# Synthesis of C-Glycosylindazoles by 1,3-Dipolar Cycloaddition of α-Diazoketoses to Benzynes

*E. García-Abbad, M. T. García-López, G. García-Muñoz (1) and M. Stud*

Instituto Química Médica, Juan de la Cierva, 3, Madrid-6, Spain

Received July 2, 1976

A number of *C*-glycosylindazoles were prepared by 1,3-dipolar cycloaddition of several α-diazoketoses to benzyne. When the cycloaddition reaction was carried out with benzyne derivatives the two possible isomeric indazoles were obtained in most of the cases. Structural assignments were made on the basis of nmr data.

*J. Heterocyclic Chem.*, **13**, 1241 (1976).

Our continued interest in the preparation of *C*-nucleosides and analogous compounds (2) has led us to study the synthesis of *C*-glycosylindazoles.

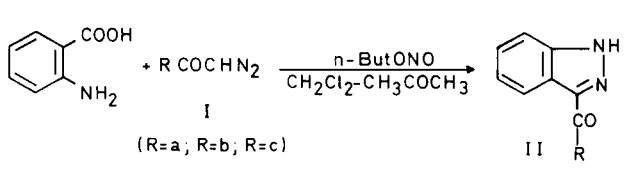
It is known that 1,3-dipolar cycloaddition of diazo compounds to *C*-glycosylacetylenes (2a, 2c, 3) or 1-diazo-1-deoxysugars to alkynes (2c, 4) is a fruitful method for the preparation of pyrazole *C*-nucleosides and analogs. Moreover, reaction of ethyl diazoacetate and diazoketones with benzyne affords indazole derivatives (5).

The present paper describes the 1,3-dipolar cycloaddition of acyclic 1-diazo-1-deoxy-2-ketosugars (I) (R = a; R = b) (6) to benzyne and various substituted benzynes to give *C*-glycosylindazoles with the carbohydrate moiety in the acyclic form. It also describes the addition of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-ribohexofuranosid-5-ulose (I) (R = c) (6) to benzyne to yield the compound II (R = c) in which the indazole system is attached to the C-5 of the sugar.

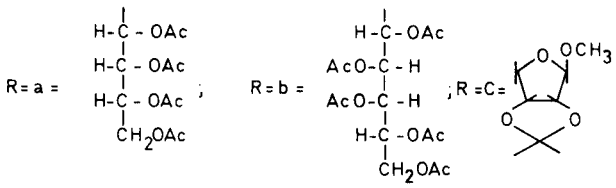
Benzyne was generated following the experimental procedure of Reynolds (8) starting from anthranilic acid and using a mixture of boiling methylene chloride-acetone as the solvent. In the case of being substituted anthranilic acids the aryne precursors, more energical conditions were required, hence a higher boiling solvent (acetonitrile) was employed and the *n*-butyl nitrite was added concurrently with the solution of the corresponding anthranilic acid to minimize the thermally induced decomposition of the alkyl nitrite (9).

In the first series of reactions the α-diazoketoses I (R = a; R = b; R = c) were added to benzyne to afford the expected indazole *C*-nucleoside analogs II (R = a; R = b; R = c) (Scheme I).

SCHEME I



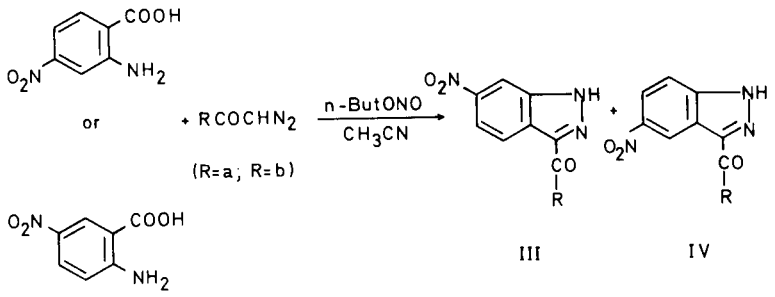

In all the schemes:



