be reported in the critical discussion being prepared.) The reaction mixture was then stirred for 30 min with 100 ml of a saturated calcium hydroxide solution. The precipitate which had formed during the reaction disappeared during this treatment with base. Carbon dioxide was bubbled through the solution until it was neutral, and the calcium carbonate was removed by filtration. The layers were separated and evaporated under reduced pressure. Chromatographic examination of the chloroform layer revealed no carbohydrates. The water layer was stirred with a mixed ion-exchange resin and, after filtration and evaporation, a syrup was obtained [0.125 g (100%)]. Analysis of the syrup by tlc and glpc showed the product to be identical with an authentic sample of D-glucitol.

D.—Methyl terminal 4-*O*-methylmaltooligosaccharides have been prepared in this laboratory.[1] A homologous series (0.100 g) was dissolved in 50 ml of chloroform maintained at 0–10° in an open beaker. Bromine (0.28 ml, 5.40×10^{-3} mol) was added dropwise over a 15-min period, while the stirred mixture was irradiated with a 60-W incandescent bulb. After 1.5 and 3.0 hr, respectively, additional 0.28-ml portions of bromine were added. After a total of 6.0 hr, the reaction mixture, which contained a precipitate, was worked up as described for the D-glucitol reaction to yield 0.04 g. Tlc analysis of the resulting syrup showed the components to be identical with the products obtained when the same compounds were treated with excess Raney nickel.[1] The syrup was hydrolyzed with 30 ml of 2 *N* sulfuric acid for 36 hr. After neutralization (resin) and evaporation, the products were converted into their per(trimethylsilyl) derivatives and analyzed by glpc. Only D-glucose and 4-*O*-methyl-D-glucose were indicated to be present.

E.—Tri-*O*-benzylamylose has been prepared in this laboratory.[1] This substance (0.172 g) was dissolved in 50 ml of chloroform maintained at 0–10° in an open beaker. Bromine (0.2 ml, 3.86×10^{-3} mol) was added all at once, while the stirred reaction mixture was irradiated with a 60-W incandescent light. After 1.5 and 3.0 hr, respectively, additional 0.2-ml portions of bromine were added. After a total of 4.5 hr, the reaction mixture, which contained a precipitate, was worked up as described for the D-sorbitol reaction to yield 0.08 g. Tlc analysis of this product showed no degradation products (D-glucose, D-gluconic acid, or D-gluconolactone). Infrared analysis showed the absence of benzyl ether groups. The product gave a blue color on treatment with iodine solution, indicating that amylose (DP >20) was present.

Registry No.—Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside, 17791-36-5; methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside, 17791-37-6; hexa-*O*-benzyl-D-glucitol, 17791-38-7.

Acknowledgments.—Grateful acknowledgment is given to the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, for Contract No. 12-14-100-7161(71) which supported this work, and to the Shell Chemical Co. for gifts of Sulfolane.

Steroid Tetrazoles[1]

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Research Laboratories Syntex, S. A., Mexico, D. F., Mexico

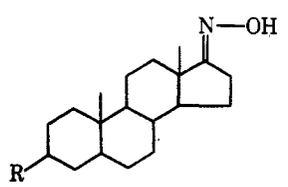
Received May 9, 1968

Tetrazoles are known to be formed when an excess of azide is used in the Schmidt reaction,[2,3] and by the reaction of oximes with sodium azide in the presence of sulfuric acid or chlorosulfonic acid.[3,4]

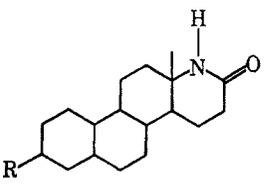
In this Note we wish to report the reaction of sodium azide with steroidal C-17 oximes, which proceeds with concomitant ring D rearrangement, to yield pentacyclic steroid tetrazoles.

Reaction of hydrazoic acid (generated by the action of sodium azide on chlorosulfonic acid) with 5α-androstan-17-one oxime (**1a**) afforded a mixture of lactam **2a** and tetrazole **3a**. The nuclear magnetic resonance (nmr) spectrum of this compound (**3a**), as well as that of the other tetrazoles described here, is characterized by the strong deshielding of the 18-methyl protons (1.36 ppm) by the tetrazole ring.

