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# SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—V

## SYNTHESIS OF KRYPTOGENIN, DIOSGENIN AND YAMOGENIN

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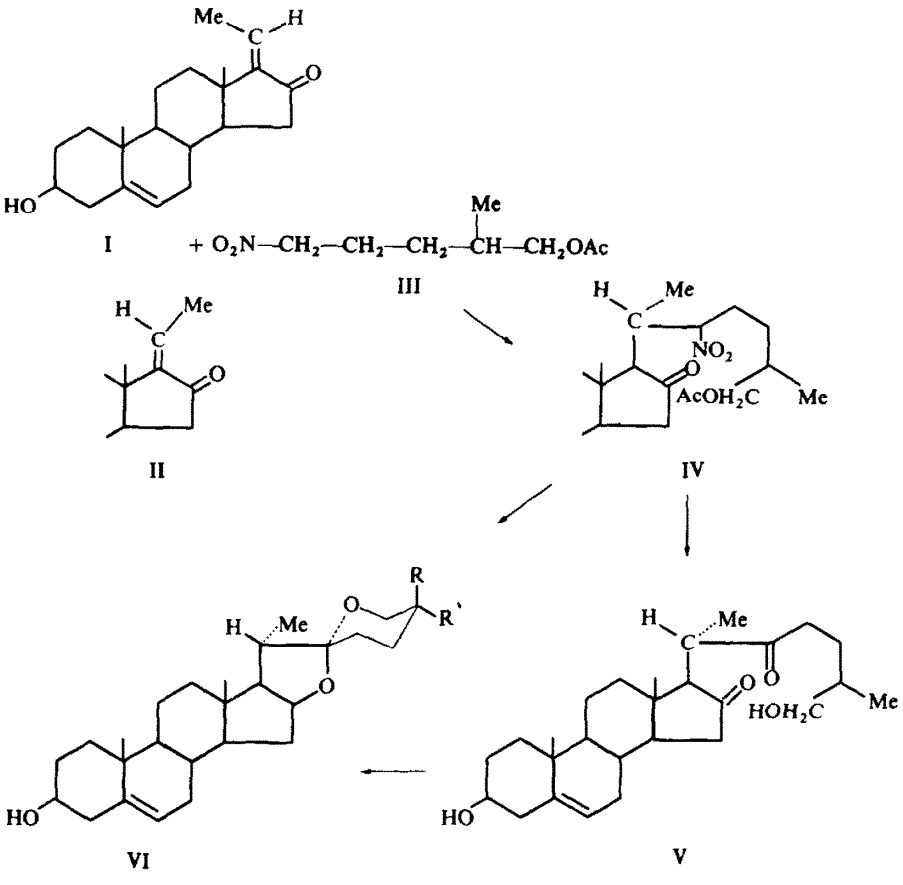
**Abstract**—Michael addition of 1-acetoxy-5-nitro-2-methylpentane to *cis*-5,17(20)-pregnadien-3β-ol-16-one furnishes adducts which readily lead to steroidal sapogenins. By using nitroacetates of appropriate configuration, stereoselective syntheses of kryptogenin, diosgenin and yamogenin have been affected.

STEROIDAL sapogenins occur widely in nature as glycosides,[1] but in contrast to extensive degradative and correlative studies, the only successful synthetic effort is the elegant work of Mazur *et al.*[2] Now a versatile approach to the spirostane structure has been developed in this laboratory.[3]