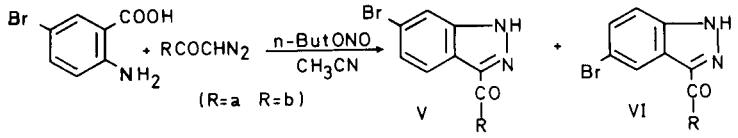

When asymmetrically substituted anthranilic acids were the generating arynes a mixture of the two possible isomeric indazoles was obtained in most of the cases. Thus, reaction of 3,4,5,6,7-penta-*O*-acetyl-1-diazo-1-deoxy-keto-D-*galacto*heptulose (I) (R = b) with 4-nitroanthranilic acid gave the pair of isomers III (R = b) and IV (R = b) in 15% and 10% yields, respectively. The same compounds were obtained (14% of III (R = b) and 6% of IV (R = b)) starting from 5-nitroanthranilic acid. Similar treatment of 3,4,5,6-tetra-*O*-acetyl-1-diazo-1-deoxy-keto-D-psicose (I) (R = a) with 4- or 5-nitroanthranilic acid led in both cases to the isomer III (R = a) in 5% or 3% yield and only traces of the other isomer IV (R = a) were obtained which was identified by means of its nmr spectrum (Scheme II).

In a similar way the addition of the α-diazoketoses I (R = a; R = b) to 5-bromoanthranilic acid gave in both cases the two possible isomeric *C*-glycosylindazoles V (R = a; R = b) and VI (R = a; R = b) (Scheme III).

SCHEME II

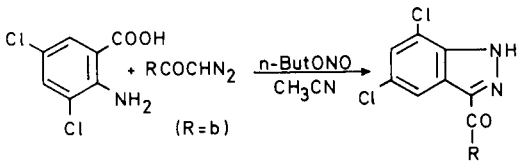



SCHEME III




Finally, when I (R = b) was treated with 3,5-dichloroanthranilic acid under the same conditions as above, only one compound was formed which was identified as VII (R = b) from its nmr spectrum as discussed below (Scheme IV).

SCHEME IV




VII

The structures of the *C*-glycosylindazoles obtained were established on the basis of elemental analysis, infrared data (3260 $cm^{-1}$ NH; 1685 $cm^{-1}$ C=O; 1745 OAc) and nuclear magnetic resonance evidence. The use of nmr was adequate to distinquish the positional isomers taking account of the value of the coupling constant for $H_4$. So, in the case of 5-substituted indazoles (IV, VI and VII) this value was consistent with *meta*-coupled protons ($J_{4,6} \sim 2$ Hz), while those 6-substituted indazoles (III and V) showed for this proton a coupling constant characteristic for an *ortho*-coupling ($J_{4,5} \sim 9$ Hz). It should be noted that, in agreement with the case of the indazole (10), the chemical shift of $H_4$ is the lowest of those of the benzenic ring in all the compounds obtained, exception being III (R = a) in which the chemical shift of $H_7$ is the lowest due to the nitro group in position *ortho* to this proton.

Further work on the reduction of the keto group, deacetylation and subsequent cyclization of the carbohydrate moiety is in progress.

## EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 100 MHz on a Varian XL-100 spectrometer using TMS as internal standard, ultraviolet spectra with a Perkin-Elmer 350 spectrophotometer and the infrared spectra with a Perkin-Elmer 257 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Analytical thin layer chromatography was performed with 0.25 mm chromatoplates of silica gel $GF_{254}$ (Merck) and preparative layer chromatography on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel $PF_{254}$ (Merck). The compounds were detected with uv light of 254 nm or by spraying with sulfuric acid in ethanol, 30%.

General Procedure for the Preparation of the *C*-Glycosylindazoles.

To a stirred, refluxing solution of 6 mmoles of the α-diazoketose and 15 mmoles of recently distilled *n*-butyl nitrite in methylene chloride (25 ml.), a solution of 12 mmoles of anthranilic acid in acetone (15 ml.) was added in the course of two hours. Once the addition was completed, the dark colored mixture was refluxed for two additional hours.

The crude reaction product showed on tlc some starting material (α-diazoketoses), strongly fluorescent products and the expected *C*-glycosylindazole.

The syrupy product that was obtained by evaporation of the solvents under reduced pressure was purified by preparative tlc using the conditions specified in each case.

2,3,4,5-Tetra-*O*-acetyl-1-(indazol-3-yl)-keto-D-ribopentulose (II, R = a).

