem. Soc.*, **80**, 6238 (1958).

[18] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 213.



fraction II, m.p. 126–127°. Only fraction I was obtained under mild reaction conditions. The recovered starting material, from the mild reaction, was treated with phosphorus pentachloride to obtain IV and V in a 4:1 ratio. It was thus evident that the N-methyl lactam formed under mild conditions was N-methyl-3-aza-5α-cholestan-2-one (VIII), and fraction II was N-methyl-2-aza-5α-cholestan-3-one (VII). These results indicate that the 19-methyl group is able to inhibit methylation of IIIa.

A mixture of N-nitroso lactams (IX) was obtained from III by the addition of sodium nitrite to a solution of III in glacial acetic acid–acetic anhydride. III was reduced with lithium aluminum hydride to obtain an oil (X) which resisted crystallization. X was obtained as the crystalline hydrobromide. The isomers of these products were not successfully separated.

Experimental[19]

2-Aza-5α-cholestan-3-one and 3-Aza-5α-cholestan-2-one (III). A. **From A-Nor-5α-cholestan-2-one.**—Four grams (0.011 mole) of A-nor-5α-cholestan-2-one (I)[20] was stirred into 120 g. of polyphosphoric acid and heated to 50–60° with stirring. After the ketone dissolved in the polyphosphoric acid, 0.95 g. (0.014 mole) of sodium azide was added with stirring. The mixture was heated and stirred periodically for 10 hr.[16]

The mixture was poured over cracked ice and, after solution was effected, a white precipitate formed which was collected by filtration. The precipitate was dissolved in chloroform, washed with water, dried over sodium sulfate, and filtered, and the chloroform was removed *in vacuo*. The residue was dissolved in hot methanol, filtered, concentrated, and allowed to crystallize. White granular crystals (3.5 g.), m.p. 215–217°, were collected. Three recrystallizations from methanol yielded 3.10 g. (77%) of III: m.p. 220–221°; $[\alpha]^{25}\text{D}$ +48.4° (*c* 1.0, chloroform); $\lambda_{\max}^{\text{KBr}}$ 2.90 and 6.05 μ.

Anal. Calcd. for $C_{26}H_{45}NO$: C, 80.56; H, 11.70; N, 3.61. Found: 80.20; H, 11.53; N, 4.04.

B. **From A-Nor-5α-cholestan-2-one Oxime.**—A-Nor-5α-cholestan-2-one oxime (II)[20] (3.25 g., 0.008 mole) was stirred into 100 g. of polyphosphoric acid. The mixture was heated in an oil bath to a temperature of 120–130°. The oxime dissolved. This temperature was maintained with stirring for 40 min.[16] The solution was cooled and poured onto crushed ice. The polyphosphoric acid dissolved leaving a tan oil floating on the surface. The mixture was extracted with chloroform. The extracts were washed with water and dried over sodium sulfate. The residue, obtained by removing the solvent *in vacuo*, was dissolved in hot methanol, filtered, and allowed to crystallize. The crystals, which were contaminated with an oily residue, were dissolved in cyclohexane and placed on a column of neutral alumina, activity grade I. The lactam fraction was eluted from the column with ethyl acetate. This fraction was crystallized four times from methanol to yield 0.70 g. (30%) of III, m.p. 218–220°. This product was shown to be identical with that obtained by method A by mixture melting point and a comparison of infrared spectra and optical rotation data.

4,4-Dichloro-2-aza-5α-cholestan-3-one (IV) and 1,1-Dichloro-3-aza-5α-cholestan-2-one (V).—Two grams (0.005 mole) of III was dissolved in 100 ml. of xylene. The solution was cooled with an ice bath and an excess of phosphorus pentachloride (3.5 g.) was added in small portions. The mixture was refluxed for 6 hr., during which the evolution of hydrogen chloride was observed.[17] The xylene was removed *in vacuo* and the dark oily residue was poured into a 10% solution of sodium carbonate. The precipitate which separated was extracted with ether and the extracts were washed with water and dried over sodium sulfate. The ether was removed *in vacuo* and the colorless oil was crystallized from 95% ethanol to yield 1.05 g., m.p. 225–227°. This product was chromatographed and crystallized again from ethanol to yield 0.90 g. of white granular crystals: m.p. 227–229°; $[\alpha]\text{D}$ +35° (*c* 1.0, chloroform); $\lambda_{\max}^{\text{KBr}}$ 2.95 and 5.93 μ.

Anal. Calcd. for $C_{26}H_{43}Cl_2NO$: C, 68.40; H, 9.49; Cl, 15.53. Found: C, 68.31; H, 9.55; Cl, 15.38.

Another fraction, fraction II, was purified by chromatographing on neutral alumina, activity grade I, the filtrate remaining from the first crystallization above. The product was eluted with ethyl acetate and recrystallized from methanol to yield 0.8 g. of V as white needles: m.p. 210–211°; $[\alpha]\text{D}$ +44° (*c* 1.0, chloroform); $\lambda_{\max}^{\text{KBr}}$ 2.95 and 5.93 μ.