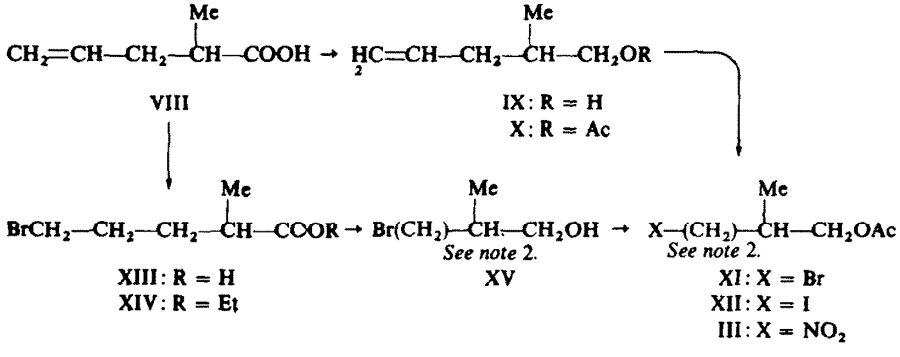
Our starting material, dehydropregnenolone, can be converted into *cis*-5,17(20)-pregnadien-3β-ol-16-one (I) by a three-step sequence.[3] Michael addition[4] of 1-acetoxy-5-nitro-2-methylpentane (III) to this α,β-unsaturated ketone furnishes the key intermediate, IV, having functional groups suitably juxtaposed for elaboration to spirostanes on one hand and to spirosolanes and solanidanes on the other.

Although four new asymmetric centres are generated in the adduct IV, no difficulty was expected on this account. The stereochemistry at C-25 could be controlled by use of nitro addenda of appropriate configuration, whereas asymmetry at C-22 was to be eliminated in a subsequent reaction. Theoretically and on the basis of analogy with nitromethane addition[5] to I, the desired β-orientation of the side chain at C-17 and the natural *S* configuration at C-20 were predicted in IV. Even if *cis-trans* isomerization of the substrate intervened to give some 20*R* product, the known preference of C-16, C-22 dicarbonyl compounds for 20*S* arrangement[6] could be exploited after the Nef reaction. Later in the sequence another asymmetric centre arises on reduction of C-16 carbonyl function. Here too, the correct β-hydroxyl orientation was expected on the basis of back-side attack.

For synthesis of the nitro addendum IIIa, bromo acid XIIIa was obtained from partially resolved 2-methyl-4-pentenoic acid (VIIIa) by peroxide catalysed addition of hydrogen bromide. Its ethyl ester was then reduced with LAH in the presence of aluminium chloride[7] to the bromo alcohol XVa which on acetylation afforded XIa. The nitro compound IIIa could be secured by direct reaction of this bromide with sodium nitrite in DMF, or better through the iodide XIIa by conventional silver nitrite reaction. The yield in reduction of the bromo ester XIVa was not entirely satisfactory. This route, however, had to be adopted since the halides XI and XII when obtained through hydrogen bromide addition to olefin acetate X were invariably contaminated with an impurity which could be eliminated only by repeated fractionation. This material was identified as a nitrite from the absorption at 6·1 μ in the




VI: R = H; R′ = Me
VII: R = Me; R′ = H




Series a, Absolute configuration *R*.

Series b, Absolute configuration *S*.

IR spectrum. The formation of substantial proportions of nitrite, especially with the silver nitrite procedure, is unusual with primary halides.[8] Therefore, it seems that in comparison to acid VIII, peroxide catalysed hydrogen bromide addition to X gives considerable amounts of secondary bromide. [See note 3].

The nitro adduct IVa, obtained by addition of IIIa to I, with the Nef reaction afforded a diketone in modest yield. This material corresponded to kryptogenin in physical properties. Although reduction of kryptogenin to diosgenin is known,[2, 9] for efficient conversion of IVa to spirostanes it was considered advisable to reduce the C-16 keto group prior to Nef reaction. Reaction of IVa with sodium borohydride[10] in ethanol at room temperature gave a material which still showed considerable IR absorption in the carbonyl region. The reduction was, therefore, attempted in refluxing ethanol. On acidification of the reaction mixture a crystalline solid separated which, to our delight, turned out to be diosgenin.* Apparently in one operation reduction, virtual Nef reaction, removal of acetyl group and cyclization had all proceeded. Efficient transformation of a nitro to carbonyl function† at the hindered C-22 position[12] is particularly gratifying in view of the difficulty usually experienced in effecting a Nef reaction at sterically congested sites.[13]