After ten consecutive developments with a mixture of ether-petroleum ether (1:1), from the second moving band starting from the origin, a syrup was obtained which was crystallized from ethyl acetate-petroleum ether to give II (R = a), m.p. 132°, $[\alpha]_D$ -67 (c 0.94, chloroform), yield, 55%; uv λ max (ethanol): 237 (ε, 8,200), 242 (ε, 8,000), 302 nm (ε, 10,100); nmr (deuteriochloroform): τ 1.81 (dd, 1, $H_4$ indazole ring); 2.62 (broad m, 3,

indazole ring).

*Anal.* Calcd. for $C_{20}H_{22}O_9N_2$: C, 55.29; H, 5.10; N, 6.44. Found: C, 55.51; H, 5.31; N, 6.54.

2,3,4,5,6-Penta-*O*-acetyl-1-(indazol-3-yl)-keto-D-galactohexulose (II, R = b).

The plates were developed twice with a mixture of ether-petroleum ether (2:1), twice with chloroform and three times with a mixture of ether-petroleum ether (1:1). The second moving band starting from the origin gave a syrup which after treatment with active charcoal and successive crystallizations from ethyl acetate-petroleum ether afforded pure II (R = b), m.p. 165-166°, $[\alpha]_D$ +13 (c 0.80, chloroform), yield, 56%; uv λ max (ethanol): 236 (ε, 10,500), 242 (ε, 10,100), 302 nm (ε, 12,700); nmr (deuteriochloroform): τ 1.93 (m, 1, $H_4$ indazole ring), 2.88 (m, 3, indazole ring).

*Anal.* Calcd. for $C_{23}H_{26}O_{11}N_2$: C, 54.54; H, 5.17; N, 5.53. Found: C, 54.62; H, 5.40; N, 5.68.

Methyl 5-Deoxy-5-keto-2,3-*O*-isopropylidene-5-(indazol-3-yl)-β-D-ribotetrafuranoside (II, R = c).

As in the previous cases, the dark oil which was obtained by removal of the solvents was purified by preparative tlc. After three developments with a mixture of ethyl acetate-petroleum ether (1:1) the main fraction furnished a syrup which was treated with active charcoal and crystallized to give II (R = c), m.p. 135° (from methanol-water), $[\alpha]_D$ -18 (c 0.92, chloroform), yield, 20%; uv λ max (ethanol): 215 (ε, 11,100), 237 (ε, 9,100), 242 (ε, 8,700), 302 nm (ε, 10,900); nmr (deuteriochloroform): τ 1.67 (dd, 1, $H_4$ indazole ring), 2.51 (m, 3, indazole ring), 4.32 (d, $J_{4',3'}$ = 1 Hz, 1, $H_4'$), 4.40 (dd, $J_{3',2'}$ = 6 and $J_{3',4'}$ = 1 Hz, 1, $H_3'$), 4.84 (s, 1, $H_1'$), 5.34 (d, $J_{2',3'}$ = 6 Hz, 1, $H_2'$), 6.84 (s, 3, $OCH_3$), 8.36 and 8.60 (s, 6, $CH_3$ isopropylidene group).

*Anal.* Calcd. for $C_{16}H_{18}O_5N_2$: C, 60.36; H, 5.69; N, 8.80. Found: C, 60.48; H, 5.58; N, 8.80.

General Procedure for the Preparation of the Substituted *C*-Glycosylindazoles.

To a mechanically stirred refluxing solution of 2.5 mmoles of the α-diazoketosugar in acetonitrile (15 ml.), contained in a three-necked flask, 5 mmoles of the corresponding substituted anthranilic acid in acetonitrile (50 ml.) and 6.2 mmoles of freshly distilled *n*-butyl nitrite was added dropwise over a period of one hour. Once the addition was completed, the dark colored mixture was refluxed for two hours.

The crude reaction product showed on tlc some starting materials, strongly fluorescent products and the expected indazole-*C*-nucleoside analogs which were separated and purified using the conditions specified in each case.

2,3,4,5-Tetra-*O*-acetyl-1-(6-nitroindazol-3-yl)-keto-D-ribopentulose (III, R = a).