Anal. Calcd. for $C_{26}H_{43}Cl_2NO$: C, 68.40; H, 9.49; Cl, 15.53. Found: C, 68.63; H, 9.66; Cl, 15.02.

4-Chloro-2-aza-4-cholesten-3-one (VI).—IV (0.50 g.) was dissolved in 10 ml. of freshly distilled collidine and refluxed 3 hr. The residue, obtained by distilling the collidine, was dissolved in ether and washed with water, dilute (2%) hydrochloric acid, and again with water. The solvent was removed, after drying over sodium sulfate, and the residue was crystallized three times from acetone–methanol to yield 0.3 g. of VI as white crystals: m.p. 239–242°; $[\alpha]\text{D}$ +56° (c 1.0, chloroform); $\lambda_{\max}^{\text{KBr}}$ 2.95, 5.95, and 6.23 μ.

Anal. Calcd. for $C_{26}H_{42}ClNO$: C, 74.34; H, 10.08; Cl, 8.44. Found: C, 73.77; H, 10.33; Cl, 8.62.

Prolonged treatment of fraction II with refluxing collidine yielded only starting material, V. No dehydrohalogenation occurred.

N-Methyl-2-aza-5α-cholestan-3-one (VII) and N-Methyl-3-aza-5α-cholestan-2-one (VIII).—To a solution of III (3.0 g., 0.008 mole) in 100 ml. of dry benzene was added a 10% excess of sodium hydride. The mixture was refluxed with stirring for 6 hr. and cooled to 0–5° with an ice bath, and a threefold excess of methyl iodide was added. The mixture was stirred at room temperature for 8 hr. and was then refluxed 2 hr. The mixture was filtered, washed with water, and dried over sodium sulfate. The residue obtained by removing the benzene was chromatographed on neutral alumina. The N-methyl lactam fraction was eluted with ethyl acetate. The isomers were separated by fractional crystallization from acetonitrile. Fraction I, m.p. 137–138°, $[\alpha]^{25}\text{D}$ +76° (1.2 g., 38%), crystallized at room temperature. Fraction II, m.p. 126–127°, $[\alpha]^{25}\text{D}$ +60° (1.4 g., 44%), was obtained by concentrating the acetonitrile filtrate and cooling to 0°. Each product absorbed at 6.14 μ but showed

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(19) Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were obtained from Weiler and Strauss Microanalytical Laboratories and Schwarzkopf Microanalytical Laboratories. Infrared spectra were obtained with a Perkin-Elmer Infracord.

(20) A. Windaus, *Ber.*, **47**, 2384 (1914).

no NH absorption in the infrared. A mixture melting point of the two fractions occurred at 115–118°.

Anal. Calcd. for $C_{27}H_{47}NO$: C, 80.73; H, 11.79; N, 3.49. Found for fraction I: C, 80.70; H, 11.93; N, 3.45. Found for fraction II: C, 80.47; H, 11.66, N, 3.64.

Fraction I was subsequently shown to be VIII and fraction II was shown to be VII. It was noted that, if the reaction time in the N-methylation were 1 hr., only one N-methyl derivative was recovered. It was identical with fraction I and accounted for approximately 30% of the starting material. The remainder of the material recovered was unsubstituted lactam, m.p. 217–219°, $[\alpha]^{25}D$ +54° (*c* 1.0, chloroform). The recovered unsubstituted lactam was treated with phosphorus pentachloride as described earlier in this paper (see IV and V). Two fractions were obtained but the ratio of IV to V was 4:1. These dichlorolactams accounted on a weight basis for 45% of the starting material used in the preparation of the N-methyl lactam under mild conditions. These results established that the N-methyl lactam (fraction I) formed under mild conditions was VIII. Fraction II was therefore VII.

N-Nitroso-2-aza-5α-cholestan-3-one and N-Nitroso-3-aza-5α-cholestan-2-one (IX′).—Two grams (0.0051 mole) of III was dissolved in a mixture of 50 ml. of glacial acetic acid and 80 ml. of acetic anhydride. The solution was cooled in an ice bath and 4 g. (10% excess) of sodium nitrite was added in small quantities with stirring.[21] A yellow precipitate began to separate immediately. After 24 hr. the yellow mixture was diluted with water and extracted with chloroform. The solvents were removed after drying over sodium sulfate. The residue was crystallized from acetone to yield 1.8 g. (85%) of IX as yellow platelets: m.p. 148–150°; $[\alpha]^{25}D$ +62° (*c* 1.0, chloroform); λ^{KBr}_{max} 5.82, 6.55, and 6.80 μ. Attempts to separate the isomers were unsuccessful.

Anal. Calcd. for $C_{26}H_{44}N_2O_2$: C, 74.95; H, 10.65; N, 6.72. Found: C, 75.14; H, 10.66; N, 6.11.