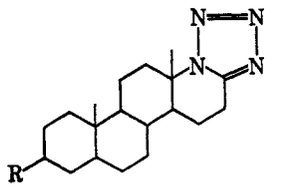
The same reaction with the 3β-acetoxy 17-oxime (**1b**)[5] provided a mixture containing 48% lactam **2b** and 9.5% the expected tetrazole (**3b**). Alkaline hydrolysis of the 3-acetoxyl group in **3b**, gave the corresponding alcohol (**3c**) which was oxidized with chromic acid in acetone[6] to the 3 ketone (**3d**). The latter was



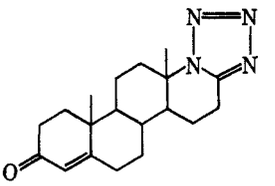
1a, R = H
b, R = AcO



2a, R = H
b, R = AcO



3a, R = H
b, R = AcO
c, R = OH
d, R = ketone
e, 2,4-dibromo; R = ketone



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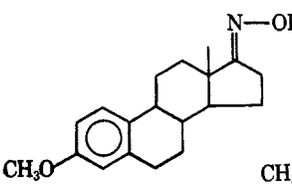

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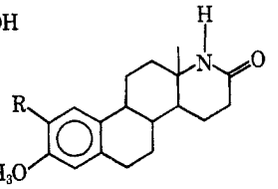
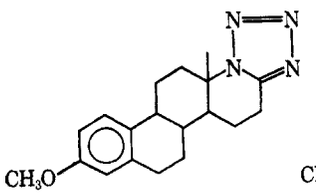


6a, R = H
b, R = SO_2Cl



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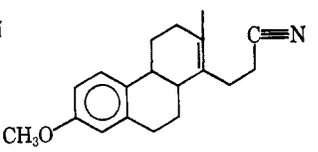

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(1) Publication no. 332 from the Syntex Institute of Steroid Chemistry. For no. 331, see P. Crabbé, H. Carpio, A. Cervantes, J. Iriarte, and L. Tökes, *Chem. Commun.*, **2**, 79 (1968).

(2) M. A. Spielman and F. L. Austin, *J. Amer. Chem. Soc.*, **59**, 2658 (1937).

(3) For a leading reference, see H. Wolff, *Org. Reaction*, **3**, 307 (1946).

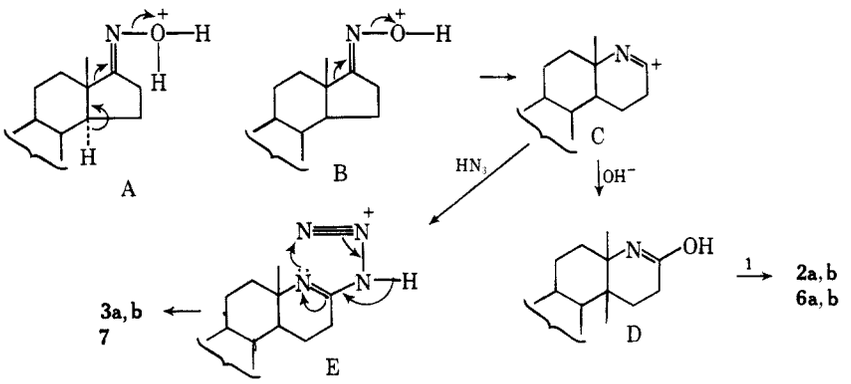
(4) See also (a) K. F. Schmidt, German Patent 855,711 (Nov 17, 1952); *Chem. Abstr.*, **52**, 15592g (1958); (b) Fr. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(5) R. Anliker, M. Müller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **38**, 1404 (1955).

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

(7) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

SCHEME I



converted to the dibromide (**3e**) and then, by conventional methods,[7] to the Δ^4-3-ketotetrazole (**4**).