A. From 4-Nitroanthranilic Acid.

The residue obtained by evaporation of the solvent under reduced pressure was chromatographed on preparative tlc plates (ethyl acetate-petroleum ether, 1:1, three developments). The following moving band to the α-diazoketosugar I (R = a) starting from the origin furnished a glass which was rechromatographed (ether-petroleum ether, 1:1, three developments) to give III (R = a) as a homogeneous syrup which crystallized on standing, m.p. 135°, $[\alpha]_D$ -74 (c 0.57, chloroform), yield, 5%; uv λ max (ethanol): 225 (ε, 7,400) (sh), 272 (ε, 22,500), 335 nm (ε, 3,000) (sh); nmr (deuteriochloroform): τ 1.48 (d, $J_{7,5}$ = 2 Hz, 1, $H_7$ indazole ring), 1.74 (d, $J_{4,5}$ = 9 Hz, 1, $H_4$ indazole ring), 1.94 (dd, 1, $H_5$ indazole ring).

*Anal.* Calcd. for $C_{20}H_{21}O_{11}N_3$: C, 50.10; H, 4.41; N, 8.76. Found: C, 50.27; H, 4.39; N, 8.97.

Traces were found of the other possible isomer, less polar than III (R = a), namely 2,3,4,5-tetra-*O*-acetyl-1-(5-nitroindazol-3-yl)-keto-D-ribopentulose (IV) (R = a); nmr (deuteriochloroform): τ 1.07 (d, $J_{4,6}$ = 2 Hz, 1, $H_4$ indazole ring), 1.78 (dd, 1, $H_6$ indazole ring), 2.42 (d, 1, $H_7$ indazole ring). This compound was not further investigated because of the very small amount.

B. From 5-Nitroanthranilic Acid.

Preparative tlc of the residue obtained after evaporation of the solvent (ether-petroleum ether, 1:1, five developments) gave III (R = a) in 3% yield and traces of IV (R = a), identical with those compounds above described.

2,3,4,5,6-Penta-*O*-acetyl-1-(6-nitroindazol-3-yl)-keto-D-galactohexulose (III, R = b) and 2,3,4,5,6-Penta-*O*-acetyl-1-(5-nitroindazol-3-yl)-keto-D-galactohexulose (IV, R = b).

A. From 4-Nitroanthranilic Acid.

The solvent was removed and the residue was chromatographed by preparative tlc using four times a mixture of ether-petroleum ether (3:1). The more polar isomer III (R = b) was rechromatographed (ether-petroleum ether, 3:1, three developments). Treatment with active charcoal and crystallization from benzene-cyclohexane gave III (R = b), m.p. 142-143°, $[\alpha]_D$ + 14 (c 0.49, chloroform), yield, 15%; uv λ max (ethanol): 229 (ε, 7,000) (sh), 273 (ε, 23,300), 340 nm (ε, 3,000) (sh); nmr (deuteriochloroform): τ 1.86 (d, $J_{4,5}$ = 9 Hz, 1, $H_4$ indazole ring), 2.10 (m, 2, indazole ring).

*Anal.* Calcd. for $C_{23}H_{25}O_{13}N_3$: C, 50.09; H, 4.56; N, 7.62. Found: C, 49.83; H, 4.33; N, 7.37.

The less polar isomer IV (R = b) was rechromatographed (ether-petroleum ether, 3:1, three developments). After treatment with active charcoal and crystallization afforded pure IV (R = b), m.p. 97-99° (from benzene-petroleum ether), $[\alpha]_D$ +6 (c 0.52, chloroform), yield, 10%; uv λ max (ethanol): 234 (ε, 11,000), 265 (ε, 10,700), 310 nm (ε, 6,500); nmr (deuteriochloroform): τ 1.14 (d, $J_{4,6}$ = 1.5 Hz, 1, $H_4$ indazole ring), 2.00 (dd, 1, $H_6$ indazole ring), 2.78 (d, 1, $H_7$ indazole ring).

*Anal.* Calcd. for $C_{23}H_{25}O_{13}N_3$: C, 50.09; H, 4.56; N, 7.62. Found: C, 50.27; H, 4.80; N, 7.50.

B. From 5-Nitroanthranilic Acid.

Thick layer chromatography after two developments with ether-petroleum ether (2:1) and two developments with ether-petroleum ether (4:1) was successful in resolving the mixture of the crude reaction product.