Starting with 2*S*-allylpropionic acid, synthesis of yamogenin followed on parallel lines. The adduct IVb was obtained as an oil which on reaction with sodium borohydride readily afforded yamogenin. Identity of this and diosgenin was established by comparison with natural samples.‡ Because 2-allylpropionic acid of good optical purity was used for synthesis of yamogenin, the 20% over-all yield from starting dehydropregnenolone can be taken as standard for this conversion.

IR spectra of the crude products obtained by sodium borohydride reduction of IV do not reveal the presence of 20*R* sapogenins,[14, 15] and it may be concluded that Michael addition of III to *cis*-ketone I furnishes, primarily, products of 20*S* configuration.§ This may seem surprising as partial isomerization of I to *trans*-ketone II occurs during the addition. On the basis of rear-side attack, the later (II) should give a 20*R* product. However, the rate of addition to the *cis*-isomer is expected[5] to be much faster and, therefore, the main reaction should proceed *via* this even in presence of *cis-trans* equilibration.

The work described in this paper formally constitutes a total synthesis of kryptogenin, diosgenin and yamogenin, as the starting material is available by a totally synthetic route.[16] In comparison to the earlier method[2] the present approach is considerably shorter, allows selective entry into the neo or iso series, and is easily amenable to synthesis of sapogenins with additional functions.

## EXPERIMENTAL

*2-Methyl-4-penten-1-ol* (IX). This alcohol, b.p. 145–146°, $n_D^{18}$ 1·4345, was prepared (70% yield) from α-allylpropionic acid by the method of Fray and Polgar.[17]

* If crude IVa is reduced as such the sapogenin obtained is contaminated by a neo isomer as shown by ratio of IR absorption intensities at 10·98 and 11·1 μ.[11]

† The mode of this conversion is currently under investigation.

‡ We are grateful to Prof. Schreiber and Dr. Ronsch of Gatersleben for a sample of natural yamogenin containing about 5% diosgenin. The synthetic product is free of this impurity as seen by a comparison of IR spectra.

§ Isomerization to 20*S* configuration during $NaBH_4$ reaction is not likely as the postulated intermediate, keto diol, is devoid of driving C-16, C-22 dicarbonyl interaction.[6] Further, 20-isosapogenin, if formed would not be expected to isomerize on contact with dil HCl at room temp.

*2-Methyl-4-pentenol-1-acetate* (X). Acetyl chloride (10 g) was added with stirring to an ice-cold mixture of IX (11·5 g), pyridine (10 g) and ether (50 ml). After stirring at room temp for 3 hr the mixture was heated to reflux for 2 hr and then cooled. Iced water (50 ml) was added. The ethereal layer was separated and washed with dil HCl, water, $NaHCO_3$ aq and water. The residue, obtained after drying and stripping the solvent, on distillation gave a pleasant smelling liquid (14 g), b.p. 159°, $n_D^{35}$ 1·4164. (Found: C, 67·85; H, 9·45. $C_8H_{14}O_2$ requires: C, 67·57; H, 9·93%.)

*5-Bromo-2-methylpentanol-1 acetate* (XI). Dry HBr was bubbled through a mixture of X (14 g), pet. ether (20 ml, 80–100°), benzoyl peroxide (100 mg), benzene (0·5 ml) and a drop of water. Every 15 min supply of gas was discontinued and dry air passed through the mixture for 1 min. After 2 hr water (50 ml) was added and the aqueous layer extracted with ether. The combined organic layer was washed with $Na_2CO_3$ aq, dried and the solvent removed. The residue on fractionation afforded a colourless oil (13 g), b.p. 76–78°/2 mm, $n_D^{35}$ 1·4544. (Found: C, 43·20; H, 6·97; Br, 36·05. $C_8H_{15}O_2Br$ requires: C, 43·09; H, 6·72; Br, 35·80%.)