Treatment of the oxime **5**[8] with sodium azide and chlorosulfonic acid afforded three compounds, the tetrazole **7** and the lactam **6a**,[8] isolated in 2 and 38% yield, respectively, as well as 9% D-secocyano derivative **8**. Furthermore, a fourth substance, *i.e.*, the chlorosulfonated steroid **6b**, was isolated in 14% yield when the reaction was run at higher temperature (see Experimental Section).

Structure **8**, assigned to the cyano compound, is supported by the C≡N absorption at 2230 cm^{-1}, as well as by the vinylic 13-methyl protons resonance at 1.73 ppm. The location of the newly introduced chlorosulfonyl group at C-2 in the lactam **6b** is inferred from the absence of C-2 aromatic proton in the nmr spectrum.

The fragmentation leading to the seco steroid **8**, is reminiscent of the reported cleavage of oximes by treatment with *p*-toluenesulfonyl chloride,[9] and probably proceeds by concerted fragmentation of the protonated oxime, as indicated in A. Since the lactams (**2a**, **2b**, and **6a**) were recovered unchanged on attempted reaction with HN_3, one may assume that both the lactams and the tetrazoles are formed by action of hydrazoic acid on an azomethine cation intermediate of type C, formed by rearrangement of the oxime and elimination of OH^-, as indicated in B (Scheme I).

Experimental Section[10]

5α-Androstan-17-one Oxime (1a).—A solution of 2 g of 5α-androstan-17-one in 75 ml of ethanol was refluxed for 2 hr with a mixture of 0.9 g of hydroxylamine hydrochloride, 1.07 g of sodium acetate, and 28 ml of ethanol.

Evaporation of the solvent and extraction with ethyl acetate gave 1.5 g of crude 5α-androstan-17-one oxime. Purification by recrystallization from acetone provided the analytical sample: mp 173–175°; $[\alpha]_D$ +14°; ν_{max} 3250 cm^{-1}; nmr 0.77 (19 H), 1.14 (18 H), 5.95 ppm (C=N—OH).

Anal. Calcd for $C_{19}H_{31}ON$: C, 78.84; H, 10.80; N, 4.84. Found: C, 79.19; H, 10.76; N, 5.19.

17a-Aza-D-homo-5α-androstane-17,17a-e-tetrazole (3a).—To 585 mg of sodium azide suspended in 10 ml of ethylene chloride 2.7 ml of chlorosulfonic acid was slowly added. The mixture was stirred for 1 hr, and an additional 585 mg of sodium azide was then added. After 15 min a solution of 1.5 g of 5α-androstan-17-one oxime (**1a**) in 20 ml of ethylene chloride was slowly added, and the reaction mixture was stirred at room temperature for 2 hr. Addition of water and extraction with ethyl acetate gave a dark oil which was chromatographed over 150 g of Florisil. By elution with a mixture of hexane–ethyl acetate (8:2), 280 mg of tetrazole (**3a**) was isolated. After three crystallizations from methylene chloride–hexane, 140 mg of pure tetrazole (**3a**) was obtained. The analytical sample showed mp 185–187°; $[\alpha]_D$ +67°; ν_{max} 3350 cm^{-1}; nmr 0.81 (19 H), 1.36 ppm (18 H).

Anal. Calcd for $C_{19}H_{30}N_4$: C, 72.56; H, 9.62; N, 17.82. Found: C, 72.35; H, 9.93; N, 18.02.

Further elution with hexane–ethyl acetate (2:3) furnished 600 mg of 13α-amino-13,17-seco-5α-androstan-17-oic acid lactam (**2a**). Purification by recrystallization from methylene chloride–ether provided 430 mg of pure lactam (**2a**): mp 314–315°; $[\alpha]_D$ +14°; ν_{max} 3110, 3025, 1675, 1610 cm^{-1}; nmr 0.80 (19 H), 0.90 (18 H), 5.50 ppm (NH).

Anal. Calcd for $C_{19}H_{31}ON$: C, 78.84; H, 10.80; N, 4.84. Found: C, 78.54; H, 10.93; N, 5.04.