Each indazole-*C*-nucleoside analog was purified as in A to give 14% yield of III (R = b) and 6% yield of IV (R = b) identical with those above described.

2,3,4,5-Tetra-*O*-acetyl-1-(6-bromoindazol-3-yl)-keto-D-ribopentulose (V, R = a) and 2,3,4,5-Tetra-*O*-acetyl-1-(5-bromoindazol-3-yl)-keto-D-ribopentulose (VI, R = a).

The solvent was removed and the residue applied on preparative tlc plates which were developed three times with a mixture of ethyl acetate-petroleum ether (1:1).

The more polar isomer V (R = a) was rechromatographed (ethyl acetate-petroleum ether, 1:1, three developments), treated with active charcoal and crystallized from ethyl acetate-petroleum ether, m.p. 168-169°, $[\alpha]_D$ -59 (c 0.58, chloroform), yield, 15%; uv λ

max (ethanol): 222 ($\epsilon$, 14,000), 244 ($\epsilon$, 14,000), 249 ($\epsilon$, 14,000), 301 nm ($\epsilon$, 11,800); nmr (deuteriochloroform): $\tau$ 2.03 (d, $J_{4,5}$ = 9 Hz, 1, $H_4$ indazole ring), 2.35 (d, 1, $H_7$ indazole ring), 2.71 (dd, 1, $H_5$ indazole ring).

*Anal.* Calcd. for $C_{20}H_{21}BrO_9N_2$: C, 46.78; H, 4.12; N, 5.45; Br, 15.58. Found: C, 46.61; H, 4.19; N, 5.35; Br, 15.73.

The less polar isomer VI (R = a) was obtained from the first chromatography as a chromatographically homogeneous amorphous solid, $[\alpha]_D$ -34 (c 0.90, chloroform), yield, 5%, uv $\lambda$ max (ethanol): 222 ($\epsilon$, 14,500), 241 ($\epsilon$, 10,000), 248 ($\epsilon$, 9,900), 292 ($\epsilon$, 7,200) (sh), 301 nm ($\epsilon$, 9,200); nmr (deuteriochloroform): $\tau$ 1.81 (d, $J_{4,6}$ = 2 Hz, 1, $H_4$ indazole ring), 2.60 (m, 2, indazole ring).

*Anal.* Calcd. for $C_{20}H_{21}BrO_9N_2$: C, 46.78; H, 4.12; N, 5.45; Br, 15.58. Found: C, 47.01; H, 4.27; N, 5.70; Br, 15.84.

2,3,4,5,6-Penta-*O*-acetyl-1-(6-bromoindazol-3-yl)-keto-D-galactohexulose (V, R = b) and 2,3,4,5,6-Penta-*O*-acetyl-1-(5-bromoindazol-3-yl)-keto-D-galactohexulose (VI, R = b).

The residue obtained after removal of the solvent was chromatographed on silica gel plates which were developed one time in a mixture of ethyl acetate-petroleum ether (1:2) and three times in a mixture of ethyl acetate-petroleum ether (1:1).

Subsequent purification of the more polar acyclic-sugar nucleoside derivative V (R = b) by preparative tlc (ethyl acetate-petroleum ether, 1:1, four developments) and treatment with active charcoal afforded V (R = b), m.p. 94-96° (from methanol-water), $[\alpha]_D$ +18 (c, 0.72, chloroform), yield, 5%; uv $\lambda$ max (ethanol): 222 ($\epsilon$, 12,500), 243 ($\epsilon$, 12,600), 249 ($\epsilon$, 12,500), 301 nm ($\epsilon$, 10,500); nmr (deuteriochloroform): $\tau$ 2.09 (d, $J_{4,5}$ = 9 Hz, 1, $H_4$ indazole ring), 2.73 (dd, 1, $H_5$ indazole ring), 2.93 (d, 1, $H_7$ indazole ring).

*Anal.* Calcd. for $C_{23}H_{25}BrO_{11}N_2$: C, 47.18; H, 4.30; N, 4.78; Br, 13.65. Found: C, 47.46; H, 4.43; N, 4.46; Br, 13.38.