*5-Idodo-2-methylpentanol-1 acetate* (XII). The bromoacetate XI (8 g) was refluxed with NaI (6·4 g) in dry acetone (100 ml) for 2 hr. Acetone was removed by distillation, the reaction mixture was diluted with water and extracted with ether. The ethereal soln was washed with $Na_2S_2O_3$ aq, water, dried and the solvent removed. The residue distilled with decomposition liberating $I_2$, b.p. 90–92°/2·5 mm, $n_D^{35}$ 1·4839. The distillate was washed again with $Na_2S_2O_3$ aq and distilled, but the $I_2$ colour reappeared.

*5-Nitro-2-methylpentanol-1 acetate* (XIII). A soln of the above iodo compound (4·5 g) in ether (50 ml) was added dropwise in the dark with stirring, to a cooled (0°) suspension of $AgNO_2$ (7 g) in ether (50 ml) over a period of 2 hr. Stirring was continued for 24 hr at 0° and for 36 hr at room temp. The suspended solid was removed and washed with ether. The solvent was distilled off from the combined ethereal soln. The residue was distilled to collect two fractions: (a) b.p. 90–105°/3 mm; (b) b.p. 110–125°/3 mm. The second fraction on redistillation gave a light yellow liquid (880 mg, 20%), $\nu_{max}$ 5·75, 6·1, 6·45, 8·1 μ, $n_D^{35}$ 1·4425. (Found: N, 7·48. $C_8H_{15}NO_4$ requires: N, 7·4%.)

*Reaction of* XI *with sodium nitrite in dimethylformamide.* A mixture of XI (4 g), $NaNO_2$ (2·5 g), urea (3 g) and freshly distilled DMF (50 ml) was stirred at room temp for 5 hr. It was then poured into iced water and extracted with ether. The solvent was removed after washing and drying the organic layer. Fractionation of the residue furnished impure III (1 g), b.p. 115–125°/3 mm, $\nu_{max}$ 5·75, 6·1, 6·45 μ.

*2R- and 2S-Methylpent-4-enoic acid* (VIIIa *and* VIIIb). 2-Methylpent-4-enoic acid was resolved with quinine alkaloid according to method of Ställberg.[18] 2*S*-methylpent-4-enoic acid (VIIIb), $[\alpha]_D$ +7·9°) was secured by decomposition of the salt obtained after nine crystallizations from acetone.

Partially resolved VIIIa, $[\alpha]_D$ −4·6°) was obtained by decomposition of the first two mother liquors in the above resolution. It (10 g) reacted with (+)-1-phenylethylamine[19] (10·4 g) in dry ether (3·15 ml). The reaction mixture was chilled overnight at −10°. The precipitated salt was collected and decomposed with HCl to give VIIIa, $[\alpha]_D$ −6·5°.

*5-Bromo-2R-methylpentanoic acid* (XIIIa). HBr was passed through a mixture of VIIIa (2·8 g), pet. ether (6 ml, 80–100°), benzoyl peroxide (30 mg) and a drop of water as before. Working up gave XIIIa (3·9 g), b.p. 110–112°/1 mm, $n_D^{36}$ 1·4736, $[\alpha]_D$ −9·33°. Lt.[20] (DL) b.p. 142/2 mm.

To ascertain the orientation of addition, DL—XIII was prepared by HBr addition to DL-2-methylpent-4-enoic acid and from diethyl 3-bromo-propylmethylmalonate by hydrolysis with 38% HBr. The two bromo acids had identical IR spectra and their anilides showed no depression in m.p. on admixture. Anilide m.p. 85–86°. (Found: N, 5·1. $C_{12}H_{16}NOBr$ requires: N, 5·2%.)