17a-Aza-3β-hydroxy-D-homo-5α-androstane-17,17a-e-tetrazole Acetate (3b).—To a stirred suspension of 6 g of sodium azide in 100 ml of ethylene chloride, 18 ml of chlorosulfonic acid was added dropwise. After 1 hr an additional 6 g of sodium azide was added; 16 min later a solution of 10 g of 3β-acetoxy-17-oximino-5α-androstane (**1b**)[6] in 150 ml of ethylene chloride was slowly added. The reaction mixture was stirred at room temperature for 2 hr and then worked up by addition of water and extraction with methylene chloride. The product was filtered through Florisil, with hexane–ethyl acetate (65:35), yielding 1 g of tetrazole (**3b**). Repeated crystallizations from methylene chloride–ether provided the pure sample: mp 254–256°; $[\alpha]_D$ +40°; ν_{max} 1738, 1527, 1455 cm^{-1}; nmr 0.86 (19 H), 1.36 (18 H), 2.0 ppm (3β OAc).

Anal. Calcd for $C_{21}H_{32}O_2N_4$: C, 67.71; H, 8.66. Found: C, 67.42; H, 8.61.

Further elution with ethyl acetate gave 4.8 g of 13α-amino-3β-acetoxy-13,17-seco-5α-androstan-17-oic acid lactam (**2b**). Crystallization from methylene chloride–methanol gave the pure product (**2b**): mp 263–265°; $[\alpha]_D$ −9°; ν_{max} 3130, 3020, 1740, 1680, 1610 cm^{-1}; nmr 0.81 (19 H), 1.13 (18 H), 2.01 (3 OAc), 4.50–4.83 (3α H), 6.81 ppm (–NH–).

Anal. Calcd for $C_{21}H_{33}O_3N$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.44; H, 9.91; N, 4.17.

17a-Aza-D-homo-5α-androstan-3-one-17,17a-e-tetrazole (3d).—3-Acetoxytetrazole **3b**, 3.1 g, was hydrolyzed at room temperature with 90 ml of 1% solution of potassium hydroxide in methanol for 18 hr under nitrogen. Dilution with water and extraction with methylene chloride gave 3 g of the crude alcohol (**3c**) which, without further purification, was dissolved in 200 ml of acetone and treated with stirring at 8° with 3 ml of 8 *N* chromic acid,[6] for 45 min. Aqueous sodium bisulfite was added, and the

(8) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956).

(9) See (a) R. M. Carman and D. Cowley, *Aust. J. Chem.*, **18**, 213 (1965); (b) J. Klinot and A. Vystrčil, *Collect. Czech. Chem. Commun.*, **27**, 377 (1962); (c) J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1219 (1967); (d) E. S. Olson and J. H. Richards, *J. Org. Chem.*, **33**, 434 (1968).

(10) Microanalyses were done by Dr. A. Bernhardt, Mülheim, Germany. Melting points were determined in capillary tubes with a Mel-Temp apparatus; they are corrected. Rotations were taken between 16 and 22°, in chloroform solution, with a 1-dm tube at sodium D line. Infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer with a NaCl prism in KBr pellets. 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 steroid in chloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies are quoted as parts per million downfield from the TMS reference and are accurate to ±0.01 ppm; coupling constants, *J*, in cycles per second, are accurate to ±0.5 cps. Mass spectra (MS) were determined on an Atlas CH-4 spectrometer by direct insertion of the sample into the ion source; the ionizing energy was 70 eV, and a 3-kV accelerating potential was used. We are indebted to Dr. L. Throop and his staff for nmr and MS measurements.

mixture was extracted with methylene chloride to yield 2.25 g of an homogeneous product. Recrystallization from methylene chloride–hexane gave the pure sample of (**3d**): mp 262–264°; $[\alpha]_D$ +71°; ν_{max} 1705, 1520, 1450 cm^{-1}; nmr 1.06 (19 H), 1.39 ppm (18 H).