2-Aza-5α-cholestane and 3-Aza-5α-cholestane (X).—One gram (0.0026 mole) of III was dissolved in 200 ml. of freshly distilled dioxane. Lithium aluminum hydride (4.0 g.) was added in small portions to the resultant solution. The mixture was refluxed 8 hr. and cooled and the excess hydride was carefully decomposed with water. The inorganic salts were filtered and washed with 400 ml. of ether. The filtrate and washings were combined, dried over sodium sulfate, and filtered, and the solvent was removed *in vacuo*. Crystallization from acetone gave 0.2 g. of a product that melted over a wide range, 80–110°. An infrared spectrum of the product showed complete reduction of the lactam carbonyl. Attempts to purify this product or to separate the isomers were unsuccessful.

Hydrobromide Salt.—The product was dissolved in dry ether and treated with HBr. The precipitate was washed with dry ether after filtration and crystallized from ethanol–acetone to yield 1.0 g. (85%) of the hydrobromide of X as white crystals: m.p. 235–245°; $[\alpha]^{25}D$ +42° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{26}H_{48}BrN$: C, 68.69; H, 10.64; Br, 17.58. Found: C, 68.39; H, 10.72; Br, 17.50.

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[21] W. Hartman and L. Roll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 460.

6α-Azido-3α,5α-cyclocholestane

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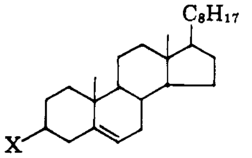
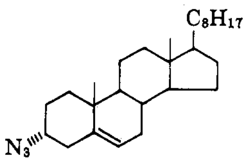
The need for preparative methods for syntheses of steroid amines prompted an investigation of recently reported reactions leading to steroid azides.[1,2] Alkyl azides can readily be reduced to amines with retention of configuration of the carbon–nitrogen bond.[3]

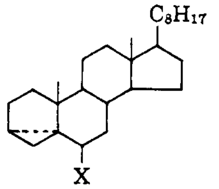
This investigation has resulted in the observation that cholesteryl 3β-*p*-toluenesulfonate (Ia) reacts with the strongly nucleophilic azide ion in various solvents to give, not only the known 3β-azidocholest-5-ene (Ib) and 6β-azido-3α,5α-cyclocholestane (IIIa), but also the undescribed 6α-azido-3α,5α-cyclocholestane (IVa). Depending on the solvent used, 3α-azido-cholest-5-ene (II) was also obtained. The yields of isomeric azides were determined in each of the solvents methanol, dimethyl sulfoxide (DMSO), and N-methylacetamide (NMA), and represent kinetically controlled product distributions, because the most labile epimer IIIa did not rearrange when subjected to the reaction conditions. The four azides were readily separated over Florisil columns by elution with *n*-pentane and *n*-pentane–benzene mixtures. They showed no tendency to rearrange during chromatography.[4]



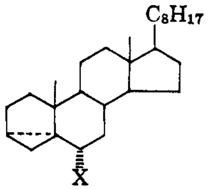
Ia, X = OTs
b, X = N_3



II



IIIa, X = N_3
b, X = OCH_3



IVa, X = N_3
b, X = $NHCOCH_3$

The structures of the steroid azides Ib, II, and IIIa were determined earlier by Jones,[5] who converted them to the known amines. Infrared and n.m.r. spectra of the azides fully confirmed these structural assignments.

The structure of IVa was determined from the following data. The presence of a cyclopropane ring was indicated by both the n.m.r. spectrum,[6] which showed a complex pattern between 0.6 and 0.0 p.p.m. and the infrared spectrum, which showed absorptions at 3069, 3028, and 3002 cm.$^{-1}$.[7] The n.m.r. spectrum showed no vinyl hydrogen. The presence of an azide group was indicated by the nitrogen analysis and by an intense asymmetric azide stretching band at 2100 cm.$^{-1}$.[8] A single-proton resonance occurred at 3.72 p.p.m. as a quartet with J_{ae} = 4.6 c.p.s. and J_{aa} = 12.0 c.p.s. An identical spin–spin coupling pattern was obtained by Tadanier and Cole[9] for the C-6 proton of 6α-substituted

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[1] D. H. R. Barton and L. R. Morgan, *J. Chem. Soc.*, 622 (1962).

[2] R. Goutarel, A. Cavé, L. Tan, and M. Leboeuf, *Bull. soc. chim. France*, 646 (1962).

[3] J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954), and references cited therein.

[4] The rearrangement of IIIa was observed by D. N. Jones during chromatography on an alumina column. See ref. 5.

[5] D. N. Jones, *Chem. Ind.* (London), 179 (1962).

[6] The n.m.r. spectra were determined at 60 Mc./sec. in deuteriochloroform using tetramethylsilane as an internal reference. Chemical shifts are reported in parts per million measured from tetramethylsilane (0.0 p.p.m.) in the direction of decreasing field.

[7] M. Hórak, J. Smejkal, and J. Farkas, *Collection Czech. Chem. Commun.*, **28**, 2280 (1963).

[8] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 263.

[9] J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).