The less polar acyclic-sugar nucleoside derivative VI (R = b) was further purified in identical way with V (R = b) above described, m.p. 155° (from methanol), $[\alpha]_D$ +21 (c 0.70, chloroform), yield, 4%; uv $\lambda$ max (ethanol): 220 ($\epsilon$, 16,100), 240 ($\epsilon$, 9,500), 247 ($\epsilon$, 9,100), 290 ($\epsilon$, 6,700) (sh), 320 nm ($\epsilon$, 8,300); nmr (deuteriochloroform): $\tau$ 1.85 (d, $J_{4,6}$ = 2 Hz, 1, $H_4$ indazole ring), 2.81 (dd, 1, $H_6$ indazole ring), 3.20 (d, 1, $H_7$ indazole ring).

*Anal.* Calcd. for $C_{23}H_{25}BrO_{11}N_2$: C, 47.18; H, 4.30; N, 4.78; Br, 13.65. Found: C, 47.37; H, 4.27; N, 4.86; Br, 13.70.

2,3,4,5,6-Penta-*O*-acetyl-1-(5,7-dichloroindazol-3-yl)-keto-D-galactohexulose (VII, R = b).

This compound was isolated by preparative tlc (ethyl acetate-petroleum ether, 3:1, three developments) from the residue obtained after removal of the solvent. Crystallization from ethyl acetate-petroleum ether gave VII (R = b), m.p. 157-159°, $[\alpha]_D$ +7 (c 0.51, chloroform), yield, 12%; uv $\lambda$ max (ethanol): 217 ($\epsilon$, 17,300), 244 ($\epsilon$, 8,900), 250 ($\epsilon$, 9,200), 295 ($\epsilon$, 5,800) (sh), 316 nm ($\epsilon$, 8,200); nmr (deuteriochloroform): $\tau$ 1.98 (d, $J_{4,6}$ = 2 Hz, 1, $H_4$ indazole ring), 2.93 (d, 1, $H_6$ indazole ring).

*Anal.* Calcd. for $C_{23}H_{24}Cl_2O_{11}N_2$: C, 48.00; H, 4.17; N, 4.86; Cl, 12.34. Found: C, 48.30; H, 4.17; N, 4.70; Cl, 12.46.

## REFERENCES AND NOTES

(1) The present paper is dedicated to the memory of Professor García-Muñoz.

(2a) M. T. García-López, G. García-Muñoz and R. Madroñero, *J. Heterocyclic Chem.*, **8**, 525 (1971); (b) M. Fuertes, M. T. García-López, G. García-Muñoz and R. Madroñero, *J. Carbohydr. Nucleosides, Nucleotides*, **2**, 277 (1975); (c) M. T. García-López, G. García-Muñoz and R. Madroñero, *An. Quim.*, in press; (d) M. Fuertes, M. T. García-López, G. García-Muñoz and M. Stud, *J. Org. Chem.*, in press.

(3) F. G. de las Heras, S. Y-K. Tam, R. S. Klein and J. J. Fox, *J. Org. Chem.*, **41**, 84 (1976).

(4) E. M. Acton, K. J. Ryan, D. W. Henry and L. Goodman, *Chem. Commun.*, 986 (1971); M. Bobek, J. Farkas and F. Sorm, *Tetrahedron Letters*, 4611 (1970); J. Farkas and F. Sorm, *Collect. Czech. Chem. Commun.*, **37**, 2798 (1972); M. Sprinzi and J. Farkas, *ibid.*, **32**, 3787 (1967).

(5) R. Huisgen and R. Knorr, *Naturwissenschaften*, **48**, 716 (1961); W. Ried and M. Schön, *Ann. Chem.*, **689**, 141 (1965).

(6) M. L. Wolfrom, A. Thompson and E. F. Evans, *J. Am. Chem. Soc.*, **67**, 1795 (1945); M. L. Wolfrom, J. M. Berkebile and A. Thompson, *ibid.*, **71**, 2360 (1949).

(7) A. Hampton, F. Perini and P. J. Harper, *Carbohydr. Res.*, **37**, 359 (1974).

(8) G. A. Reynolds, *J. Org. Chem.*, **29**, 3733 (1964).

(9) L. Friedman and F. M. Logullo, *ibid.*, **34**, 3089 (1969).

(10) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **16**, 105 (1963).