Anal. Calcd for $C_{19}H_{28}ON_4$: C, 69.47; H, 8.59; N, 17.06. Found: C, 69.58; H, 8.75; N, 16.90.

17a-Aza-D-homoandrost-4-en-3-one-17,17a-e-tetrazole (4).—A solution of 2 g of the 3 ketone (**3d**) in 75 ml of acetic acid was treated dropwise with 1.92 g of bromine in 6.2 ml of acetic acid. Three drops of a saturated solution of hydrogen bromide in acetic acid was added, and the mixture was stirred for 18 hr. The reaction mixture was then poured into water, and the precipitated solid was extracted with methylene chloride. The extract was washed to neutrality, dried, and evaporated *in vacuo* to yield 2.6 g of the corresponding 2,4-dibromo compound **3e** which, without further purification, was treated with chromous acetate as follows.[7]

Zinc dust (10 g) was amalgamated by shaking with a solution of 0.8 g of mercuric chloride, 10 ml of water, and 0.5 ml of hydrochloric acid for 5 min and decanting the supernatant. Addition of a solution of 5 g of chromic chloride in 20 ml of water and 2 ml of hydrochloric acid under an atmosphere of carbon dioxide gave a dark blue solution of chromous chloride which was immediately transferred to a three-necked flask (under a rapid stream of carbon dioxide) provided with gas inlet and outlet tubes, a dropping funnel, and a sintered-glass filtering stick tube which could be lowered or raised through a rubber stopper. This filter tube was connected to the vacuum line.[7]

A solution of 9.2 g of sodium acetate in 18 ml of deoxygenated water was added through the dropping funnel without stirring. The blue solution turned to crystals of deep red chromous acetate. The suspension was stirred; the filter was lowered and the liquid phase was withdrawn; and the precipitate was washed with two portions of ethanol, and finally with ether. To the dry powder was added with stirring 2.6 g of the dibromo compound **3e** dissolved in 75 ml of acetic acid and 18 ml of chloroform. After 8 min, air was blown through the flask to oxidize the excess of chromous acetate. The mixture was then poured into cold water, extracted with methylene chloride, washed several times with water, dried and evaporated *in vacuo*. There was obtained 1.9 g of an oily product which was dissolved in 6 ml of dimethylacetamide and added to a boiling suspension of 0.8 g of calcium carbonate in 18 ml of dimethylacetamide under a stream of nitrogen. After 30 min the mixture was cooled, poured into water, and extracted with methylene chloride, then washed with a 2% solution of hydrochloric acid and finally with water to neutrality.

The residue was purified by preparative thin layer chromatography to yield 630 mg of **4**. Recrystallization from methylene chloride–ether yielded 450 mg of the analytical sample: mp 236–238°; $[\alpha]_D$ +120°; λ_{max} 240 mμ (log ε 4.15); ν_{max} 3350, 1665, 1615, 1520, 1455 cm^{-1}; nmr 1.25 (19 H), 1.43 (18 H), 5.73 ppm (4 H).

Anal. Calcd for $C_{19}H_{26}ON_4$: C, 69.90; H, 8.03; N, 17.17. Found: C, 69.95; H, 8.07; N, 17.41.

17a-Aza-3-hydroxy-D-homoestra-1,3,5(10)-triene-17,17a-e-tetrazole,3-Methyl Ether (7).—Chlorosulfonic acid (13 ml) was added dropwise with stirring to a suspension of 6 g of sodium azide in 100 ml of ethylene chloride. After 1 hr, more sodium azide (6 g) was added, and, 15 min later, a solution of 10 g of estrone methyl ether 17-oxime (**5**)[8] was added slowly. The mixture was stirred for 2 hr and then poured into water, and the product extracted with methylene chloride. The residue was dissolved in methylene chloride and filtered through a column on Florisil. Elution with hexane–ethyl acetate (95:5) afforded 1 g of the cyano derivative **8**, which after two crystallizations from methanol–water showed mp 68–69°; $[\alpha]_D$ −84°; λ_{max} 278, 287 mμ (log ε 3.31, 3.27); ν_{max} 2230, 1605, 1580 cm^{-1}; nmr 1.73 (18 H, vinylic methyl), 3.75 (3 OCH_3), 6.67 (4 H), 6.67, 6.80 (2 H), 7.16, 7.31 ppm (1 H); MS 281 (M^+).