*Ethyl 5-bromo-2R-methylpentanoate* (XIVa). The above bromo acid (11·5 g) was esterified with EtOH to give XIVa (12 g), b.p. 74–76°(1·5 mm, $n_D^{36}$ 1·4495, $[\alpha]_D$ −10·74°. (Found: C, 43·23; H, 6·53. $C_8H_{15}O_2$ requires: C, 43·05; H, 6·73%.)

*5-Bromo-2R-methylpentanol-1* (XVa). A soln of anhyd $AlCl_3$ (5·34 g) in ether (100 ml) was added slowly to a suspension of LAH (1·5 g) in ether (250 ml) at 0°. After stirring for 20 min a soln of XIVa (9 g) in ether (50 ml) was added dropwise. The reaction mixture was stirred for 6 hr at room temp and then decomposed by dropwise addition of water (6 ml). The mixture was filtered and the cake extracted with ether. The solvent was removed from the combined ether layers. The residue on distillation afforded XVa (3·5 g), b.p. 79–80°/1·5 mm, $n_D^{26}$ 1·4783, $[\alpha]_D$ −11·45°. (Found: C, 39·76; H, 7·14. $C_6H_{13}OBr$ requires: C, 39·88; H, 7·18%.)

*5-Bromo-2R-methylpentanol-1 acetate* (XIa). Acetyl chloride (5 ml) was added, dropwise with stirring, to a cooled (5°) soln of XVa (5 g) in benzene. The reaction mixture was left overnight, refluxed for 1 hr and then decomposed with water. The benzene layer was washed with $NaHCO_3$ aq and the solvent

removed. Distillation of the residue furnished XIa (5·8 g), b.p. 70–72°/1·5 mm, $n_D^{29}$ 1·4582, $[\alpha]_D$ −2·96°. (Found: C, 42·97; H, 6·8. $C_8H_{15}O_2Br$ requires: C, 43·09; H, 6·72%.)

*5-Iodo-2R-methylpentanol-1 acetate* (XIIa). The compound XIIa was prepared in 90% yield, by reaction of XIa with NaI as above, b.p. 93–95°/2 mm, $n_D^{32}$ 1·4765. (Found: C, 35·31; H, 5·54; I, 47·4. $C_8H_{15}O_2I$ requires: C, 35·55; H, 5·53; I, 47·04%.) No liberation of $I_2$ was noticed in this case.

*5-Nitro-2R-methylpentanol-1 acetate* (IIIa). The nitro acetate was obtained from XIIa by reaction with $AgNO_2$ as before. In contrast, pure IIIa was obtained in 50% yield, b.p. 124–125°/2 mm, $n_D^{26}$ 1·412, $[\alpha]_D$ +4·1°, $\nu_{max}$ 5·75, 6·45, 8·1 μ (liquid film). (Found: C, 50·56; H, 7·87; N, 7·25. $C_8H_{15}O_4N$ requires: C, 50·80; H, 7·90; N, 7·40%.)

This nitro acetate was also prepared in 25% yield by $NaNO_2$ reaction of XIa, as before.

*Michael addition of* IIIa *to cis-5,17(20)-pregnadien 3β-ol-16-one* (I). A soln of potassium salt of IIIa (from IIIa, 570 mg, K metal, 50 mg) in t-butyl alcohol (5 ml) was added to a soln of the *cis*-ketone I (625 mg) in t-butyl alcohol (5 ml). The clear soln was allowed to stand at room temp. After one day a solid separated and the process was complete in about a week. Periodically a small portion of the heterogenous mixture was withdrawn, neutralized with dil AcOH, diluted with water and extracted with $CH_2Cl_2$. The extract was washed with $NaHCO_3$ aq and water, dried and the solvent stripped off. Progress of the reaction could be followed by TLC of this residue. *trans*-Ketone II could be detected after 2 days and both I and II were absent after 8 days. Then the whole reaction mixture was neutralized with 10% AcOH and shaken for 1 hr. The solid (400 mg, 40%) was removed and washed with dry ether, m.p. 199–205°. Crystallization from EtOH furnished pure IVa, m.p. 229–230°, $[\alpha]_D$ −157°, $\nu_{max}$ 2·85, 5·75, 6·45 μ. (Found: C, 69·57; H, 8·74; N, 2·75. $C_{29}H_{45}NO_6$ requires: C, 69·15; H, 9·01; N, 2·78%.)

The mother liquor from the above reaction mixture on dilution with water gave an oil which was extracted with $CH_2Cl_2$. After washing and drying, the solvent was removed. The residual gum could not be crystallized ($\nu_{max}$ 2·85, 5·75, 6·45 μ; no absorption at 5·85 and 6·0 μ corresponding to the α,β-unsaturated ketone) nor could any solid be obtained by chromatography on alumina.

*Nef reaction on 25R-26-acetoxy-22-nitro-5-cholesten-3β-ol-16-one* (IVa). A mixture of IVa (100 mg), NaOEt (from sodium metal, 250 mg), ethanol (125 ml) and water (10 ml) was allowed to stand at room temp for 6 hr and then cooled to 0°. It was added in 30 min, dropwise with stirring, to a cold (0°) soln of $H_2SO_4$ (11 ml) in water (50 ml). Stirring was continued for 30 min and the mixture allowed to stand overnight. Then it was diluted with water (800 ml) and extracted with ether. The ethereal soln was washed free of acid and dried. Removal of solvent left a semi-solid which crystallized on Trituration with pet. ether; 3 crystallizations from AcOEt afforded colourless Va (15 mg, 20%), m.p. 186–188°, $\nu_{max}$ 2·9, 5·75, 5·84 μ (KBr). (Found: C, 75·62; H, 9·63. $C_{27}H_{42}O_4$ requires: C, 75·35; H, 9·83%.) Lit. m.p.[21] of kryptogenin, 187–189°, $\nu_{max}$ 5·75, 5·85 μ.

*Diosgenin* (VI). A soln of IVa (50 mg) in EtOH was refluxed with $NaBH_4$ for 3 hr. The mixture was allowed to stand overnight and then decomposed by adding HCl. After 2 hr the separated solid was collected, washed with water and dried (35 mg), m.p. 202–204°. Its IR spectrum corresponded with that of diosgenin. Two crystallizations from acetone furnished a pure sample, m.p. 207–208°, $[\alpha]_D$ −215°; mixed m.p. 207–209°, superimposable IR and identical $R_f$ values.*

*5-Nitro-2S-methylpentanol-1-acetate* (IIIb). This nitro acetate, b.p. 124°/2 mm, $n_D^{23}$ 1·4412, $[\alpha]_D$ −5·0° was obtained from VIIIb *via* the same steps as used for IIIa.

*5-Bromo-2S-methylpentanoic acid* (XIIIb). b.p. 110–112°/1 mm, $n_D^{36}$ 1·4736, $[\alpha]_D$ +11·5°.

*Ethyl-5-bromo-2S-methylpentanoate* (XIVb). b.p. 74–76°/1·5 mm, $n_D^{36}$ 1·4495, $[\alpha]_D$ +13·2°.

*5-Bromo-2S-methylpentanol-1* (XVb). b.p. 79·80°/1·5 mm, $n_D^{26}$ 1·4783, $[\alpha]_D$ +14·0°.

*5-Bromo-2S-methylpentanol-1 acetate* (Xb). b.p. 70–72°/1·5 mm, $n_D^{29}$ 1·4285, $[\alpha]_D$ +3·7°.

*5-Iodo-2S-methylpentanol-1 acetate* (XIIb). b.p. 93–95°/2 mm, $n_D^{32}$ 1·4765.