Anal. Calcd for $C_{19}H_{23}ON$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.83; H, 8.19; N, 5.35.

Further elution with 30% ethyl acetate in hexane, gave 200 mg of **7**. Crystallization from methylene chloride–ether gave the analytical sample: mp 245–247°; $[\alpha]_D$ +107°; λ_{max} 278, 287 mμ (log ε 3.21, 3.17); ν_{max} 1610, 1580, 1500 cm^{-1}; nmr 1.4 (18 H), 3.75 (3 OCH_3), 6.6 (4 H), 6.8 (2 H), 7.1–7.3 ppm (1 H, doublet, J_H = 8 cps).

Anal. Calcd for $C_{19}H_{24}ON_4$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.12; H, 7.68; N, 17.10.

Elution with ethyl acetate–hexane (1:1) provided 3.8 g of 3-methoxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oic acid 13,17-lactam (**6a**): mp 222–224°; $[\alpha]_D$ +93°; λ_{max} 278, 287 mμ (log ε 3.25, 3.25). Regan and Hayes[8] report mp 222–224°; $[\alpha]_D$ +95°; λ_{max} 279, 286 mμ (log ε 3.30, 3.26).

2-Chlorosulfonyl-3-methoxy-13α-amino-13,17-secoestra-1,3,5(10)-trien-17-oic Acid 13,17-Lactam (6b).—The above reaction was carried out with 2 g of estrone methyl ether oxime (**5**),[8] with larger amounts of chlorosulfonic acid, first heating at 35° for 1 hr and then at 50° for a second hour. After cooling, the reaction mixture was poured into water and extracted with methylene chloride. The organic layer was washed, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The slightly soluble compound **6b** was recrystallized from methylene chloride–ether. There was obtained 400 mg of pure sulfonated lactam **6b**: mp 258–260°; $[\alpha]_D$ +76°; λ_{max} 306 mμ (log ε 3.47); nmr 1.2 (18 H) 4.01 (3 OCH_3), 6.87 (4 H), 7.85 ppm (1 H).

Anal. Calcd for $C_{19}H_{24}O_4NSCl$: C, 57.34; H, 6.08; N, 3.52; S, 8.06. Found: C, 57.26; H, 6.17; N, 3.95; S, 7.83.

Registry No.—**1a**, 1035-62-7; **2a**, 17556-10-4; **2b**, 2232-15-7; **3a**, 17556-03-5; **3b**, 17556-04-6; **3d**, 17556-05-7; **4**, 17556-06-8; **6b**, 17556-11-5; **7**, 17556-07-9; **8**, 17556-08-0.

Acknowledgment.—We wish to thank Dr. J. Fried for helpful discussions.

Fluoronitroaliphatics. III. Preparation of Some Negatively Substituted Halonitromethanes[1]

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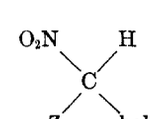
Received May 22, 1968

For a recent study of the effect of α-fluorine on C–H acidities,[3] the negatively substituted monofluoronitromethanes, Ia–IIIa, and the corresponding monochloro derivatives, Ib–IIIb, were required. We wish now to record the syntheses and some properties of these materials.



Ia, Z = COOEt; hal = F Ib, hal = Cl
IIa, Z = $CONH_2$; hal = F IIb, hal = Cl
IIIa, Z = Cl; hal = F IIIb, hal = Cl

Direct halogenation of the parent compounds, Z–CH_2NO_2, did not appear to be a promising route to I–III in view of the fact that dihalogenation, in particular difluorination, had frequently been observed with such systems. Thus, Inman and coworkers had reported the difluoro derivatives as the only products of the fluorination of the sodium salts of diethyl malonate, ethyl acetoacetate, and 2,4-pentanedione with

(1) Part II: M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).
(2) Deceased.
(3) H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966).