*Michael addition of* IIIb *to cis-5,17(20)-pregnadien-3β-ol-16-one* (I). A soln of the potassium salt of IIIb (from IIIb, 335 mg, K metal, 25 mg) in t-butyl alcohol (2 ml) was added to a soln of the *cis*-ketone (300 mg) in t-butyl alcohol (2 ml), The mixture was allowed to stand at room temp for 10 days and then acidified with 10% AcOH. As no solid separated, excess water was added and the organic material was taken up in $CH_2Cl_2$. The organic layer was washed, dried and the solvent was evaporated to obtain an oil which was triturated with two 3 ml portions of ether–pet. ether (1:1). The residual gum (375 mg) could not be induced to crystallize, $\nu_{max}$ 5·75, 6·45 μ (film), no absorption at 5·85, 6·0 μ.

* Diosgenin obtained from CIPLA Laboratories, Bombay, was crystallized twice from acetone to get sample for comparison.

*Yamogenin* (VII). A soln of IVb (100 mg) in EtOH (10 ml) was refluxed with $NaBH_4$ for 3 hr. Work up of the reaction afforded a crystalline solid (70 mg) m.p. 195–197°. Two crystallizations from acetone furnished pure yamogenin, mixed m.p. 200–201°, identical IR spectra and $R_f$ values.

## REFERENCES


[1] For a review see L. F. Fieser and M. Fieser, *Steroids* Chap. 21. Reinhold, New York, N.Y. (1959), and C. W. Shopee, *Chemistry of Steroids* (Second Edition), London (1964).
[2] Y. Mazur, N. Danieli and F. Sondheimer, *J. Am. Chem. Soc.* **82**, 5889 (1960).
[3] Part III of this series.
[4] For a general discussion of Michael reaction with nitro alkanes see M. C. Kloetzel, *J. Am. Chem. Soc.* **69**, 2271 (1947), and subsequent papers.
[5] S. V. Kessar, Y. P. Gupta, R. K. Mahajan and A. R. Rampal, *Tetrahedron*
[6] F. Sondheimer and Y. Mazur, *Experientia* **16**, 181 (1960).
[7] R. F. Nystrom, *J. Am. Chem. Soc.* **81**, 610 (1959).
[8] We are grateful to Prof. N. Kornblum of Purdue University for discussion on this point.
[9] F. C. Uhle, *J. Am. Chem. Soc.* **83**, 1460 (1961).
[10] H. Shechter, D. E. Ley and L. Zeldin, *Ibid.* **74**, 3667 (1952).
[11] cf. M. E. Wall *et al.*, *Analyt. Chem.* **24**, 1337 (1952).
[12] W. Cole and P. Jullian, *J. Am. Chem. Soc.* **67**, 1369 (1945).
[13] W. E. Noland, *Chem. Rev.* **55**, 137 (1955).
[14] C. R. Eddy, M. Barnes and C. S. Fenske, *Analyt. Chem.* **27**, 1067 (1955).
[15] J. B. Ziegler, W. E. Rosen and A. C. Shabica, *J. Am. Chem. Soc.* **77**, 1223 (1955).
[16] H. Cardwell, J. Cornforth, S. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.* 361 (1953).
[17] G. I. Fray and N. Polgar, *J. Chem. Soc.* 2036 (1956).
[18] S. Ställberg-Stenhagen, *Arkiv. Kemi. Mineral. Geol.* **A23**, 14 (1946); C.A. **41**, 5443 (1947). S. Ställberg-Stenhagen and E. Stenhagen, *Ibid.* **43B**, 6 (1947); C.A. **42**, 7711 (1948).
[19] G. Ställberg, *Acta. Chem. Scand.* **11**, 1430 (1957).
[20] F. Salmon-Legagneur and C. Neven, *Bull. Soc. Chim. Fr.* 400 (1957).
[21] R. E. Marker, R. B. Wagner, D. P. J. Goldsmith, P. R. Ulshafer and C. H. Rouf, *J. Am. Chem. Soc.* **65**, 779 (1943).